Cardiology Research and Practice

Hemodynamic Monitoring

Guest Editors: Antoine Vieillard-Baron, Anthony McLean, Paul Mayo, and Philippe Vignon

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Editorial Board

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Editorial
Hemodynamic Monitoring

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This special issue is dedicated to hemodynamic monitoring. Papers include didactic papers and original clinical studies which originate from 6 countries in 3 continents (USA, Sweden, England, France, Portugal, and Australia). This reflects the worldwide interest of ICU physicians for this type of monitoring. This renewed interest for the hemodynamic monitoring is presumably due to the emergence of new technologies and concepts which can easily be implemented on clinical grounds by the intensivist to better guide acute therapy in shocked patients. New concepts, because functional hemodynamic monitoring and preload responsiveness, rather than the traditional preload assessment, are widely proposed as an attractive alternative to the conventional static approach of hemodynamic assessment. New technologies, because minimally or noninvasive techniques, such as, echocardiography, have yet gained wide acceptance and provide unparalleled information when compared to conventional invasive monitoring techniques (right-heart catheterization). For instance, critical care echocardiography has been defined as an echocardiography performed by intensivists themselves at the bedside to evaluate hemodynamics [1, 2].

This special issue emphasizes the recent conceptual evolution of hemodynamic monitoring in the ICU setting. Historically, hemodynamic monitoring was based on a quantitative approach which relied on static parameters obtained by invasive methods, whereas the modern approach is rather functional and based on dynamic indices derived from heart-lung interactions, especially in mechanically ventilated patients. Accordingly, this special issue may help the reader to understand step by step this in-depth conceptual evolution.

A. Napoli reviewed most of these concepts. In their contribution, S. Huang and A. Mclean focused on a practical approach of hemodynamic monitoring based on transthoracic echocardiography, while M. Chew proposed a larger routine use of echocardiography. P. Squara and C. Waldmann suggested that the development of new monitors allowing to less invasively measure cardiac output should be integrated in clinical practice to obtain an exhaustive, real-time, hemodynamic assessment which they coined "intelligent hemodynamic monitoring". How to guide fluid resuscitation is also debated, either when using $ScVO_2$ as suggested by S. Nebout and R. Pirracchio, or by testing the circulatory system to identify fluid responsiveness. L. Levitov and P. Marik reviewed the echocardiographic assessment of fluid responsiveness, using either the transthoracic or the transesophageal route. S. Préau et al. proposed to use pulse pressure variations and respiratory changes of peak velocity of Doppler arterial flow to identify potential fluid responders in spontaneously breathing patients during a standardized deep inspiration effort. F. Pissarra et al. reviewed the clinical value of transesophageal echocardiography in the operating room to optimize hemodynamics. R. Maharaj reviewed the clinical interest of extravascular lung water assessment in patients with acute lung injury.

Overall, the current special issue on hemodynamic monitoring emphasizes its clinical utility and describes currently

available tools, while discussing the evolving concepts which mainly rely on the use of combined parameters to predict fluid responsiveness and on the assessment of both the efficacy and tolerance of blood volume expansion to guide fluid therapy and ultimately patient's acute care.

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References

[1] P. H. Mayo, Y. Beaulieu, P. Doelken et al., "American college of chest physicians/la societédé réanimation de langue française statement on competence in critical care ultrasonography," *Chest*, vol. 135, no. 4, pp. 1050–1060, 2009.

[2] Expert round table on ultrasound in ICU, "International expert statement on training standards for critical care ultrasonography," *Intensive Care Medicine*, vol. 37, no. 7, pp. 1077–1083, 2011.

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Clinical Study

Transoesophageal Echocardiography for Monitoring Liver Surgery: Data from a Pilot Study

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A pilot study aimed to introduce intraoperative monitoring of liver surgery using transoesophageal echocardiography (TEE) is described. A set of TEE measurements was established as a protocol, consisting of left atrial (LA) dimension at the aortic valve plane; mitral velocity flow integral, calculation of stroke volume and cardiac output (CO); mitral annular plane systolic excursion; finally, right atrial area. A total of 165 measurements (on 21 patients) were performed, 31 occurring during hypotension. The conclusions reached were during acute blood loss LA dimension changed earlier than CVP, and, in one patient, a dynamic left ventricular (LV) obstruction was observed; in 3 patients a transient LV systolic dysfunction was documented. The comparison between 39 CO paired measurements obtained by TEE and PiCCO2 revealed a statistically significant correlation ($P < 0.001$, $r = 0.83$). In this pilot study TEE successfully answered the questions raised by the anesthesiologists. Larger cohort studies are needed to address this issue.

1. Introduction

In major surgery haemodynamic complications are likely to occur; hence for this reason monitoring is necessary to trace physiological parameters. There are several commercially available monitoring systems, but transoesophageal echocardiography (TOE) was not as extensively studied in noncardiac [1] as it was in cardiac surgery [2–5]. Due to its unique ability for cardiac imaging, assessing left ventricular (LV) function and right heart chambers dimensions, it is considered promising [5].

The questions faced by anaesthesiologists in noncardiac surgery are quite different from those in cardiac surgery, where valvular diseases, prosthesis placement and complications are the most relevant. Questions on LV function or acute change in volume status and hypotension are more concerning in noncardiac surgery. Good candidates for such monitoring are patients submitted to major surgery, especially those undergoing liver surgery or even transplantation [6–8]. During this type of surgery, haemodynamic instability can occur during liver manipulation or due to associated blood loss.

In our centre, the usual means for monitoring include the continuous monitoring of the central venous pressure (CVP) and, in selected cases, the continuous monitoring of cardiac output (CO) through the use of the PiCCO system. Pulmonary artery catheters, used more often in the past, are now seldom used. As resident anaesthesiologists felt an increasing need for a more accurate monitoring, a pilot study aimed to introduce intraoperative monitoring of liver surgery using TOE was performed. This study was aimed to evaluate the place of TOE for liver surgery monitoring and to compare efficiency of TOE measurements with PVC and PiCCO to diagnose hemodynamic instability causes. A set of TOE measurements was established as a protocol, after previous discussion with the anaesthesiology staff about the required information. A comparison between the information derived from the monitoring devices used was also performed.

2. Material and Methods

2.1. Patients. This was a 1-year prospective study, which included patients submitted to liver surgery and enrolled without previous selection, although limited to the availability of

the anesthesiologists (FP and AO), intensive care specialist with expertise in the area (PM), and echocardiography equipment. This pilot study was open with the anaesthesiologists being aware of TOE information. All data was digitally recorded for later visualisation, if deemed necessary.

Patients were characterized by age, gender, and body surface area. Main diagnoses (for surgical purposes) and comorbidities were also collected. The main demographic and clinical characteristics of the enrolled patients are presented in Table 1.

The study protocol was reviewed by the local Ethics Board, and an informed statement was obtained previous to surgery.

2.2. Methods. During liver surgery, hypotension and liver manipulation (reported by the surgeons) were the most regarded situations. Hypotension was considered when mean arterial blood pressure was 60 mmHg or lower, and data was thoroughly analysed. Blood loss was considered either by the reports from the surgeons or by a decrease in haemoglobin levels of more than 2 gr/dL. Other possible aetiologies were evaluated according to the available monitoring devices.

Patients were anaesthetised using a general balanced anaesthesia, having been intubated after anaesthesia induction.

CVP monitoring was performed continuously using a central venous line connected to a Philips M4 monitor, where the arterial pressure and heart rate were also registered. The arterial pressure was monitored invasively using an arterial catheter inserted into a radial or femoral artery. The invasive CO, when used, was determined using a PiCCO 2 system, for which a central venous line and a femoral arterial line were inserted and then calibrated according to the manufacturer's instructions.

2.3. Echocardiography. The TOE monitoring was performed using a Siemens ACCUSON X300 and a General Electric LOGIC P6, both equipped with a multiplane transoesophageal probe.

Before the study started, a consensus was established with the anaesthesiologists to determine the information needed for monitoring. The information considered necessary was previous surgery knowledge of the heart anatomy and function; CO; left ventricular (LV) performance; data on volume status; right heart chamber evaluation. Special concern was addressed to the TOE parameters; they needed to be easily obtained, not time consuming, in order to permit quick therapeutic decisions. It was also established that intragastric views should not be used so as to avoid interference with the surgical field. The choice of invasive monitoring was carried out by the anaesthesiologist's judgement and independent of study purposes.

After anaesthesia induction, a transoesophageal probe was inserted and the first images obtained. A global examination was first performed and global and segmental wall motion abnormalities were evaluated, as well as valvular regurgitations. The following sets of measurements were chosen in order to obtain the information previously required by the anaesthesiologists. The CO was obtained through the mitral velocity time integral (VTI), measured as follows. First the left ventricular influx by evaluation of the mitral E/A ratio in the 4-chamber view was analysed. Secondly, left ventricular CO was assessed by measuring the mitral VTI, calculating the stroke volume index (SVI) and multiplying it by heart rate (Figure 1). Necessary information with regards to the width of the mitral valve orifice was measured in the same view (Figure 2). The LV function was assessed through the external mitral annulus systolic excursion (MAPSE, considered the most feasible parameter compared to ejection fraction and other volumetric parameters) obtained in the same 4-chamber view. At the aortic valve plane, during diastole when the three aortic cuspids were visible, visible left atrium (LA) area and dimension, obtained from the LA first echo to aortic valve (Figure 3), were determined. Lastly, the assessment of right heart chambers was performed; the probe was repositioned for the assessment of the right atrium and ventricle. The measurement of the right atrial area was emphasized (Figure 4). All TOE measurements were performed at end-expiration, and other changes detected during TOE were registered. TOE evaluation was performed routinely every 15 minutes of surgery or whenever considered necessary if hypotension, blood loss, or liver manipulation were reported.

An LV systolic dysfunction was considered whenever MAPSE was <15 mm, and CO <2,4 L/m^2. LA and RA dimensions were considered the TOE surrogates for volume status and preload determination and regarded as changes from the previous measurements.

2.4. Statistical Analysis. All variables are presented as mean and standard deviations. To compare continuous variables, parametric and nonparametric statistical tests were used, calculating the correlation index (r) and P value, which were considered significant if <0.05. The statistical program used was an SPSS for Windows, version 18.0 (SPSS Inc, Chicago, Illinois). Comparisons were made between data from TOE and usual monitored parameters. The parameters compared were CO analysis by PiCCO and TOE whenever available and preload assessment comparing CVP with LA and RA measurements, as well as its changes during acute phenomena.

Table 1: Demographic and clinical characterization of studied patients ($n = 21$).

Age (years, mean, and sd)	54.1 ± 17.6
Male (n)	12
Body surface area (m^2, mean and sd)	1.73 ± 0.17
Liver resection due to metastatic disease (n)	14
Liver resection due to other diseases (n)	4
Liver transplant (n)	3
Past history:	
Coronary artery disease	1
Hypertension	2
Diabetes mellitus	2
Other	1

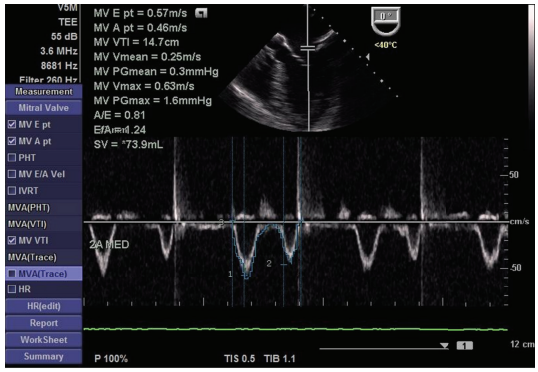

Figure 1: Determination of the mitral VTI.

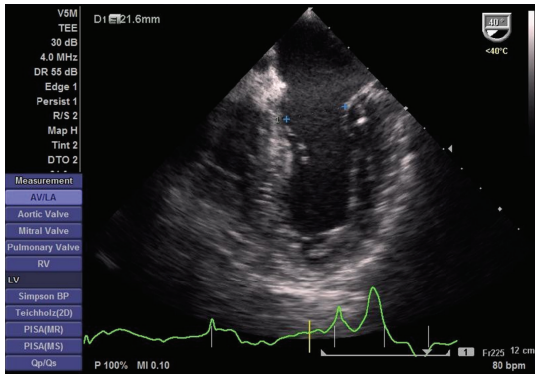

Figure 2: Determination of the mitral annulus diameter.

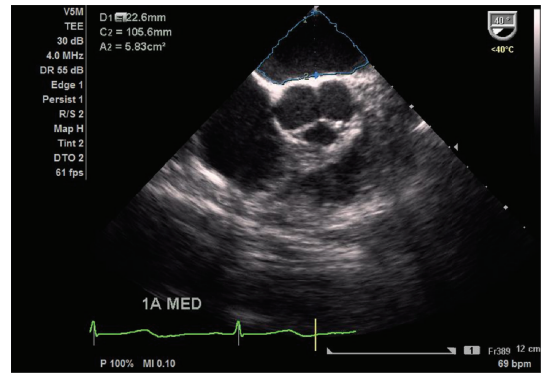

Figure 3: Determination of visible LA area and dimension (distance from the first echo from LA to aortic valve) in the aortic plane.

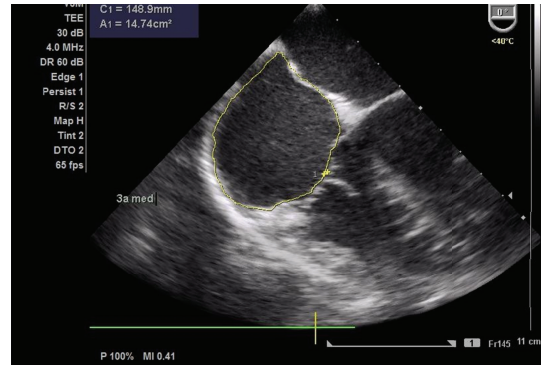

Figure 4: Determination of the right atrial area.

3. Results

Overall, 165 TEE dataset measurements were performed, and in 5 patients a PiCCO2 system was present. Overall, 31 registries were performed during hypotension. Of these, 16 (5 patients) were due to hemorrhage, 9 (5 patients) without obvious cause, and 6 (4 patients) due to liver manipulation.

In the haemorrhage evaluation the LA and RA dimensions decreased in all patients, as well as CVP, but it occurred simultaneously in only two occasions. In the remaining measurements ($n = 29$), TOE modifications preceded CVP changes by 10 to 15 minutes. In Table 2, and in Figure 5, a graphic representing a registry during an acute blood loss and changes in CVP and visible LA area and dimension is presented. It was also observed that the LA dimension decreased almost uniformly by nearly 20% (19.8% ± 0.9). The comparative data of the parameters previous to haemorrhage and during haemorrhage is presented.

There were 6 cases of liver manipulation. In two episodes hypotension occurred without changes in CVP. Interestingly, LA and RA dimensions decreased during liver manipulation, but CVP and CO remained unchanged. The comparative data obtained previous to and during liver manipulation are presented in Table 3.

In 9 cases (5 patients), a hypotensive episode was documented without blood loss. Within this group, in two cases a typical change in volume status was detected by TOE, but not by CVP; in one case, a decreased volume status was identified by both methods; in two cases there was no change observed by the two methods; in three episodes (3 patients) a systolic dysfunction was detected by TOE (decrease in CO and MAPSE) in patients with previous normal LV contractility. This LV dysfunction was transient and, due to global LV hypokinesia, the recovery was observed within a few minutes. No apparent cause for this phenomenon was detected.

Only one patient presented an LV dysfunction, detected previous to surgery, suffering from ischemic heart disease. During surgery, hypotension was detected during a massive blood loss, and LV dysfunction exacerbated, along with exacerbated wall motion abnormalities. Vasopressor and inotropic support was started, some recovery of LV contractility was observed but the patient remained hypotensive. This patient died in the early postoperative period in the Intensive Care Unit.

Overall, TOE-derived CO varied more markedly than PiCCO2-derived; the mitral E/A wave form changed during anaesthesia induction and remained less than one during most part of the surgery. The first obtained mean values for this parameter were 0.99 ± 0.47 and for the remaining 0.83 ± 0.36 ($P = 0.001$). However no relevant information could be obtained from this parameter during surgery, even during hypotension/blood losses.

By linear regression analysis, considering CVP as a dependent variable and LA dimension and RA area as in-

Table 2: Comparison of hemodynamic and echocardiographical data in hypotension due to blood losses (16 sets of measurements in 5 patients).

Parameter	Data before hypotension	Data during hypotension	P
HR (bpm)	71.7 ± 9.4	74 ± 11.8	ns
CVP (mmHg)	6.7 ± 1.9	5.2 ± 2.2	0.01
LA area (cm^2)	9.1 ± 3.5	5.4 ± 2.2	0.001
LA dimension (mm)	28.5 ± 4.7	22.8 ± 4.3	0.001
RA area (cm^2)	15.1 ± 2.4	13.8 ± 2.6	0.01
Mitral E/A	0.73 ± 0.33	0.76 ± 0.34	ns
PiCCO CO (mL/min)	4322 ± 452	3921 ± 404	0.001
TOE CO (L/min)	4571 ± 472	3622 ± 463	<0.001
MAPSE (mm)	16.2 ± 0.9	16.1 ± 1.3	ns

HR: heart rate, bpm: best per minute, CVP: central venous pressure, LA: left atrium, RA: right atrium, TOE: transoesophageal echocardiography, MAPSE: mitral annulus systolic excursion, cm^2: squared centimetres, mm: millimeters, and mL/min: mililiters per minute.

Table 3: Comparison of hemodynamic and echocardiographical data during liver manipulation (6 sets of measurements in 4 patients).

Parameter	Data before liver manipulation	Data during liver manipulation	P
HR (bpm)	69 ± 7.6	72.2 ± 9.1	ns
CVP (mmHg)	6.1 ± 1.1	6.1 ± 1.8	ns
LA area (cm^2)	9.9 ± 3.2	6.2 ± 3.4	0.003
LA dimension (mm)	28.4 ± 3.9	25.2 ± 4.1	0.005
RA area (cm^2)	15.6 ± 2.2	15.3 ± 2	ns
Mitral E/A	0.77 ± 0.3	0.84 ± 0.39	ns
PiCCO CO (mL/min)	4020 ± 397	4150 ± 425	ns
TEE CO (L/min)	4286 ± 438	4481 ± 467	ns
MAPSE (mm)	16.4 ± 01.1	15.4 ± 1.2	ns

HR: heart rate, bpm: best per minute, CVP: central venous pressure, LA: left atrium, RA: right atrium, TOE: transoesophageal echocardiography, MAPSE: mitral annulus systolic excursion, cm^2: squared centimetres, mm: millimeters, and mL/min: milliliters per minute.

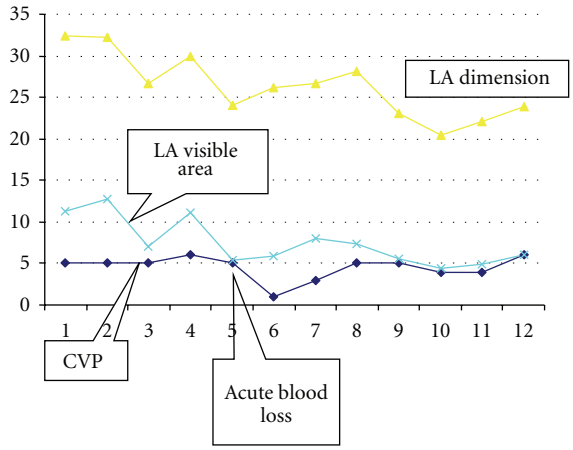

Figure 5: Line graphic of a patient with an episode of acute blood loss, comparing the time of CVP, LA dimension, and visible LA area changes. Note that the LA parameters changed earlier than CVP.

dependent variables, a significant association was found between CVP and RA area ($P = 0.001$), but not between CVP and LA dimension ($P = 0.07$).

In 5 patients a comparison of the CO by TEE and PiCCO was possible, consisting in 39 paired simultaneous measurements. In Figure 6 the linear correlation is presented; the P value is <0.001, and the correlation coefficient was 0.83 (Figure 6). The mean error between CO obtained by TOE and PiCCO2 was 63.6 ± 528.2 (limits: −1722 to 1230).

4. Discussion

Data from this pilot study highlighted several possibilities of TOE as an intraoperative monitoring tool for liver surgery. It also brings some new data that would be subjected to further studies and analyses. The hypotension episodes observed tested the clinical utility of TOE monitoring. It could effectively detect changes in CO and detected changes in volume status earlier than comparative pressure-derived methods, along with the LV function monitoring.

The assessment of volume status is a major concern for any surgery. CVP monitoring was the "standard" method used. The comparative analysis of invasive and noninvasive parameters revealed some new data. In most cases of acute volume loss, as seen in major haemorrhage, LA dimensions changes were observed earlier, by 10 to 15 minutes, which

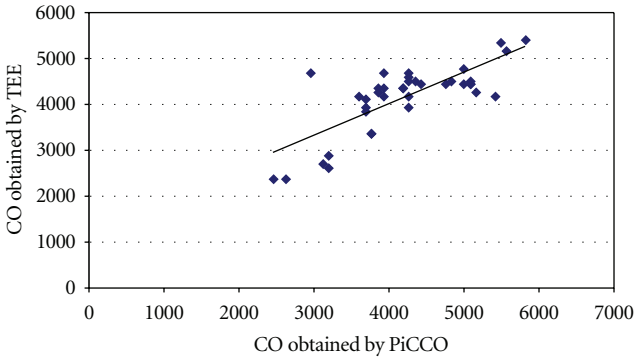

Figure 6: Dispersion graphic comparing the cardiac output obtained by PiCCO2 and TEE ($P < 0.001$, $r = 0.83$).

may be considered an early adaptive phenomenon in order to ensure LV filling pressure (during volume loss the decrease in LA dimension prevents further decrease in LA pressure and consequent LV filling pressure). Interestingly, the same changes were observed during liver manipulation, which results in decreased preload due to vascular compression. This information is important and allows the anaesthesiologist to anticipate adequate therapeutic actions. To our knowledge, this finding has not yet been described in the literature. However, RA area was the parameter with a statistically significant association with CVP, not the LA dimension.

The present study evaluated preload not preload dependency, using comparative data from static parameters. Among the possible parameters, left ventricular end diastolic area (LVEDA) could not be considered as transgastric views were not obtained [9]. Dynamic concepts for fluid administration [10, 11] and preload dependency were not also considered in the present study. Only when PiCCO system was inserted could the anaesthesiologists evaluate the systolic volume variation, and fluids were often administered whenever this parameter was >15%, regardless of haemodynamic status. Several TOE parameters can be used to assess preload dependency [12, 13], and in some settings they were used to guide intraoperative fluid administration. In this regard we must consider that the protocol was formulated in order to detect and characterize acute changes, not to guide fluid administration. The emphasis was acute volume loss mainly blood losses that should be rapidly treated. In other words, we focused on acute phenomena.

CO has gained particular attention as a way of accessing the global circulatory status, but how accurately this variable measures the adequacy of circulatory flow is yet to be established. Perhaps the usefulness of CO consists in detecting changes in this variable during surgery, especially during episodes of instability. Considering this as the main use of CO monitoring, the changes are more important than its absolute value. Using TEE, CO was monitored through the mitral pulsed-Doppler influx, an occasionally used method [14, 15]. In this method mitral valve annulus was used as a surrogate for cross-sectional area. The accuracy of mitral valve stroke volume is debatable. The mitral valve orifice does not have a perfect geometrical shape; thus it is not used by investigators. As we decided not to use intragastric views in order not to interfere with surgery, this was the possible, non-time-consuming method. The correlation obtained with the PiCCO system was statistically significant ($P < 0.001$), with r value of 0.83. Although the methods are different the importance of this parameter is its changes during acute events, and in this regard both methods were reliable, although TOE-derived CO presented greater variability than PiCCO-derived CO.

Left ventricular function was monitored through mitral valve annular plane systolic excursion, a method widely used and tested [16, 17]. The LV function monitoring ability is perhaps one of the most important features of TOE monitoring. No other means is comparable not even the classic methods. It was a valuable tool in the approach of hypotension in one patient, guiding inotropic and vasopressor support and detecting a transient LV dysfunction in other 3 episodes of hypotension. This detection was only possible because TOE monitoring was present, and we could not detect a cause for this phenomenon. Also, we could not find a similar description in the literature. Although an experienced observer could detect changes in LV function subjectively, MAPSE was used in this pilot study as an objective measurement. One should remember that LV systolic dysfunction can also be easily detected by simultaneous changes in mitral VTI and MAPSE.

Other possibilities of TOE were not observed in this study, for example, the detection of right heart overload and alterations in cardiac chambers, mainly due to gas embolism or thrombus formation. In a larger cohort study they could possibly be observed.

5. Study Limitations

In this pilot study the preload determination was considered rather than preload dependency. The invasive counterpart for preload dependency estimation can be the systolic volume variation, and several TOE parameters can be used to evaluate, such as the analysis of superior vena cava, an easy procedure to carry out during TOE examination. This need was not particularly expressed by anaesthesiologists, more focused on acute and life-threatening phenomena and LV function. But in future protocols this item can be used. Some other measurements could be considered but, as we limited the information to a non-time-consuming acquisition in order to describe an easy-to-use tool during anaesthesia, most information was limited. More complex data can be obtained through this technique which, yet due to time constraints typical of an operating theatre, went beyond the scope of this study.

In the future it is also necessary to enrol patients who present atrial fibrillation, in order to fully understand the limitations of TOE monitoring.

Another question regards TOE possibilities. Right heart dysfunction and/or overload could not be detected in the patients studied, but it can be an advantage in the use of TOE. Other conditions resulting from the cardiac imaging (valvular regurgitations, intracardiac masses or thrombi) can also present an advantage, not observed in the studied patients.

6. Conclusion

The use of a TOE monitoring was possible during liver surgery, in order to assess volume status, LV function, and CO. In five patients monitored with the PiCCO system, a statistically significant correlation between CO obtained by mitral valve VTI was obtained. TOE was also useful during episodes of hypotension, detecting changes in volume status earlier than invasive tools.

TOE is a possible and valuable tool in monitoring liver surgery, and its use by anaesthesiologists should be encouraged. More data is needed to establish its role in other noncardiac surgery monitoring.

References

[1] E. Catena and D. Mele, "Role of intraoperative transesophageal echocardiography in patients undergoing noncardiac surgery," *Journal of Cardiovascular Medicine*, vol. 9, no. 10, pp. 993–1003, 2008.

[2] M. Minhaj, K. Patel, D. Muzic et al., "The effect of routine intraoperative transesophageal echocardiography on surgical management," *Journal of Cardiothoracic and Vascular Anesthesia*, vol. 21, no. 6, pp. 800–804, 2007.

[3] N. Kolev, R. Brase, J. Swanevelder et al., "The influence of transoesophageal echocardiography on intra-operative decision making. A European multicentre study. European Perioperative TOE Research Group," *Anaesthesia*, vol. 53, pp. 767–773, 1998.

[4] A. A. Klein, A. Snell, S. A. M. Nashef, R. M. O. Hall, J. D. Kneeshaw, and J. E. Arrowsmith, "The impact of intraoperative transoesophageal echocardiography on cardiac surgical practice," *Anaesthesia*, vol. 64, no. 9, pp. 947–952, 2009.

[5] D. C. Oxorn, "Intraoperative echocardiography," *Heart*, vol. 94, no. 9, pp. 1236–1243, 2008.

[6] Y. Ozier and J. R. Klinck, "Anesthetic management of hepatic transplantation," *Current Opinion in Anaesthesiology*, vol. 21, no. 3, pp. 391–400, 2008.

[7] A. J. Burtenshaw and J. L. Isaac, "The role of tras-esophageal echocardiography for perioperative cardiovascular monitoring during orthotopic liver transplantation," *Liver transplantation*, vol. 12, pp. 1577–1583, 2006.

[8] D. B. Wax, A. Torres, C. Scher, and A. B. Leibowitz, "Transesophageal echocardiography utilization in high-volume liver transplantation centers in the United States," *Journal of Cardiothoracic and Vascular Anesthesia*, vol. 22, no. 6, pp. 811–813, 2008.

[9] J. Renner, M. Gruenewald, P. Brand et al., "Global end-diastolic volume as a variable of fluid responsiveness during acute changing loading conditions," *Journal of Cardiothoracic and Vascular Anesthesia*, vol. 21, no. 5, pp. 650–654, 2007.

[10] P. E. Marik, R. Cavallazzi, T. Vasu, and A. Hirani, "Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature," *Critical Care Medicine*, vol. 37, no. 9, pp. 2642–2647, 2009.

[11] B. Tavernier, O. Makhotine, G. Lebuffe, J. Dupont, and P. Scherpereel, "Systolic pressure variation as a guide to fluid therapy in patients with sepsis-induced hypotension," *Anesthesiology*, vol. 89, no. 6, pp. 1313–1321, 1998.

[12] N. G. Goddard, L. T. Menadue, and H. G. Wakeling, "A case for routine oesophageal Doppler fluid monitoring during major surgery becoming a standard of care," *British Journal of Anaesthesia*, vol. 99, no. 4, p. 599, 2007.

[13] T. D. Phan, H. Ismail, A. G. Heriot, and K. M. Ho, "Improving perioperative outcomes: fluid optimization with the esophageal doppler monitor, a metaanalysis and review," *Journal of the American College of Surgeons*, vol. 207, no. 6, pp. 935–941, 2008.

[14] W. E. Miller, K. L. Richards, and M. H. Crawford, "Accuracy of mitral Doppler echocardiographic cardiac output determinations in adults," *American Heart Journal*, vol. 119, no. 4, pp. 905–910, 1990.

[15] P. Nissen, J. J. Van Lieshout, S. Novovic, M. Bundgaard-Nielsen, and N. H. Secher, "Techniques of cardiac output measurement during liver transplantation: arterial pulse wave versus thermodilution," *Liver Transplantation*, vol. 15, no. 3, pp. 287–291, 2009.

[16] Y. Cevik, M. Degertekin, Y. Basaran, F. Turan, and O. Pektas, "A new echocardiographic formula to calculate ejection fraction by using systolic excursion of mitral annulus," *Angiology*, vol. 46, no. 2, pp. 157–163, 1995.

[17] M. F. Elnoamany and A. K. Abdelhameed, "Mitral annular motion as a surrogate for left ventricular function: correlation with brain natriuretic peptide levels," *European Journal of Echocardiography*, vol. 7, no. 3, pp. 187–198, 2006.

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Review Article

Appreciating the Strengths and Weaknesses of Transthoracic Echocardiography in Hemodynamic Assessments

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Transthoracic echocardiography (TTE) is becoming the choice of hemodynamic assessment tool in many intensive care units. With an ever increasing number of training programs available worldwide, learning the skills to perform TTE is no longer a limiting factor. Instead, the future emphasis will be shifted to teach the users how to recognize measurement errors and artefacts (internal validity), to realize the limitations of TTE in various applications, and finally how to apply the information to the patient in question (external validity). This paper aims to achieve these objectives in a common area of TTE application—hemodynamic assessments. We explore the strengths and weaknesses of TTE in such assessments in this paper. Various methods of hemodynamic assessments, such as cardiac output measurements, estimation of preload, and assessment of fluid responsiveness, will be discussed.

1. Introduction

Hemodynamic assessments form an indispensable part in optimizing fluid status, with the objective of improving adequate tissue perfusion in critically ill patients. In the last decade or two, the practice of critical care medicine is slowly moving away from traditional high-risks invasive procedures wherever possible. Echocardiography, especially transthoracic echocardiography (TTE), has been gaining popularity due to its noninvasiveness where the benefit far outweighs the risk [1]. Its ability to provide vital information about the cardiovascular and hemodynamic status of the patients within a short time frame (within 30 minutes) is another attraction for its use in the critical care setting [2]. A proper focused bedside assessment of cardiac function by TTE can provide answers to important questions about the cardiac function within 10–15 minutes [3]. Assessment for fluid status can also be done within 10–15 minutes. At present, there are no other bedside investigative tools that provide the same level and amount of information as echocardiography. That said, it is important to realize that echocardiography has its strengths and weaknesses. It can suffer from internal and external validity problems. Internal validity refers to the errors associated with the study procedure such as artefacts and measurement errors, and external validity refers to the applicability of the study findings to a particular patients. This article will discuss some of the strengths and validities of TTE in hemodynamic assessments.

2. Hemodynamics

The term "hemodynamics" is not very well defined but is generally used to refer to "the physics of blood circulation". It involves the study of the control of circulation and the factors that alter it. Figure 1 shows the general scheme of hemodynamics in the body. The main function of blood circulation is to ensure adequate tissue perfusion, which is related to two important factors: cardiac output and vascular resistance. Cardiac output is the product of stroke volume and heart rate, where the former can be affected by preload, afterload and cardiac contractility. Afterload, or the tension on myocardial wall during systole, depends on the blood pressure downstream and is determined by the intravascular volume and the resistance of the vasculature where the vasomotor tone is under continuous control by various neurohumoral and local factors. On the other hand, preload,

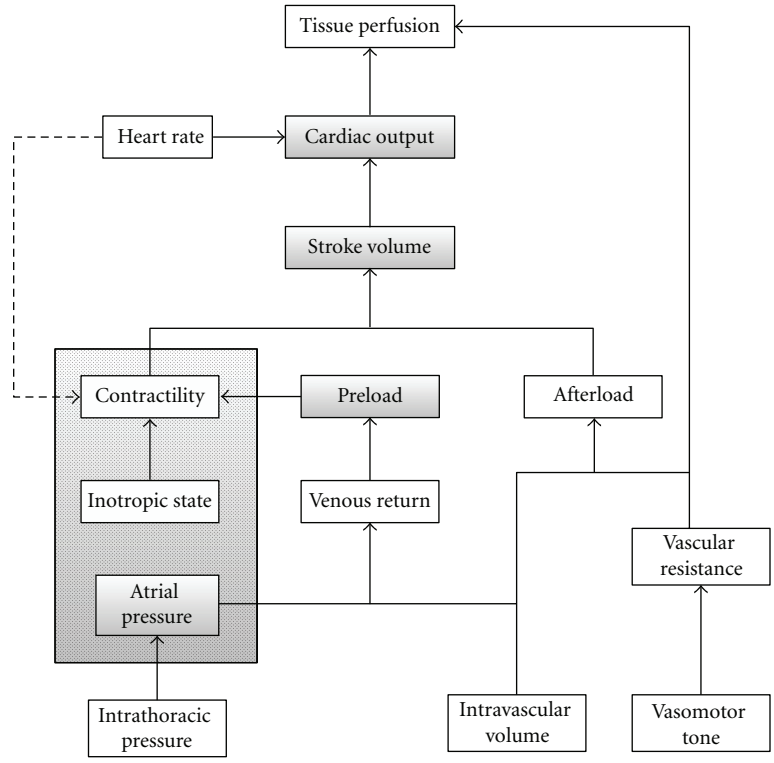

Figure 1: General scheme of hemodynamics.

or the tension on the myocardial wall during end-diastole, is determined largely by the venous pressure hence intravascular volume. Cardiac contractility is influenced by (1) the inotropic state, (2) preload by way of the Frank-Starling mechanism, and (3) to a lesser extent, heart rate and rhythm. LV geometry may also affect stroke volume and is best depicted by TTE when compared to blind invasive monitoring system. It is apparent that all these factors are intimately connected.

Left and right heart function aside, the expression "hemodynamics" is often used to denote the assessments of cardiac output, fluid status, and intravascular pressures, the latter often being used as surrogates for afterload (e.g., arterial blood pressure) and preload (e.g., central venous pressure and pulmonary artery occlusion pressure). While vascular resistance can be assessed by various methods, it is based on information derived from other measurements, such as cardiac output and mean arterial blood pressure. It is therefore not a direct measurement and its clinical value is unclear.

3. Hemodynamic Assessments by TTE

The use of TTE in hemodynamic assessment is an attractive approach because the procedure is noninvasive and a focused assessment takes less than 20 minutes. However, the biggest drawbacks are (1) it is not a continuous monitoring technique and (2) study quality can be limited by a number of factors including patient's position and habitus, comorbidities, mechanical ventilation, operator expertise, and machine quality. Fortunately, reasonable study quality can usually be obtained in majority of the cases provided that the operator is reasonable skillful such as attained level 1 or basic ultrasound training [3]. Most hemodynamic parameters and other useful information can be extracted even with suboptimal image quality. A standard TTE provides vital information about the heart function (Table 1), the estimation of cardiac output and assessment of preload (fluid status) and fluid responsiveness.

3.1. Measurement of Cardiac Output (CO). Cardiac output is the most often used surrogate for monitoring hemodynamic in intensive care unit (ICU). It is used for guiding treatment especially in patients with shock. TTE can provide a point estimate ("snapshot") of the CO. CO can be determined by either 2D volumetric methods such as the Simpson's method or Doppler echocardiography. Unfortunately, the 2D image qualities of the critically ill are usually suboptimal hence precluding the use of Simpson's method. Instead, CO can be more reliably determined using Doppler TTE. CO is measured at the left ventricular outflow tract (LVOT), and is based on the mathematical relation of CO = SV $\times$ HR, where SV and HR are stroke volume and heart rate, respectively. Echocardiographically, three parameters are needed to work out the CO: (a) LVOT velocity time integral (VTI_{LVOT}), (b) LVOT cross-sectional area (CSA), and (c) HR [4]. The VTI is the summation of all velocities per heartbeat and is represented by the area under the curve for each heartbeat. The LVOT velocity is obtained by placing the pulsed-wave Doppler sample gate in the LVOT in apical-5-chamber

Table 1: Common cardiac information which can be provided by a standard TTE.

Left heart	(i) Dimensions: chamber sizes and thickness (ii) Left ventricular ejection fraction (iii) Regional wall motion abnormalities
Right heart	(i) Dimensions: chamber size and thickness (ii) Right ventricular systolic function: FAC or TAPSE (iii) Signs of pressure or volume overload
Valvular pathologies	(i) Regurgitations (ii) Stenoses (iii) Prolapses (iv) Presence of vegetation
Aorta	(i) Dilatation (ii) Dissection
Estimation of pressures	(i) Pulmonary artery systolic pressure (ii) Left ventricular filling pressure (iii) Transvalvular pressure gradients
Other	Pericardial effusion and tamponade

FAC: fractional area contraction; TAPSE: tricuspid annular plane systolic excursion.

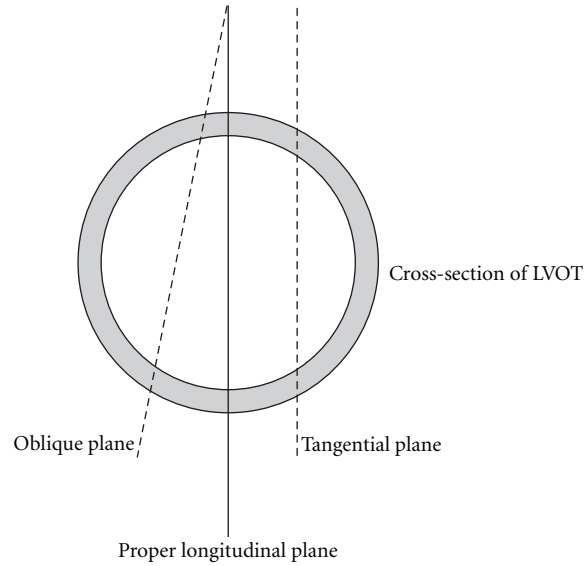

Figure 2: Schematic diagram showing proper and improper ultrasound longitudinal planes in measuring left ventricular outflow tract (LVOT) diameter. Oblique plane is resulted from a tilted angle from the proper plane, while a parallel shift in ultrasound plane results in a tangential planes. Both oblique and tangential planes give rise to underestimation of LVOT diameter. The same is true for measuring inferior vena cava diameter.

window. VTI_{LVOT} is obtained by manually tracing the Doppler velocity spectrum. The process of summation of the velocities is however automated. An average of 3 to 5 consecutive VTI_{LVOT} is normally used to minimize variability. The CSA of the LVOT is calculated from the diameter of the LVOT obtained from the parasternal long axis window. Measurement of the diameter is done manually, but the calculation of area is automated. Heart rate is obtained by measuring the R-R interval. If accurately done, the TTE obtained CO is comparable to pulmonary artery catheter thermodilution method [5].

Limitations. The major limitations of TTE CO measurement are listed in Table 2. One of the major limitations is the lack of continuous tracking ability. Serial measurements can be done, but is laborious and "round-the-clock" availability of sonographers is a problem in many units. Sudden and rapid changes in hemodynamic status mean finding the right operator and setting up the ultrasound machine may be too late in some instances. Interobserver variability may also be an issue.

Other limitations are related to measurement errors of which there are two: errors in LVOT diameter measurement and in Doppler velocity measurement (Doppler angle error). Measurement of LVOT diameter relies on obtaining a proper longitudinal plane of the LVOT. Slight angulation or lateral misplacement of the transducer will result in obtaining an oblique or tangential plane of the LVOT, hence underestimating the LVOT diameter (Figure 2). Incorrectly identifying the tissue-blood interface may result in under- or overestimation of the diameter. Since the CSA is proportional to the square of the diameter [$CSA = \pi \times (\text{diameter}/2)^2$], any error made will also be squared. A 10% error in diameter will result in approximately 20% error in CSA, hence CO.

Table 2: Limitations of cardiac output measurements in ICU by TTE.

Cannot provide continuous monitoring
Measurements and accuracies can be affected by:
(i) Patient's position
(ii) Patient's condition: for example, lung hyperinflation, cutaneous emphysema, trauma, wound
(iii) Effects of mechanical ventilation
(iv) Suboptimal ultrasound windows: poor image quality
(v) Heart plane motion during measurements
(vi) Doppler angle error: poor angle alignment
(vii) Arrhythmias

Accurate Doppler measurements demand the ultrasound beam being parallel to the blood flow (i.e., Doppler angle = 0°). Deviation from this will result in underestimation of blood flow velocity. While a Doppler angle of 20° results in an acceptable 6% error, a 30° angle will end up with greater than 10% error. It is often forgotten that blood is flowing in a three-dimensional perspective—the 2-dimensional (X-Y) plane as seen on the screen plus a Z-plane which is perpendicular to the screen. Angle correction (for the X-Y plane) is seldom used in echocardiography as the error in Z-plane is unknown. The only remedy is to ensure a proper apical-5-chamber window is used for measurements, and the transducer should be tilted or moved around slightly

to obtain the maximal velocity. Foreshortening apical-5-chamber window should be avoided; otherwise CO should not be measured. Of note, motion artefact due to respiration can also lead to angle error by tilting the heart plane up and down. Sometimes, it is difficult to differentiate this motion artefact from the SV variation (see below) in a fluid-depleted but responsive patient. The operator may see alternating 4- and 5-chamber views in concert with the respiratory phase if it is due to motion artefact.

Arrhythmias is another factor that can lead to an measurement error. For patients with atrial fibrillation, the VTI_{LVOT} measurement should be averaged over at least 5 consecutive cardiac cycles. The HR should also be averaged. Ectopic beats should be avoided.

3.2. Estimation of Right Atrial Pressure. In the classical Guyton's theory, cardiac output not only depends on the cardiac mechanics, but also on the venous return which determines the right atrial pressure (RAP) which can be approximated by central venous pressure (Figure 3). The inferior vena cava (IVC) has long been used to predict RAP in nonventilated patients [6]. In response to a change in intrathoracic pressure during respiration the IVC diameter changes. The diameter is the largest during expiration, and is the smallest during inspiration or sniffing. The IVC collapsibility index, defined as the difference in IVC diameters (during expiration and inspiration) divided by the maximal diameter (or $(D_{\text{expiration}} - D_{\text{inspiration}})/D_{\text{expiration}}$ where D is the diameter), has been shown to be correlated to RAP [6, 7]. Various cutoffs have been used to predict RAP [6, 8].

The IVC collapsibility index is obtained from the subcostal window. The patients are asked to perform a brief rapid inspiration or a sniff. The maximum diameter of the IVC is obtained during expiration, and minimum diameter is obtained during an inspiratory or a sniff maneuver.

Limitations. Contrary to traditional belief, RAP and central venous pressure have been proven to be poor predictors for fluid status (or blood volume) in critically ill patients [9, 10]. Since IVC diameter and collapsibility index are used as surrogates to estimate RAP, it follows that such information will not be very useful in predicting fluid status in critically ill patients despite the fact that IVC collapsibility index correlates with RAP.

The main limitation of the applicability of IVC collapsibility index is its applicability in mechanically ventilated patients. Studies that demonstrated good correlations between IVC collapsibility index and RAP were mostly performed in spontaneously breathing patients [6, 7]. The correlations in mechanical ventilated patients were poor [11, 12]. Compounded to the mechanical ventilation effects are a number of confounding factors that also affect the IVC diameter and collapsibility in critically ill patients. For example, right heart failure, significant tricuspid regurgitation, and supine body position, which are common in critically ill patients, are known to dilate the IVC [12–15]. Despite these, an IVC diameter of ≤12 mm has 100% specificity, with only 25% sensitivity, of predicting an RAP of 10 mmHg or less in mechanically ventilated patients [12].

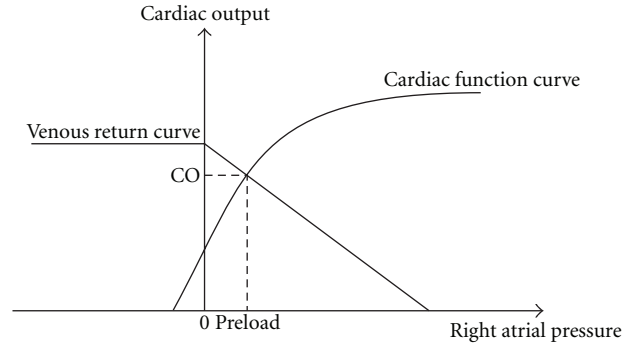

Figure 3: The relationship of venous return and cardiac function in determining cardiac output. As depicted in the venous return curve, venous return reduces with increasing right atrial pressure. The cardiac function curve illustrates the effect of increasing right atrial pressure on cardiac output (CO). Increasing right atrial pressure causes as increase in CO until a plateau (flat portion) is reached. At equilibrium, CO is determined by the point where two curves cross each other. The right atrial pressure at this point is the preload. The cardiac function curve is also known as the Frank-Starling curve.

The main technical limitation results from motion artefact are due to diaphragmatic and abdominal wall movements. IVC is commonly displaced inferiorly by the diaphragm during inspiration or sniffing, and affects the measurements especially when M-mode is used. Abdominal wall motion during sniffing can displace the transducer, hence the ultrasound plane, during the measurements. Care must therefore be taken to minimize such displacements while maintaining the ability to capture the changes in diameter during inspiration or sniffing. Measurements are best done in 2D mode with high frame rate to minimize such measurement errors.

4. Determination of Fluid Responsiveness

It is a well-known fact that administering fluid to patients whose hearts are operating at the flat (top) portion of the Frank-Starling (preload versus SV) curve is harmful to patients [16]. Various techniques have been developed to identify those "fluid responsive" patients who will benefit from fluid administration, that is, those whose ventricles are operating at the steep (ascending) part of the Frank-Starling curve (Figure 4). In a systematic review and meta-analysis of clinical study, it was found that approximately half (52.9%) of the study population were responders [17]. Two approaches have been adopted to predict fluid responsiveness: (a) volume expansion and (b) respiratory variation in SV or its surrogates.

4.1. Volume Expansion. The volume expansion approach utilizes the fact that if preload is increased acutely in those who will benefit from fluid administration, an accompanying increase in SV (or CO) should be observed (Figure 4) [18]. Volume expansion can be achieved via (a) passive leg raising

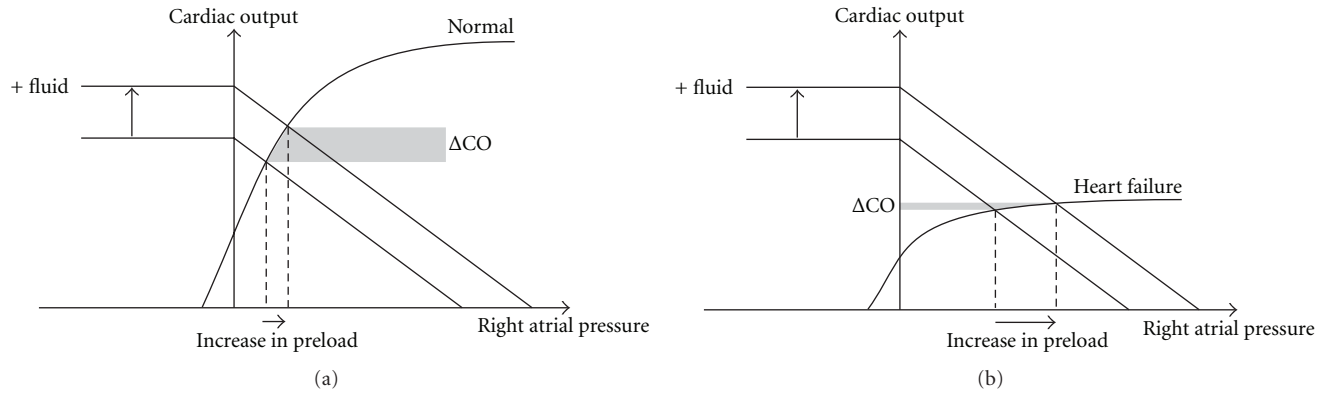

Figure 4: The effect of fluid administration on cardiac output. Fluid administration results in an upward shift in venous return curve. As a result, there is an increase in preload hence cardiac output (ΔCO) (a). Note that the crossing points between the two curves are on the steep part of the cardiac function (Frank-Starling) curve. In heart failure, the Frank-Starling curve is lowered, and the crossing point is at the flat portion of the curve (b). Fluid administration, although it increases the preload, does not result in an increase in CO in the latter case.

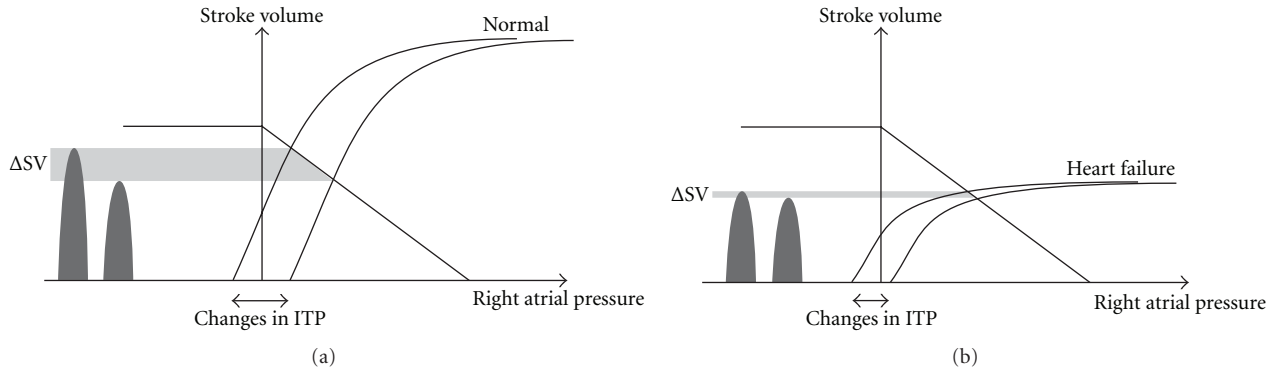

Figure 5: The effect of intrathoracic pressure on cardiac output. Both spontaneous breathing and mechanical ventilation result in a cyclical change in intrathoracic pressure (ITP). Depending on the mode of ventilation, the change in ITP is accompanied by a cyclical shift in the Frank-Starling (cardiac function) curve which results in a cyclical change in preload. If the crossing point is on the steep part of the curve, shifting of the curve would result in a change in stroke volume (SV) (or cardiac output). This respiratory induced cyclical change in SV is known as SV variation (a). In heart failure, such change in SV may be less apparent because the crossing point is at the flat portion of the curve (b).

(PLR) or (b) volume challenge—rapid infusion of a fixed volume (e.g., 500 mL) of fluid within 15–30 min [19]. In response to acute volume expansion, an increase in SV or its surrogates, such as echocardiographic LVOT or aortic flow VTI (and CO), are expected. In patients whose ventricles are operating at the flat portion of the Frank-Starling curve, the change in stoke volume is less apparent (Figure 4). Studies involving the use of PLR reported that an increase in CO by 12–15% offers high specificities (>90%) and sensitivities (>80%) in discriminating fluid responder from nonresponder [17]. PLR-induced increase in SV or CO displays a good correlation with volume challenge [17, 19]. While SV and CO are reported, their surrogates such as VTI_{LVOT} or aortic flow VTI (VTI_{aortic}) are normally used. VTI_{aortic} can be measured either in the apical-5-chamber window or the suprasternal window using continuous wave Doppler.

4.2. Respiratory Variation. During steady respiratory effort, changes in intrathoracic pressure alters the heart-lung interaction mechanics leading to a regular fluctuation of SV [20]. In mechanically ventilated patients, the LV SV is at its greatest at the end of the inflation period. This is due to an increase in pleural pressure and LV preload. During expiration, the reduction in LV preload decreases the SV. This respiratory variation in SV (SV variation or SVV) is exaggerated in fluid responders whose ventricles are operating at the steep part of the Frank-Starling curve (Figure 5). For those (non-responders) whose ventricles are operating at the flat portion of the curve, the SVV is blunted (Figure 5) [19]. SVV is defined as $(SV_{max} - SV_{min})SV_{mean} \times 100\%$, where the subscripts max, min, and mean stand for maximum, minimum, and average, respectively. In TTE, the percentage variation in VTI_{LVOT} or VTI_{aortic} is normally used as a surrogates for SVV [21, 22].

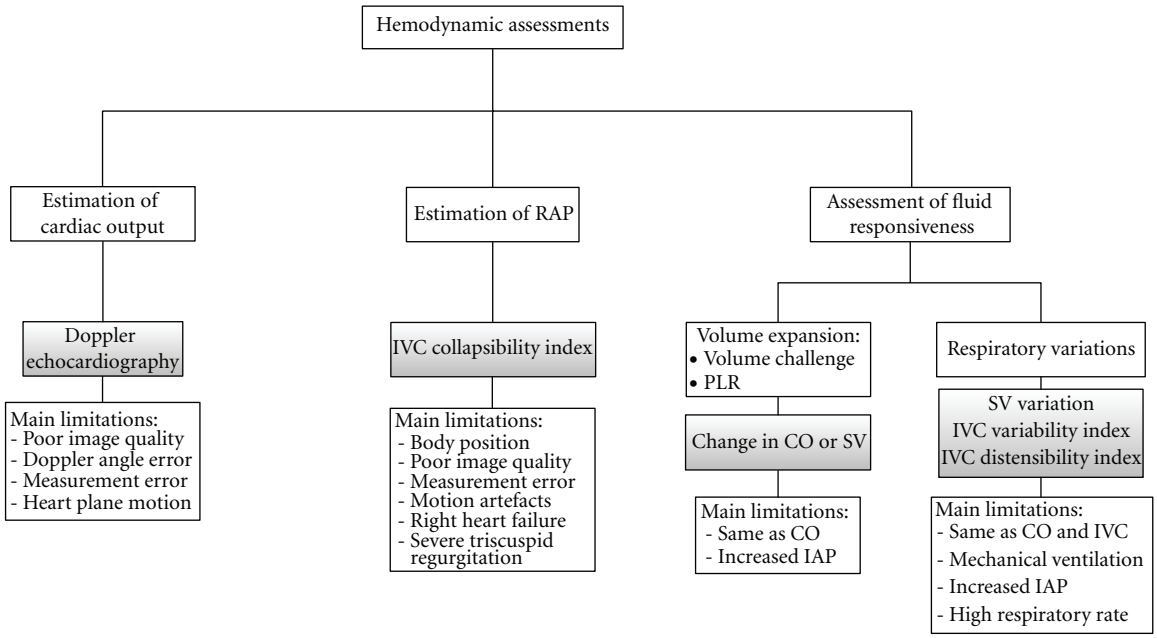

Figure 6: Summary of hemodynamic assessment by transthoracic echocardiography.

Respiratory variation in right atrial pressure has also been used to predict fluid responsiveness [23, 24]. As a surrogate for RAP, the changes in IVC diameter with respiratory variation has also been shown to be a satisfactory predictor for fluid responsiveness in mechanically ventilated patients. Barbier et al. demonstrated a percentage distensibility of IVC, defined as $(IVC_{max} - IVC_{min})IVC_{min}$, of 18% offers 90% sensitivity and specificity in discriminating fluid responders from non-responders [25]. On the other hand, Feissel et al. found that a percentage variation in IVC, defined as $(IVC_{max} - IVC_{min})IVC_{mean}$, of 12% can predict fluid responder with >90% sensitivity and specificity [26]. Of note, IVC distensibility and variability should not be confused with IVC collapsibility (see above). While the former two predict fluid responsiveness, the latter predicts RAP. The use of superior vena cava (SVC) collapsibility index has also been used, but transesophageal echocardiography is necessary to visualize the SVC [27].

4.3. Limitations. One of the main concerns of using respiratory variation is its applicability in spontaneously breathing patients or in those not in mandatory controlled mode [28]. In one study, SVV was found to be a poor predictor for fluid responder in patients with septic shock on pressure support mode [29]. Breath-by-breath changes in inspiratory effort may alter the intrathoracic pressure hence the regular SVV or IVC variations required for such analysis. Further, variations in tidal volume and duration of respiratory cycle in noncontrolled mode may negate the use of SVV or IVC variations. Charron et al., however, showed that VTI_{aortic} was still a satisfactory predictor for fluid responsiveness even when the tidal volume was increased [30]. However, no follow-up study was done in this regard.

Elevated intraabdominal pressure is another confounding factor for assessment of fluid responsiveness. Intra-abdominal hypertension has been shown to render the use of PLR useless in predicting fluid responsiveness [31]. Animal studies also demonstrated that the normal cutoffs for SVV are not helpful in predicting fluid responsiveness [32, 33]. Increase in respiratory rate in mechanically ventilated patients reduces the VTI_{aortic} variations rendering the use of SVV useless [34]. Intra-abdominal hypertension can also affect the size of IVC and its response to respiration.

5. Conclusion

TTE has proven itself to be an indispensible critical care tool in recent years. Although its main uses are for exploring the cardiac function, its applications in hemodynamic assessment are increasingly popular. Estimations of cardiac output and right atrial pressure, and ascertaining the fluid status of the patients, are common uses of TTE (Figure 6).

Hemodynamic assessment by TTE is confronted by two major limitations: internal and external validities. Internal validity stems mainly from technical limitations including image quality and measurement errors. Some of these can be minimized by quality control and skill improvement over time. External validity concerns with the applicability and appropriateness of using a particular TTE measurement to answer a specific hemodynamic question. In face of the issue of external validity, the operator should constantly ask himself or herself whether a particular TTE measurement is valid (suitable) for the patient in question. The power of echocardiography can only be unleashed through the understanding of its strength and limitations more fully.

References

[1] S. J. Huang and A. S. McLean, "Do we need a critical care ultrasound certification program? Implications from an Australian medical-legal perspective," *Critical Care*, vol. 14, no. 3, p. 313, 2010.

[2] A. S. McLean, "Echocardiography and the intensive care unit," *Critical Care and Resuscitation*, vol. 1, no. 3, pp. 231–231, 1999.

[3] A. S. McLean, "International recommendations on competency in critical care ultrasound: pertinence to Australia and New Zealand," *Critical Care and Resuscitation*, vol. 13, no. 1, pp. 56–58, 2011.

[4] W. A. Zoghbi and M. A. Quinones, "Determination of cardiac output by Doppler echocardiography: a critical appraisal," *Herz*, vol. 11, no. 5, pp. 258–268, 1986.

[5] A. S. McLean, A. Needham, D. Stewart, and R. Parkin, "Estimation of cardiac output by noninvasive echocardiographic techniques in the critically ill subject," *Anaesthesia and Intensive Care*, vol. 25, no. 3, pp. 250–254, 1997.

[6] B. J. Kircher, R. B. Himelman, and N. B. Schiller, "Noninvasive estimation of right atrial pressure from the inspiratory collapse of the inferior vena cava," *American Journal of Cardiology*, vol. 66, no. 4, pp. 493–496, 1990.

[7] O. Yildirimturk, Y. Tayyareci, R. Erdim et al., "Assessment of right atrial pressure using echocardiography and correlation with catheterization," *Journal of Clinical Ultrasound*, vol. 39, no. 6, pp. 337–343, 2011.

[8] J. M. Brennan, J. E. Blair, S. Goonewardena et al., "Reappraisal of the use of inferior Vena Cava for estimating right atrial pressure," *Journal of the American Society of Echocardiography*, vol. 20, no. 7, pp. 857–861, 2007.

[9] C. R. Shippy, P. L. Appel, and W. C. Shoemaker, "Reliability of clinical monitoring to assess blood volume in critically ill patients," *Critical Care Medicine*, vol. 12, no. 2, pp. 107–112, 1984.

[10] P. E. Marik, M. Baram, and B. Vahid, "Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares," *Chest*, vol. 134, no. 1, pp. 172–178, 2008.

[11] S. F. Nagueh, H. A. Kopelen, and W. A. Zoghbi, "Relation of mean right atrial pressure to echocardiographic and Doppler parameters of right atrial and right ventricular function," *Circulation*, vol. 93, no. 6, pp. 1160–1169, 1996.

[12] J. Jue, W. Chung, and N. B. Schiller, "Does inferior vena cava size predict right atrial pressures in patients receiving mechanical ventilation?" *Journal of the American Society of Echocardiography*, vol. 5, no. 6, pp. 613–619, 1992.

[13] S. K. Dutta, G. D. Plotnick, R. Williams, and F. Morris, "Massive dilation of the inferior vena cava. Association with tricuspid regurgitation," *Journal of the American Medical Association*, vol. 239, no. 2, pp. 135–136, 1978.

[14] R. S. Meltzer, J. McGhie, and J. Roelandt, "Inferior vena cava echocardiography," *Journal of Clinical Ultrasound*, vol. 10, no. 2, pp. 47–51, 1982.

[15] F. Mookadam, T. A. Warsame, H. S. Yang, U. R. Emani, C. P. Appleton, and S. F. Raslan, "Effect of positional changes on inferior vena cava size," *European Journal of Echocardiography*, vol. 12, no. 4, pp. 322–325, 2011.

[16] S. Magder, "Fluid status and fluid responsiveness," *Current Opinion in Critical Care*, vol. 16, no. 4, pp. 289–296, 2010.

[17] F. Cavallaro, C. Sandroni, C. Marano et al., "Diagnostic accuracy of passive leg raising for prediction of fluid responsiveness in adults: systematic review and meta-analysis of clinical studies," *Intensive Care Medicine*, vol. 36, no. 9, pp. 1475–1483, 2010.

[18] J. L. Vincent and M. H. Weil, "Fluid challenge revisited," *Critical Care Medicine*, vol. 34, no. 5, pp. 1333–1337, 2006.

[19] X. Monnet, M. Rienzo, D. Osman et al., "Passive leg raising predicts fluid responsiveness in the critically ill," *Critical Care Medicine*, vol. 34, no. 5, pp. 1402–1407, 2006.

[20] F. Michard and J. L. Teboul, "Using heart-lung interactions to assess fluid responsiveness during mechanical ventilation," *Critical Care*, vol. 4, no. 5, pp. 282–289, 2000.

[21] C. Charron, V. Caille, F. Jardin, and A. Vieillard-Baron, "Echocardiographic measurement of fluid responsiveness," *Current Opinion in Critical Care*, vol. 12, no. 3, pp. 249–254, 2006.

[22] M. Slama, H. Masson, J. L. Teboul et al., "Respiratory variations of aortic VTI: a new index of hypovolemia and fluid responsiveness," *American Journal of Physiology Heart and Circulatory Physiology*, vol. 283, no. 4, pp. H1729–H1733, 2002.

[23] S. Magder, G. Georgiadis, and T. Cheong, "Respiratory variations in right atrial pressure predict the response to fluid challenge," *Journal of Critical Care*, vol. 7, no. 2, pp. 76–85, 1992.

[24] S. Magder, D. Lagonidis, and F. Erice, "The use of respiratory variations in right atrial pressure to predict the cardiac output response to PEEP," *Journal of Critical Care*, vol. 16, no. 3, pp. 108–114, 2001.

[25] C. Barbier, Y. Loubieres, C. Schmit et al., "Respiratory changes in inferior vena cava diameter are helpful in predicting fluid responsiveness in ventilated septic patients," *Intensive Care Medicine*, vol. 30, no. 9, pp. 1740–1746, 2004.

[26] M. Feissel, F. Michard, J. P. Faller, and J. L. Teboul, "The respiratory variation in inferior vena cava diameter as a guide to fluid therapy," *Intensive Care Medicine*, vol. 30, no. 9, pp. 1834–1837, 2004.

[27] A. Vieillard-Baron, K. Chergui, A. Rabiller et al., "Superior vena caval collapsibility as a gauge of volume status in ventilated septic patients," *Intensive Care Medicine*, vol. 30, no. 9, pp. 1734–1739, 2004.

[28] P. Vignon, "Evaluation of fluid responsiveness in ventilated septic patients: back to venous return," *Intensive Care Medicine*, vol. 30, no. 9, pp. 1699–1701, 2004.

[29] A. Perner and T. Faber, "Stroke volume variation does not predict fluid responsiveness in patients with septic shock on pressure support ventilation," *Acta Anaesthesiologica Scandinavica*, vol. 50, no. 9, pp. 1068–1073, 2006.

[30] C. Charron, C. Fessenmeyer, C. Cosson et al., "The influence of tidal volume on the dynamic variables of fluid responsiveness in critically ill patients," *Anesthesia and Analgesia*, vol. 102, no. 5, pp. 1511–1517, 2006.

[31] Y. Mahjoub, J. Touzeau, N. Airapetian et al., "The passive leg-raising maneuver cannot accurately predict fluid responsiveness in patients with intra-abdominal hypertension," *Critical Care Medicine*, vol. 38, no. 9, pp. 1824–1829, 2010.

[32] D. Jacques, K. Bendjelid, S. Duperret, J. Colling, V. Piriou, and J. -. Viale, "Pulse pressure variation and stroke volume variation during increased intra-abdominal pressure: an experimental study," *Critical Care*, vol. 15, no. 1, article 33, 2011.

[33] J. Renner, M. Gruenewald, R. Quaden et al., "Influence of increased intra-abdominal pressure on fluid responsiveness predicted by pulse pressure variation and stroke volume variation in a porcine model," *Critical Care Medicine*, vol. 37, no. 2, pp. 650–658, 2009.

[34] D. de Backer, F. S. Taccone, R. Holsten, F. Ibrahimi, and J. L. Vincent, "Influence of respiratory rate on stroke volume variation in mechanically ventilated patients," *Anesthesiology*, vol. 110, no. 5, pp. 1092–1097, 2009.

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Review Article

Haemodynamic Monitoring Using Echocardiography in the Critically Ill: A Review

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Physicians caring for the critically ill are now expected to acquire competence in echocardiography. It has become an indispensable diagnostic and monitoring tool in acute care settings where it is generally accepted to have therapeutic impact. There are a number of indications for a critical care echocardiographic study, and the most important queries include those pertaining left and right ventricular function and filling status. Focused examinations are increasing in popularity and provide a means for systematic study, and can be easily learned and practiced by novices. This paper addresses the indications, therapeutic impact, and some of the most common questions that can be answered using echocardiography the in critically ill patient.

1. Introduction

Echocardiography is now considered an indispensable tool for diagnosis and haemodynamic monitoring in critically ill patients. Indications for performing echocardiography in the ICU have expanded and it is now considered a requirement for critical care physicians to acquire competence in this mode of monitoring. Reflecting this are the numerous competency guidelines published in recent years [1–4].

Potential advantages and disadvantages of echocardiography compared to invasive haemodynamic monitoring (e.g., pulmonary artery catheter and arterial waveform analysis) in the critically ill are listed in Table 1.

This paper is not intended to be a comprehensive review of echocardiographic techniques. It does not include a review of left ventricular diastolic function, or lung ultrasound, a rapidly growing and increasingly important imaging modality [5].

Instead it addresses the indications, therapeutic impact, and some of the most common questions that can be answered using echocardiography in critically ill patients.

2. Therapeutic Impact

There are no randomized trials/metaanalyses regarding the impact of echocardiography on critically ill patients. A number of studies attest to the usefulness of echocardiography in the intensive care unit [6–9]. For example in Vignon et al., TTE and TEE led to therapeutic changes in approximately 25% of critically ill, mechanically ventilated patients [6], a finding supported by later studies [8, 9]. There are a number of societal guidelines with evidence-based recommendations for the use of echocardiography in a variety of clinical situations, including intraoperative settings and in critically ill patients [10]. The best evidence for the therapeutic impact of echocardiography in this context is found for perioperative TEE where improved clinical outcomes have been well documented [10].

3. Indications for Echocardiography in the Critically Ill

Echocardiography in critical care settings may be indicated for (1) diagnostic purposes, (2) guiding interventions and therapy, and (3) monitoring and followup.

The most important indications within the critical care context include diagnosis of major valvulopathies, major structural abnormalities (e.g., intracardiac masses, ventricular and atrial septal defects), endocarditis, pericardial effusion, and tamponade. It is also indicated for the evaluation of chest pain and unexplained shortness of breath, suspected pulmonary embolism, and respiratory failure of uncertain aetiology. It is used for the evaluation of shock

Table 1: Potential advantages and disadvantages of echocardiography versus invasive monitoring.

	Echocardiography	Invasive haemodynamic monitoring
Invasiveness	TTE noninvasive TEE semi-invasive	PAC invasive arterial waveform analysis semi-invasive
Portability	Scanners easily moved to patient	Generally not portable
Use in acute care	Yes, also documented for ED	No
Diagnostic value	Yes	Yes
Monitoring capability	Yes	Yes
User dependent	Very user dependent	Less user dependent, some methods require calibration

PAC: pulmonary artery catheter; TTE: transthoracic echocardiography; TEE: transoesophageal echocardiography.

or haemodynamic instability, where the determination of filling status and left and right ventricular function are key questions. In terms of monitoring, echocardiography may be used to assess responses to fluid and vasoactive therapies.

In the latest publication of the American College of Cardiology Appropriate Use Taskforce, appropriate use criteria were established for the use of TTE for cardiovascular evaluation in the acute care setting [11] (Table 2). Of note, assessment of volume status received an Appropriate Use Score of only 5 (of 9) points.

Table 2: Indications for echocardiography in acute care settings, evaluated using appropriate use scores (AUS).

Indication	AUS
Hypotension/haemodynamic instability of uncertain or suspected cardiac aetiology	A
Assessment of volume status in critically ill patient	U
Acute chest pain with suspected MI, inconclusive ECG during pain	A
No chest pain but laboratory and/or other features indicative of MI	A
Suspected complication of MI	A
Respiratory failure/hypoxemia of uncertain aetiology	A
Respiratory failure/hypoxemia when noncardiac aetiology is already established	U
To establish diagnosis of suspected PE	I
To guide therapy of known acute PE	A
Routine surveillance of prior PE, with normal RV function and PAP	I
Reevaluation of known PE after therapy for change RV function and PAP	A
Severe deceleration injury/chest trauma with suspected or possible pericardial effusion, valvular, or cardiac injury	A
Routine evaluation in mild chest trauma without ECG or biomarker changes	I

I: inappropriate test for that indication (not generally acceptable and not a reasonable approach. Score 1–3 out of 9); U: uncertain for specific indication (may be acceptable and may be a reasonable approach. Also implies that further patient information/research needed to classify indication definitively. Score 4–6 out of 9); A: appropriate test for that indication. Test is generally acceptable and is a reasonable approach for the indication. Score 4–6 out of 9). MI: myocardial infarction, PE: pulmonary embolism, RV: right ventricle, PAP: pulmonary arterial pressure. Adapted from Douglas et al. [11].

4. A Practical Approach

In recent years, several focused echocardiography protocols have been introduced [12]. These studies can usually be carried out by novice operators after a modest amount of training. For more complex examinations, consultation with the local echocardiography service is recommended if no specific competence is available in the intensive care unit.

There are several ways of approaching the echocardiographic examination of the critically ill. While several focused protocols exist, two such protocols, RACE and FATE, have gained widespread popularity and are described here.

This author finds RACE (rapid assessment by cardiac echo) useful for the initial echocardiographic evaluation of the unstable critically ill patient. This method ensures that the examination is conducted systematically, and stresses that findings be put within the context of the patient's clinical status. Two modes (M-mode and 2Dimensional imaging) and 5 views (parasternal long axis, parasternal short axis, apical 4-chamber, apical 2-chamber, and subcostal views) are used to answer the following four questions.

(1) What is the left ventricular function?

(2) What is the right ventricular function?

(3) Is there any evidence of pericardial effusion and cardiac tamponade?

(4) What is the fluid status?

The authors of RACE also stress that it is not a full TTE study, does not include Doppler measurements, and that a full transthoracic echocardiographic assessment should be requested if considered clinically necessary. Nevertheless, RACE is a good initial approach to the evaluation of the haemodynamically unstable patient and provides a skill set that can be easily learned by novices.

Another focused echocardiographic protocol is FATE (focused assessed transthoracic echocardiography) [13]. The purpose of FATE is to screen for significant pathology and to obtain information about volume status and cardiac contractility. FATE is similar to RACE in that it offers a systematic and focused approach to the echocardiographic examination of the critically ill patient, and provides a skill set that can be easily learned by novices. FATE differs from RACE in that it is not designed to answer a specific set of questions, and is rather used as a "rapid and systematic protocol for cardiopulmonary screening and monitoring"

[13]. Another key difference is that in FATE other modalities such as Doppler may be applied as the user sees fit. Further, the examination may be interrupted before it is complete whereas RACE concentrates on answering the set of 4 questions systematically in every view.

5. Specific Areas of Interest in the Critically Ill

This paper will not include details of a full echocardiographic examination and the reader is referred instead to the numerous publications available with special focus areas [14–19]. However, a few key areas of interest to the critical care physician are outlined below. The importance of obtaining consistent and good quality images cannot be stressed enough. This is often a challenge in the critically ill, mechanically ventilated patient. Pathology should be confirmed from at least two views/windows. Less emphasis should be placed on obtaining direct measurements, for example, using Doppler methods due to the numerous associated pitfalls. The user is instead advised to conduct a systematic examination, obtain good quality images, and interpret the echocardiographic findings within the clinical context before embarking on various Doppler-based measurements.

5.1. LV Function. Assessment of global LV contractility may be quickly obtained by "eyeballing" from the parasternal long- and short-axis, apical 2- and 4-chamber and subcostal views [17, 18]. Experienced users may supplement this information by further assessments using a combination of ejection fraction/fractional shortening, Doppler patterns of ventricular filling, and tissue Doppler imaging [19]. It is important to use several windows as no single view can provide a comprehensive picture of contractility. In mechanically ventilated patients, obtaining parasternal views in particular may be challenging. In such patients, the subcostal view is often helpful since it minimizes signal attenuation from air in the lungs and the rib cage.

Two other modes of imaging that are relatively easy to obtain for the assessment of LV function are the atrioventricular plane displacement (AVPD) and systolic tissue Doppler velocities (sTD) (Figure 1) [20–22]. Both of these are accessible from the apical window. Of note these measurements are dependent on preload, and only reflect components of LV contractility.

In addition to contractility, assessments of chamber size and LV wall thickness are made. These serve as an indication of fluid status, cardiomyopathies, and the presence of nonviable myocardium. Left atrial size is evaluated as an enlarged LA may indicate significant mitral and aortic valve disease, intra-atrial shunting and atrial fibrillation, all of which may contribute or cause haemodynamic instability. Further, LA size may provide an indication of elevated LV filling pressures.

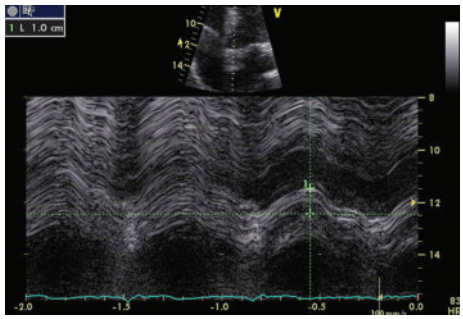
Finally, the aortic and mitral valves are made to complete the examination of left ventricular function. Measurement of stenotic areas and regurgitant volumes are difficult and highly variable in the critically ill patients with varying volume status and mechanical ventilation. For this reason, echocardiographic evaluation of the critically ill should identify major pathology, but quantification of such should be made by experienced operators only, and taking into consideration the clinical context. A focused critical care echocardiographic examination should be able to identify, but not quantify, major valvulopathies that may contribute to or explain haemodynamic instability, such as significant aortic stenosis and mitral regurgitation, using 2D and colour Doppler imaging.

5.2. RV Function. Assessment of right ventricular function is of particular interest in critical care due to the effects of fluid loading and mechanical ventilation on the right heart. Due to ventricular interdependence [15], impaired RV function may lead to decreased left ventricular output. It is estimated that approximately 25% of patients with ARDS have right ventricular dysfunction and pulmonary hypertension [23]. Importantly, right ventricular failure is independently associated with mortality in critically ill patients [24].

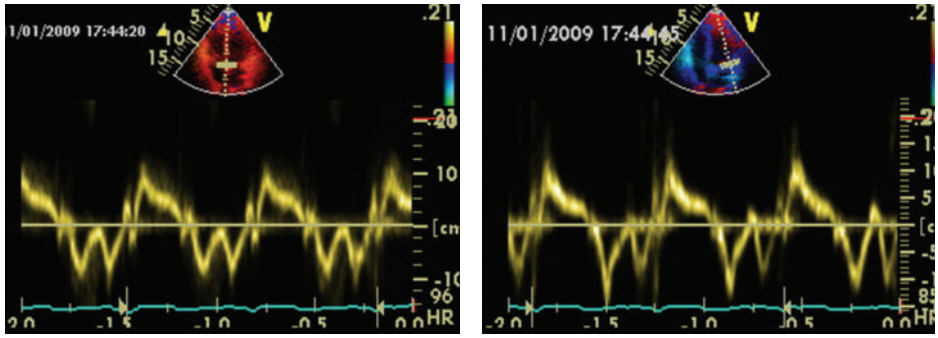
RV function is assessed initially from its size, wall thickness, and contractility. Comprehensive guidelines for the echocardiographic assessment of the right heart are given in a recent report of the American Society of Echocardiography [25]. For the critical care physician conducting an echocardiographic examination in mechanically ventilated patients, a more pragmatic approach may be adopted. Direct measurement of RV size by endocardial border tracing is difficult and not recommended due to its complex geometry and the presence of trabeculations within the RV chamber. Subjective assessment of the right ventricular area compared to left ventricular area in the apical 4-chamber view may be used instead. The RV should be smaller than the LV, and an RV : LV end diastolic area ratio of >0.6 indicates a dilated right ventricle, consistent with pressure or volume overload. Mechanical ventilation and pulmonary hypertension are common conditions causing RV dilatation in the critically ill patient. The right ventricular wall is normally thin, and hypertrophy indicates prior disease. RV contractility is assessed by eyeballing from the parasternal long-axis, apical 4-chamber, and subcostal views. Direct measurements such as the tricuspid annular plane systolic excursion (TAPSE) are easy to obtain and helpful, and provide a useful adjunct to eyeballing [25] (Figure 2).

The right atrium (RA) is examined for size and abnormal masses. A dilated RA may be indicative of fluid overload, interatrial shunts, tricuspid disease, and increased pulmonary pressures. Atrial fibrillation and mechanical ventilation may also cause a dilated RA. Finally the tricuspid and pulmonary valves are examined for abnormalities.

Measurement of the tricuspid regurgitant velocity is a relatively simple procedure and is used for the estimation of pulmonary arterial systolic pressure using the simplified Bernoulli equation [12, 14]. Typically this is made from the apical 4-chamber view (Figure 3). If this is not accessible, the tricuspid regurgitant flow jet may also be insonated



(a)



(b)

Figure 1: Methods for measuring LV function. (a) Atrioventricular plane displacement (septal wall) using M-mode, showing abnormal (decreased) displacement. (b) Systolic tissue Doppler measurement at the septal and lateral walls using tissue velocity imaging with pulsed wave Doppler, showing normal velocities.

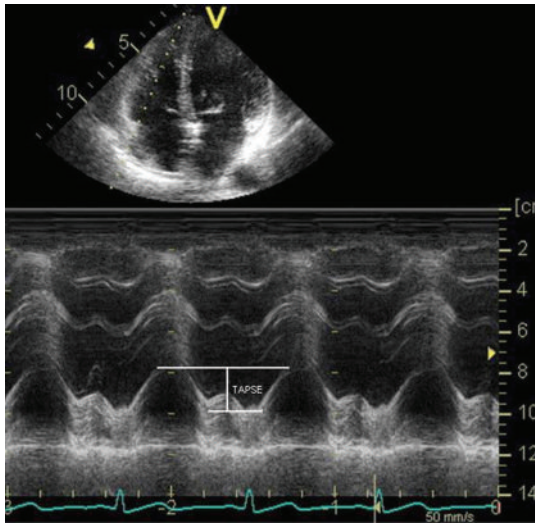


Figure 2: Tricuspid annular plane systolic excursion (TAPSE) for evaluating right ventricular contractility.

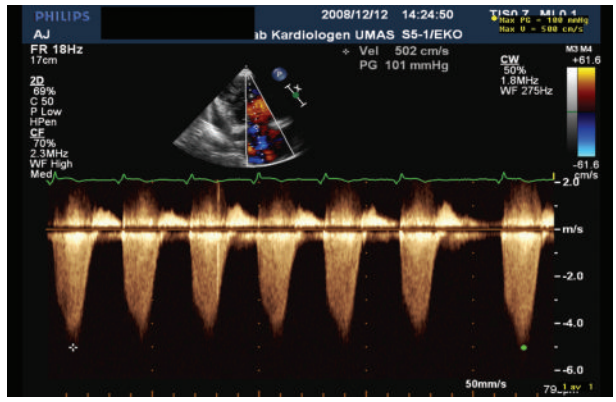


Figure 3: Estimation of the pulmonary arterial systolic pressure (PASP) from the tricuspid regurgitant jet (V_{TR}). The latter is measured using continuous wave Doppler. PASP is calculated from simplified Bernoulli equation, $PASP = 4 \times V_{TR}^2$.

from the parasternal and subcostal views. Estimation of pulmonary arterial systolic pressure using this method assumes the absence of significant pulmonary stenosis, and may be inaccurate in patients with decreased right ventricular contractility.

5.3. Fluid Status. Estimation of preload by assessment of ventricular volumes is one of the most challenging areas in critical care echocardiography. Firstly, altering compliance complicates the pressure-volume relationship [26]. Added to this are the varying effects of mechanical ventilation on the heart. Generally preload assessment may be made by examination of the left ventricle, the right heart, and the inferior vena cava. The critical care physician may generally assess preload by measuring left ventricular volumes. The left

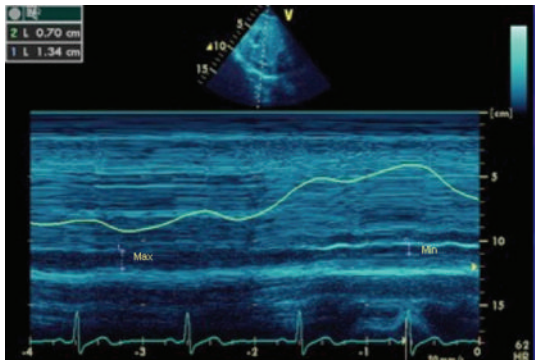


Figure 4: IVC diameter, measured using M-mode from the subcostal view. The minimum and maximum diameters are used to calculate the IVC distensibility and/or variability index. (Courtesy of A. McLean, S. Huang, and I. Ting, Nepean Critical Care Echo Group, Nepean Hospital, Sydney University, Australia).

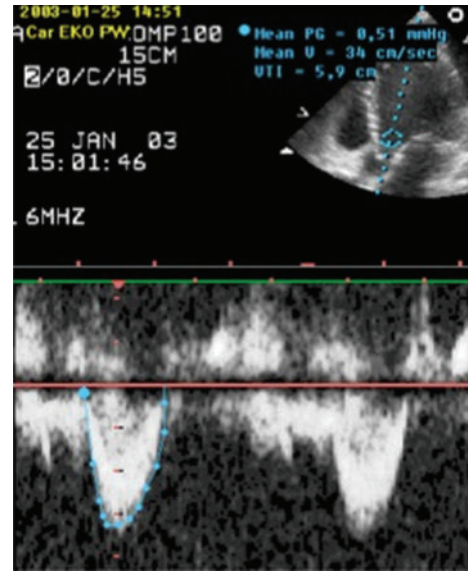


Figure 5: Measurement of LVOT VTI from the apical 5-chamber plane.

ventricular end-diastolic area (LVEDA) may be "eyeballed" or measured using the Simpson's biplane method [27]. The latter requires identification of the endocardial border and may be difficult in the presence of mechanical ventilation. In the case of a hypovolaemic patient, a simpler approach is to look for obliteration of the LV cavity, also known as "kissing ventricles."

The right ventricular dimensions are normally smaller than those of the LV. While RV dilatation may indicate volume overload, it is not specific for this. RV dilatation may occur for example due to mechanical ventilated with high PEEP. The RA size may be increased and an enlarged RA with bowing of the intra-atrial septum towards the left is indicative of elevated right atrial pressure. The triad of a "kissing" LV, small LV and RV size, along with a normal or small RA is strongly suggestive of hypovolaemia.

A method for assessing fluid responsiveness in patients with controlled mechanical ventilation, that is, not on assist modes, is the distensibility index of the inferior vena cava (IVC_{DI}). This is defined as

$$\frac{D_{max} - D_{min}}{D_{min}} \times 100\%, \quad (1)$$

where D_{max} and D_{min} are the minimum and maximum diameters of the inferior vena cava obtained from the subcostal view. A value exceeding 18% is predictive of fluid responsiveness in mechanically ventilated patients [28] (Figure 4). Another method which may be used is the variability index of the inferior vena cava (IVC_{VI}) [29], defined as

$$\frac{D_{max} - D_{min}}{D_{mean}}, \quad (2)$$

where D_{max} and D_{min} are the minimum and maximum diameters of the inferior vena cava obtained from the subcostal view, and D_{mean} is the average of the two. A value >12% indicates fluid responsiveness in ventilated patients (Figure 4).

IVC_{DI} and IVC_{VI} should be distinguished from the commonly used inferior vena cava collapsibility index, defined as $D_{max} - D_{min}/D_{max}$. A small D_{max} (<20 mm) with greater than 55% collapsibility is indicative of hypovolaemia [30]. However, this is relevant only in spontaneously breathing patients.

Finally the variation in the velocity time integral at the left ventricular outflow tract or aortic blood flow may predict volume responsiveness better than static indices. Generally thresholds around 15% have been shown to be predictive with sensitivities and specificities exceeding 90% [31–33].

5.4. Cardiac Output. Cardiac output (CO) measurements are occasionally made in the critical care setting, since an adequate CO is a prerequisite for tissue oxygen delivery. While a low CO is always a source of concern, there is no preset absolute value for adequate CO. Hence in some situations a "high" CO of 10 L/min may be adequate, and conversely a seemingly "normal" CO of 5 L/min may be inadequate for optimal tissue oxygen delivery. There are several ways of measuring CO echocardiographically. One commonly used and reliable method relies on the measurement of the velocity time integral from the left ventricular outflow tract (LVOT VTI) in an apical 5-chamber plane (Figure 5) [26, 34]. The diameter of the aortic annulus is measured from the parasternal long-axis view, and its area was calculated. Multiplying this area with the LVOT VTI gives the stroke volume, and multiplying stroke volume with heart rate gives the CO.

5.5. Pericardial Effusion and Tamponade. Echocardiography is the tool of choice for evaluating the pericardial sac and the presence of tamponade. The diagnosis of a pericardial effusion is made from the observation of an echo-free space between the parietal and visceral pericardium seen from the parasternal, apical, and/or subcostal views.

The presence of haemodynamically significant pericardial fluid is typically assessed by examination of the RA and RV. RA collapse during early systole and RV collapse during early diastole indicate that intrapericardial pressure exceeds right heart pressures. These findings, together with a dilated IVC are signs of a haemodynamically significant tamponade [35].

6. Conclusion

Echocardiography is important development in critical care. However, as with any diagnostic and monitoring tool, echocardiography is subject to errors in interpretation, and there is a range of individual responses for any given study. No single tool is complete; however, echo provides some distinct advantages compared to invasive monitoring, not least of which are noninvasiveness and the ability to conduct a direct anatomic evaluation of the heart and its component parts in real time.

There are a number of focused approaches designed to facilitate the conduct of a systematic echocardiographic study. A number of guidelines have been issued for training and competency, which are designed to enforce standards and define core skill sets required for examination of the critically ill patient. The most important of these have been addressed in this review.

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References

[1] P. H. Mayo, Y. Beaulieu, P. Doelken et al., "American college of chest physicians/ la societédé réanimation de langue francais statement on competence in critical care ultrasonography," *Chest*, vol. 135, no. 4, pp. 1050–1060, 2009.

[2] Expert Round Table on Ultrasound in ICU, "International Expert Statement on Standards for Critical Care Ultrasonography," *Intensive Care Medicine*, vol. 37, no. 7, pp. 1077–1083, 2011.

[3] L. Neri, E. Storti, and D. Lichtenstein, "Toward an ultrasound curriculum for critical care medicine," *Critical Care Medicine*, vol. 35, supplement 5, pp. S290–S304, 2007.

[4] S. Price, G. Via, E. Sloth et al., "Echocardiography practice, training and accreditation in the intensive care: document for the World Interactive Network Focused on Critical Ultrasound (WINFOCUS)," *Cardiovascular Ultrasound*, vol. 6, article 49, 2008.

[5] D. Lichtenstein, I. Goldstein, E. Mourgeon, P. Cluzel, P. Grenier, and J.-J. Rouby, "Comparative diagnostic performances of auscultation, chest radiography, and lung ultrasonography in acute respiratory distress syndrome," *Anesthesiology*, vol. 100, no. 1, pp. 9–15, 2004.

[6] P. Vignon, H. Mentec, S. Terré, H. Gastinne, P. Gueret, and F. Lemaire, "Diagnostic accuracy and therapeutic impact of transthoracic and transesophageal echocardiography in mechanically ventilated patients in the ICU," *Chest*, vol. 106, no. 6, pp. 1829–1834, 1994.

[7] J. Tam, J. Nichol, A. MacDiarmid, N. Lazarow, and K. Wolfe, "What is the real clinical utility of echocardiography? A prospective observational study," *Journal of the American Society of Echocardiography*, vol. 12, no. 9, pp. 689–697, 1999.

[8] L. K. Stanko, E. Jacobsohn, J. W. Tam, C. J. de Wet, and M. Avidan, "Transthoracic echocardiography: impact on diagnosis and management in tertiary care intensive care units," *Anaesthesia and Intensive Care*, vol. 33, no. 4, pp. 492–496, 2005.

[9] R. M. Orme, M. P. Oram, and C. E. McKinstry, "Impact of echocardiography on patient management in the intensive care unit: an audit of district general hospital practice," *British Journal of Anaesthesia*, vol. 102, no. 3, pp. 340–344, 2009.

[10] M. D. Cheitlin, W. F. Armstrong, G. P. Aurigemma et al., "ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: summary article: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (ACC/AHA/ASE committee to update the 1997 guidelines for the clinical application of echocardiography)," *Journal of the American College of Cardiology*, vol. 42, no. 5, pp. 954–970, 2003.

[11] P. Douglas, M. J. Garcia, D. E. Haines et al., "ACCF/ASE/ASNC/HFSA/HRS/SCAI/SCCM/SCCT/SCMR 2011 Appropriate use criteria for echocardiography," *Journal of the American College of Cardiology*, vol. 57, pp. 1126–1166, 2011.

[12] F. A. Khasawneh and R. D. Smalligan, "Focused transthoracic echocardiography," *Postgraduate Medicine*, vol. 122, no. 3, pp. 230–237, 2010.

[13] M. B. Jensen, E. Sloth, K. M. Larsen, and M. B. Schmidt, "Transthoracic echocardiography for cardiopulmonary monitoring in intensive care," *European Journal of Anaesthesiology*, vol. 21, no. 9, pp. 700–707, 2004.

[14] M. I. Burgess, R. J. Bright-Thomas, and S. G. Ray, "Echocardiographic evaluation of right ventricular function," *European Journal of Echocardiography*, vol. 3, no. 4, pp. 252–262, 2002.

[15] A. Vieillard-Baron, "Assessment of right ventricular function," *Current Opinion in Critical Care*, vol. 15, no. 3, pp. 254–260, 2009.

[16] S. N. Ahmed, F. M. Syed, and D. T. Porembka, "Echocardiographic evaluation of hemodynamic parameters," *Critical Care Medicine*, vol. 35, supplement 8, pp. S323–S329, 2007.

[17] L. Bergenzaun, P. Gudmonsson, H. Öhlin et al., "Assesing left ventricular systolic function in shock: evaluating of echocardiographic parameters in intensive care," *Critical Care*, vol. 15, p. R200, 2011.

[18] P. Gudmundsson, E. Rydberg, R. Winter, and R. Willenheimer, "Visually estimated left ventricular ejection fraction by echocardiography is closely correlated with formal quantitative methods," *International Journal of Cardiology*, vol. 101, no. 2, pp. 209–212, 2005.

[19] S. Price, E. Nicol, D. G. Gibson, and T. W. Evans, "Echocardiography in the critically ill: current and potential roles," *Intensive Care Medicine*, vol. 32, no. 1, pp. 48–59, 2006.

[20] R. Willenheimer, C. Cline, L. Erhardt, and B. Israelsson, "Left ventricular atrioventricular plane displacement: an echocardiographic technique for rapid assessment of prognosis in heart failure," *Heart*, vol. 78, no. 3, pp. 230–236, 1997.

[21] M. Alam, J. Wardell, E. Andersson, B. A. Samad, and R. Nordlander, "Characteristics of mitral and tricuspid annular velocities determined by pulsed wave Doppler tissue imaging in healthy subjects," *Journal of the American Society of Echocardiography*, vol. 12, no. 8, pp. 618–628, 1999.

[22] B. Lind, M. Eriksson, S. Roumina, J. Nowak, and L.-Å. Brodin, "Longitudinal isovolumic displacement of the left ventricular myocardium assessed by tissue velocity echocardiography in healthy individuals," *Journal of the American Society of Echocardiography*, vol. 19, no. 3, pp. 255–265, 2006.

[23] A. Vieillard-Baron, J.-M. Schmitt, R. Augarde et al., "Acute cor pulmonale in acute respiratory distress syndrome submitted to protective ventilation: incidence, clinical implications, and prognosis," *Critical Care Medicine*, vol. 29, no. 8, pp. 1551–1555, 2001.

[24] D. Osman, X. Monnet, V. Castelain et al., "Incidence and prognostic value of right ventricular failure in acute respiratory distress syndrome," *Intensive Care Medicine*, vol. 35, no. 1, pp. 69–76, 2009.

[25] L. G. Rudski, W. W. Lai, J. Afilalo et al., "Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography. Endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography," *Journal of the American Society of Echocardiography*, vol. 23, no. 7, pp. 685–713, 2010.

[26] J. I. Poelaert and G. Schüpfer, "Hemodynamic monitoring utilizing transesophageal echocardiography. The relationships among pressure, flow, and function," *Chest*, vol. 127, no. 1, pp. 379–390, 2005.

[27] R. M. Lang, M. Bierig, R. B. Devereux et al., "Recommendations for chamber quantification: a report from the American Society of Echocardiography's guidelines and standards committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology," *Journal of the American Society of Echocardiography*, vol. 18, no. 12, pp. 1440–1463, 2005.

[28] C. Barbier, Y. Loubières, C. Schmit et al., "Respiratory changes in inferior vena cava diameter are helpful in predicting fluid responsiveness in ventilated septic patients," *Intensive Care Medicine*, vol. 30, no. 9, pp. 1740–1746, 2004.

[29] M. Feissel, F. Michard, J.-P. Faller, and J. L. Teboul, "The respiratory variation in inferior vena cava diameter as a guide to fluid therapy," *Intensive Care Medicine*, vol. 30, no. 9, pp. 1834–1837, 2004.

[30] J. M. Brennan, J. E. Blair, S. Goonewardena et al., "Reappraisal of the use of inferior vena cava for estimating right atrial pressure," *Journal of the American Society of Echocardiography*, vol. 20, no. 7, pp. 857–861, 2007.

[31] M. Slama, H. Masson, and J.-L. Teboul, "Respiratory variations of arotic VTI: a new index of hypovolemia and fluid responsiveness," *American Journal of Physiology: Heart and Circulatory Physiology*, vol. 283, pp. H1729–H1733, 2002.

[32] X. Monnet, M. Rienzo, D. Osman et al., "Esophageal Doppler monitoring predicts fluid responsiveness in critically ill ventilated patients," *Intensive Care Medicine*, vol. 31, no. 9, pp. 1195–1201, 2005.

[33] M. Feissel, F. Michard, I. Mangin, O. Ruyer, J.-P. Faller, and J.-L. Teboul, "Respiratory changes in aortic blood velocity as an indicator of fluid responsiveness in ventilated patients with septic shock," *Chest*, vol. 119, no. 3, pp. 867–873, 2001.

[34] M. S. Chew and J. Poelaert, "Accuracy and repeatability of pediatric cardiac output measurement using Doppler: 20-Year review of the literature," *Intensive Care Medicine*, vol. 29, no. 11, pp. 1889–1894, 2003.

[35] B. D. Hoit, "Pericardial disease and pericardial tamponade," *Critical Care Medicine*, vol. 35, supplement 8, pp. S355–S364, 2007.

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Clinical Study

Hemodynamic Changes during a Deep Inspiration Maneuver Predict Fluid Responsiveness in Spontaneously Breathing Patients

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Objective. We hypothesized that the hemodynamic response to a deep inspiration maneuver (DIM) indicates fluid responsiveness in spontaneously breathing (SB) patients. *Design*. Prospective study. *Setting*. ICU of a general hospital. *Patients*. Consecutive nonintubated patients without mechanical ventilation, considered for volume expansion (VE). *Intervention*. We assessed hemodynamic status at baseline and after VE. *Measurements and Main Results*. We measured radial pulse pressure (PP) using an arterial catheter and peak velocity of femoral artery flow (VF) using continuous Doppler. Changes in PP and VF induced by a DIM (ΔPPdim and ΔVFdim) were calculated in 23 patients. ΔPPdim and ΔVFdim $\geq$12% predicted responders to VE with sensitivity of 90% and specificity of 100%. *Conclusions*. In a restricted population of SB patients with severe sepsis or acute pancreatitis, ΔPPdim and ΔVFdim are accurate indices for predicting fluid responsiveness. These results should be confirmed in a larger population before validating their use in current practice.

1. Introduction

Blood volume is a determinant of hemodynamic stability, which regulates oxygen supply to the tissues. Volume expansion (VE) is frequently the first-line therapeutic measure for improving the hemodynamic status of patients with acute circulatory failure. Absence of VE and excessive fluid loading can lead to inadequate tissue oxygenation, organ failure, and sometimes death [1]. Unfortunately, only 40–70% of critically ill patients with acute circulatory failure significantly increase their stroke volume (SV) in response to VE regardless of the respiratory conditions [2]. This emphasizes the need for factors that predict fluid responsiveness in order to distinguish patients who might benefit from VE, as well as to avoid ineffective VE.

Cardiac preload estimation is not accurate for predicting fluid responsiveness in patients with acute circulatory failure [3]. Dynamic indices, based on the analysis of SV preload dependence, have been validated to predict fluid responsiveness in mechanically ventilated patients [3]. However, only a few studies, yielding conflicting results, tested VE responsiveness indices in spontaneously breathing (SB) patients [4–8].

The passive leg-raising maneuver has been reported to provide valid assessment of fluid responsiveness in a broad population, including patients with cardiac arrhythmias or spontaneous respiratory movements [9]. Nevertheless, depending on the method used, this test may not increase cardiac preload enough to detect preload dependence and/or may not be possible to perform with all types of beds and stretchers [9, 10].

During spontaneous breathing (SB), inspiration decreases intrathoracic pressure and increases intra-abdominal pressure, increasing the preload of the right ventricle, resulting in

an increase in right ventricular SV, and an expiratory increase in left ventricular SV [11–13] if the heart is preload-responsive. As reported during mechanical ventilation using low tidal volume, possibly masking biventricular preload dependence [14–16], respiratory changes in intrathoracic pressure during SB may be insufficient to modify loading conditions of the ventricles to the extent that respiratory changes in left ventricular SV can be measured [4]. Consequently, a deep inspiration maneuver (DIM) might improve the predictive value of SB-induced SV variations for detecting fluid responsiveness. To our knowledge, DIM-induced hemodynamic changes have never been previously tested for detecting fluid responsiveness in SB patients.

As previously described, the velocity peak of femoral artery flow (VF) and radial pulse pressure (PP) are reliable surrogates of left ventricular SV for detecting SV changes during preload responsiveness assessment [7].

We thus conducted a prospective study to assess whether DIM-induced changes in PP and VF (ΔPPdim and ΔVFdim, resp.) can predict fluid responsiveness in SB patients with acute circulatory failure. Moreover, to determine physiological hemodynamic changes during the specific DIM used in this study, ΔPPdim and ΔVFdim were assessed in 6 healthy volunteers prior to patient analyses.

2. Patients and Methods

2.1. Ethical Considerations. This study was submitted to the institutional review board for human subjects of our institutions. Protocol was approved and considered to be part of the routine practice. Healthy subjects and patients gave informed consent prior to inclusion in the study. Healthy subjects and consecutive patients hospitalized in the intensive care unit of the General Hospital Center in Valenciennes (France) were prospectively assessed for a 12-month period until February 2009.

2.2. Healthy Volunteers. Criteria for inclusion of healthy volunteers included no chronic diseases and a stable physical state for at least 6 weeks prior to the study. Subjects were examined after overnight fasting.

2.3. Patients. We selected for inclusion all nonintubated SB patients without ventilatory support and with acute circulatory failure, for whom the attending physician decided to perform fluid challenge. This decision was based on the presence of at least one clinical sign of inadequate tissue perfusion and absence of contraindications for fluid infusion. Clinical signs of inadequate tissue perfusion were defined as follows: systolic arterial pressure (SAP) of 90 mm Hg (or a decrease of 40 mm Hg in previously hypertensive patients), urine output of 0.5 mL/kg/h for at least 1 h, tachycardia (heart rate ≥100/min), and mottled skin. Cardiac rhythm had to be regular. Each patient had a 3-Fr radial catheter (Seldiflex Plastimed; Division Prodimed, Saint-Leu-La-Foret, France) inserted prior to the study as part of standard hemodynamic monitoring.

Patients were not included in the study if they displayed accessory muscle use (sternocleidomastoid, scalene, pectoralis major, trapezius, internal intercostals, and abdominal muscles), if the respiratory rate was over 30 or if they could not sustain an inspiration strain for over 5 s.

Eligible patients were secondarily excluded if they had high-grade aortic insufficiency, if transthoracic echogenicity was not satisfactory, or if mechanical ventilation was warranted.

2.4. Measurements (Systemic Arterial Pressure, Stroke Volume, Femoral Artery Flow). Noninvasive (healthy volunteers) and invasive (patients) arterial pressures, heart rate, and respiratory rate were measured with offline recordings on a central monitor (Information Center M3155; Philips Medical System, Andover, MA, USA) connected to bedside monitors (IntelliVue MP70; Philips Medical System, Boeblingen, Germany). For respiratory rate measurements, thoracic impedance recordings were used.

For patients, systolic and diastolic arterial pressures (SAP and DAP) were measured with a radial catheter. Mean arterial pressure (MAP) was calculated as MAP = (SAP + 2DAP)/3. Arterial PP was calculated as SAP minus DAP.

All echographic measurements were made on-line with commercially available echocardiographic HDI 3000 equipment (Philips Medical System; Bothell, WA, USA) with a 2-MHz transthoracic transducer. Aortic blood flow was recorded with a pulsed Doppler at the aortic valve so that the click of aortic closure was obtained. The velocity time integral of aortic blood flow was measured. The aortic valve area was calculated from the diameter of the aortic orifice, measured at insertion of the aortic cusps, as aortic area = π* aortic diameter^2/4. SV was calculated as SV = aortic valve area * the velocity time integral of aortic blood flow [18].

Femoral blood flow was recorded with a continuous Doppler at the common femoral artery. One of the two common femoral arteries was identified with echographic 2-dimensional and color Doppler's modes. VF was measured with a continuous Doppler.

An average of 10 consecutive cardiac cycles over at least one respiratory cycle was used for measurement of SAP, DAP, MAP, PP, SV, and VF.

2.5. Respiratory Variations during Quiet SB. Maximal and minimal values for PP and VF were determined over a respiratory cycle during quiet SB. Respiratory variations in PP and VF (ΔPP and ΔVF, resp.) were calculated as previously described [19]: respiratory variation within a respiratory cycle = (maximal value − minimal value)/((maximal value − minimal value)/2). Three consecutive measurements were averaged.

2.6. Respiratory Variations during DIM. All patients received a brief training (<5 min) to make them familiar with the performance of DIM. After passive exhalation, DIM consisted of slow continuous inspiration strain (5–8 s) followed by slow passive exhalation. Then, normal quiet breathing was resumed. Inspiration and exhalation durations were controlled

at the bedside with the echograph chronometer and off-line with thoracic impedance recording. Maximal values of DIM-induced PP and VF were recorded as the maximal value of PP and VF during the deep inspiration strain and the following exhalation. DIM-induced changes in PP and VF (ΔPPdim and ΔVFdim, resp.) were calculated as follow.

DIM-induced changes = (maximal value during DIM − minimal value during quiet SB prior to DIM)/((maximal value during DIM − minimal value during quiet SB prior to DIM)/2). Three consecutive measurements were averaged. The variability of ΔPPdim and ΔVFdim measurements was tested. ΔVFdim was measured three times in all healthy volunteers by the same observer (intraobserver variability) and by a second observer (interobserver variability). ΔPPdim and ΔVFdim were measured three times in 10 patients by the same observer (intraobserver variability).

2.7. Study Design. Patients were studied in a semirecumbent position. Supportive therapies and vasopressors, if present, remained unchanged throughout the study. All hemodynamic and echocardiographic measurements during quiet SB and DIM were performed at baseline and immediately after a 30 min VE using 500 mL of 6% hydroxyethyl starch. Patients were considered as responders to VE if their SV increased by 15%. Because the aortic valve area is not affected by VE, this 15% cut-off value was defined prior to beginning the study as twice the intraobserver variability of the velocity time integral of aortic valve flow, measured by transthoracic echocardiography in previous studies [4–7]. Tested parameters and SV were recorded consecutively within 5 min by 2 different investigators, before and after VE.

2.8. Statistical Analysis. Numerical data are given as means ± SD unless otherwise indicated. The Shapiro-Wilk test was used to test for normal distribution. Comparison of means within groups was performed using a paired-sample Student's *t*-test or a paired-sample Wilcoxon's test. Comparison of means between groups was performed using an independent sample Student's *t*-test or Mann-Whitney's *U*-test. Qualitative variables were reported as number and percentage and compared between groups using a Fisher test. Linear correlations were tested using the Pearson test. Receiver-operating characteristic curves ± SE were compared using the Hanley-McNeil test [20]. Cut-off values for ΔPP, ΔPPdim, ΔVF, and ΔVFdim were chosen to correspond to the best respective Youden's index [21]. A $P \leq .05$ was considered statistically significant. Statistical analysis was performed using SPSS 13.0.1 software (SPSS, Chicago, IL, USA).

3. Results

3.1. Healthy Volunteers. VF time course was assessed during DIM in 6 healthy volunteers, and mean clinical characteristics are summarized in Table 1. During inspiration strain, VF immediately decreased (phase 1), then increased (phase 2), and eventually again decreased (phase 3). During slow passive exhalation immediately following inspiration strain, VF increased (phase 4). After quiet SB was resumed, VF returned to baseline level within 30 s. The maximum value of DIM-induced VF was recorded during phase 2 or 4 (Figure 1). VF Values during SB and DIM are reported in Table 2. Intraobserver and interobserver variabilities for ΔVFdim were, respectively, 4.7% ± 3.4% and 7.1% ± 6.5%.

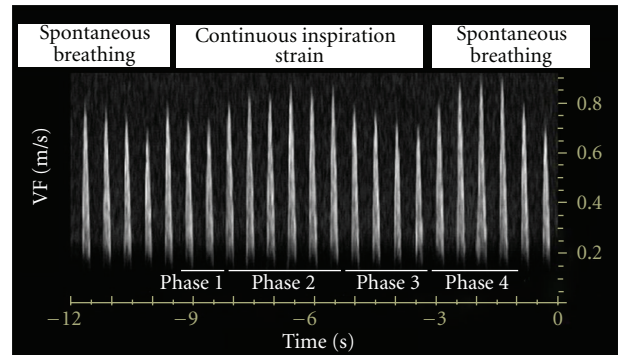

Figure 1: Velocity peak of femoral artery flow (VF) during a deep inspiration maneuver (DIM). Phase 1, 2, 3, and 4 of the DIM.

Table 1: Main characteristics of healthy volunteers.

	$n = 6$
Age, years	35 ± 3
Sex ratio, M/F	4/2
Body mass index	23.6 ± 3.2
Body surface area, m^2	1.83 ± 0.18
HR, beats/min	72 ± 9
RR, cycles/min	17 ± 5
MAP, mm Hg	85 ± 11
PP, mm Hg	44 ± 12
SAP, mm Hg	114 ± 17
DAP, mm Hg	70 ± 8
SVi, mL/m^2	33 ± 7
VF, cm/s	74.2 ± 9.8

HR, heart rate; RR, respiratory rate; MAP, mean arterial pressure; PP, pulse pressure; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; SVi, stroke volume index; VF, velocity peak of femoral artery flow. Values are expressed as mean ± SD.

3.2. Patients. Among 250 consecutive patients hospitalized during the study, 30 (5.8%) were evaluated for inclusion in the study. Among them, 4 (13.3%) were not included because of accessory muscles use ($n = 3$), respiratory rate of ≥ 30 ($n = 1$), and/or inspiration strain below 5 s ($n = 4$). Among the 26 eligible patients, 3 (11.5%) were excluded because of transthoracic poor insonation. Thus, 23 patients (7 females and 16 males) with a mean age of 50 ± 5 years were included in the study (Table 3). Glasgow's coma score was 15/15 for all patients. Mean simplified acute physiological score II was 31 ± 12, and 2 (8.7%) patients died during hospitalization.

For the group as a whole, SV was significantly increased by VE, from 53.2 ± 12.2 mL to 62.8 ± 14 mL ($P < 0.0001$). Ten patients (43.5%) were considered responders to VE. The general characteristics of the two groups were similar prior

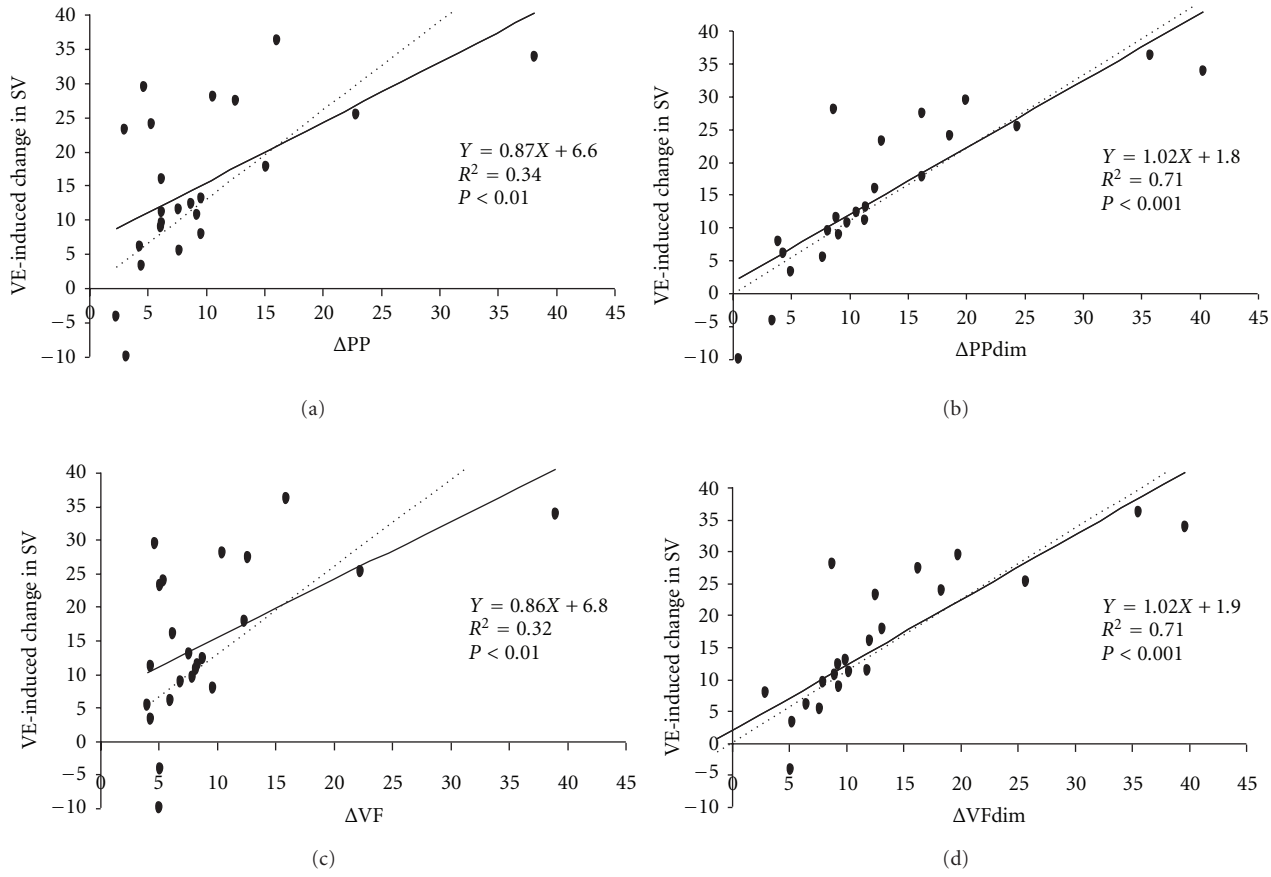

Figure 2: Linear correlation between respiratory change in pulse pressure (ΔPP), respiratory change in velocity peak of femoral artery flow (ΔVF), deep inspiration maneuver-induced change in pulse pressure (ΔPPdim), deep inspiration maneuver-induced change in velocity peak of femoral artery flow (ΔVFdim)- and volume expansion- (VE-) induced change in stroke volume (SV).

Table 2: Velocity peak of femoral artery flow during quiet spontaneous breathing and deep inspiration maneuver in healthy volunteers.

N	VF during quiet spontaneous breathing (cm/s)		VF during deep inspiration maneuver (cm/s)				ΔVF (%)	ΔVFdim (%)
	Inspiration	Exhalation	Phase 1	Phase 2	Phase 3	Phase 4		
1	81.2	92.2	73.2	92.1	64	92.9	12.7	13.4
2	64	72.3	59	71.2	55.4	76.5	12.2	17.8
3	71.8	82.8	62.1	82.9	51.7	88	14.2	20.3
4	75.7	83.5	68.1	82.6	52.1	87.8	9.8	14.8
5	56.1	61.3	50	66.9	36.4	64.8	8.9	17.6
6	86.8	91.6	81.3	99.6	76.3	88.8	5.4	13.7
Mean ± SD	72.6 ± 11.2	80.6 ± 11.9	65.6 ± 11	82.6 ± 12.3	56 ± 13.4	83.1 ± 10.5	10.5 ± 3.2	16.2 ± 2.7[a]

VF, velocity peak of femoral artery flow; ΔVF, respiration-induced change in VF; ΔVFdim, deep-inspiration-maneuver-induced change in VF. [a]$P < 0.05$ versus ΔVF. Values are expressed as mean ± SD.

to VE (Table 3). Invasive arterial pressure and femoral blood flow were recorded in all patients. Intraobserver variability for ΔPPdim and ΔVFdim were, respectively, 5.9% ± 4.6% and 6.3% ± 5.8%. ΔPP, ΔPPdim, ΔVF, and ΔVFdim were higher in responders than those in nonresponders (Table 4), and each was positively correlated with a VE-induced increase in SV (Figure 2). Moreover, VE-induced changes in SV were negatively correlated with VE-induced changes in ΔPP ($R^2 = 0.23$; $P = 0.02$), VE-induced changes in ΔPPdim ($R^2 = 0.55$; $P < 0.01$), VE-induced changes in ΔVF ($R^2 = 0.24$; $P = 0.02$), and VE-induced changes in ΔVFdim ($R^2 = 0.56$; $P < 0.01$).

AUROC ± SE for ΔPPdim (0.95 ± 0.05) and ΔVFdim (0.95 ± 0.05) were higher than AUROC ± SE for ΔPP (0.71 ± 0.12) and ΔVF (0.74 ± 0.11); $P < 0.05$. ΔPPdim and ΔVFdim of ≥12% predicted fluid responsiveness with a sensitivity of 90% and specificity of 100% (Table 5, Figure 3). No adverse effect of DIM was reported.

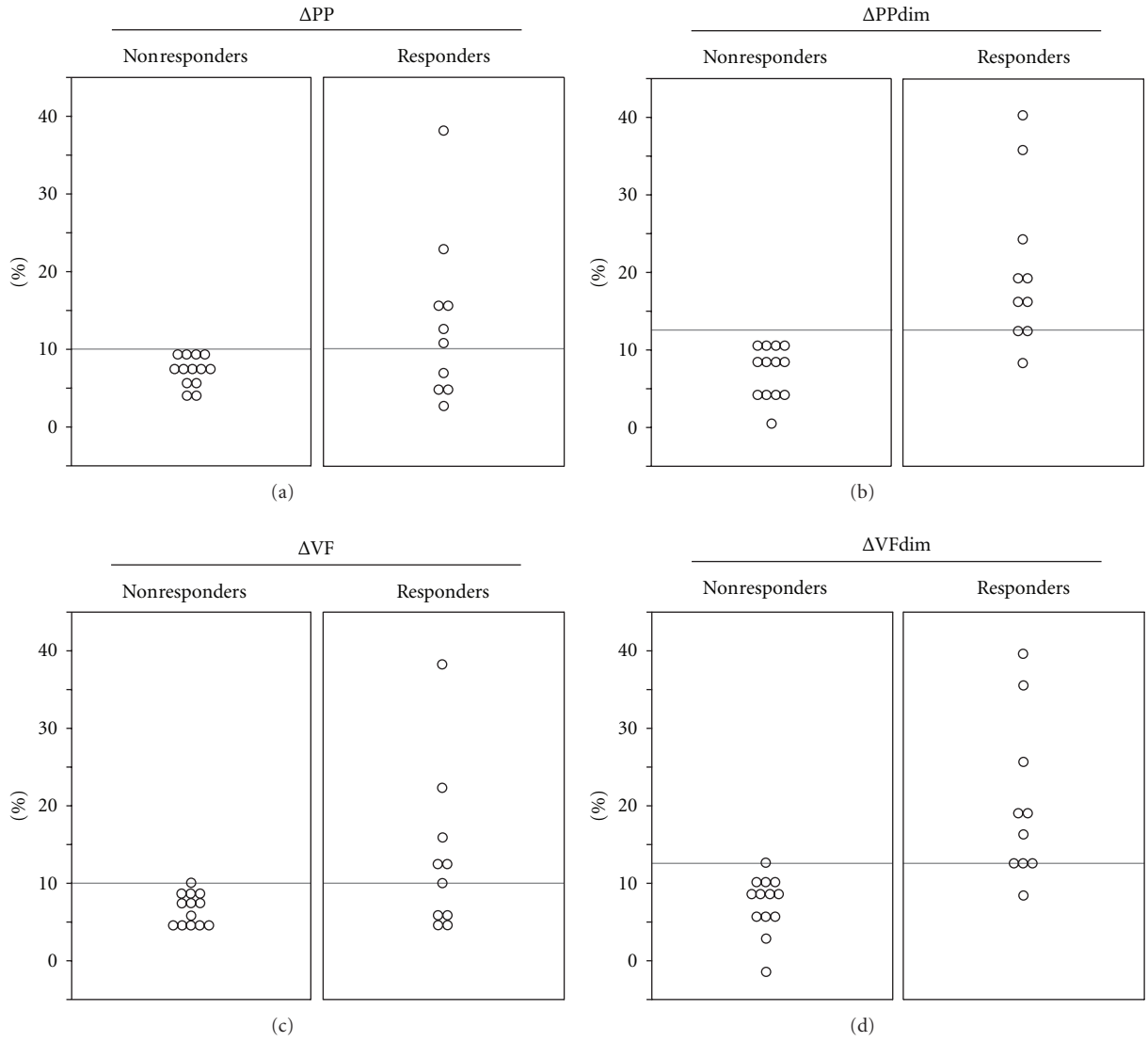

Figure 3: Individual baseline values for each indicator, respiratory change in pulse pressure (ΔPP), respiratory change in velocity peak of femoral artery flow (ΔVF), deep inspiration maneuver-induced change in pulse pressure (ΔPPdim), and deep inspiration maneuver-induced change in velocity peak of femoral artery flow (ΔVFdim) in patients with volume expansion-induced changes in SV ≥ 15% (responders) and <15% (nonresponders).

4. Discussion

The main finding of this study was that ΔVFdim and ΔPPdim enable safe and accurate bedside prediction of preload responsiveness in SB patients without ventilatory support with sepsis or acute pancreatitis. ΔVFdim and ΔPPdim of ≥12% were predictive of a positive hemodynamic response to VE induced by rapid fluid infusion. Furthermore, we demonstrated that ΔVFdim and ΔPPdim are more accurate makers of fluid responsiveness than ΔVF or ΔPP. The search for predictive factors of fluid responsiveness in SB patients was justified, since fluid responsiveness occurred in only 43.5% of patients. Thus, as previously described in SB patients, VE does not consistently improve hemodynamics [4–8].

In mechanically ventilated patients, positive pressure inspiration induces cyclic increases in right atrial pressure, causing, in turn, inverse changes in venous return, right ventricular preload and ejection, and ultimately left ventricular preload. In preload-dependent patients, these cyclic changes in ventricular filling induce cyclic changes in SV, PP, and arterial blood flow, enabling prediction of a positive response to VE [19]. In SB patients without mechanical ventilatory support, negative pressure inspiration induces cyclic decreases in right atrial pressure, causing cyclic increases in venous return, right ventricular preload and ejection, and ultimately left ventricular preload. Although SB and mechanical ventilation have inversed physiological effects on cardiac preload, respiratory changes in SV or surrogates are correlated with VE-induced changes in SV [4]. As previously described [4], the sensitivity of ΔVF and ΔPP in our study was lower than that in mechanically ventilated patients [19, 22]. Nevertheless, the predictive value of ΔPP in mechanically ventilated

Table 3: Descriptive clinical data of the patients.

	Responders $n = 10$	Nonresponders $n = 13$	P
Age, years	47 ± 22	53 ± 22	0.69
Sex ratio, M/F	6/4	10/3	0.65
SAPS II	31 ± 15	30 ± 10	0.82
ICU stay before inclusion, days[a]	1 [0–3]	1 [0–4]	0.90
Abdominal compartment syndrome [17]	0 (0%)	0 (0%)	1
OALL	0 (0%)	0 (0%)	1
COPD	0 (0%)	1 (8%)	1
Arterial hypertension	1 (10%)	3 (23%)	0.6
LVEF <45%	2 (20%)	1 (8%)	0.56
Indication for ICU stay (on the day of inclusion)			
Sepsis	9 (90%)	11 (85%)	1
Pulmonary infections	9 (90%)	7 (54%)	0.77
Urinary tract infections	0 (0%)	1 (8%)	0.57
Abdominal infections	0 (0%)	1 (8%)	0.57
Other infections	0 (0%)	2 (15%)	0.31
Nosocomial infections	2 (20%)	6 (46%)	0.20
Acute pancreatitis	1 (10%)	2 (8%)	1
Clinical hemodynamic parameters			
Vasoactive drugs	0 (0%)	2 (16%)	0.49
Arterial hypotension	4 (40%)	7 (54%)	0.68
Oliguria	5 (50%)	6 (46%)	1
Tachycardia	8 (80%)	9 (69%)	0.66
Mottled skin	3 (30%)	4 (31%)	1

SAPS II, Simplified Acute Physiologic Score II; ICU, intensive care unit, OALL, obliterating arteriopathy of the lower limbs; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction. [a]Values expressed as median and interquartile range (25th-75th percentiles). Values are expressed as number (%) or mean ± SD.

Table 4: Hemodynamic parameters before and after volume expansion in responders and nonresponders.

$n = 23$	Before volume expansion	After volume expansion
RR, cycles/min		
Nonresponders	23 ± 4	22 ± 4
Responders	23 ± 4	22 ± 4
HR, beats/min		
Nonresponders	97 ± 22	97 ± 23
Responders	112 ± 22	107 ± 18[b]
MAP, mm Hg		
Nonresponders	79 ± 13	83 ± 13[b]
Responders	80 ± 14	90 ± 16[b]
PP, mm Hg		
Nonresponders	66 ± 19	68 ± 20
Responders	63 ± 22	71 ± 26[b]
VF, mm Hg		
Nonresponders	82.1 ± 20.5	87.5 ± 22.9[b]
Responders	79.2 ± 27.8	94.6 ± 33.4[b]
SVi, mL/m^2		
Nonresponders	28.7 ± 4.9	31.3 ± 5.4[b]
Responders	28.9 ± 10.7	39 ± 14.1[b]
ΔPP, %		
Nonresponders	6.6 ± 2.5[a]	4.5 ± 2.2[b]
Responders	13.5 ± 10.6	5.5 ± 2.5[b]
ΔPPdim, %		
Nonresponders	7.2 ± 3.5[a]	5.7 ± 2.5[a]
Responders	20.6 ± 10	10.2 ± 6.1[b]
ΔVF, %		
Nonresponders	6.6 ± 1.9[a]	5.1 ± 1.1[b]
Responders	13.4 ± 10.6	6.6 ± 3.1[b]
ΔVFdim, %		
Nonresponders	7.4 ± 3[a]	6.3 ± 1.8[a]
Responders	20.4 ± 10.1	10.9 ± 5.2[b]

RR, respiratory rate; HR, heart rate; MAP, mean arterial pressure; PP, pulse pressure; VF, velocity peak of femoral artery flow; SVi, stroke volume index; ΔPP, respiration-induced change in PP; ΔPPdim, deep inspiration maneuver-induced change in PP; ΔVF, respiration-induced change in VF; ΔVFdim, deep inspiration maneuver-induced change in VF; responders, patients with volume expansion-induced changes in stroke volume ≥ 15%. [a]$P < 0.05$ versus responders; [b]$P < 0.05$ versus before volume expansion. Values given as mean ± SD.

patients can be altered when tidal volume is low [14]. Since low tidal volume may attenuate ΔVF and ΔPP values in SB patients, we hypothesized that DIM may sensitize these indices for predicting fluid responsiveness. Our results confirm that a transient increase in tidal volume due to a standardized DIM can increase ΔVF and ΔPP sensitivity for predicting responders to VE. The main strength of the specific DIM performed in this study is that it does not necessitate specific material such as a certain type of bed [9], spirometry transducers [8], or inspiratory threshold devices [23]. The main weakness of the maneuver is the lack of respiratory parameter measurements to control whether the inspiration strain is sufficient to increase venous return to the heart. Attention should be directed to the specific population selected in our study. Indeed, ΔVFdim and ΔPPdim predicted fluid responsiveness with high sensitivity provided patients were able to understand and perform an inspiratory strain of >5 s. This prerequisite may have enabled selection of patients with appropriate inspiratory capacity, permitting accurate DIM and thus accurate fluid responsiveness prediction. However, this hypothesis should be confirmed in further studies before ΔVFdim and ΔPPdim can be routinely used at the bedside to predict fluid responsiveness in SB patients.

Continuous inspiration strain leads to a significant increase in caval blood flow [24], thus increasing cardiac preload. Although the DIM performed in this study may increase cardiac preload, hemodynamic effects are more complex and DIM-induced changes in left ventricular SV are not entirely driven by preload responsiveness of the heart. As described previously, inspiration during SB not only decreases intrathoracic pressure but also increases intraabdominal pressure and lung volume. Combined effects

Table 5: Accuracy of hemodynamic parameters for predicting fluid responsiveness.

	Threshold value	Sensitivity	Specificity	PPV	NPV	PLR	NLR	AUROC ± SE
ΔPP	10%	60%	100%	100%	76%	∞	0.4	0.71 ± 0.12
ΔPPdim	12%	90%	100%	100%	93%	∞	0.1	0.95 ± 0.05[a,b]
ΔVF	10%	60%	100%	100%	76%	∞	0.4	0.74 ± 0.11
ΔVFdim	12%	90%	100%	100%	93%	∞	0.1	0.95 ± 0.05[a,b]

ΔPP, respiratory change in pulse pressure; ΔPPdim, deep inspiration maneuver-induced change in pulse pressure; ΔVF, respiratory change in velocity peak of femoral artery flow; ΔVFdim, deep inspiration maneuver-induced change in velocity peak of femoral artery flow [a]$P < 0.05$ versus ΔPP; [b]$P < 0.05$ versus ΔVF.

of the three physiologic phenomena lead to an increase not only in right ventricular preload but also in right and left ventricular afterloads [25, 26]. Therefore, DIM-induced left ventricular SV changes over time are the integrative consequence of DIM-induced changes in preload and afterload changes. First, the inspiration strain-induced increase in left ventricular afterload leads to an immediate decrease in left ventricular SV, PP and VF (phase 1 of the DIM) [26–28]. Second, if the heart is preload-responsive despite increases in right and left ventricular afterload, the increase in right ventricular preload results in an increase in right ventricular SV and, 2 or 3 heartbeats later due to pulmonary transit time of blood, in an increase in left ventricular SV, PP, and VF (phase 2 of the DIM) [11–13]. Third, the inspiration strain-induced increase in right and left ventricular afterloads overwhelms preload-dependent effects, leading to a decrease in left ventricular SV, PP, and VF (phase 3 of the DIM). As previously described during deep inspiration, global equilibrium between increased venous return and increased cardiac afterload leads to an increase in intrathoracic blood volume [27, 28] and, thus, cardiac preload. Therefore, if the heart is preload-responsive, passive exhalation immediately following deep inspiration leads to an increase in left ventricular SV, PP, and VF (phase 4 of the DIM). Thus, DIM-induced increases in PP and VF during phase 2 or 4 may correlate with cardiac preload responsiveness if their relationships with left ventricular SV are not significantly altered [7]. The high sensitivity and specificity values of ΔVFdim and ΔPPdim for predicting fluid responsiveness suggest that the relationship between left ventricular SV, PP, and VF may not be significantly altered during DIM. However, it must be underlined that no patient had abdominal compartment syndrome in this study. As intraabdominal pressure may alter hemodynamic effects of DIM, these results should not be extended to patients with suspected or confirmed abdominal compartment syndrome.

Although specificity of ΔVFdim and ΔPPdim was highly efficient at detecting VE responders, false positives may occur. As previously described, a high ΔPP baseline value could reflect either preload dependence or right ventricular dysfunction [29, 30]. Indeed, in case of obstructive lung disease and/or acute right ventricular dysfunction, an inspiratory decrease in left-ventricular diastolic compliance results in an exaggeration of the normal inspiratory decrease in PP referred to as pulsus paradoxus [31]. Therefore, ΔVFdim, and ΔPPdim might be high despite the absence of preload responsiveness and may expose patients to ineffective or deleterious fluid loadings. Evaluation of right ventricular function may help to predict false positives of ΔVFdim and ΔPPdim. Unfortunately, the study population comprised few or no patients with chronic obstructive pulmonary disease or reduced right ventricular function. Consequently, further studies are needed to determine reliability of ΔVFdim and ΔPPdim in a larger population comprising patients with obstructive lung disease and acute right ventricular dysfunction.

Eventually, it must be underlined that arrhythmia leads to misinterpretation of respiratory changes in arterial blood flow parameters, and; thus, these results cannot be extended to patients without regular cardiac rhythm.

In summary, our findings suggest that in a restricted population of SB patients with severe sepsis or acute pancreatitis, ΔVFdim and ΔPPdim are accurate indices of fluid responsiveness. Analysis of ΔPPdim or ΔVFdim is easy to perform in patients who have an indwelling arterial catheter or when echographic equipment is available. However, false negatives and false positives may occur in different clinical conditions. These results should be confirmed in a larger population before validating their use in current practice.

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References

[1] G. Mion and J. Y. Lefrant, "Adverse effects of blood volume expansion," *Reanimation*, vol. 13, no. 4, pp. 273–278, 2004.

[2] F. Michard and J. L. Teboul, "Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence," *Chest*, vol. 121, no. 6, pp. 2000–2008, 2002.

[3] J. L. Teboul, "SRLF experts recommendations: indicators of volume resuscitation during circulatory failure," *Reanimation*, vol. 13, no. 4, pp. 255–263, 2004.

[4] S. Soubrier, F. Saulnier, H. Hubert et al., "Can dynamic indicators help the prediction of fluid responsiveness in spontaneously breathing critically ill patients?" *Intensive Care Medicine*, vol. 33, no. 7, pp. 1117–1124, 2007.

[5] J. Maizel, N. Airapetian, E. Lorne, C. Tribouilloy, Z. Massy, and M. Slama, "Diagnosis of central hypovolemia by using passive leg raising," *Intensive Care Medicine*, vol. 33, no. 7, pp. 1133–1138, 2007.

[6] B. Lamia, A. Ochagavia, X. Monnet, D. Chemla, C. Richard, and J. L. Teboul, "Echocardiographic prediction of volume res-

ponsiveness in critically ill patients with spontaneously breathing activity," *Intensive Care Medicine*, vol. 33, no. 7, pp. 1125–1132, 2007.

[7] S. Préau, F. Saulnier, F. Dewavrin, A. Durocher, and J. L. Chagnon, "Passive leg raising is predictive of fluid responsiveness in spontaneously breathing patients with severe sepsis or acute pancreatitis," *Critical Care Medicine*, vol. 38, no. 3, pp. 819–825, 2010.

[8] M. I. Monge García, A. Gil Cano, and J. C. Díaz Monrové, "Arterial pressure changes during the Valsalva maneuver to predict fluid responsiveness in spontaneously breathing patients," *Intensive Care Medicine*, vol. 35, no. 1, pp. 77–84, 2009.

[9] J. L. Teboul and X. Monnet, "Prediction of volume responsiveness in critically ill patients with spontaneous breathing activity," *Current Opinion in Critical Care*, vol. 14, no. 3, pp. 334–339, 2008.

[10] K. Lakhal, S. Ehrmann, I. Runge et al., "Central venous pressure measurements improve the accuracy of leg raising-induced change in pulse pressure to predict fluid responsiveness," *Intensive Care Medicine*, vol. 36, no. 6, pp. 940–948, 2010.

[11] M. R. Pinsky, "Cardiovascular issues in respiratory care," *Chest*, vol. 128, no. 5, supplement 2, pp. 592S–597S, 2005.

[12] S. W. Patterson and E. H. Starling, "On the mechanical factors which determine the output of the ventricles," *The Journal of Physiology*, vol. 48, pp. 357–379, 1914.

[13] D. D. Glower, J. A. Spratt, N. D. Snow et al., "Linearity of the Frank-Starling relationship in the intact heart: the concept of preload recruitable stroke work," *Circulation*, vol. 71, pp. 994–1009, 1985.

[14] D. De Backer, S. Heenen, M. Piagnerelli, M. Koch, and J. L. Vincent, "Pulse pressure variations to predict fluid responsiveness: influence of tidal volume," *Intensive Care Medicine*, vol. 31, no. 4, pp. 517–523, 2005.

[15] D. A. Reuter, J. Bayerlein, M. S. G. Goepfert et al., "Influence of tidal volume on left ventricular stroke volume variation measured by pulse contour analysis in mechanically ventilated patients," *Intensive Care Medicine*, vol. 29, no. 3, pp. 476–480, 2003.

[16] A. Szold, R. Pizov, E. Segal, and A. Perel, "The effect of tidal volume and intravascular volume state on systolic pressure variation in ventilated dogs," *Intensive Care Medicine*, vol. 15, no. 6, pp. 368–371, 1989.

[17] M. L. N. G. Malbrain, M. L. Cheatham, A. Kirkpatrick et al., "Results from the international conference of experts on intra-abdominal hypertension and abdominal compartment syndrome. I. Definitions," *Intensive Care Medicine*, vol. 32, no. 11, pp. 1722–1732, 2006.

[18] J. F. Lewis, L. C. Kuo, J. G. Nelson, M. C. Limacher, and M. A. Quinones, "Pulsed Doppler echocardiographic determination of stroke volume and cardiac output: clinical validation of two new methods using the apical window," *Circulation*, vol. 70, no. 3, pp. 425–431, 1984.

[19] F. Michard, S. Boussat, D. Chemla et al., "Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure," *American Journal of Respiratory and Critical Care Medicine*, vol. 162, no. 1, pp. 134–138, 2000.

[20] J. A. Hanley and B. J. McNeil, "A method of comparing the areas under receiver operating characteristic curves derived from the same cases," *Radiology*, vol. 148, no. 3, pp. 839–843, 1983.

[21] W. J. Youden, "Index for rating diagnostic tests," *Cancer*, vol. 3, no. 1, pp. 32–35, 1950.

[22] M. I. Monge García, A. Gil Cano, and J. C. Díaz Monrové, "Brachial artery peak velocity variation to predict fluid responsiveness in mechanically ventilated patients," *Critical Care*, vol. 13, no. 5, p. R142, 2009.

[23] M. K. Dahl, S. T. Vistisen, J. Koefoed-Nielsen, and A. Larsson, "Using an expiratory resistor, arterial pulse pressure variations predict fluid responsiveness during spontaneous breathing: an experimental porcine study," *Critical Care*, vol. 13, no. 2, article no. R39, 2009.

[24] R. S. Kuzo, R. A. Pooley, J. E. Crook, M. G. Heckman, and T. C. Gerber, "Measurement of caval blood flow with MRI during respiratory maneuvers: implications for vascular contrast opacification on pulmonary CT angiographic studies," *American Journal of Roentgenology*, vol. 188, no. 3, pp. 839–842, 2007.

[25] T. S. Hakim, R. P. Michel, and H. K. Chang, "Effect of lung inflation on pulmonary vascular resistance by arterial and venous occlusion," *Journal of Applied Physiology Respiratory Environmental and Exercise Physiology*, vol. 53, no. 5, pp. 1110–1115, 1982.

[26] A. J. Buda, M. R. Pinsky, N. B. Ingels Jr., G. T. Daughters II, E. B. Stinson, and E. L. Alderman, "Effect of intrathoracic pressure on left ventricular performance," *The New England Journal of Medicine*, vol. 301, pp. 453–459, 1979.

[27] M. Karam, R. A. Wise, and T. K. Natarajan, "Mechanism of decreased left ventricular stroke volume during inspiration in man," *Circulation*, vol. 69, no. 5, pp. 866–873, 1984.

[28] S. M. Scharf, R. Brown, N. Saunders, and L. H. Green, "Effects of normal and loaded spontaneous inspiration on cardiovascular function," *Journal of Applied Physiology Respiratory Environmental and Exercise Physiology*, vol. 47, no. 3, pp. 582–590, 1979.

[29] Y. Mahjoub, C. Pila, A. Friggeri et al., "Assessing fluid responsiveness in critically ill patients: false-positive pulse pressure variation is detected by Doppler echocardiographic evaluation of the right ventricle," *Critical Care Medicine*, vol. 37, no. 9, pp. 2570–2575, 2009.

[30] J. N. Cohn, A. L. Pinkerson, and F. E. Tristani, "Mechanism of pulsus paradoxus in clinical shock," *Journal of Clinical Investigation*, vol. 46, no. 11, pp. 1744–1755, 1967.

[31] R. Shabetai, N. O. Fowler, J. C. Fenton, and M. Masangkay, "Pulsus paradoxus," *Journal of Clinical Investigation*, vol. 44, no. 11, pp. 1882–1898, 1965.

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Review Article

Nonconvective Forces: A Critical and Often Ignored Component in the Echocardiographic Assessment of Transvalvular Pressure Gradients

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Echocardiography is routinely used to assess ventricular and valvular function, particularly in patients with known or suspected cardiac disease and who have evidence of hemodynamic compromise. A cornerstone to the use of echocardiographic imaging is not only the qualitative assessment, but also the quantitative Doppler-derived velocity characteristics of intracardiac blood flow. While simplified equations, such as the modified Bernoulli equation, are used to estimate intracardiac pressure gradients based upon Doppler velocity data, these modified equations are based upon assumptions of the varying contributions of the different forces that contribute to blood flow. Unfortunately, the assumptions can result in significant miscalculations in determining a gradient if not completely understood or they are misapplied. We briefly summarize the principles of fluid dynamics that are used clinically with some of the inherent limitations of routine broad application of the simplified Bernoulli equation.

1. Introduction

Echocardiography has become an invaluable tool for the qualitative and quantitative assessment of cardiac function. The ability to evaluate ventricular function and valve pathology in real time, its portability, lack of ionizing radiation, and relatively low cost are all factors that have contributed to echocardiography becoming more common in the physiologic and hemodynamic assessment of sick patients. While 2-dimensional and, more recently, 3-dimensional imaging of cardiac structures are part of a routine qualitative assessment; both continuous and pulsed wave Doppler are often used for quantitative assessment of intracardiac flows depending on the magnitude of flow velocity and the need for spatial resolution [1]. While Doppler waveforms are routinely used to determine the magnitude of normal, regurgitant, and stenotic (restrictive) intracardiac flow, the limitations of the assumptions of the equations routinely used are rarely considered [2].

2. Theoretical Basis for the Assessment of Intracardiac Pressure Gradients

A primary application of the pulsed Doppler waveforms has been the estimation of pressure gradients, typically across both native and prosthetic valves [3]. The theoretical basis of this stems from the Navier-Stokes equations for incompressible fluid that describes three-dimensional flow [4]. The Navier-Stokes equations can then be rewritten and simplified to describe two-dimensional flow across a streamline; this is known as Euler's equation (1) and relates the instantaneous local pressure (∂p) and velocity (∂v) relationships as a function of distance (∂s) and time (∂t)

$$\frac{\partial p}{\partial s} = -\rho\left[\frac{\partial v}{\partial t} + v\frac{\partial v}{\partial s}\right]. \quad (1)$$

Integrating Euler's equation between 2 points along a pathway (such as within the heart between a point in the

left atrium (S_{LA}) and ventricle (S_{LV})) results in the unsteady Bernoulli equation

$$\Delta p = \frac{1}{2}\rho(v_2^2[t] - v_1^2[t]) + \rho \int_{S_{LA}}^{S_{LV}} \frac{\partial v[s,t]}{\partial t} ds + G. \quad (2)$$

Similarly, the unsteady Bernoulli equation (also known simply as "the Bernoulli equation") can be rewritten as

$$\Delta p(t) = \frac{1}{2}\rho\Delta(v_2^2 - v_1^2) + M\frac{dv}{dt} + R(v) + G, \quad (3)$$

in which $\Delta p(t)$ is the drop in pressure as a function of time (t) between the two points of interest, ρ is blood density ($1.05\,g/cm^3$), v is the velocity of blood between the two points of interest (v_1 and v_2), and M is the inertance term of blood flow. R is a resistive term reflecting the effects of viscosity along the path. G is the term that describes the effects of gravity and, in the context of intracardiac blood flow, is considered negligible and is typically ignored [5]. Similarly, since these applications often describe blood flow originating in either the right or left atrium for the assessment of transtricuspid or transmitral applications, the initial velocity within the left atriums have also been shown to be negligible and can be ignored [6]. This assumption of an initial minimal upstream velocity is a recurrent source of error in the assessment of intracardiac blood flow, regardless of the equations used.

The complete form of the unsteady Bernoulli equation (3) consists of 4 terms [6] that describe the contributions of different forces that determine a pressure gradient:

(1) a convective term ($\Delta p_{conv} = (1/2)\rho\Delta(v_2^2 - v_1^2)$) accounts for the fall in pressure and the simultaneous rise in the kinetic energy as fluid (i.e., blood) increases velocity across an orifice (i.e., a valve);

(2) an inertial or nonconvective term ($\Delta p_{int} = M(dv/dt)$) describes the pressure change that is required to accelerate a mass of blood across the valve;

(3) a gravitational (G) term that describes the effects of gravitational forces on the mass;

(4) a viscous term ($\Delta p_{visc} = R(v)$) that describes the loss of energy from the viscous interactions between the fluid/blood along the walls.

3. Resistive or Viscous Forces

The contribution of resistive or viscous forces is based upon the Poiseuille equation (4)

$$\Delta p_{visc} = \frac{4\mu V_{max} L}{r^2}. \quad (4)$$

The viscous resistance to flow (Δp_{visc}) is a function of the viscosity of blood (μ), the peak velocity (V_{max}), and the length of the column (L), divided by the radius squared (r^2). For cardiac applications, and assuming steady-state laminar flow, for the range of human cardiac output (2–6 liters/minute), over the distance measured (typically only several centimeters within the heart), and for the range of valvular or tubular diameters (also typically only several centimeters), the contribution of the resistance term ranges from 0.006 mmHg (for a radius of 0.7 cm and a cardiac output of 2 liters/min) to 0.14 mmHg (for a diameter of 1.0 cm and a cardiac output of 6 liters/min) [5]. Hence, as mentioned, in the context of intracardiac flow and pressures, viscous forces are considered negligible and are typically ignored.

4. Inertance (Nonconvective) Forces

The inertance term, M, is a function of the energy required to accelerate a mass of blood (dv/dt), and it can be described by rewriting the unsteady Bernoulli equation

$$M \approx \frac{\Delta P_{act} - \Delta P_{conv}}{dv/dt}. \quad (5)$$

M can be approximated as the difference between the actual pressure gradient (ΔP_{act}) and the convective component of the pressure gradient ($\Delta P_{conv} = (1/2)\rho\Delta[v^2]$) as a function of the changes in velocity over time (again assuming negligible viscous and gravitational forces). For routine applications, M is also typically ignored because it requires being able to derive the change in velocity (acceleration) over a distance, a task that is very difficult to accurately accomplish when measuring intracardiac blood flow. This spatial acceleration is not available by conventional 2D Doppler velocity data (which only provides the velocity characteristics of blood at a point/region of interest). Color M-mode Doppler, unlike conventional Doppler imaging that provides a velocity at a specific point within the heart, provides encoded velocities over an entire scanline with the colors displayed directly correlating to that specific velocity on the scanline. The scanline provides the distances while real-time recording adds the component of time. Recording these scanline velocity characteristics over time allows for determining the nonconvective or inertial forces [7]. While sophisticated analysis of color M-mode imaging has demonstrated the ability to determine the spatial acceleration of blood and the inertial component, these tools are not easily available and therefore not part of routine clinical applications. Furthermore, acquisition of these images requires the scanline to be directly oriented in a 90 degree angle to the direction of flow to prevent underestimation of velocities by off-angle measurements. While in theory Doppler scan-line orientation can have a significant impact on underestimating true velocities, and hence true pressure gradients, the magnitude and significance of off-angle measurements are unclear [8]. Furthermore, in routine clinical applications, either with transthoracic or transesophageal imaging, the ability to accurately orient the Doppler scanline in a patient can be technically challenging. Much like gravitational and viscous forces are often considered negligible as are inertance forces, in part because of the difficulty in measuring them accurately; however, inertance forces have been shown to be physiologically complex, incompletely understood, and considerably variables in ways that can lead to a substantial underestimation of the overall pressure gradient which needs to be considered [9].

For routine clinical applications, the estimation of a pressure gradient within the heart typically only considers the easy-to-measure convective term. It is this convective term that is commonly referred to as the "modified" Bernoulli equation that is the complete Bernoulli equation (3) minus the inertial, gravitational, and viscous/resistance terms. When converted into appropriate scientific units, it becomes familiar: $\Delta p = 4v^2$ [3], in which v is the Doppler-derived velocity in m/sec and Δp is the estimated pressure gradient in mmHg. Again, an additional assumption is that the initial velocities, for example, in the left atrium, are minimal, and hence, only the final velocity is considered—a concept that is not necessarily valid.

For nonrestrictive orifices, such as a normal valves and "larger" conduits, these assumptions do not apply. Because of the relatively large amount of blood that must pass through a nonrestrictive mitral valve with each cardiac cycle, the inertial term is presumed to play a significant role in describing the overall transmitral pressure gradient [10]. Although previous investigators have demonstrated the importance of the inertial component of the Bernoulli equation when applied to transmitral flow, it is a term that is commonly ignored both clinically and in research [11, 12].

5. Clinical Data

Animal and human data regarding the absolute or relative contributions of transvalvular inertance and nonconvective forces are limited, with most work having been performed in the context of transmitral valvular pressure gradients (transaortic gradients and velocities are much higher and the inertial components contribute relatively less and probably have less clinical significance). Human *in situ* experiments, with high-fidelity pressure transducers placed across the mitral valve, in which actual pressure gradients are compared with the convective components (as determined using the modified Bernoulli equation from echo Doppler velocities) under a wide-spectrum of physiologic conditions, are used to estimate the inertance components [13]. In these human experiments, the actual catheter derived transmitral pressure gradients ranging from 1.04 to 14.24 mmHg. However, using simultaneously derived Doppler velocity, the inertance component ($M(dv/dt)$) ranged from 0.6 to 12.9 mmHg. A previously validated numerical model of the cardiovascular system [14] was then used to predict those physiologic and echocardiographic determinants of M (not to be confused with the complete inertial component, $M(dv/dt)$) [11]. The results of mathematical modeling demonstrated, using a multivariate analysis, that the strongest predictors of transmitral M was (1) maximum left atrial volume (an index of the "mass" of blood that needs to be accelerated) and (2) the ratio of pulmonary venous S/D wave velocities (an index of the initial kinetic/potential energy of blood within the left atrium that needs to be moved across the mitral valve). Overall, the inertial energy, on average, consisted of 74% of the actual pressure gradient as predicted using only the convective term [13].

In a similar set of human experiments, in 8 patients undergoing cardiac surgery, 56 cardiac cycles from 16 hemodynamic stages were studied. Actual pressure gradients were recorded with high-fidelity multisensor pressure transducers (Millar, Houston, Tex, USA) across a normal mitral valve. These actual gradients were correlated with noninvasive echocardiograph color M-mode images. This study demonstrated, for a large range of physiologic conditions, that the Δp_{conv} consistently underestimated Δp_{act} ($r = 0.72$, $P < 0.05$), and, in fact, Δp_{act} overall poorly correlated with Δp_{conv} ($r = 0.35$). However, color M-mode-derived gradients (which included both convective and inertance components) correlated closely with actual pressure gradients ($y = 0.95x + 0.24$, $r = 0.96$) [11]. These findings are consistent with previous canine, human, and numerical modeling studies in which, under normal loading conditions, ignoring the inertance components underestimated transmitral gradients by as much as 12 mmHg [9, 12, 13].

This data suggests that in "sicker" patients (i.e., those with greater left atrial volumes, mitral valve dysfunction, and abnormal filling pressures) the inertance contribution to transmitral pressure gradients is greater and thereby implying the Doppler-derived gradients significantly underestimate, and more so with larger LA volume, the actual gradient. Conversely, a decreased pulmonary venous S/D ratio in the setting of "normal" transmitral Doppler waveforms, which is a marker for heart failure [15], predicts a lower inertial component to the actual transmitral gradient, and hence the convective term more closely approximates the true gradient. These findings and concepts are consistent with separate studies performed by Nakatani et al. [12] in which physiologic predictors of transmitral M included systolic LV pressures and actual transmitral gradients.

Flachskampf and colleagues, in an *in vitro* model, showed that inertance depended on the orifice diameter and conduit length more than the actual gradients. This explains, in part, the basis of the limitations of the modified Bernoulli equation in larger orifices and lower pressure/velocity scenarios, like a normal mitral valve. In the context of the heart, he suggested that M was a function of geometrical characteristics of the mitral valve area and apparatus length [10]. Even though these results might appear contradictory, chronic adverse changes in ventricular loading conditions are linked to pathologic changes in the mitral valve function and geometry.

While these experiments demonstrate the role of nonconvective, or inertial, forces for transmitral flow, it is important to consider that the same principles apply for other applications that measure pressure gradients within the heart, such as intraventricular pressure gradients [16, 17], right ventricular filling pressures [18], intracardiac shunts, and pulmonary hypertension [19]. For example, while Doppler velocities are routinely used to derive pulmonary artery pressures [20], it is well known that these pressures typically correlate poorly with actual catheter-derived measurements [21]. In these studies, even when right atrial pressures are included in these estimates, there is still a significant (~8 mmHg) source of error in more than 50% of patients that cannot be explained by routinely measured clinical parameters and are hypothesized to be only accounted for by nonconvective forces [22]. Clearly, further

studies are needed to substantiate and better understand these complex complementary or conflict determinants to intracardiac pressure gradients.

6. Conclusions

The use of echocardiography in the evaluation of cardiac disease and the critically ill is becoming ubiquitous. It is standard of care for intraoperative management of patients undergoing valve surgery without contraindications [23]. Unfortunately, clinically useful tools to accurately quantitatively determine the contributing factors to nonconvective forces, or the inertial components of intracardiac blood flow, are lacking which potentially further explains why this parameter is typically ignored when determining intracardiac pressure gradients. Nevertheless, as outlined, these nonconvective forces remain a variable and critical contribution to the determination of pressure gradients. A thorough understanding of the principles of fluid dynamics, the limitations of Doppler echocardiography, and the assumptions of the modified Bernoulli equation are critical in accurate interpretation of clinical data.

References

[1] R. O. Bonow, B. A. Carabello, K. Chatterjee et al., "ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients with Valvular Heart Disease) - Developed in collaboration with the Society of Cardiovascular Anesthesiologists," *Circulation*, vol. 114, no. 5, pp. e84–e231, 2006.

[2] P. J. Currie, J. B. Seward, and G. S. Reeder, "Continuous-wave Doppler echocardiographic assessment of severity of calcific aortic stenosis: a simultaneous Doppler-catheter correlative study in 100 adult patients," *Circulation*, vol. 71, no. 6, pp. 1162–1169, 1985.

[3] R. B. Stamm and R. P. Martin, "Quantification of pressure gradients across stenotic valves by Doppler ultrasound," *Journal of the American College of Cardiology*, vol. 2, no. 4, pp. 707–718, 1983.

[4] G. K. Batchelor, *An Introduction to Fluid Dynamics*, Cambridge University Press, New York, NY, USA, 2000.

[5] P. S. Teirstein, P. G. Yock, and R. L. Popp, "The accuracy of Doppler ultrasound measurement of pressure gradients across irregular, dual, and tunnellike obstructions to blood flow," *Circulation*, vol. 72, no. 3, pp. 577–581, 1985.

[6] "Principles of flow," in *Principles and Practice of Echocardiography*, A. R. Weyman, Ed., pp. 184–200, Lea & Febiger, Philadelphia, Pa, USA, 2nd edition, 1994.

[7] J. D. Thomas and A. E. Weyman, "Numerical modeling of ventricular filling," *Annals of Biomedical Engineering*, vol. 20, no. 1, pp. 19–39, 1992.

[8] Neil L. Greenberg, Krucinski, and James D. Thomas, "Significance of color Doppler M-mode scanline orientation in the non-invasive assessment of intraventricular pressure gradients," *Computers in Cardiology*, pp. 605–608, 1997.

[9] N. L. Greenberg, P. M. Vandervoort, and J. D. Thomas, "Instantaneous diastolic transmitral pressure differences from color Doppler M mode echocardiography," *American Journal of Physiology—Heart and Circulatory Physiology*, vol. 271, no. 4, pp. H1267–H1276, 1996.

[10] F. A. Flachskampf, L. Rodriguez, C. Chen, J. L. Guerrero, A. E. Weyman, and J. D. Thomas, "Analysis of mitral inertance: a factor critical for early transmitral filling," *Journal of the American Society of Echocardiography*, vol. 6, no. 4, pp. 422–432, 1993.

[11] M. S. Firstenberg, P. M. Vandervoort, N. L. Greenberg et al., "Noninvasive estimation of transmitral pressure drop across the normal mitral valve in humans: importance of convective and inertial forces during left ventricular filling," *Journal of the American College of Cardiology*, vol. 36, no. 6, pp. 1942–1949, 2000.

[12] S. Nakatani, M. S. Firstenberg, N. L. Greenberg et al., "Mitral inertance in humans: critical factor in Doppler estimation of transvalvular pressure gradients," *American Journal of Physiology—Heart and Circulatory Physiology*, vol. 280, no. 3, pp. H1340–H1345, 2001.

[13] M. S. Firstenberg, N. L. Greenberg, N. G. Smedira, P. M. McCarthy, M. J. Garcia, and J. D. Thomas, "Noninvasive assessment of mitral inertance: clinical results with numerical model validation," *Computers in Cardiology*, pp. 613–616, 2001.

[14] J. D. Thomas, J. Zhou, N. Greenberg, G. Bibawy, P. M. Mccarthy, and P. M. Vandervoort, "Physical and physiological determinants of pulmonary venous flow: numerical analysis," *American Journal of Physiology—Heart and Circulatory Physiology*, vol. 272, no. 5, pp. H2453–H2465, 1997.

[15] R. Nagano, T. Masuyama, J. M. Lee et al., "Transthoracic Doppler assessment of pattern of left ventricular dysfunction in hypertensive heart disease: combined analysis of mitral and pulmonary venous flow velocity patterns," *Journal of the American Society of Echocardiography*, vol. 7, no. 5, pp. 493–505, 1994.

[16] J. D. Thomas and Z. B. Popović, "Intraventricular pressure differences: a new window into cardiac function," *Circulation*, vol. 112, no. 12, pp. 1684–1686, 2005.

[17] R. Yotti, J. Bermejo, M. M. Desco et al., "Doppler-derived ejection intraventricular pressure gradients provide a reliable assessment of left ventricular systolic chamber function," *Circulation*, vol. 112, no. 12, pp. 1771–1779, 2005.

[18] C. Cortina, J. Bermejo, R. Yotti et al., "Noninvasive assessment of the right ventricular filling pressure gradient," *Circulation*, vol. 116, no. 9, pp. 1015–1023, 2007.

[19] M. R. Fisher, P. R. Forfia, E. Chamera et al., "Accuracy of doppler echocardiography in the hemodynamic assessment of pulmonary hypertension," *American Journal of Respiratory and Critical Care Medicine*, vol. 179, no. 7, pp. 615–621, 2009.

[20] P. G. Yock and R. L. Popp, "Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation," *Circulation*, vol. 70, no. 4, pp. 657–662, 1984.

[21] J. M. Testani, S. M. G. S. John, S. E. Wiegers, A. V. Khera, R. P. Shannon, and J. N. Kirkpatrick, "Accuracy of noninvasively determined pulmonary artery systolic pressure," *American Journal of Cardiology*, vol. 105, no. 8, pp. 1192–1197, 2010.

[22] K. Isaaz, "Expanding the frontiers of Doppler echocardiography for the noninvasive assessment of diastolic hemodynamics," *Journal of the American College of Cardiology*, vol. 36, no. 6, pp. 1950–1952, 2000.

[23] American Society of Anesthesiologists and Society of Cardiovascular Anesthesiologists Task Force on Transesophageal Echocardiography, "Practice guidelines for perioperative transesophageal echocardiography," *Anesthesiology*, vol. 112, no. 5, pp. 1084–1096, 2010.

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Review Article

Should We Monitor $ScVO_2$ in Critically Ill Patients?

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Hemodynamic monitoring has become a real challenge in the intensive care unit. As an integrative parameter for oxygen supply/demand, venous oxygen saturation (SvO_2) provided by pulmonary artery catheterization is one of the most popular parameters to assess the adequacy of cardiac output. However, technical limitations and potential iatrogenic complications constitute important limits for a widespread use. Regular central venous catheters coupled with a fiberoptic lumen for central venous oxygen saturation ($ScvO_2$) monitoring have been proposed as a surrogate for SvO_2 monitoring. The purpose of the present article is to review the physiological backgrounds of circulation, the pathophysiology of circulatory failure and subsequent venous oxygen saturation alterations, and finally the merits and the limits of the use of $ScvO_2$ in different clinical situations.

1. Introduction

Hemodynamic monitoring has become a common practice in the intensive care unit. Besides blood pressure measurement, most industrial efforts have concentrated on providing devices for cardiac output monitoring. However, adequate adaptation of these macrohemodynamic parameters is somehow challenging. Indeed, as cardiac output is an adaptive parameter, it is always difficult to judge whether a *given value* at a *given time* for a *given patient* is appropriate or not. Similarly, which value should be considered an appropriate goal for blood pressure, considering regional perfusion specificities (e.g., autoregulation or flow/pressure dependency), patient's age, history of hypertension, and so on. Therefore, considering that O_2 supply to the tissue is the basic objective, intensivists have been trying to find out an integrative parameter that would be more suitable to globally assess hemodynamic status of their patients. As a surrogate for evaluating O_2 demand/supply adequacy, central oxygen venous saturation ($ScvO_2$) has become a popular parameter. As explained for the dummies, oxygen venous saturation is interpreted as a bank statement at the end of the month: "if the balance is negative, you can consider two explanations: you spend too much money or you earn not enough." The aim of the present paper is precisely to critically analyze the physiological basements for such an interpretation, the data that support its use in clinical practice, and finally the limits that should be kept in mind while using such a parameter at the bedside.

2. Physiological Background

2.1. Normal Circulation Physiology. One of the main goals of blood circulation is to ensure oxygen supply to organs and tissues. The determinants of arterial oxygen delivery (DO_2) are

(i) cardiac output (CO);

(ii) arterial content in oxygen (CaO_2).

The arterial content in oxygen has 2 components.

(1) The main component is oxygen bound to hemoglobin (Hb).

(2) The secondary component is dissolved oxygen.

The first one depends on hemoglobin concentration, hemoglobin affinity for oxygen (which varies for Hb isotypes

and with environmental conditions such as temperature, pH, or 2.3 DPG concentrations), and, therefore, Hb oxygen saturation. The second component depends on arterial partial pressure of oxygen (PaO_2) and is considered as negligible because of the very solubility coefficient of oxygen in plasma. It is then possible to set the equations:

(i) $CaO_2 = (Hb \times 1.34 \times SaO_2) + (0.003 \times PaO_2)$,

(ii) $DO_2 = CO \times CaO_2$.

By ignoring the dissolved oxygen component, we get

(i) $DO_2 = CO \times 1{,}34 \times SaO_2$.

Arterial blood is then deoxygenated in tissues. Tissue oxygen extraction depends on their demand but also on their ability for oxygen extraction. Therefore, after peripheral oxygen extraction, venous oxygen content depends on arterial content and tissue oxygen extraction.

2.2. Pathophysiology of Circulatory Failure. Shock is one of the leading causes of admission in the intensive care unit. It is usually defined as a mean arterial pressure (MAP) <60 mmHg or a systolic arterial pressure (SAP) <90 mmHh, or a decrease in SAP greater than 40 mmHg as compared to the usual SAP [1]. For many years, hemodynamic management has focused on "macrocirculatory" parameters such as blood pressure or cardiac output. Though the magnitude of macrocirculatory disorders is well known to be related to prognosis [2], its optimization seems mandatory [3] but insufficient [4]. Indeed, in septic shock patients, Sakr et al. observed that after 24 h hours of intensive care, the values of MAP, cardiac index (CI), and central venous pressure (CVP) did not discriminate survivors from nonsurvivors.

Hence, shock can be defined as a *macrohemodynamic* instability leading to an inappropriate oxygen supply/demand balance. Schematically, as represented in Figure 1, any fall in DO_2 is initially compensated by an increase in tissue oxygen extraction (EO_2), explaining that tissue VO_2 is initially maintained. However, when tissue oxygen extraction capacity is overtaken, oxygen consumption begins to fall and lactate concentration increases, indicating a switch of the cellular metabolism from aerobic glycolysis to cytoplasmic anaerobic glycolysis. This threshold immediately precedes the onset of clinical organ failures.

Considering such a pathophysiological scheme, hemodynamic support in shock should aim at correcting macrocirculatory but also microcirculatory parameters in order to avoid any local fall in O_2 supply below this crucial threshold. Therefore, a parameter such as venous oxygen saturation (SvO_2), that should reflect the inadequacy in oxygen supply, might be of great help.

2.3. Physiological Determinants for Venous Oxygen Saturation. Oxygen extraction in the tissues can be mathematically defined as follows:

(i) $EO_2 = CO \times (CaO_2 - CvO_2)$,

(ii) $EO_2 = VO_2/DO_2$,

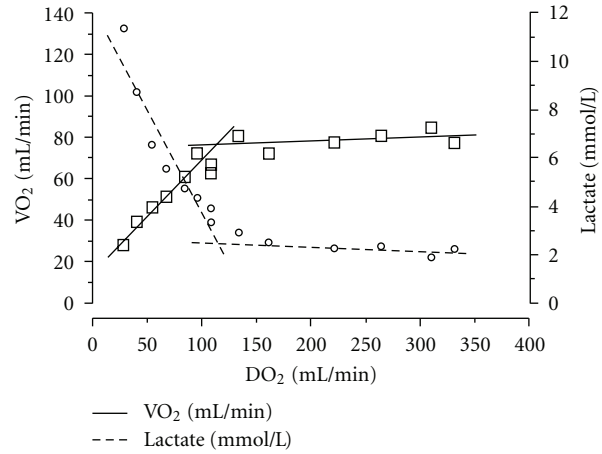

Figure 1: Evolution of oxygen consumption when oxygen delivery decreases. From Vincent and De Backer [5] with permission. Note the presence of a DO_2 threshold located at approximately 100 mL/min. Below this value, oxygen consumption begins to fall and lactate concentration increases, indicating a switch from aerobic to anaerobic metabolism.

with CvO_2 being venous oxygen content and VO_2 being oxygen consumption.

Then, venous oxygen saturation can then be calculated using the following formula:

(i) $SvO_2 = SaO_2 - (VO_2/(CO \times Hb \times 1.34))$.

Hence, any decrease in venous oxygen saturation should be explained by

(i) a decrease in SaO_2;

(ii) a decrease in cardiac output;

(iii) a decrease in hemoglobin level;

(iv) an increase of oxygen consumption (VO_2).

Thus, providing that SaO_2, oxygen consumption, and haemoglobin level are in normal ranges, SvO_2 can be used as a surrogate for cardiac output.

Likewise, if

(i) $EO_2 = CO \times (CaO_2 - CvO_2)$,

(ii) $EO_2 = VO_2/DO_2$,

then,

(i) $EO_2 = (SaO_2 - SvO_2)/SaO_2$.

Consequently, when $SaO_2 = 100\%$, then $EO_2 = 1 - SvO_2$ and $SvO_2 = 1 - EO_2$.

Then, SvO_2 is also a good surrogate for EO_2.

In shock, decrease in tissue oxygen supply is mostly related to a decrease in tissue blood flow, would it be relative (as in distributive shocks) or real (as in hemorrhagic shock). The first recommended measure in international guidelines for shock resuscitation consists in optimizing cardiac output by repeated fluid challenges [6], in order to correct oxygen supply/demand imbalance. In this aspect, SvO_2 measurements could help guiding fluid challenges in shock patients.

3. SvO_2—$ScvO_2$: Is It the Same?

The reference technique to assess the adequacy of oxygen supply is the mixed venous oxygen saturation (SvO_2), provided by pulmonary artery catheter (a.k.a. Swan-Ganz catheter) [7]. However, limitations related to difficulties of insertion and placement, but also to potential complications related with such a catheter, lead to a substantial decrease in its use. In the meantime, industrials have developed regular central venous catheter coupled with a fiberoptic lumen for continuous haemoglobin saturation monitoring. Placed through a jugular of a subclavian vein, at the confluent of the superior vena cava and the right auricle, such catheters actually monitor the central venous oxygen saturation ($ScvO_2$) [8].

However, one should ask whether SvO_2 and $ScvO_2$ provide the same information. Actually, taken in pulmonary artery, SvO_2 is a surrogate for global tissue oxygenation, whereas $ScvO_2$ essentially reflects the oxygenation of the upper part of the body (head, neck upper limbs, and upper part of the trunk) and of a lower proportion of the lower part of the body (lower part of the trunk and lower limbs), depending on the exact position of the catheter's extremity. Anyhow, $ScvO_2$ does not include venous blood coming from coronary sinus commonly located in the right auricle. Thus, taken at the confluent of the vena cava in the right auricle (i.e., upstream from the coronary sinus), $ScvO_2$ does not include myocardial oxygenation. On the contrary, SvO_2 concerns venous blood from pulmonary artery, that is, by definition, after the coronary venous sinus. Such a difference might highly impact the observed values, given that (1) venous blood from the coronary sinus, with a saturation of oxygen close to 40%, is the most deoxygenated venous blood of the body [9] and (2) that in critically ill patients, myocardial oxygen supply/demand imbalance is likely to occur.

4. $ScvO_2$: A Validated Monitoring Parameter

4.1. Experimental Validation. Many studies have compared the $ScvO_2$ and SvO_2 values in the same patients (Table 1). Most of them showed a good correlation between $ScvO_2$ and SvO_2 and a similar trend in the temporal evolution. In 1989, Reinhart et al. [10] reported, in a dog model, a correlation coefficient between $ScvO_2$ and SvO_2 of 0.96. In this study, the two values exhibited less than 5% difference in 77% of the cases. Later on, Reinhart et al. [11] confirmed their results in ICU patients: $ScvO_2$ and SvO_2 had similar evolution in 90% of the cases and had a correlation coefficient of 0.81 ($P < 0.001$). Similarly, Martin et al. [12] reported a parallel evolution of $ScvO_2$ and SvO_2 in 75% of the cases. Considering such results, it seems that $ScvO_2$ and especially its evolution over time could be used as an interesting surrogate for SvO_2 monitoring. However, the impact of $ScvO_2$ monitoring on the prognosis of critically ill patients remained to be demonstrated.

4.2. Clinical Validation. Some authors, therefore, focused on evaluating the connection between $SvcO_2$ and prognosis and especially the benefits turnoff considering $SvcO_2$ optimization as a goal for resuscitation. Pearse et al. [23] observed in a cohort of 118 postoperative patients from major surgery that a decrease in $ScvO_2$ during the first 8 hours was associated with an increase in 28-day morbidity and mortality. Consistently, Futier et al. [24] showed in major abdominal surgery that a $ScvO_2$ <70% was associated with postoperative complications. In addition, $ScvO_2$ seems to be a reliable and sensitive parameter to detect hemorrhage in trauma patients admitted to the Emergency Room [25], while other series suggest that $ScvO_2$ could be a prognosis marker in myocardial infarction [26], acute heart failure [27], as well as in severe sepsis patients [28].

But the great clinical advantage related to early $ScvO_2$has been suggested by Rivers et al. [29]. Indeed, these authors reported that, in severe sepsis patients, an early and aggressive therapy that aimed at normalizing in the first hours the values of $ScvO_2$ MAP and CVP achieved a reduction in in-hospital mortality from 46.5% to 30.5% (relative risk 0.58 (0.38–0.87), $P = 0.009$). These results were later confirmed by two large studies [30, 31] conducted, respectively, on 15,022 and 330 patients that both showed a mortality reduction related to the implementation of $ScvO_2$ as a resuscitation goal. Though Levy's et al. study [30] failed to show any survival improvement specifically related to $ScvO_2$ implementation, the global target implementation did (lactate measure, blood culture before antibiotics, broad spectrum antibiotics, fluid and vasopressors, CVP >8 mmHg, and $ScvO_2$ >70%). This could be partly explained by the fact that, among those 6 resuscitation targets, $ScvO_2$ >70% was the less commonly achieved, both after the first quarter of patients was included and after the final quarter of patients was included (resp., in 13.3% and 24.3% of the cases). Recently, Jones et al. [32] showed, in 300 septic shock patients, that the mortality of patients who benefited from a $ScvO_2$ goal-directed therapy was low (23% (17–30%)) and similar to those who were treated using a lactate clearance goal-directed therapy (17% (11–24%)).

$ScvO_2$ is considered as a suitable prognosis factor in many clinical situations in the critically ill patients. The Surviving Sepsis Campaign [33], gathering all European guidelines regarding severe sepsis and sepsis shock patients management, suggested including $ScvO_2$ as a goal parameter in the first 6 hours of management ($ScvO_2$ >70%).

5. $ScvO_2$ Limits

5.1. Theoretical Limits. The first limit of using $ScvO_2$ refers to its ignorance of the coronary sinus venous blood saturation. As the extremity of the $ScvO_2$ catheter usually stands upstream from the joining point of coronary sinus in the right auricle, the $ScvO_2$ value does not take into account the myocardial oxygen supply/demand adequacy. As myocardial oxygen extraction is physiologically basically high, venous coronary blood is one of the most deoxygenated venous bloods [9] of the body. This explains that the value of mixed

Table 1: Summary of the studies comparing SvO_2 and $ScvO_2$ in humans or in experimental models.

Author (year)	Type of patients (n)	Conclusion	Correlation coefficient
Tahvanainen et al. [13] (1982)	Intensive care (42)	$ScvO_2 = SvO_2$	NC
Wendt et al. [14] (1990)	Intensive care (19)	$ScvO_2 \sim SvO_2$	0,78
Kong et al. [15] (1990)	Kidney failure (8)	$ScvO_2 \sim SvO_2$	NC
Berridge et al. [16] (1992)	Intensive care (51)	$ScvO_2 = SvO_2$	0,92
Herrera et al. [17] (1993)	Thoracic surgery (23)	$ScvO_2 = SvO_2$	NC
Pieri et al. [18] (1995)	Major surgery (39)	$ScvO_2 \neq SvO_2$, nonsubstituable	0,90
Ladakis et al. [19] (2001)	Intensive care (61)	$ScvO_2 = SvO_2$	0,94
Reinhart et al. [11] (2004)	Intensive care (32)	$ScvO_2 \sim SvO_2$	0,81
Chawla et al. [20] (2004)	Intensive care (53)	$ScvO_2 > SvO_2$	0.88
Dueck et al. [21] (2005)	Neurosurgery (70)	$ScvO_2 \neq SvO_2$, substituable evolution	$\geq$0,75
Ho et al. [22] (2010)	Intensive care	$ScVO_2 \neq SvO_2$, nonsubstituable	NC

venous blood saturation of oxygen (SvO_2), which actually takes into account venous coronary blood, is usually lower than the $ScvO_2$. Moreover, any major increase in myocardial oxygen consumption could lead to a critical myocardial oxygen extraction that would have no impact on $ScvO_2$ monitoring. Besides, $ScvO_2$, just as SvO_2, is a global oxygenation parameter. So any local change in tissue oxygenation is at risk of being "diluted" in the rest of venous blood and then becoming undetectable. Similarly, in the case of a drop in regional venous saturation responsible for a drop of $ScvO_2$, it would not be possible to assess the affected territory without further exploration. Then, theoretically, the distal extremity of the central venous catheter is supposed to be placed at the joining point of vena cava and the right auricle to enable a suitable assessment of tissue oxygenation of inferior and superior territories. However, checking the position of the catheter's distal extremity with chest X-ray is not accurate enough. Moreover, as venous saturation from the superior vena cava is systematically lower than inferior vena cava, any variation in the position of the catheter's tip could have a major influence on the measures and therefore lead to $ScvO_2$ misinterpretation. Ultimately, as previously reported, $ScvO_2$ depends on tissue oxygen extraction and hemoglobin affinity for oxygen. Experiments report that septic patients could suffer from a decrease in oxygen extraction capacity [34, 35], a rise in capillary shunt [34], as well as changes in hemoglobin affinity for oxygen [36]. All these changes may alter the theoretical relationship between $SvcO_2$, and cardiac output, such as $ScvO_2$ interpretation, to guide hemodynamic therapy becomes more complex.

5.2. Clinical Limits. First of all, one could argue that $ScvO_2$ measurement requires a central venous catheter, which is an invasive technique, exposing patients to complications such as infection or hemorrhage. However, central venous lines are often needed for critically patients and could therefore be used for $ScvO_2$ monitoring. However, in severe sepsis and septic shock, tissue hypoperfusion should lead to particularly low $ScvO_2$ values, as observed by Rivers et al. in the early stage of sepsis. However, after the first hours of resuscitation, this situation is rarely met [37], and $ScvO_2$ values tend to be paradoxically normal or even raised. This could be explained by the physiological modification induced by sepsis and previously described (decrease in tissue oxygen extraction capacity, rise of capillary shunt, and changes in hemoglobin affinity for oxygen). Consistently, in such situations, the agreement between SvO_2 and $ScvO_2$ seems much less satisfactory, especially in the context of septic shock [22, 38, 39]. Besides, $ScvO_2$ clinical validation is mainly based on one single study [29], which is a single centre study, and its results are still controversial. As a matter of fact, van Beest et al. [37], in a Dutch prospective multicenter study, reported that only 1% of the patients meeting the inclusion criteria required by Rivers et al. [29] had a $ScvO_2$ <50%. Ho et al. [40], in a retrospective study, as well as the ARISE group (Australian Resuscitation of Sepsis Evaluation), in a multicenter study [41], reported an in-hospital mortality of 26–28% in patients who did not benefit from an early goal-directed therapy but that met the inclusion criteria for Rivers' trial. This mortality rate is much lower than the one observed by Rivers in his control group. Finally, the low CVP values (5-6 mmHg) observed by Rivers et al. suggest that their patients were probably highly hypovolemic.

5.3. Global versus Regional Circulation. If global hemodynamic optimization is considered as an essential prerequisite to ensure adequate tissue perfusion, it may not be always sufficient to avoid the development of organ failure. The poor accuracy for global oxygen venous saturation monitoring to detect changes in regional oxygenation has been well described in animal models [42–44]. For instance, Legrand et al. [42] recently showed in a rat model that LPS-induced endotoxemia could induce alterations in microvascular perfusion and oxygenation in the renal cortex in rats, which appeared to be only weakly dependent on systemic and renal macrohemodynamic alterations. Consistently, Vallet et al. [44] and Lagoa et al. [43] reported, in endotoxemic dogs, that after resuscitation skeletal VO_2 is maintained when blood flow within the gut is significantly disturbed with mucosal hypoxia. In human beings, as described by Sakr et al. [4]. global hemodynamic parameters fail to discriminate

survivors from nonsurvivors after 24 hours of intensive care in septic shock patients. One illustrative example is the lack of accuracy of global SvO_2 to detect cerebral venous desaturations [45]. In this perspective, global $ScvO_2$ might face some limitations with respect to local inadequacy in the DO_2/VO_2 balance. Indeed, local SvO_2 might not be detected by global oxygen saturation monitoring, the signal being *diluted* among a global normally saturated venous blood. Therefore, regional SvO_2 could be an interesting supplementary target parameter. However, while regional SVO_2 monitoring might be feasible at the bedside for some organ, such as jugular venous oxygen monitoring [46–48], it is much more difficult for others such as the kidney or the gut, for example. In such situation, some alternative parameters for regional monitoring could be of interest.

6. Candidate Parameter to Reflect Regional Inadequate Oxygen Supply

As for now, no biological or technical parameter has been proved to directly reflect regional oxygen supply inadequacy. Nevertheless, some parameters appear to be good surrogate candidate, such as tissue oxygen saturation (StO_2) and regional carbon dioxide partial pressure (pCO_2).

6.1. Tissue Oxygen Saturation (StO_2). StO_2 can be estimated by near-infrared spectroscopy (NIRS) using the differential absorption properties of oxygenated and deoxygenated hemoglobin. Near-infrared light (wave length 680–800 nm) easily crosses biological tissue and is only absorbed by hemoglobin, myoglobin, and oxidized cytochrome, but the contribution of myoglobin and oxidized cytochrome in light absorption is very low [49, 50]. Light tissue penetration is dependant on the space between the illumination fiber and the detection fiber. With a 25 mm space, 95% of the light signals detected come from a 0–23 mm depth.

The steady StO_2 value is a reflection of oxygen saturation of the haemoglobin present in the tissue volume crossed by the near-infrared light, containing a mix of arteriolar, capillary, and venous blood. It is then a complicated integrative parameter, but it has been shown to be correlated to the microcirculation state and is therefore considered as an acceptable parameter for tissue perfusion [51].

During shock from various origins, the relationship between StO_2 values at the forearm and the prognosis has been extensively studied during the past decade [52–55]. During shock states, as StO_2 drops correlate with fall in central venous, mixed venous oxygen saturation, or oxygen delivery [56–59], StO_2 seems to be a good marker of regional DO_2/VO_2 imbalance, with the advantage of being applicable to different regional territories such as the brain [60], the liver [61], or the muscle [62], for example. However, this technique suffers some limitations, the major one being its poor sensitivity to rule out tissue hypoperfusion [55]. In order to improve its sensitivity, vascular occlusion tests (transient upper arm arterial occlusion with a pneumatic cuff) have been proposed [63]. By continuously monitoring StO_2 during the test, a pattern curve is obtained with an initial decrease of StO_2 during occlusion, followed after cuff deflation by an increase of StO_2 usually transiently reaching higher values than baseline (hyperemic response) before returning to baseline. The slope of the decreasing part of the curve is the StO_2 desaturation rate and is correlated to the tissue oxygen consumption, whereas the slope of the increasing part of the curve is the StO_2 recovery rate and is correlated to the quality of the microvascular bedside [64].

6.2. Carbon Dioxide Partial Pressure. Regional capnography relies on the principle that cellular oxygen consumption through oxidative phosphorylation produces proportional amount of carbon dioxide. In this perspective, any decrease in blood flow would result in a CO_2 accumulation detected by a capnograph. Tissue pCO_2 could then be used as a surrogate for regional blood flow and oxygen consumption combined [65]. However, regional $pCO_2$is difficult to interpret, because CO_2 production also depends on cellular metabolism level and arterial glucose concentration. This probably explains the fact that, despite appealing, this parameter is still rarely used in clinical practice.

7. Conclusion

In conclusion, $ScvO_2$ measurement seems to be an interesting tool, especially in the early phase of shock to guide fluid management and blood transfusion or inotropic support. Nevertheless, a large knowledge of its determinants and the physiology of circulation seem to be essential to ensure a reliable interpretation in clinical practice. When $ScvO_2$ is low, it reflects an adaptive mechanism to an unsuitable supply in oxygen and should lead doctors to understand the reasons for it and to propose an appropriate optimization strategy. As well, in clinical situations such as septic shock, after the first hours of management, a "normal" or even a high $ScvO_2$ can be falsely reassuring.

Conflict of Interests

The author declares that there is no conflict of interests.

References

[1] M. M. Levy, M. P. Fink, J. C. Marshall et al., "2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference," *Critical Care Medicine*, vol. 31, no. 4, pp. 1250–1256, 2003.

[2] J. Valles, J. Rello, A. Ochagavia, J. Garnacho, and M. A. Alcala, "Community-acquired bloodstream infection in critically ill adult patients: impact of shock and inappropriate antibiotic therapy on survival," *Chest*, vol. 123, no. 5, pp. 1615–1624, 2003.

[3] M. Antonelli, M. Levy, P. J. Andrews et al., "Hemodynamic monitoring in shock and implications for management: International Consensus Conference, Paris, France, 27-28 April 2006," *Intensive Care Medicine*, vol. 33, no. 4, pp. 575–590, 2007.

[4] Y. Sakr, M. J. Dubois, D. De Backer, J. Creteur, and J. L. Vincent, "Persistent-microcirculatory alterations are associated

with organ failure and death in patients with septic shock," *Critical Care Medicine*, vol. 32, no. 9, pp. 1825–1831, 2004.

[5] J. L. Vincent and D. De Backer, "Oxygen transport—the oxygen delivery controversy," *Intensive Care Medicine*, vol. 30, no. 11, pp. 1990–1996, 2004.

[6] J. L. Vincent and M. H. Weil, "Fluid challenge revisited," *Critical Care Medicine*, vol. 34, no. 5, pp. 1333–1337, 2006.

[7] K. Reinhart and F. Bloos, "The value of venous oximetry," *Current Opinion in Critical Care*, vol. 11, no. 3, pp. 259–263, 2005.

[8] M. M. Scheinman, M. A. Brown, and E. Rapaport, "Critical assessment of use of central venous oxygen saturation as a mirror of mixed venous oxygen in severely ill cardiac patients," *Circulation*, vol. 40, no. 2, pp. 165–172, 1969.

[9] T. Miyairi, T. Miwa, T. Takayama, K. Ka, and K. Itoh, "Continuous monitoring of coronary sinus oxygen saturation during warm heart surgery," *Journal of Thoracic and Cardiovascular Surgery*, vol. 108, no. 4, pp. 795–796, 1994.

[10] K. Reinhart, T. Rudolph, D. L. Bredle, L. Hannemann, and S. M. Cain, "Comparison of central-venous to mixed-venous oxygen saturation during changes in oxygen supply/demand," *Chest*, vol. 95, no. 6, pp. 1216–1221, 1989.

[11] K. Reinhart, H. J. Kuhn, C. Hartog, and D. L. Bredle, "Continuous central venous and pulmonary artery oxygen saturation monitoring in the critically ill," *Intensive Care Medicine*, vol. 30, no. 8, pp. 1572–1578, 2004.

[12] C. Martin, J. P. Auffray, C. Badetti, G. Perrin, L. Papazian, and F. Gouin, "Monitoring of central venous oxygen saturation versus mixed venous oxygen saturation in critically ill patients," *Intensive Care Medicine*, vol. 18, no. 2, pp. 101–104, 1992.

[13] J. Tahvanainen, O. Meretoja, and P. Nikki, "Can central venous blood replace mixed venous blood samples?" *Critical Care Medicine*, vol. 10, no. 11, pp. 758–761, 1982.

[14] M. Wendt, T. Hachenberg, A. Albert, and R. Janzen, "Mixed venous versus central venous oxygen saturation in intensive medicine," *Anasth Intensivther Notfallmed*, vol. 25, no. 1, pp. 102–106, 1990.

[15] C. H. Kong, F. D. Thompson, and F. J. Imms, "Cardiac output and oxygen uptake in patients with renal failure," *Clinical Science*, vol. 78, no. 6, pp. 591–596, 1990.

[16] J. C. Berridge, "Influence of cardiac output on the correlation between mixed venous and central venous oxygen saturation," *British Journal of Anaesthesia*, vol. 69, no. 4, pp. 409–410, 1992.

[17] A. Herrera, A. Pajuelo, M. J. Morano, M. P. Ureta, J. Gutierrez-Garcia, and M. de las Mulas, "Comparison of oxygen saturations in mixed venous and central blood during thoracic anesthesia with selective single-lung ventilation," *Revista Española de Anestesiología y Reanimación*, vol. 40, no. 6, pp. 349–353, 1993.

[18] M. Pieri, L. S. Brandi, R. Bertolini, M. Calafà, and F. Giunta, "Comparison of bench central and mixed pulmonary venous oxygen saturation in critically ill postsurgical patients," *Minerva Anestesiologica*, vol. 61, no. 7-8, pp. 285–291, 1995.

[19] C. Ladakis, P. Myrianthefs, A. Karabinis et al., "Central venous and mixed venous oxygen saturation in critically ill patients," *Respiration*, vol. 68, no. 3, pp. 279–285, 2001.

[20] L. S. Chawla, H. Zia, G. Gutierrez, N. M. Katz, M. G. Seneff, and M. Shah, "Lack of equivalence between central and mixed venous oxygen saturation," *Chest*, vol. 126, no. 6, pp. 1891–1896, 2004.

[21] M. H. Dueck, M. Klimek, S. Appenrodt, C. Weigand, and U. Boerner, "Trends but not individual values of central venous oxygen saturation agree with mixed venous oxygen saturation during varying hemodynamic conditions," *Anesthesiology*, vol. 103, no. 2, pp. 249–257, 2005.

[22] K. M. Ho, R. Harding, J. Chamberlain, and M. Bulsara, "A comparison of central and mixed venous oxygen saturation in circulatory failure," *Journal of Cardiothoracic and Vascular Anesthesia*, vol. 24, no. 3, pp. 434–439, 2010.

[23] R. Pearse, D. Dawson, J. Fawcett, A. Rhodes, R. M. Grounds, and E. D. Bennett, "Changes in central venous saturation after major surgery, and association with outcome," *Critical Care*, vol. 9, no. 6, pp. R694–R699, 2005.

[24] E. Futier, E. Robin, M. Jabaudon et al., "Central venous O_2 saturation and venous-to-arterial CO_2 difference as complementary tools for goal-directed therapy during high-risk surgery," *Critical Care*, vol. 14, no. 5, article R193, 2010.

[25] T. M. Scalea, R. W. Hartnett, A. O. Duncan et al., "Central venous oxygen saturation: a useful clinical tool in trauma patients," *The Journal of Trauma*, vol. 30, no. 12, pp. 1539–1543, 1990.

[26] A. M. Hutter Jr. and A. J. Moss, "Central venous oxygen saturations: value of serial determinations in patients with acute myocardial infarction," *The Journal of the American Medical Association*, vol. 212, no. 2, pp. 299–303, 1970.

[27] D. S. Ander, M. Jaggi, E. Rivers et al., "Undetected cardiogenic shock in patients with congestive heart failure presenting to the emergency department," *The American Journal of Cardiology*, vol. 82, no. 7, pp. 888–891, 1998.

[28] M. Y. Rady, E. P. Rivers, G. B. Martin, H. Smithline, T. Appelton, and R. M. Nowak, "Continuous central venous oximetry and shock index in the emergency department: use in the evaluation of clinical shock," *American Journal of Emergency Medicine*, vol. 10, no. 6, pp. 538–541, 1992.

[29] E. Rivers, B. Nguyen, S. Havstad et al., "Early goal-directed therapy in the treatment of severe sepsis and septic shock," *The New England Journal of Medicine*, vol. 345, no. 19, pp. 1368–1377, 2001.

[30] M. M. Levy, R. P. Dellinger, S. R. Townsend et al., "The surviving sepsis campaign: results of an international guideline-based performance improvement program targeting severe sepsis," *Intensive Care Medicine*, vol. 36, no. 2, pp. 222–231, 2010.

[31] H. B. Nguyen, S. W. Corbett, R. Steele et al., "Implementation of a bundle of quality indicators for the early management of severe sepsis and septic shock is associated with decreased mortality," *Critical Care Medicine*, vol. 35, no. 4, pp. 1105–1112, 2007.

[32] A. E. Jones, N. I. Shapiro, S. Trzeciak, R. C. Arnold, H. A. Claremont, and J. A. Kline, "Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial," *The Journal of the American Medical Association*, vol. 303, no. 8, pp. 739–746, 2010.

[33] R. P. Dellinger, M. M. Levy, J. M. Carlet et al., "Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2008," *Critical Care Medicine*, vol. 36, no. 1, pp. 296–327, 2008.

[34] P. W. G. Elbers and C. Ince, "Bench-to-bedside review: mechanisms of critical illness—classifying microcirculatory flow abnormalities in distributive shock," *Critical Care*, vol. 10, no. 4, article 221, 2006.

[35] R. J. Levy and C. S. Deutschman, "Cytochrome c oxidase dysfunction in sepsis," *Critical Care Medicine*, vol. 35, no. 9, pp. S468–S475, 2007.

[36] J. J. Lehot, C. Elarby, J. J. Vallon, and J. Motin, "Oxyhaemoglobin dissociation curve and 2,3-diphosphoglycerate

in septic shock," *Annales Francaises d'Anesthesie et de Reanimation*, vol. 3, no. 2, pp. 85–89, 1984.

[37] P. A. van Beest, J. J. Hofstra, M. J. Schultz, C. E. Boerma, P. E. Spronk, and M. A. Kuiper, "The incidence of low venous oxygen saturation on admission to the intensive care unit: a multi-center observational study in The Netherlands," *Critical Care*, vol. 12, no. 2, article R33, 2008.

[38] P. Kopterides, S. Bonovas, I. Mavrou, E. Kostadima, E. Zakynthinos, and A. Armaganidis, "Venous oxygen saturation and lactate gradient from superior vena cava to pulmonary artery in patients with septic shock," *Shock*, vol. 31, no. 6, pp. 561–567, 2009.

[39] M. Varpula, S. Karlsson, E. Ruokonen, and V. Pettilä, "Mixed venous oxygen saturation cannot be estimated by central venous oxygen saturation in septic shock," *Intensive Care Medicine*, vol. 32, no. 9, pp. 1336–1343, 2006.

[40] B. C. H. Ho, R. Bellomo, F. McGain et al., "The incidence and outcome of septic shock patients in the absence of early-goal directed therapy," *Critical Care*, vol. 10, no. 3, article R80, 2006.

[41] "The outcome of patients with sepsis and septic shock presenting to emergency departments in Australia and New Zealand," *Critical Care and Resuscitation*, vol. 9, no. 1, pp. 8–18, 2007.

[42] M. Legrand, R. Bezemer, A. Kandil, C. Demirci, D. Payen, and C. Ince, "The role of renal hypoperfusion in development of renal microcirculatory dysfunction in endotoxemic rats," *Journal of Intensive Care Medicine*, vol. 37, no. 9, pp. 1534–1542, 2011.

[43] C. E. Lagoa, L. F. de Figueiredo, R. J. Cruz, E. Silva, and M. Rocha e Silva, "Effects of volume resuscitation on splanchnic perfusion in canine model of severe sepsis induced by live *Escherichia coli* infusion," *Critical Care*, vol. 8, no. 4, pp. R221–R228, 2004.

[44] B. Vallet, N. Lund, S. E. Curtis, D. Kelly, and S. M. Cain, "Gut and muscle tissue PO2 in endotoxemic dogs during shock and resuscitation," *Journal of Applied Physiology*, vol. 76, no. 2, pp. 793–800, 1994.

[45] N. Nagdyman, T. Fleck, S. Barth et al., "Relation of cerebral tissue oxygenation index to central venous oxygen saturation in children," *Intensive Care Medicine*, vol. 30, no. 3, pp. 468–471, 2004.

[46] Z. Feldman and C. S. Robertson, "Monitoring of cerebral hemodynamics with jugular bulb catheters," *Critical Care Clinics*, vol. 13, no. 1, pp. 51–77, 1997.

[47] M. O. Gayle, T. C. Frewen, R. F. Armstrong et al., "Jugular venous bulb catheterization in infants and children," *Critical Care Medicine*, vol. 17, no. 5, pp. 385–388, 1989.

[48] E. L. Gibbs, W. G. Lennox, L. F. Nims, and F. A. Gibbs, "Arterial and cerebral venous blood: arterial-venous differences in man," *The Journal of Biological Chemistry*, vol. 144, no. 2, pp. 325–332, 1942.

[49] R. Boushel and C. A. Piantadosi, "Near-infrared spectroscopy for monitoring muscle oxygenation," *Acta Physiologica Scandinavica*, vol. 168, no. 4, pp. 615–622, 2000.

[50] D. M. Mancini, L. Bolinger, H. Li, K. Kendrick, B. Chance, and J. R. Wilson, "Validation of near-infrared spectroscopy in humans," *Journal of Applied Physiology*, vol. 77, no. 6, pp. 2740–2747, 1994.

[51] M. Podbregar and H. Mozina, "Skeletal muscle oxygen saturation does not estimate mixed venous oxygen saturation in patients with severe left heart failure and additional severe sepsis or septic shock," *Critical Care*, vol. 11, no. 1, article R6, 2007.

[52] S. M. Cohn, A. B. Nathens, F. A. Moore et al., "Tissue oxygen saturation predicts the development of organ dysfunction during traumatic shock resuscitation," *The Journal of Trauma*, vol. 62, no. 1, pp. 44–54, 2007.

[53] J. Creteur, T. Carollo, G. Soldati, G. Buchele, D. De Backer, and J. L. Vincent, "The prognostic value of muscle StO2 in septic patients," *Intensive Care Medicine*, vol. 33, no. 9, pp. 1549–1556, 2007.

[54] M. Leone, S. Blidi, F. Antonini et al., "Oxygen tissue saturation is lower in nonsurvivors than in survivors after early resuscitation of septic shock," *Anesthesiology*, vol. 111, no. 2, pp. 366–371, 2009.

[55] A. Rodriguez, T. Lisboa, I. Martin-Loeches et al., "Mortality and regional oxygen saturation index in septic shock patients: a pilot study," *The Journal of Trauma*, vol. 70, no. 5, pp. 1145–1152, 2011.

[56] L. Heyer, A. Mebazaa, E. Gayat et al., "Cardiac troponin and skeletal muscle oxygenation in severe post-partum haemorrhage," *Critical Care*, vol. 13, supplement 5, article S8, 2009.

[57] J. Mesquida, G. Gruartmoner, M. L. Martínez et al., "Thenar oxygen saturation (StO2) and invasive oxygen delivery measurements in critically ill patients in early septic shock," *Shock*, vol. 35, no. 5, pp. 456–459, 2011.

[58] J. Mesquida, J. Masip, G. Gili, A. Artigas, and F. Baigorri, "Thenar oxygen saturation measured by near infrared spectroscopy as a noninvasive predictor of low central venous oxygen saturation in septic patients," *Intensive Care Medicine*, vol. 35, no. 6, pp. 1106–1109, 2009.

[59] K. E. Mulier, D. E. Skarda, J. H. Taylor et al., "Near-infrared spectroscopy in patients with severe sepsis: correlation with invasive hemodynamic measurements," *Surgical Infections*, vol. 9, no. 5, pp. 515–519, 2008.

[60] J. M. Murkin and M. Arango, "Near-infrared spectroscopy as an index of brain and tissue oxygenation," *British Journal of Anaesthesia*, vol. 103, supplement 1, pp. i3–i13, 2009.

[61] E. Nahum, P. W. Skippen, R. E. Gagnon, A. J. Macnab, and E. D. Skarsgard, "Correlation of transcutaneous hepatic near-infrared spectroscopy readings with liver surface readings and perfusion parameters in a piglet endotoxemic shock model," *Liver International*, vol. 26, no. 10, pp. 1277–1282, 2006.

[62] M. Girardis, L. Rinaldi, S. Busani, I. Flore, S. Mauro, and A. Pasetto, "Muscle perfusion and oxygen consumption by near-infrared spectroscopy in septic-shock and non-septic-shock patients," *Intensive Care Medicine*, vol. 29, no. 7, pp. 1173–1176, 2003.

[63] C. Mayeur, S. Campard, C. Richard, and J. L. Teboul, "Comparison of four different vascular occlusion tests for assessing reactive hyperemia using near-infrared spectroscopy," *Critical Care Medicine*, vol. 39, no. 4, pp. 695–701, 2011.

[64] A. Lima, J. van Bommel, K. Sikorska et al., "The relation of near-infrared spectroscopy with changes in peripheral circulation in critically ill patients," *Critical Care Medicine*, vol. 39, no. 7, pp. 1649–1654, 2011.

[65] F. Vallée, J. Mateo, G. Dubreuil et al., "Cutaneous ear lobe PCO_2 at 37°C to evaluate microperfusion in patients with septic shock," *Chest*, vol. 138, no. 5, pp. 1062–1070, 2010.

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Review Article

Echocardiographic Assessment of Preload Responsiveness in Critically Ill Patients

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Fluid challenges are considered the cornerstone of resuscitation in critically ill patients. However, clinical studies have demonstrated that only about 50% of hemodynamically unstable patients are volume responsive. Furthermore, increasing evidence suggests that excess fluid resuscitation is associated with increased mortality. It therefore becomes vital to assess a patient's fluid responsiveness prior to embarking on fluid loading. Static pressure (CVP, PAOP) and echocardiographic (IVC diameter, LVEDA) parameters fails to predict volume responsiveness. However, a number of dynamic echocardiographic parameters which are based on changes in vena-caval dimensions or cardiac function induce by positive pressure ventilation or passive leg raising appear to be highly predictive of volume responsiveness.

1. Introduction

Shock (hemodynamic failure) is ubiquitous in the modern intensive care unit (ICU). Venodilation, transudation of fluid from the vascular space into the interstitium and increased insensible losses result in hypovolemia early in the course of patients with sepsis. Early goal-directed therapy (EGDT) emphasizes aggressive fluid resuscitation of septic patients during the initial 6 hours of presentation [1]. Persistent hypotension after initial fluid resuscitation is common and poses the dilemma of whether the patient should receive additional fluid boluses or a vasopressor agent should be initiated. Persistent signs of organ hypoperfusion such as oliguria make this decision crucial. While number of technologies including pulse counter analysis [2], transpulmonary thermodilution [3] and bioreactance [4] have all shown promise in evaluation of volume status of septic patients, bedside ultrasonography has already established itself as useful technique to evaluate cardiac function [5]. Applying the same echocardiographic techniques to dynamically assess the physiological response to spontaneous or mechanical ventilation, bedside maneuvers and the response to therapeutic interventions will likely become a cornerstone of hemodynamic monitoring in the modern ICU.

2. Benefits and Pitfalls of Fluid Resuscitation

When hypovolemia (either absolute or relative) is suspected, fluid resuscitation will provide benefit to the patient by increasing venous return, cardiac output, arterial blood pressure and ultimately tissue perfusion. The rapidity, with which euvolemia is reestablished may be a decisive factor in the eventual outcome [1]. That being said, there is an increasing body of evidence suggesting that fluid resuscitation is not without serious and possibly lethal complications. Those complications may be related to preexisting conditions such as systolic or diastolic heart failure, cor pulmonale, or the development of sepsis-related cardiac dysfunction [6]. Extravasation of fluids may result in worsening of acute respiratory distress syndrome (ARDS) and prolonged mechanical ventilation [7]. Anemia and clotting disorders occur with hemodilution. Excessive fluid resuscitation can be positively correlated with increased mortality in the ICU [8–10]. Given the risk to benefit ratio of volume expansion, the key question is whether the patient would benefit from additional fluid boluses. It is essential to make this determination as clinical studies have repeatedly demonstrated that only about 50% of hemodynamically unstable ICU patients are volume responsive (see definitions below).

3. Fluid Challenge versus Volume Responsiveness

Previously this question was answered by administering a "fluid challenge" of 30 mL/kg of crystalloid solution, and the patients clinical (blood pressure, heart rate, urine output) and hemodynamic response (CVP, PAOP) to the challenge was evaluated. Importantly, because a fluid challenge has to be given to assess volume responsiveness, and hypervolemia is associated with significant complications, one would suggest that the increase in mortality associated with invasive hemodynamic monitoring [11] may be attributed to this approach. Therefore, given the increased mortality associated with excessive fluid resuscitation it seems prudent to be able to predict the response to a fluid bolus prior to administering the bolus; a concept known as volume responsiveness.

The standard definition of volume responsiveness is a >15% increase in cardiac output in response to volume expansion. Although the volume of the fluid bolus has not been well standardized, a volume of between 500 mL to 1000 mL of crystalloid solution has been most studied. One or more baseline hemodynamic parameters are measured and evaluated for the ability to discriminate between responders and nonresponders.

4. Static Parameters

A static parameter is measured under a single ventricular loading condition and is presumed to reliably estimate the preload of the right ventricle (RV), left ventricle (LV), or both ventricles. This estimation is used to evaluate the probability of responsiveness to ventricular filling, by assuming that a lower preload increases the probability of a response to volume expansion. Several static parameters of ventricular preload have been used in the ICU; some are based on direct pressure measurements, while others use echocardiographic indices.

4.1. Static Pressure Parameters. The traditional approach to fluid resuscitation consists of measuring a pressure parameter such as the central venous pressure (CVP) or pulmonary artery occlusion pressure (POAP) together with a cardiac output determination. The clinician would then prescribe a "fluid challenge" and reassess the above mentioned parameters. This approach has been largely discredited by the data suggesting a poor or no correlation between the CVP or PAOP and volume responsiveness as well as intravascular volume [12]. Nevertheless, the vast majority of intensivists still utilize the CVP to assess volume status [13] and the major critical care societies advocate for CVP as a measure of successful fluid resuscitation [14]. Several studies have demonstrated that the response to a fluid challenge even in healthy volunteers cannot be predicted by either the CVP or PAOP. In a study by Kumar et al. [15] in healthy subjects, static indices of ventricular preload (CVP,PAOP, LVEDV index, and RVEDV index) and cardiac performance indices (cardiac index, stroke volume index) were measured before and after 3 liters of normal saline loading. In this study, there was no correlation between baseline static pressure parameters and changes in the cardiac performance indices (cardiac index and stroke volume index) after fluid loading. Similarly, there was no correlation between changes in the CVP and PAOP and changes in cardiac performance [16]. A meta-analysis by Coudray et al. [17] reviewed five studies on a mixed population of spontaneously breathing critically ill patients and demonstrated the absence of a correlation between the initial PAOP and the response to a crystalloid infusion (an average of 1 liter).

4.2. Static Echocardiographic Parameters. As echocardiography is noninvasive, it has advantages over pressure-derived parameters particular those obtained from pulmonary artery catheterization. Transthoracic echocardiography (TTE) is preferred; however, in certain circumstance transesophageal echocardiography (TEE) may be required. The CVP and PAOP (left atrial pressure) can be approximated by echocardiography. In spontaneously breathing patients, there is a fairly good correlation between the size of the IVC and the CVP. However, Feissel et al. demonstrated that the absolute IVC size failed to predict fluid responsiveness in patients with septic shock [18].

PAOP (left atrial pressure) estimates involve the use of Doppler mitral flow E/A ratio, pulmonary venous flow, tissue Doppler (E/Ea ratio), or colored coded Doppler (E/Vp ratio). While beyond the expertise level of most American intensivists, the estimated left atrial pressure can be estimated as part of a comprehensive echocardiographic examination performed by an experienced operator. However, it is worth noting that the PAOP fails to predict volume responsiveness whether measured directly or by echocardiography. The RV and LV diastolic diameter or area has been used as a measure of preload. However, Tavernier et al. and Feissel et al. [19, 20] have demonstrated that LV size (left ventricular end diastolic area LVEDA) is not a useful predictor of fluid responsiveness in patients on mechanical ventilation, unless LV is very small and hyperkinetic. A meta-analysis by Marik et al. [21] demonstrated the failure of the LVEDA to predict volume responsiveness in mechanically ventilated patients. Generally speaking, static parameters appear to be poor predictors of volume responsiveness except in patients with relatively obvious hypovolemia, which is a relatively uncommon event in modern ICU practice. It can, therefore, be concluded, that standard static indices of preload are not useful in predicting volume responsiveness in ICU patients. This observation may be due to dynamic changes in left (LV) and to a lesser degree right ventricular (RV) compliance, making the diastolic pressure-volume relationship nonlinear, unpredictable, and perhaps subject to change during resuscitation itself. Systolic left ventricular function is also a subject to change in critically ill patients, even those, without preexistent cardiac disease. Vieillard-Baron and coauthors demonstrated the development of systolic left ventricular dysfunction in 60% of patient with septic shock [6]. Changing left ventricular function makes it difficult to predict the position of the patient on his/her Frank-Starling

curve. It is even difficult to estimate which family of Frank-Starling relationships should be utilized to predict fluid responsiveness (see Figure 1). Furthermore, the development of acute right ventricular failure (acute cor pulmonale), particularly in patients receiving mechanical ventilation with high plateau pressures (>27 cm H_2O), further confounds the issue [22]. Unrecognized acute right ventricular failure can mimic hypovolemia hemodynamically but would not respond or even get worse with volume expansion. Dynamic hemodynamic parameters offer the intensivists the best opportunity of predicting response to fluid resuscitation.

5. Dynamic Parameters of Volume Responsiveness

Dynamic parameters are used to determine the patients position on his/her Frank-Starling curve (Figure 1) and specifically to determine whether the patient is situated on the ascending portion of the Frank-Starling curve where an increase of preload results in increase of stroke volume (SV) (preload-dependent situation), or on the plateau portion where a variation of preload does not alter SV (preload-independent situation). Several approaches can be used to determine on what portion of the preload/stroke volume relationship the ventricle is functioning to establish the diagnosis of preload dependence or independence. Most utilize observation of cardiac response to either mechanical or spontaneous breathing cycle and breathing related variations in intrathoracic pressure. These pressure changes directly effect RV and LV preload and provides a tool to correlate these preload changes to SV. Alternatively, bedside maneuvers such as passive leg raising (PLR) result in alterations of RV and LV preload can be utilized to establish similar correlations.

5.1. Ventilated versus Spontaneously Breathing Patient. By significantly increasing RV preload, spontaneous breathing is crucial to maintaining normal hemodynamic status. Mechanical ventilation substantially increases intrathoracic pressure, decreasing RV preload and thus has predictably negative hemodynamic consequences. Moreover, traditional positive pressure ventilation also reverses inspiration/expiration phases from a hemodynamic point of view, changing many breathing related phenomena (i.e., paradoxical pulse) to its opposite (reverse pulsus paradoxus) [23].

5.2. Dynamic Echocardiographic Parameters in Patients on Mechanical Ventilation. Analysis of the respiratory changes of LV stroke volume during mechanical ventilation provides a dynamic, biventricular evaluation of preload dependence. The respiratory changes of stroke volume can be estimated by Doppler analysis of velocity-time integral (VTI) during TTE or TEE. In clinical studies, maximal ascending aortic flow velocity or VTI variation measured with TEE predict, with high sensitivity and specificity, increases in cardiac output after fluid infusion in patients with septic shock. A cut-off value of respiratory cycle changes of 12% for maximal flow velocity and 20% for aortic VTI-discriminated responders from nonresponders [20]. Similar information that can be obtained from interrogation of ascending aorta with TTE (Figure 2) or descending aorta. Another approach to identify volume responsiveness used 2D images. Cannesson et al. [24] assessed LV diastolic area (LVDA) changes by TEE from the short axis view. They found that a 16% respiratory variation of LVDA predicted fluid responsiveness with a sensitivity of 92% and a specificity of 83%. Utilizing a similar principle, IVC and superior vena cava (SVC) diameter changes during mechanical ventilation can be used to predict fluid responsiveness (see Figure 3). The inferior vena cava diameter by TTE is analyzed from a subcostal long axis view and recorded by using M mode. The superior vena cava diameter is recorded from TEE longitudinal view at 90–100°. Cut-off values of 12% (by using (max − min)/mean value)) and 18% (by using (max − min)/min value) for IVC (distensibility index) and 36% for SVC (collapsibility index) were found to accurately (sensitivity 90%, specificity 100%) separate responders and non-responders that as an intrathoracic. The potential benefit of using SVC is due to the fact that as intrathoracic organ the SVC is subject to greater respiratory variations and intrathoracic pressure resulting from mechanical ventilation. Though SVC collapsibility appears to be the most "reliable index of volume responsiveness", it does require TEE [25] and thus is out of reach of most intensivists in the United States.

Ventilator induced preload changes as predictors of volume responsiveness have only been evaluated in patients on flow limited, volume cycled ventilation and without patient ventilator dyssynchrony. Furthermore, although the level of positive end expiratory pressure (PEEP) is known to influence venous return and biventricular function the effect of PEEP on echocardiographic assessment of volume responsiveness has not been studied. Other requirements include presence of a normal sinus rhythm, normal intra-abdominal pressure and absence of significant RV dysfunction. Although a positive response to PLR seems to be predictive of volume responsiveness in mechanically ventilated patients (sensitivity 90% specificity 83%) [26] further studies are necessary to better understand the role of this bedside maneuver in this population of critically ill patients.

5.3. Dynamic Echocardiographic Parameters in Spontaneously Breathing Patients. Several publications have proposed using PLR maneuver to predict preload responsiveness (Figure 4). This maneuver rapidly mobilizes about 300–500 mL of blood from the lower limbs to the intrathoracic compartment and reproduces the effects of similar volume fluid bolus (Figure 1). Being completely reversible this maneuver is devoid of any risks associated with an actual "fluid challenge." The test consists of raising both legs of the supine patient to an angle of 45° in relation to the bed while measuring SV and cardiac output before and immediately (1–3 minutes) following the PLR maneuver. This may be accomplished by measuring the VTI of the aortic outflow with either TTE (apical five-chamber view) or TEE (deep-gastric view). Monnet et al. [27] demonstrated that when

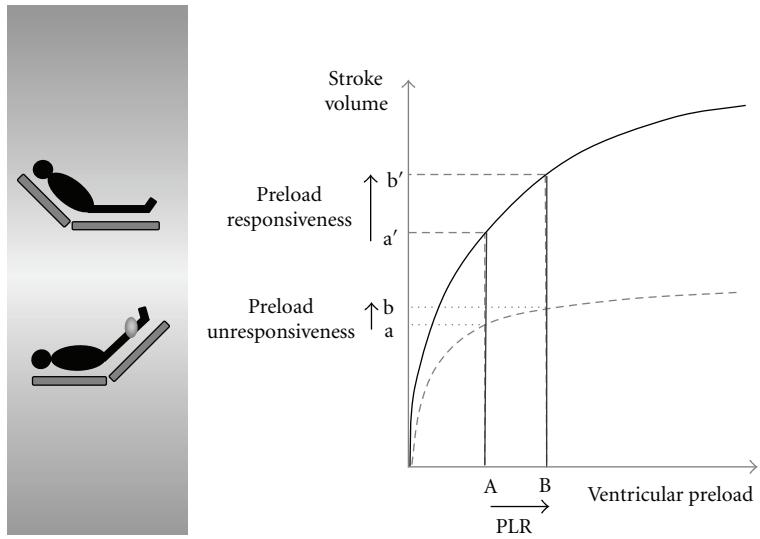


Figure 1: Depending on LV systolic function two distinct families of Frank-Starling relationships are formed, exemplified by solid and interrupted lines. Patients with hemodynamics following solid line pattern (preserved left ventricular systolic function) are more likely to benefit from preload manipulation, then those following the interrupted line pattern (reduced left ventricular systolic function). When Ventricle is functioning on the steep part of the Frank-Starling curve, there is a preload reserve. The passive leg raising (PLR) test (and a fluid challenge) increases stroke volume. By contrast, once the ventricle is operating near the flat part of the curve, there is no preload reserve and PLR (and a fluid challenge) has little effect on the stroke volume.

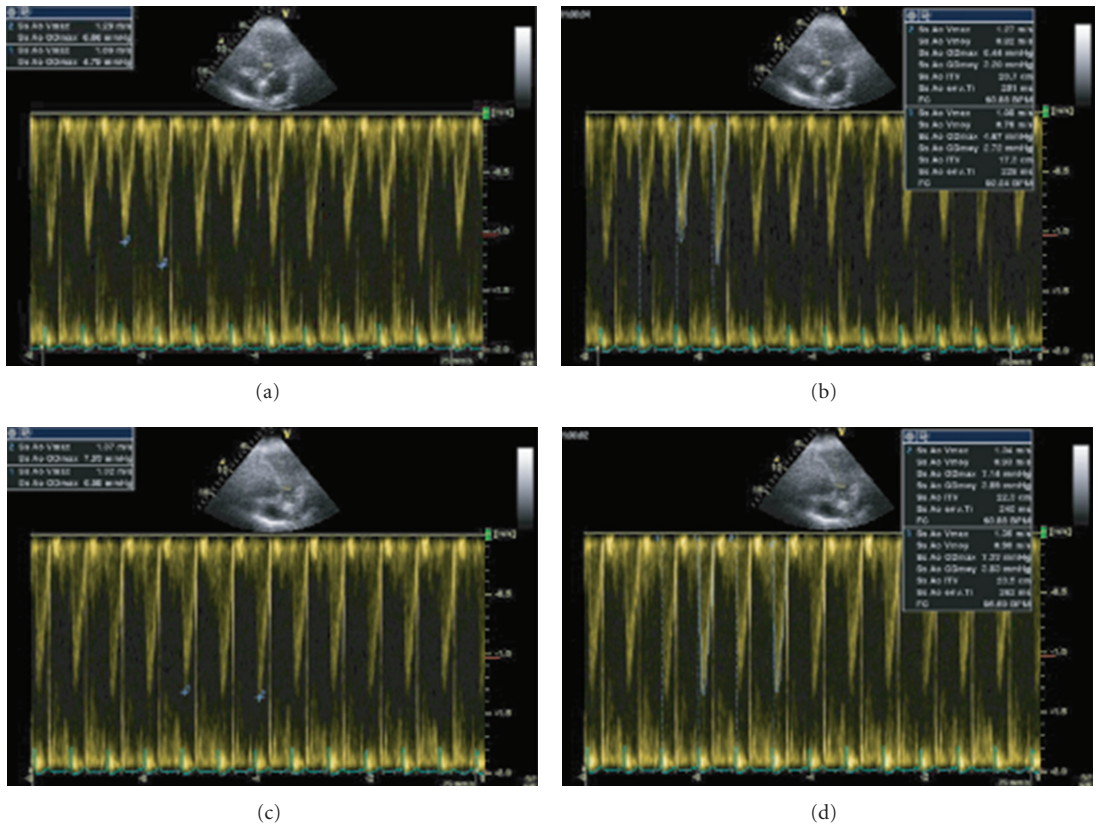
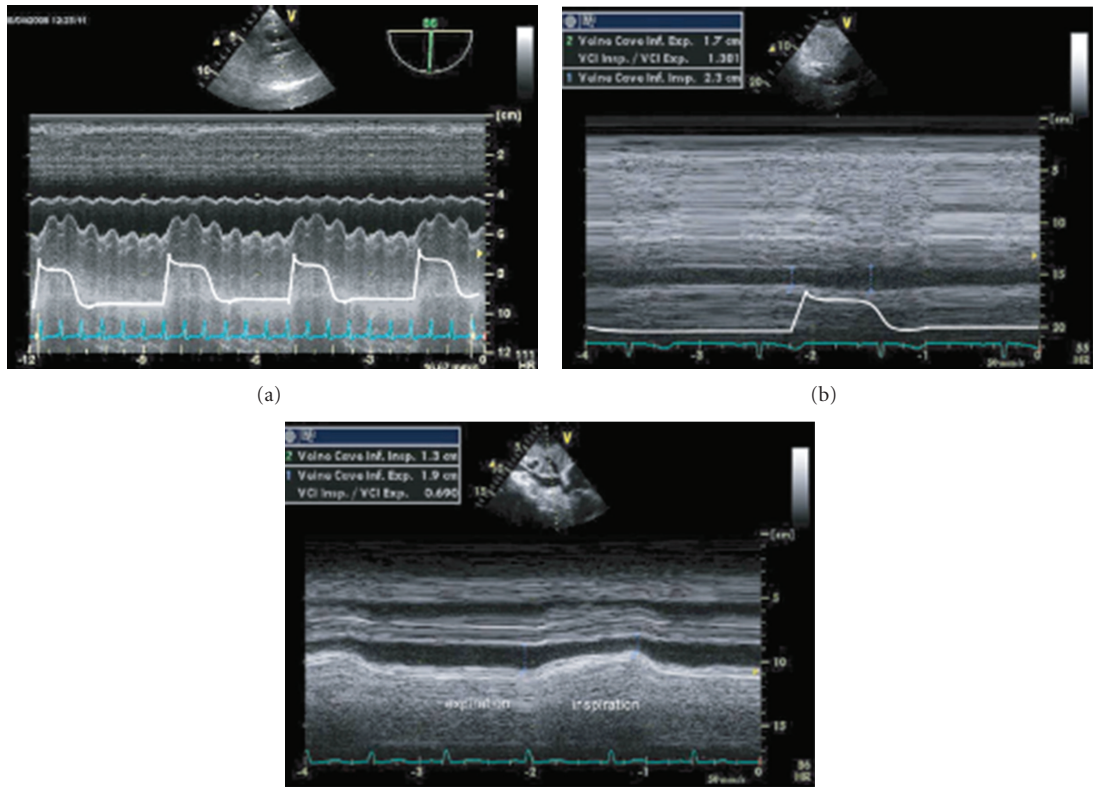


Figure 2: Respiratory variations of maximal velocity (Vmax) (a and c) and VTI (b and d) of aortic blood flow recorded with a pulsed Doppler transthoracic echocardiography in a mechanically ventilated patient (a and c). Presence of significant respiratory variations of Vmax (Vmax − Vmin/[Vmax + Vmin/2]; 1.29 − 1.09/1.19 = 17%) and VTI (VTImax − VTImin/[VTImax + VTI min/2]; 20.7 − 17.3/19 = 18%). (b and d) Same patient after volume expansion, regression of the respiratory variations: Vmax (1.37 − 1.32/1.34 = 4%), VTI (23.5 − 22.3/22.9 = 5%). Reproduced with permission from Levitov et al. "Critical care Ultrasonography" Mc Graw Hill 2009.



(a) (b)

(c)

Figure 3: Respiratory vena cava variations in different circumstances. (a) Significant superior vena cava (SVC) collapsibility recorded with transesophageal echocardiography (TEE). (b) Significant inferior vena cava (IVC) distensibility recorded with transthoracic echocardiography (TTE) in a mechanically ventilated patient. (c) Significant vena cava collapsibility recorded with transthoracic echocardiography (TTE) in a spontaneously breathing patient. Reproduced with permission from Levitov et al. "Critical care Ultrasonography" Mc Graw Hill 2009.

(a) (b) (c)

Figure 4: The realization of a passive leg raising maneuver in three steps: (a) at baseline the patient is laying in a semirecumbent position, the trunk of the patient at 45° up to the horizontal; (b) the entire bed is pivoted to obtain a head down tilt at 45°. (c) The head of the bed is adjusted to obtain a strictly horizontal.

PLR induced an increase of aortic flow of >10%, it was predictive of an increase of aortic flow of >15% in response to volume expansion (sensitivity: 97%; specificity: 94%). Volume expansion was performed with 500 mL of isotonic saline over 10 minutes. Thirty-seven (52%) of the 71 patients included in this study responded to volume expansion; 22 subjects had spontaneous breathing activity (spontaneous breathing mode with inspiratory assistance). This study also evaluated respiratory cycle induced pulse pressure variations. The authors concluded that respiratory cyclic variations of pulse pressure ≥12% were similarly predictive of an increase of aortic flow by >15% in response to volume expansion in mechanically ventilated patients (sensitivity: 88%; specificity: 93%). However, in spontaneously breathing patient's predictive value of respiratory pulse pressure variations was poor. In two other studies aortic VTI, stroke volume and cardiac output were recorded using transthoracic echocardiography in spontaneously breathing patients

during a PLR maneuver. Lamia et al. [28] demonstrated a PLR-induced increase in stroke volume of 12.5% or more predicted an increase in stroke volume of 15% or more after volume expansion, with a sensitivity of 77% and a specificity of 100%. In this study, patients were intubated with spontaneous breathing. Static indices of preload such as left ventricular diastolic area and E/Ea ratio failed to predict volume responsiveness. Maizel et al. [29] studied 34 spontaneously breathing patients; an increase of cardiac output or stroke volume by >12% during PLR was highly predictive of volume responsiveness. Sensitivity and specificity values were 63% and 89%, respectively. In addition, this study demonstrated that PLR may be used to predict volume responsiveness in patients with atrial fibrillation. Increased intraabdominal pressure, however, strongly interferes with the ability of PLR to predict fluid responsiveness [30].

In conclusion, echocardiography provides the intensivist with several methods to determine volume responsiveness in patients with hemodynamic failure. The clinician with basic skills in critical care echocardiography may use respiratory variation of IVC diameter to identify the preload-dependent patient combined with pattern recognition of small hyperdynamic LV. The intensivist with advanced TTE skill level may use respiratory variation of SV determined by Doppler echocardiography (VTI) and changes in SV following the PLR maneuver to identify volume responsiveness. Intensivist with TEE skills may effectively utilize this modality in patients presenting technical challenge for TTE. Advent of minimally invasive TEE monitoring probes might allow intensivist views of SVC not available on TTE and real time LV and RV function monitoring abilities, previously unavailable at bedside. Widespread use of newer modes of mechanical ventilation (APRV, HFOV) provides new challenges and opportunities for the evaluation of their effect of cardiac performance and volume responsiveness. Further studies are necessary to determine if this increase in physiological insight will translate into improved outcomes of critically ill patients.

Conflict of Interests

The authors declare that they have no conflict of interests.

References

[1] E. Rivers, B. Nguyen, S. Havstad et al., "Early goal-directed therapy in the treatment of severe sepsis and septic shock," *New England Journal of Medicine*, vol. 345, no. 19, pp. 1368–1377, 2001.

[2] P. E. Marik, R. Cavallazzi, T. Vasu, and A. Hirani, "Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature," *Critical Care Medicine*, vol. 37, no. 9, pp. 2642–2647, 2009.

[3] S. Boussat, T. Jacques, B. Levy et al., "Intravascular volume monitoring and extravascular lung water in septic patients with pulmonary edema," *Intensive Care Medicine*, vol. 28, no. 6, pp. 712–718, 2002.

[4] B. Benomar, A. Ouattara, P. Estagnasie, A. Brusset, and P. Squara, "Fluid responsiveness predicted by noninvasive bioreactance-based passive leg raise test," *Intensive Care Medicine*, vol. 36, no. 11, pp. 1875–1881, 2010.

[5] A. R. Manasia, H. M. Nagaraj, R. B. Kodali et al., "Feasibility and potential clinical utility of goal-directed transthoracic echocardiography performed by noncardiologist intensivists using a small hand-carried device (SonoHeart) in critically ill patients," *Journal of Cardiothoracic and Vascular Anesthesia*, vol. 19, no. 2, pp. 155–159, 2005.

[6] A. Vieillard-Baron, V. Caille, C. Charron, G. Belliard, B. Page, and F. Jardin, "Actual incidence of global left ventricular hypokinesia in adult septic shock," *Critical Care Medicine*, vol. 36, no. 6, pp. 1701–1706, 2008.

[7] H. P. Wiedemann, A. P. Wheeler, G. R. Bernard et al., "Comparison of two fluid-management strategies in acute lung injury," *New England Journal of Medicine*, vol. 354, no. 24, pp. 2564–2575, 2006.

[8] J. H. Boyd, J. Forbes, T. A. Nakada, K. R. Walley, and J. A. Russell, "Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality," *Critical Care Medicine*, vol. 39, no. 2, pp. 259–265, 2011.

[9] C. V. Murphy, G. E. Schramm, J. A. Doherty et al., "The importance of fluid management in acute lung injury secondary to septic shock," *Chest*, vol. 136, no. 1, pp. 102–109, 2009.

[10] A. L. Rosenberg, R. E. Dechert, P. K. Park, and R. H. Bartlett, "Review of a large clinical series: association of cumulative fluid balance on outcome in acute lung injury: a retrospective review of the ARDSnet tidal volume study cohort," *Journal of Intensive Care Medicine*, vol. 24, no. 1, pp. 35–46, 2009.

[11] A. F. Connors, T. Speroff, N. V. Dawson et al., "The effectiveness of right heart catheterization in the initial care of critically ill patients," *Journal of the American Medical Association*, vol. 276, no. 11, pp. 889–897, 1996.

[12] P. E. Marik, M. Baram, and B. Vahid, "Does central venous pressure predict fluid responsiveness?" *Chest*, vol. 134, no. 1, pp. 172–178, 2008.

[13] L. A. McIntyre, P. C. Hébert, D. Fergusson, D. J. Cook, and A. Aziz, "A survey of Canadian intensivists' resuscitation practices in early septic shock," *Critical Care*, vol. 11, article R74, 2007.

[14] R. P. Dellinger, M. M. Levy, J. M. Carlet et al., "Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2008," *Critical Care Medicine*, vol. 36, no. 1, pp. 296–327, 2008.

[15] A. Kumar, R. Anel, E. Bunnell et al., "Pulmonary artery occlusion pressure and central venous pressure fail to predict ventricular filling volume, cardiac performance, or the response to volume infusion in normal subjects," *Critical Care Medicine*, vol. 32, no. 3, pp. 691–699, 2004.

[16] F. Michard and J. L. Teboul, "Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence," *Chest*, vol. 121, no. 6, pp. 2000–2008, 2002.

[17] A. Coudray, J. A. Romand, M. Treggiari, and K. Bendjelid, "Fluid responsiveness in spontaneously breathing patients: a review of indexes used in intensive care," *Critical Care Medicine*, vol. 33, no. 12, pp. 2757–2762, 2005.

[18] M. Feissel, F. Michard, J. P. Faller, and J. L. Teboul, "The respiratory variation in inferior vena cava diameter as a guide to fluid therapy," *Intensive Care Medicine*, vol. 30, no. 9, pp. 1834–1837, 2004.

[19] B. Tavernier, O. Makhotine, G. Lebuffe, J. Dupont, and P. Scherpereel, "Systolic pressure variation as a guide to fluid therapy in patients with sepsis-induced hypotension," *Anesthesiology*, vol. 89, no. 6, pp. 1313–1321, 1998.

[20] M. Feissel, F. Michard, I. Mangin, O. Ruyer, J. P. Faller, and J. L. Teboul, "Respiratory changes in aortic blood velocity as an indicator of fluid responsiveness in ventilated patients with septic shock," *Chest*, vol. 119, no. 3, pp. 867–873, 2001.

[21] P. E. Marik, R. Cavallazzi, and T. Vasu, "Stroke volume variations and fluid responsiveness. A systematic review of literature," *Critical Care Medicine*, vol. 37, pp. 2642–2647, 2009.

[22] F. Jardin and A. Vieillard-Baron, "Is there a safe plateau pressure in ARDS? The right heart only knows," *Intensive Care Medicine*, vol. 33, no. 3, pp. 444–447, 2007.

[23] R. A. Massumi, D. T. Mason, Z. Vera, R. Zelis, J. Otero, and E. A. Amsterdam, "Reversed pulsus paradoxus," *New England Journal of Medicine*, vol. 289, no. 24, pp. 1272–1275, 1973.

[24] M. Cannesson, J. Slieker, O. Desebbe, F. Farhat, O. Bastien, and J. J. Lehot, "Prediction of fluid responsiveness using respiratory variations in left ventricular stroke area by transoesophageal echocardiographic automated border detection in mechanically ventilated patients," *Critical Care*, vol. 10, article R171, 2006.

[25] C. Charron, V. Caille, F. Jardin, and A. Vieillard-Baron, "Echocardiographic measurement of fluid responsiveness," *Current Opinion in Critical Care*, vol. 12, no. 3, pp. 249–254, 2006.

[26] A. Lafanechère, F. Pène, C. Goulenok et al., "Changes in aortic blood flow induced by passive leg raising predict fluid responsiveness in critically ill patients," *Critical Care*, vol. 10, no. 5, article R132, 2006.

[27] X. Monnet, M. Rienzo, D. Osman et al., "Passive leg raising predicts fluid responsiveness in the critically ill," *Critical Care Medicine*, vol. 34, no. 5, pp. 1402–1407, 2006.

[28] B. Lamia, A. Ochagavia, X. Monnet, D. Chemla, C. Richard, and J. L. Teboul, "Echocardiographic prediction of volume responsiveness in critically ill patients with spontaneously breathing activity," *Intensive Care Medicine*, vol. 33, no. 7, pp. 1125–1132, 2007.

[29] J. Maizel, N. Airapetian, E. Lorne, C. Tribouilloy, Z. Massy, and M. Slama, "Diagnosis of central hypovolemia by using passive leg raising," *Intensive Care Medicine*, vol. 33, no. 7, pp. 1133–1138, 2007.

[30] Y. Mahjoub, J. Touzeau, N. Airapetian et al., "The passive leg-raising maneuver cannot accurately predict fluid responsiveness in patients with intra-abdominal hypertension," *Critical Care Medicine*, vol. 38, no. 9, pp. 1824–1829, 2010.

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Review Article

Physiologic and Clinical Principles behind Noninvasive Resuscitation Techniques and Cardiac Output Monitoring

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Clinical assessment and vital signs are poor predictors of the overall hemodynamic state. Optimal measurement of the response to fluid resuscitation and hemodynamics has previously required invasive measurement with radial and pulmonary artery catheterization. Newer noninvasive resuscitation technology offers the hope of more accurately and safely monitoring a broader range of critically ill patients while using fewer resources. Fluid responsiveness, the cardiac response to volume loading, represents a dynamic method of improving upon the assessment of preload when compared to static measures like central venous pressure. Multiple new hemodynamic monitors now exist that can noninvasively report cardiac output and oxygen delivery in a continuous manner. Proper assessment of the potential future role of these techniques in resuscitation requires understanding the underlying physiologic and clinical principles, reviewing the most recent literature examining their clinical validity, and evaluating their respective advantages and limitations.

1. Background

Consensus recommendations, research, and meta-analyses have all questioned the efficacy of routine use of pulmonary artery catheterization in critically ill patients [1–3]. Other studies have questioned its accuracy, with limits of error of ±20–22% [4, 5]. Early adaptation of invasive protocols utilizing arterial and central venous access has become the standard in some cases [6] despite the limitations of some components of such protocols [7]. Research has long since demonstrated that traditional parameters of hemodynamic stability (heart rate and blood pressure) are poor predictors of the degree of cardiac dysfunction [8] or organ failure [9] and that physicians are poor predictors of hemodynamics in critically ill patients [10–12]. As much as 18% of "hemodynamically stable" sepsis patients (blood pressure > 90 mmHg, lactate < 4 mmol/L) can progress to severe sepsis and septic shock within 72 hours [13].

Noninvasive techniques for measuring hemodynamic variables have existed for some time; older techniques are being refined and newer techniques are being developed. Most research to date has focused on the validation of these technologies with little demonstrated efficacy, and there is a lack of multicenter trials pairing these technologies to dedicated treatment protocols [14]. Noninvasive hemodynamic monitoring and guided resuscitation has the potential to offer critical care clinicians information that is clinically compatible with pulmonary artery catheterization and potentially provide such information earlier and in a safer manner than traditional parameters used in resuscitation. The objective of this paper is to discuss the principles behind the clinical development of newer completely noninvasive techniques to assess preload dependence and the hemodynamic monitors that measure cardiac output and oxygen delivery that are available for care of the critically ill patient.

2. Preload Dependence

The Frank-Starling relationship is curvilinear; a steep and nearly linear relationship exists in the volume dependent ascending portion of the Frank-Starling curve where stroke volume (SV) is intimately related to preload, termed preload dependence [15–17]. Preload independence occurs as the Frank-Starling curve plateaus. Fluid responsiveness (FR) is generally defined as an increase of 10–15% in stroke volume

(SV), cardiac output (CO), or cardiac index (CI) in response to volume expansion and indicates unmasked hypovolemia or preload dependency [18]. 40–72% of critically ill patients respond to volume expansion with a change in stroke volume, suggesting a need for better methods of predicting fluid responsiveness [19]. The discussion that follows details the limitations of static measures of fluid responsiveness and the advantages of dynamic measurement of preload dependency.

2.1. Static Measures of Fluid Responsiveness

2.1.1. Central Venous Pressure. Central venous pressure (CVP), the most common static measure of preload, is clinically estimated by transducing the pressure in a central venous line. It serves as an important component of the management of critically ill patients [6]. However, static measures such as central venous pressure and pulmonary capillary wedge pressure are poor measures of cardiac preload and do not predict response to fluid therapy [20]. A meta-analysis of studies examining the ability of CVP to predict fluid responsiveness reported a poor association ($r = 0.18$, ROC = 0.56) and concluded "CVP should not be used to make clinical decisions regarding fluid management" [7]. CVP as a tool for predicting FR is limited because it does not account for whether the patient is in a preload dependent or preload independent part of the Frank-Starling curve. Another major limitation is that one cannot adequately account for the degree to which transmitted pressures from comorbidities (i.e., cor pulmonale) or clinical conditions (i.e., mechanical ventilation) may affect the accuracy of measurement. The ability of CVP to predict fluid responsiveness is also altered by differences in ventricular compliance or changes in ventricular contractility. A young individual with a compliant ventricle may be volume overloaded at the same central venous pressure of an older individual with a stiff ventricle who may be volume depleted. Ventricular contractility can be impaired in conditions like sepsis where a rightward and downward shift in left ventricular stroke work is present at a given volume [21–23]. The flatter curve that results from depressed LV systolic function limits the exploitation of the Frank-Starling relationship of improving stroke volume by improving preload.

CVP does, however, represent an opportunity to estimate the right atrial pressure (RAP) and the pulmonary artery pressure (PAP). CVP, measured by sonographic diameter of the inferior vena cava (IVC), is nearly equivalent to the RAP and is a fair estimate of the PAP if the peak tricuspid regurgitant flow (V_{peakTR}) is minimal:

$$\text{CVP} \approx \text{RAP}, \qquad \text{PAP} = \text{RAP} + 4 * \left(V_{\text{peakTR}}\right)^2. \quad (1)$$

This technique accurately reflects pulmonary artery pressure and performs much better than estimates of jugular venous distension [24]. The RAP can be estimated (Table 1) by utilizing the known relationship between RAP and inferior vena cava (IVC) diameter and the caval index (the fractional change in the IVC diameter during respiration) [25, 26]. A greater than 50% decrease in IVC diameter is associated with a CVP <8 mmHg ($r = 0.74$) in the early stages of resuscitation from severe sepsis [27]. The main limitation of this technique in spontaneously breathing patients is that certain clinical situations inducing changes in intrathoracic pressure (i.e., asthma, emphysema) may cause changes in IVC diameter that are more reflective of these intrathoracic pressure changes than they are preload responsiveness [28, 29]. Alternatively, the absence of respiratory variations in IVC diameter in these conditions is generally indicative of the absence of preload responsiveness. The accuracy of this technique is also dependent upon the IVC sampling location and the interrater reliability of this approach has yet to be established [30]. Thus, this represents an early adjunct in the management of acutely ill patients that is both feasible and safe but needs further validation. Recent small studies have suggested that respiratory changes in inferior vena cava diameter may be helpful as a dynamic measure of predicting FR in mechanically ventilated sepsis patients [31–33].

Table 1: Central venous pressure by ultrasonography of the inferior vena cava.

IVC diameter (cm)	Respiratory collapse	RA pressure (mmHg)*
< 1.5	Total Collapse	0–5
1.5–2.5	> 50% Collapse	5–10
1.5–2.5	< 50% Collapse	10–15
> 2.5	< 50% Collapse	15–20
> 2.5	No Collapse	> 20

IVC = inferior vena cava, RA = right atrial.

Other static measures of assessing preload have been studied. However, these methods generally require invasive monitoring (like right atrial pressure, pulmonary artery pressure, or the intrathoracic blood volume index) or techniques, like right ventricular end diastolic volume by echocardiography, that require skills not maintained by most critical care clinicians [18, 34].

2.2. Dynamic Measures of Fluid Responsiveness. Dynamic parameters can predict an increase in cardiac output from volume expansion before such volume expansion is performed and are better predictors of FR than static parameters [19]. Understanding how dynamic measures are predictors of fluid responsiveness requires an understanding of how respiratory variation can impact the preload, pulse pressure, and stroke volume. Spontaneous inspiration leads to a larger venous return to the right side of the heart but also leads to the displacement of the septum and pulmonary vein dilatation leading to reduced preload to the left side of the heart. This reduced preload results in less ventricular filling and a lower left ventricular stroke volume. Expiration leads to decreased intrathoracic pressure, higher preload, and larger stroke volumes on the left side of the heart. This increase in left cardiac preload occurs at expiration as a result of the transmission of the increase in right cardiac preload after the lung transit time. Such changes in pulse pressure during spontaneous respiration are otherwise

known as pulsus paradoxus. Changes in intrathoracic pressure from mechanical ventilation can lead to cyclic changes, but reversed—otherwise termed reverse pulsus paradoxus. These small changes in right ventricular preload induced by mechanical ventilation can lead to significant changes in stroke volume in the ascending part of the Frank-Starling curve (i.e., in preload-dependent individuals). On the left side of the heart, if arterial compliance is constant through a respiratory cycle then variations in systolic blood pressure and pulse pressure (PP) will be reflected in left ventricular stroke volume [35]:

$$C = \frac{dV}{dP} = \frac{\Delta V}{\Delta P} = \frac{\mathrm{SV}}{\mathrm{PP}}, \qquad \mathrm{SV} = C \times \mathrm{PP}. \tag{2}$$

2.2.1. Pulse Pressure Variation. Clinical study has long since established the relationship between systolic pressure variation (SPV) and FR [36, 37]. While SPV and pulse pressure variations (PPV) in mechanically ventilated patients are predictive of FR [38, 39] in sepsis patients, PPV appears to be the better measure [39]. PPV is typically represented as a percent:

$$\mathrm{PPV} = 100 * \frac{(\mathrm{PP}_{\max} - \mathrm{PP}_{\min})}{((\mathrm{PP}_{\max} + \mathrm{PP}_{\min})/2)}. \tag{3}$$

PPV is highly predictive of FR with cutoff values of 11–13% according to various studies [40, 41]. Traditional measurement of pulse pressure on a beat-to-beat basis has required arterial cannulation. However, recent literature comparing the *noninvasive* pulse oximetry waveform amplitudes to standard arterial cannulation has shown that respiratory variations in the noninvasive pulse oximetry waveform (ΔrPOP) have a high correlation with PPV ($r = 0.83$) in mechanically ventilated patients [41]. A ΔrPOP >15% roughly equates to PPV >13%. These results were validated in operating room [42] and postoperative cardiac surgery patients [43]. Clinical study has been promising [41, 44]; ΔrPOP with a cutoff of 13% predicted FR with a sensitivity of 93% and specificity of 90% [41]. Technology equipped with the capacity to calculate ΔrPOP would substantially improve the resuscitation of mechanically ventilated critically ill patients by providing a simple and noninvasive method of predicting FR. However, while the potential of a noninvasive measure like ΔrPOP supplanting arterial PPV measurement is promising, its use is limited to mechanically ventilated patients.

2.2.2. Stroke Volume Variation. Stroke volume variation (SVV) is believed to be less affected by vasomotor tone then PPV and is, therefore, likely to be a better measure of FR in mechanically ventilated patients [45, 46]. A study comparing SVV to pulmonary artery catheterization by thermodilution (PAC-TD) demonstrated SVV (ROC = 0.82) to be equivalent if not better than PPV (ROC = 0.80) in mechanically ventilated patients [47]. In both studies, CVP performed poorly as a measure of preload responsiveness [46, 47]. Most noninvasive hemodynamic monitors (discussed below) can measure stroke volume variation by way of the arterial pressure curve. SVV, much like PPV and ΔrPOP, is limited to mechanically ventilated patients, as preload is highly susceptible to changes in intrathoracic pressure.

Despite the promising results of studies of PPV and SVV in mechanically ventilated patients, limitations exist in these methodologies. In mechanically ventilated patients, a linear relationship exists between tidal volume and SVV or PPV [48]; tidal volumes of less than 8 mL/kg are no more accurate than traditional measures of preload [49]. Recent work has demonstrated that lower tidal volumes, impaired contractility, or elevated respiratory rates each independently result in lower SVV and PPV errantly leading to an increase in falsely negative tests for fluid responsiveness [50, 51]. Meanwhile, right ventricular dysfunction may cause a false positives PPV [52], a result that could lead to volume overload and deleterious affects in certain populations [53]. Interestingly, increased contractility does not influence PPV or SVV [50]. Early inspiratory augmentation of left ventricular stroke volume (often termed dUP) and irregular cardiac rhythms may affect the reliability of these parameters as well [38, 45].

2.2.3. The Preejection Period. The preejection period (PEP), the time between onset of ventricular depolarization and ventricular ejection, is a systolic time interval believed to be representative of contractility. As the Frank-Starling curve would indicate, the lower the ventricular preload the shorter the PEP. Respiratory changes in the preejection period (*r*PEP) are an accurate measure of FR in septic ventilated patients [54]. PEP, like SVV, can be measured by some currently available noninvasive monitors. However, *r*PEP has not been studied using noninvasive monitoring partly because only some noninvasive monitors simultaneously record the electrocardiogram (ECG) and the arterial pressure waveform. A noninvasive method of measuring FR in both spontaneously breathing patients and mechanically ventilated patients is needed.

2.2.4. Passive Leg Raising. Passive leg raising (PLR) is a simple, reversible maneuver that mimics a rapid volume expansion of approximately 300–500 mL [55, 56] by shifting blood from the lower extremities to the core venous circulation [57, 58]. A standard PLR is done by placing a patient in a semirecumbent position for three minutes then laying the patient supine with the legs elevated to 45 degrees for three minutes. Fluid responsiveness is generally defined as a change in cardiac index (ΔCI), cardiac output (ΔCO), or stroke volume (ΔSV) of >10–15% [18]. PLR-induced changes in SV represent a good predictor of fluid responsiveness independent of breathing conditions [56, 59–61]. A recent meta-analysis demonstrated PLR-induced changes in cardiac output was more accurate than measured changes in arterial pulse pressure, with a pooled sensitivity, specificity, correlation, and area under the receiver operator curve of 89%, 91%, 0.81, and 0.95, respectively [62]. These studies validate for the first time a technique for noninvasively measuring fluid responsiveness in ventilator-dependent and spontaneously breathing patients.

2.2.5. Utilizing Dynamic Measures of Fluid Responsiveness. Passive leg raising matched with a noninvasive technology to assess hemodynamic response would be an important advance in critical care settings where traditional management methods of critically ill individuals may not be immediately available in early resuscitation (such as measuring CVP and $ScVO_2$), of suspect accuracy (CVP in determining preload), or functionally inaccessible (i.e., hemodynamics measured by thermodilution).

Minimizing respiratory variations in stroke volume by volume loading is a good surrogate for maximizing cardiac output by volume expansion until patients reach the preload independent part of the Frank-Starling curve. However, measuring fluid responsiveness still has significant limitations. The most obvious limitation is that all of these dynamic measures of FR, with the exception of PLR, are limited to mechanically ventilated patients, ideally with tidal volumes of at least 8 mL/kg [49]. Other limitations include unstable or irregular rhythms, the necessity of a sealed chest cavity, and a normal abdominal compartment pressure. ΔrPOP is being integrated into the monitoring systems of currently available standard monitors, and it comes at a limited cost; however, its efficacy has yet to be demonstrated outside the operating room [63]. Like CVP, it is a continuous and easily interpretable number. However, none of the measures of FR provide the critical care clinician with other hemodynamics (such as cardiac output or oxygen-carrying capacity) which may be particularly helpful in managing undifferentiated shock, shock of more than one etiology, and nonfluid responders. PLR and SVV are measureable on noninvasive hemodynamic monitors, though the latter is limited to mechanically ventilated patients. Maximal effect of PLR occurs within the first minute, making it important to assess this change in conjunction with real-time stroke volume and cardiac output monitors.

3. Noninvasive Hemodynamic Monitoring

Multiple methodologies for noninvasive hemodynamic and resuscitation monitoring are available in the management of acutely ill patients in the ED. Each technology offers a unique set of advantages and limitations (summarized in Table 2). Literature questioning the efficacy of routines use of PAC-TD, it's limitations of accuracy, and the desire for noninvasive alternatives have led to wider consideration of these monitors. Bedside ultrasonography, transcutaneous doppler ultrasonography, thoracic bioimpedance, and bioreactance represent some of these alternatives discussed below.

3.1. Bedside Ultrasonography. The use of bedside ultrasonography in critically ill patients is becoming more frequent as technical advances, cost reductions, and safety concerns have led to many EDs and intensive care units (ICU) having bedside portable ultrasound. While volumetric methods of measuring stroke volume exist (termed the method of discs or Simpson's rule), a more reliable measure of cardiac output comes from simple physics. Flow is the product of the velocity (V) of a fluid moving through a certain location and the cross sectional area (CSA) of that location. Therefore, the stroke volume can be measured by calculating the velocity of blood emerging from the left ventricular outflow tract (Figure 1), such that

$$\mathrm{CO} = \mathrm{HR} * \mathrm{SV}, \tag{4}$$

$$\mathrm{SV} = \mathrm{VTI} * \mathrm{CSA}_{\mathrm{LVOT}}. \tag{5}$$

This technique is a validated, accurate measure of stroke volume that is used extensively in echocardiography [64, 65]. Physicians attempting to utilize this technique must be facile in identifying the left ventricular outflow tract, measuring the time integral of velocity through the region (VTI), and obtaining a 5-chamber apical view—all of which are difficult to do in critically ill patients. One generally measures VTI by placing a Doppler probe at the suprasternal notch and aiming it directly opposite the direction of blood flow. This technique has been utilized extensively in echocardiography and is the basis for transcutaneous doppler ultrasonography (TCDU).

Despite the difficulty in using ultrasound for the measurement of stroke volume and cardiac output, focused critical care echocardiography is increasingly being recognized as an important adjunct in the care of critically ill patients because of the wealth of information one can obtain. Multiple studies have now shown that short training programs can adequately train novice users in the necessary skills for bedside ultrasonography [66–69]. These skills include assessment of global left ventricular function, ventricular size, inferior vena cava diameters, and identifying pericardial effusions and tamponade [67, 69–72]. Assessment of right ventricular function by echocardiography is important in certain types of shock and may contribute to limited responses to fluid resuscitation [73, 74]. While transabdominal inferior vena cava collapsibility index is a promising measure of fluid responsiveness and central venous pressure [27, 32, 33], transesophageal echocardiography also offers the potential to measure superior vena cava collapsibility and may be one of the best measures of fluid responsiveness [75, 76].

3.1.1. Advantages. Skilled sonographers can utilize enhanced echocardiography to examine wall motion abnormalities and valvular disease. With proper training, one can measure SV and CVP, make qualitative assessments of ventricular function, as well as evaluate primary and secondary etiologies of hemodynamic instability (i.e., pericardial tamponade). For these reasons, independent of hemodynamic measurement, bedside ultrasonography has an important role in the resuscitation of critically ill patients.

3.1.2. Limitations. The greatest limitation of bedside ultrasonography is that it is discontinuous. Findings may lead to definitive changes in management but to utilize this technology of as a hemodynamic monitor or to monitor therapeutic effectiveness requires regular reevaluation. While multiple studies have now demonstrated the validity of short training courses and curricula for novice users, few studies

Table 2: Comparison of noninvasive techniques for hemodynamic monitoring.

Technique	Continuous	Operator dependent	Initial cost	Need for lead replacement	Supportive clinical literature for bedside hemodynamics	Correlation with TD
Ultrasound	N	+++	+++	N	+++	+++
TCDU	N	++	++	N	++	++
TEB	Y	+	++	Y	+++	++
BR	Y	+	++	Y	++	+++

Y: yes, N: No, +: fair, ++: moderate, +++: high.
TCDU: Transcutaneous Doppler ultrasound, TEB: Thoracic Electric Bioimpedance, BR: Bioreactance.

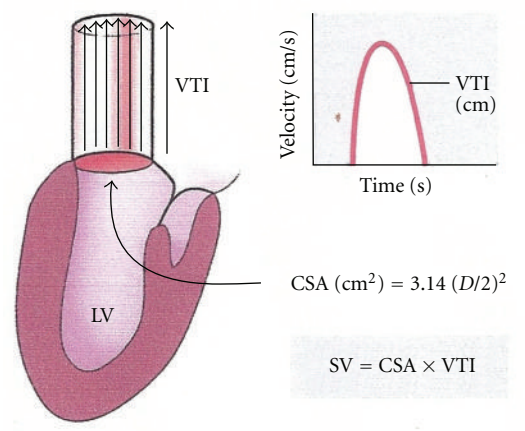


Figure 1: Doppler assessment of stroke volume via the left ventricular outflow tract. This illustration demonstrates the physiologic principle of measuring stroke volume by measuring the LVOT diameter and the VTI at that point. A characteristic curve is generated by proper placement of a probe in line with the flow of blood out of the LVOT. This figure was published in the Textbook of Clinical Echocardiography, 3rd edition, Elsevier, Ltd, 2004. Page 147, Used with permission [25].

currently exist that demonstrate the therapeutic impact of this skill set [71].

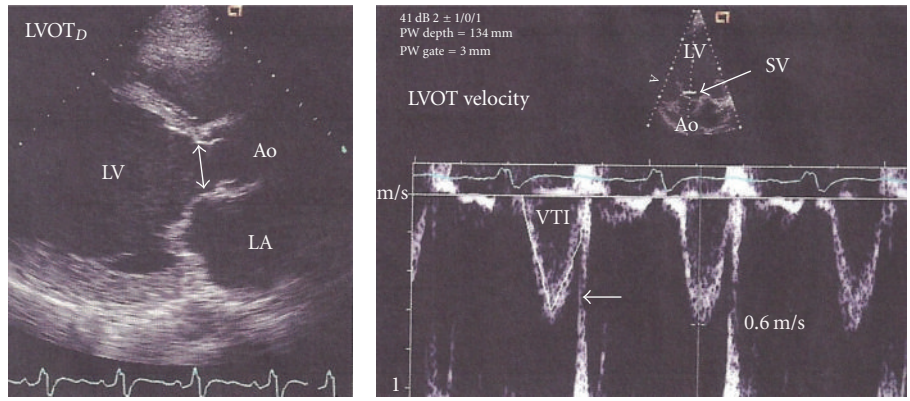
3.2. Transcutaneous Doppler Ultrasonography. Transcutaneous wave doppler ultrasonography (TCDU) is an extension of bedside echocardiography that is based on the same principle of measuring the VTI at the left ventricular outflow tract (LVOT). The relationship in cadaver studies between height and a normal LVOT diameter obviates the need to manually measure the LVOT diameter. The provider obtains the stroke volume by obtaining the patient's height and measuring the VTI using visual and auditory cues to improve positioning of a transcutaneous Doppler probe (Figure 2).

There appears to be a high correlation ($r = 0.87$) with PAC-TD, with minimal bias and limits of agreement of approximately ±1 L/min [77, 78]. Studies have demonstrated excellent interrater reliability of this technology with minimal to no training [79–81]. The corrected aortic flow time (FTc), a Doppler measure of the duration of flow during systole corrected for heart rate, has been used in conjunction with TCDU and appears to be an effective measure of FR in spontaneously breathing patients in septic shock [82]. TCDU can also predict FR when used in conjunction with PLR in critically ill patients [83].

3.2.1. Advantages. Transcutaneous doppler ultrasonography is fast, easy to learn, and has high interrater reliability even in novice users. While the initial cost of this technology is comparable with others, one of its major advantages is that there are no per-patient costs associated with disposable parts. Measurements are obtained in the suprasternal notch so there is minimal interference with patient care and patient specific factors like obesity, diaphoresis, or positioning have limited effect on the accuracy of the results.

3.2.2. Limitations. The largest limitation of this technology is that continuous monitoring is not possible. Though there are no studies demonstrating that continuous hemodynamic monitoring improves outcome in critically ill patients, noncontinuity of hemodynamic monitoring requires clinicians to decide on a preset protocol of recurrent measurement or to utilize this technology when clinical circumstances dictate. Since physicians are poor predictors of underlying hemodynamic instability, a noncontinuous monitoring technique may help direct treatment when combined with a protocol but it likely will not help alert clinicians to hemodynamic decline. Additionally, because the LVOT diameter is assumed, anatomical changes such as aortic valve regurgitation, aortic valve stenosis, or proximal aortic aneurysms/dilatation can cause significant alterations in the accuracy of the stroke volume. Though clinical exam can detect many of these abnormalities, it is not uncommon for patients to have clinically indetectable stenosis, regurgitation, or aneurysms—particularly in the critically ill. Lastly, clinical trials have largely been validations against other hemodynamic monitoring techniques or evaluations of inter-rater reliability. Few studies exist that compare this technology to other methods of measuring hemodynamics in critically ill patients; those that do question the device's accuracy [84].

3.3. Impedance Cardiography or Thoracic Bioimpedance. Impedance cardiography (ICG) or thoracic bioimpedance (TEB) is a noninvasive means for obtaining continuous hemodynamic data. This technology has been validated in over 2000 patients in multiple different settings against



(a) (b)

Figure 2: Transducer placement and characteristic waveform using transcutaneous doppler ultrasonography. This demonstrates the characteristic transducer direction and image capture using the direct measurement through the left ventricular outflow tract. One notes a characterstic waveform and manipulates the transducer to obtain maximum outflow. This figure was published in the Textbook of Clinical Echocardiography, 3rd edition, Elsevier, Ltd, 2004. Page 148, Used with permission [25].

multiple different gold standards [85]. It is based on measuring changes in thoracic impedance of high-frequency, low-magnitude alternating currents applied across the thorax. The impedance (Z) of various tissues across the chest can change with time, but the blood in the aorta is the only component in the thorax that changes over a few seconds' time. Pulse waves will, therefore, naturally travel down the aorta and be responsible for the beat-to-beat alterations in impedance, providing characteristic waveforms that can be used to calculate hemodynamic variables (Figure 3).

The area under the curve of the pulse pressure waveform represents the stroke volume. Typically, this area can be estimated by the peak pressure change during systole multiplied by the ventricular ejection time (VET), the time between opening and closing of the aortic valve. Using bioimpedance, one can estimate the stroke volume by measuring peak change in impedance ($dZ/dt_{\max}$) multiplied by the VET (Figure 4). Measurement of $dZ/dt_{\max}$ requires a pair of thoracic impedance leads and measurement of VET requires the acquisition of an ECG signal; two sets of leads are necessary—each with an adequate signal. A change in impedance between two sets of leads requires measuring the amplitude of the impedance signal at each lead *and* measuring the distance between the leads because the amplitude degrades over time. More recent research has enhanced the ease and accuracy of monitoring by (1) assuming the thorax is a cylinder or cone, (2) which makes up 17% of one's overall height (H), (3) and can be normalized by ideal body weight [86]. Therefore, the stroke volume is calculated as

$$\mathrm{SV} = c\left(\frac{(0.17 * H)^3}{4.2}\right) * \frac{dZ}{dt_{\max}} * \frac{\mathrm{VET}}{Z}. \quad (6)$$

TEB also allows for measuring central thoracic fluid volume by assessing the overall impedance (Z), as well as measuring systolic time intervals and the accelerated cardiac index, all measures that may have use in certain clinical situations [85, 87–89]. Early research was promising but inadequate for advocating routine use of TEB as a surrogate for PAC-TD because of the large limits of agreement [90]. Overtime algorithms have improved; a large multicenter study of over 2000 measurements in 861 critically ill ED, ICU, or operating room patients found a good correlation ($r = 0.85$) with a bias of $-0.12 + 0.75$ L/min/m^2 [91]. This study represents the single largest multicenter study to validate a noninvasive hemodynamic monitor in critically patients. Weighted average and meta-analytic correlation coefficients comparing TEB with other methodologies of measuring cardiac output demonstrates correlations ranging from $r = 0.61$ (Doppler Echocardiography) to $r = 0.89$ (left ventricular assist device) with an overall correlation of $r = 0.81$ ($n > 16{,}000$) and the same correlation ($r = 0.81$) in studies comparing TEB with PAC-TD ($n = 10{,}959$). The largest single study in critically ill patients found the percent limit of agreement (LOA) between TEB and PAC-TD to be 16.6% with even better performance (9.8% ± 6.7%, $r = 0.93$) when motion artifact and clinical conditions affecting the uniformity of thoracic impedance are accounted for [91].

3.3.1. Advantages. TEB technology offers the clinician a well-studied method to noninvasively, continuously monitor hemodynamics. The capacity for beat-to-beat measurement of the impedance waveform allows for a more accurate and responsive measurement of stroke volume as the measurement period can be selected by the user. TEB has the largest and widest breath of literature validating its accuracy. It also remains the only technology that has been validated, at least in part, in critically ill patients.

3.3.2. Limitations. Morbid obesity, a short neck, extensive hair, diaphoresis, and inability to localize landmarks are limitations. Clinical conditions such as pneumonia, pleural effusions, hemo/pneumothorax, or significant third spacing

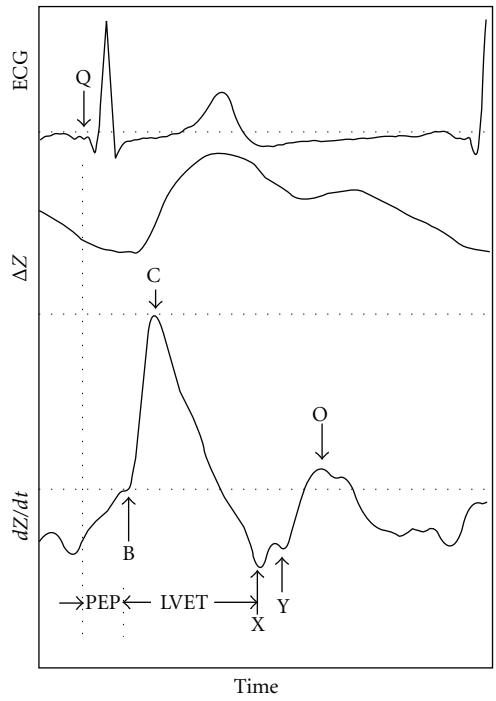


Figure 3: Characteristic waveforms for thoracic bioimpedance monitoring. Product photographs reprinted with permission from SonoSite; _electrical and mechanical change in impedance over change in time. Trademarks and logos are trademarks owned by SonoSite, Inc. PEP: preejection period, LVET: left ventricular ejection time, ΔZ: change in impedance, dZ/dt: 1st derivative of impedance waveform.

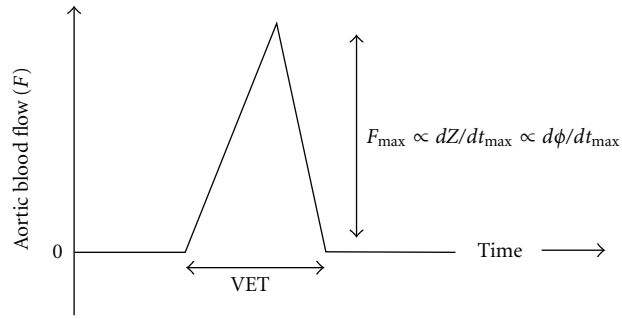


Figure 4: Determining stroke volume using thoracic bioimpedance or bioreactance. Schematic representation of stroke volume measured from aortic blood flow by measuring the change in impedance (dZ/dt_{max}) using thoracic bioimpedance or the relative phase shift ($d\phi/dt_{max}$) using bioreactance. These parameters are representative of the peak blood flow, and the stroke volume is proportional to the product of this parameter over the ventricular time (VET) for each device, respectively [92].

from late stage sepsis may also impair the accuracy [85]. Multiple small studies have also questioned the accuracy of TEB in measuring CO of mechanically ventilated patients during PEEP [94–96]. Improper placement or errors in the assumed relationship between height and thoracic length can lead to significant errors due to the mathematical relationship (7) used to determine stroke volume. Despite these limitations, inter-rater reliability is very good [81]. These known limitations and the continued variability in reports of the accuracy of this technology, particularly in critically ill subsets, have hindered the adoption of the technology.

3.4. Bioreactance. Bioreactance is the newest technique for noninvasive hemodynamic monitoring. Bioreactance (BR) is very similar to TEB in that, an electrical current of low amplitude and known frequency is applied across the chest between two leads. The difference between the two methodologies is analogous to the AM (amplitude modulated) radios (TEB) and FM (frequency modulated) radios (BR) of impedance hemodynamics. As such, the frequency of a signal does not degrade with distance, and the ability to record adequate signal intensity, therefore, becomes independent of distance. BR measures the relative phase shifts in the applied and received signal between two leads that is created by changes in intrathoracic volume resulting from blood flow. These phase shifts are also generally less susceptible to signal degradation and more amenable to high-pass filtering to eliminate ambient noise, theoretically leading to more accurate signal recovery. As opposed to TEB (7), SV with BR is not a function of the distance between leads but simply a function of (VET), the maximum phase shift over time ($d\phi/dt_{max}$), and a constant (c) (8).

$$SV_{TEB} \approx \left(\frac{L}{Z}\right)^2 * VET * \frac{dZ}{dt_{max}}, \quad (7)$$

$$SV_{BR} \approx c * VET * \frac{d\phi}{dt_{max}}. \quad (8)$$

While this technology is much newer than TEB, recent literature on the accuracy of this monitoring technique against TD and other hemodynamic monitoring is as strong if not better [92, 97, 98]. The largest single-site validation of a noninvasive hemodynamic monitor, a study of 110 consecutive postcardiac surgery patients with a total of 65,888 paired measurements between BR and PAC-TD, demonstrated a correlation of $r = 0.82$ with a bias of 0.16 ± 0.52 L/min (which equated to a percent bias of $4 \pm 11.3\%$) [98]. A subsequent multicenter validation of BR versus PAC-TD resulted in a similar correlation ($r = 0.78$) [97] with limits of agreement that were similar to those observed in prior studies of continuous versus bolus PAC-TD [99]. Early results in clinical studies in patients with septic shock that compare BR to PAC-TD suggests that the accuracy and precision are maintained in both baseline measurements ($r = 0.88$) and during PLR testing (bias $6.8 \pm 13\%$) [100].

3.4.1. Advantages. The most important advantage of BR is that frequency modulations and phase shifts are independent of the distance between the applied and detected signal. Lead placement using BR requires neither an exact distance nor an exact location on the thorax. This allows for more convenience and less interference of lead placement. Additionally, anatomic or clinical conditions such as obesity, short neck, and diaphoresis do not degrade the accuracy of a

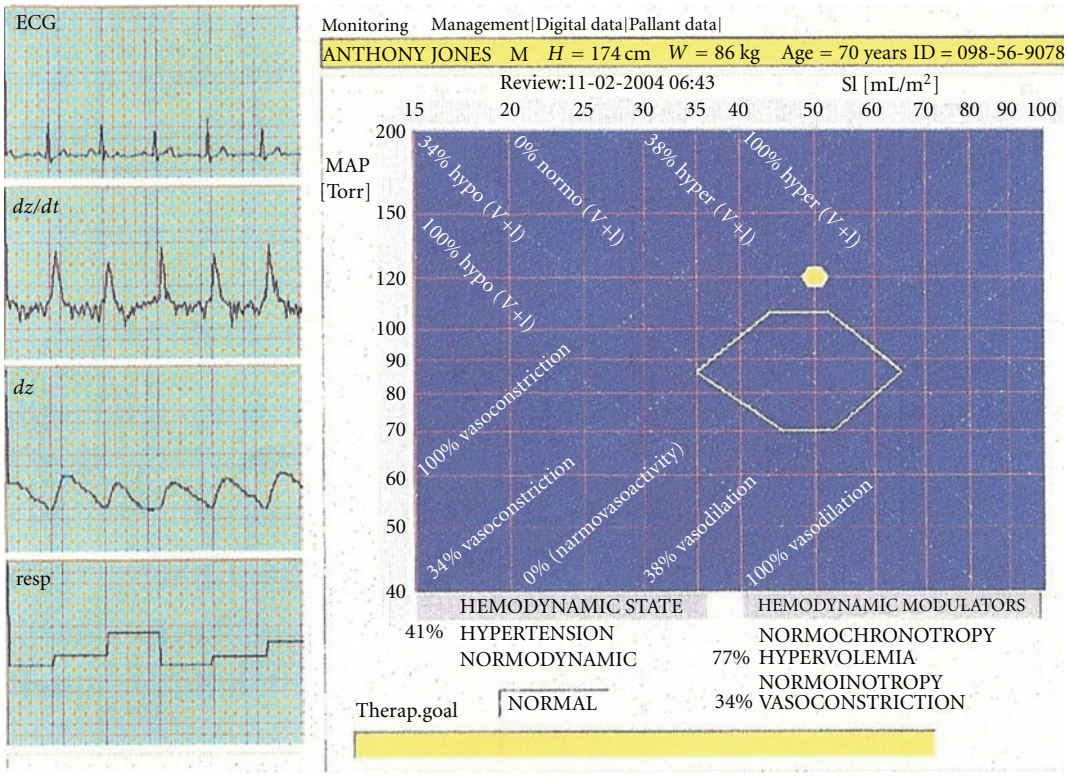


Figure 5: Graphical representation of the normalized hemodynamic modulators that determine the hemodynamic state. This is a graphical illustration of the four hemodynamic modulators (preload, afterload, inotropy, and chronotropy) that determine one's hemodynamic state. Measurement on a per-beat basis, and normalization of each measure allows for percentile representation of each modulator effect with respect to the whole [93].

frequency-modulated signal. Measurements are not affected by other voltage sources and known frequency interference (such as ambient noise) can be filtered out.

3.4.2. Limitations. This technology is fairly new, but there are few currently identifiable disadvantages. The validation literature is very strong though there are few published clinical studies to date utilizing this technology in undifferentiated or specific critically ill patient populations. TEB has a much broader experience in clinical use though its role in specific conditions or undifferentiated critically ill patients remains controversial because of the reports of variable accuracy [85, 90].

4. Conclusion and Future Directions

4.1. Per-Beat Hemodynamic Measurement. Expressing patient hemodynamics as a per-minute phenomenon is not reflective of the basic function of the cardiovascular system—to respond to ongoing metabolic demands with immediate changes in oxygen delivery. As such, per-minute hemodynamic measurement may not be reflective of ongoing changes particularly in hemodynamically unstable individuals. In spontaneously breathing patients, the thoracic pressure changes in concert with the frequency of respirations leading to varying rates of changes in thoracic pressure. Even in a steady state, 20–30% of beat-to-beat variations in heart rate and stroke index have been demonstrated [93]. While standard convention is to extrapolate measurements and represent them on a per-minute basis, measurements are not typically taken over one minute. The actual time period of measurement and consequently the number of respirations during that time are likely to be different depending on the methodology; thermodilution is measured over a set period of time while many of the noninvasive technologies use a different time period or measure over a running several beat average. As such, newer noninvasive technology may be more reflective of ongoing hemodynamic response to clinical conditions.

4.2. Modeling the Hemodynamic Response. If the hemodynamic parameters of volume, inotropy, chronotropy, and vasoactivity can be measured noninvasively and the normal values for these hemodynamic parameters are known, then these parameters can be normalized and the hemodynamic state of each patient can be graphically represented by superimposing these parameters on the same graph and representing them as percent changes from the norm (Figure 5). This would allow graphical modeling of the hemodynamic state, and clinicians may be able to more accurately respond to the individual needs of the patient with targeted therapy.

Clinicians would not need to continuously interpret the per-beat hemodynamic variables within the context of "normal" or patient body habitus. Thus, measurement of these hemodynamic parameters, indexing them by body surface area, and analyzing them all in concert may be important in the future monitoring of critically ill individuals. This technique was first proposed by Sramek et al. and has demonstrated improved outcome in antihypertensive management but has yet to be studied in critically ill patient populations [93, 101–103].

4.3. Outcomes-Based Research. While the noninvasive technology described here and the physiologic principles underlying this technology may initially be difficult to understand, this technology may be the next step in improving the resuscitation of the critically ill. Algorithms based on noninvasive hemodynamic parameters that better characterize the body's hemodynamic response to illness may be more intuitive and can potentially be applied in a larger breath of patient population. Measures of FR would improve upon measuring CVP and stroke index could augment $ScVO_2$ in management strategies like early goal directed therapy for sepsis. Most of the noninvasive hemodynamic monitoring literature to date has focused on single or multicenter validations of device accuracy, proofs of concept, or observational trials of the prognostic capacity of individual hemodynamic parameters. Future research will undoubtedly necessitate a multicenter trial utilizing hemodynamic monitoring to drive clinical interventions in protocols for the resuscitation of critically ill patients. The noninvasive hemodynamic techniques discussed here may provide the means to improve upon aggressive resuscitation while other new techniques for noninvasively measuring tissue level response to resuscitation may aid us in knowing when those efforts have succeeded [104–106].

References

[1] D. Atkins, D. Best, P. A. Briss et al., "Grading quality of evidence and strength of recommendations," *BMJ*, vol. 328, no. 1490, 2004.

[2] M. R. Shah, V. Hasselblad, L. W. Stevenson et al., "Impact of the pulmonary artery catheter in critically ill patients: meta-analysis of randomized clinical trials," *Journal of the American Medical Association*, vol. 294, no. 13, pp. 1664–1670, 2005.

[3] S. Harvey, D. A. Harrison, M. Singer et al., "Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial," *The Lancet*, vol. 366, no. 9484, pp. 472–477, 2005.

[4] J. D. Mackenzie, N. E. Haites, and J. M. Rawles, "Method of assessing the reproducibility of blood flow measurement: factors influencing the performance of thermodilution cardiac output computers," *British Heart Journal*, vol. 55, no. 1, pp. 14–24, 1986.

[5] T. Nishikawa and S. Dohi, "Errors in the measurement of cardiac output by thermodilution," *Canadian Journal of Anaesthesia*, vol. 40, no. 2, pp. 142–153, 1993.

[6] E. Rivers, B. Nguyen, S. Havstad et al., "Early goal-directed therapy in the treatment of severe sepsis and septic shock," *The New England Journal of Medicine*, vol. 345, no. 19, pp. 1368–1377, 2001.

[7] P. E. Marik, M. Baram, and B. Vahid, "Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares," *Chest*, vol. 134, no. 1, pp. 172–178, 2008.

[8] C. C. Wo, W. C. Shoemaker, P. L. Appel, M. H. Bishop, H. B. Kram, and E. Hardin, "Unreliability of blood pressure and heart rate to evaluate cardiac output in emergency resuscitation and critical illness," *Critical Care Medicine*, vol. 21, no. 2, pp. 218–223, 1993.

[9] M. Y. Rady, E. P. Rivers, and R. M. Nowak, "Resuscitation of the critically ill in the ED: responses of blood pressure, heart rate, shock index, central venous oxygen saturation, and lactate," *American Journal of Emergency Medicine*, vol. 14, no. 2, pp. 218–225, 1996.

[10] A. F. Connors Jr., N. V. Dawson, P. K. Shaw, H. D. Montenegro, A. R. Nara, and L. Martin, "Hemodynamic status in critically ill patients with and without acute heart disease," *Chest*, vol. 98, no. 5, pp. 1200–1206, 1990.

[11] O. Mimoz, A. Rauss, N. Rekik, C. Brun-Buisson, F. Lemaire, and L. Brochard, "Pulmonary artery catheterization in critically ill patients: a prospective analysis of outcome changes associated with catheter-prompted changes in therapy," *Critical Care Medicine*, vol. 22, no. 4, pp. 573–579, 1994.

[12] P. R. Eisenberg, A. S. Jaffe, and D. P. Schuster, "Clinical evaluation compared to pulmonary artery catheterization in the hemodynamic assessment of critically ill patients," *Critical Care Medicine*, vol. 12, no. 7, pp. 549–553, 1984.

[13] S. W. Glickman, C. B. Cairns, R. M. Otero et al., "Disease progression in hemodynamically stable patients presenting to the emergency department with sepsis," *Academic Emergency Medicine*, vol. 17, no. 4, pp. 383–390, 2010.

[14] M. R. Pinsky, "Hemodynamic evaluation and monitoring in the ICU," *Chest*, vol. 132, no. 6, pp. 2020–2029, 2007.

[15] R. M. Berne and M. N. Levy, *Cardiovascular Physiology*, Mosby, St. Louis, Mo, USA, 7th edition, 1997.

[16] O. Frank, "Zur dynamik des herzmuskels," *Zeitschrift für Biologie*, vol. 32, pp. 370–447, 1895.

[17] E. Starling, *The Linacre Lecture on the Law of the Heart: Given at Cambridge, 1915*, Longmans, Green and Co., London, UK, 1918.

[18] K. Bendjelid and J. A. Romand, "Fluid responsiveness in mechanically ventilated patients: a review of indices used in intensive care," *Intensive Care Medicine*, vol. 29, no. 3, pp. 352–360, 2003.

[19] F. Michard and J. L. Teboul, "Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence," *Chest*, vol. 121, no. 6, pp. 2000–2008, 2002.

[20] A. Kumar, R. Anel, E. Bunnell et al., "Pulmonary artery occlusion pressure and central venous pressure fail to predict ventricular filling volume, cardiac performance, or the response to volume infusion in normal subjects," *Critical Care Medicine*, vol. 32, no. 3, pp. 691–699, 2004.

[21] F. P. Ognibene, M. M. Parker, C. Natanson, J. H. Shelhamer, and J. E. Parrillo, "Depressed left ventricular performance: response to volume infusion in patients with sepsis and septic shock," *Chest*, vol. 93, no. 5, pp. 903–910, 1988.

[22] M. M. Parker, J. H. Shelhamer, S. L. Bacharach et al., "Profound but reversible myocardial depression in patients with septic shock," *Annals of Internal Medicine*, vol. 100, no. 4, pp. 483–490, 1984.

[23] C. R. Shippy, P. L. Appel, and W. C. Shoemaker, "Reliability of clinical monitoring to assess blood volume in critically ill

patients," *Critical Care Medicine*, vol. 12, no. 2, pp. 107–112, 1984.

[24] P. G. Yock and R. L. Popp, "Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation," *Circulation*, vol. 70, no. 4, pp. 657–662, 1984.

[25] C. Otto, *Textbook of Clinical Echocardiography*, Elsevier Saunders, Philadelphia, Pa, USA, 3rd edition, 2004.

[26] O. J. Ma and J. Mateer, *Emergency Ultrasound*, McGraw-Hill, New York, NY, USA, 2003.

[27] A. D. Nagdev, R. C. Merchant, A. Tirado-Gonzalez, C. A. Sisson, and M. C. Murphy, "Emergency department bedside ultrasonographic measurement of the caval index for noninvasive determination of low central Venous pressure," *Annals of Emergency Medicine*, vol. 55, no. 3, pp. 290–295, 2010.

[28] H. Natori, S. Tamaki, and S. Kira, "Ultrasonographic evaluation of ventilatory effect on inferior vena caval configuration," *The American Review of Respiratory Disease*, vol. 120, no. 2, pp. 421–427, 1979.

[29] B. J. Kimura, R. Dalugdugan, G. W. Gilcrease III, J. N. Phan, B. K. Showalter, and T. Wolfson, "The effect of breathing manner on inferior vena caval diameter," *European Journal of Echocardiography*, vol. 12, no. 2, pp. 120–123, 2011.

[30] D. J. Wallace, M. Allison, and M. B. Stone, "Inferior vena cava percentage collapse during respiration is affected by the sampling location: an ultrasound study in healthy volunteers," *Academic Emergency Medicine*, vol. 17, no. 1, pp. 96–99, 2010.

[31] M. Pepi, G. Tamborini, C. Galli et al., "A new formula for echo-Doppler estimation of right ventricular systolic pressure," *Journal of the American Society of Echocardiography*, vol. 7, no. 1, pp. 20–26, 1994.

[32] M. Feissel, F. Michard, J. P. Faller, and J. L. Teboul, "The respiratory variation in inferior vena cava diameter as a guide to fluid therapy," *Intensive Care Medicine*, vol. 30, no. 9, pp. 1834–1837, 2004.

[33] C. Barbier, Y. Loubières, C. Schmit et al., "Respiratory changes in inferior vena cava diameter are helpful in predicting fluid responsiveness in ventilated septic patients," *Intensive Care Medicine*, vol. 30, no. 9, pp. 1740–1746, 2004.

[34] D. A. Reuter, T. W. Felbinger, K. Moerstedt et al., "Intrathoracic blood volume index measured by thermodilution for preload monitoring after cardiac surgery," *Journal of Cardiothoracic and Vascular Anesthesia*, vol. 16, no. 2, pp. 191–195, 2002.

[35] D. D. Glower, J. A. Spratt, N. D. Snow et al., "Linearity of the Frank-Starling relationship in the intact heart: the concept of preload recruitable stroke work," *Circulation*, vol. 71, no. 5, pp. 994–1009, 1985.

[36] F. Jardin, J. C. Farcot, P. Gueret, J. F. Prost, Y. Ozier, and J. P. Bourdarias, "Cyclic changes in arterial pulse during respiratory support," *Circulation*, vol. 68, no. 21, pp. 266–274, 1983.

[37] J. J. Rick and S. S. Burke, "Respirator paradox," *Southern Medical Journal*, vol. 71, no. 11, pp. 1376–1382, 1978.

[38] B. Tavernier, O. Makhotine, G. Lebuffe, J. Dupont, and P. Scherpereel, "Systolic pressure variation as a guide to fluid therapy in patients with sepsis-induced hypotension," *Anesthesiology*, vol. 89, no. 6, pp. 1313–1321, 1998.

[39] F. Michard, S. Boussat, D. Chemla et al., "Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure," *American Journal of Respiratory and Critical Care Medicine*, vol. 162, no. 1, pp. 134–138, 2000.

[40] A. Kramer, D. Zygun, H. Hawes, P. Easton, and A. Ferland, "Pulse pressure variation predicts fluid responsiveness following coronary artery bypass surgery," *Chest*, vol. 126, no. 5, pp. 1563–1568, 2004.

[41] M. Cannesson, C. Besnard, P. G. Durand, J. Bohé, and D. Jacques, "Relation between respiratory variations in pulse oximetry plethysmographic waveform amplitude and arterial pulse pressure in ventilated patients," *Critical Care*, vol. 9, no. 5, pp. R562–R568, 2005.

[42] M. Cannesson, Y. Attof, P. Rosamel et al., "Respiratory variations in pulse oximetry plethysmographic waveform amplitude to predict fluid responsiveness in the operating room," *Anesthesiology*, vol. 106, no. 6, pp. 1105–1111, 2007.

[43] P. A. H. Wyffels, P. J. Durnez, J. Helderweirt, W. M. A. Stockman, and D. De Kegel, "Ventilation-induced plethysmographic variations predict fluid responsiveness in ventilated postoperative cardiac surgery patients," *Anesthesia and Analgesia*, vol. 105, no. 2, pp. 448–452, 2007.

[44] M. Feissel, R. Kalakhy, J. Badie, G. Robles, J. Faller, and J. L. Teboul, "Plethysmography variability index: a new fluid responsiveness parameter," *Critical Care*, vol. 13, supplement 1, p. 205, 2009.

[45] M. R. Pinsky, "Probing the limits of arterial pulse contour analysis to predict preload responsiveness," *Anesthesia and Analgesia*, vol. 96, no. 5, pp. 1245–1247, 2003.

[46] G. Marx, T. Cope, L. McCrossan et al., "Assessing fluid responsiveness by stroke volume variation in mechanically ventilated patients with severe sepsis," *European Journal of Anaesthesiology*, vol. 21, no. 2, pp. 132–138, 2004.

[47] C. K. Hofer, S. M. Müller, L. Furrer, R. Klaghofer, M. Genoni, and A. Zollinger, "Stroke volume and pulse pressure variation for prediction of fluid responsiveness in patients undergoing off-pump coronary artery bypass grafting," *Chest*, vol. 128, no. 2, pp. 848–854, 2005.

[48] D. A. Reuter, J. Bayerlein, M. S. G. Goepfert et al., "Influence of tidal volume on left ventricular stroke volume variation measured by pulse contour analysis in mechanically ventilated patients," *Intensive Care Medicine*, vol. 29, no. 3, pp. 476–480, 2003.

[49] D. De Backer, S. Heenen, M. Piagnerelli, M. Koch, and J. L. Vincent, "Pulse pressure variations to predict fluid responsiveness: influence of tidal volume," *Intensive Care Medicine*, vol. 31, no. 4, pp. 517–523, 2005.

[50] H. K. Kim and M. R. Pinsky, "Effect of tidal volume, sampling duration, and cardiac contractility on pulse pressure and stroke volume variation during positive-pressure ventilation," *Critical Care Medicine*, vol. 36, no. 10, pp. 2858–2862, 2008.

[51] D. De Backer, F. S. Taccone, R. Holsten, F. Ibrahimi, and J. L. Vincent, "Influence of respiratory rate on stroke volume variation in mechanically ventilated patients," *Anesthesiology*, vol. 110, no. 5, pp. 1092–1097, 2009.

[52] Y. Mahjoub, C. Pila, A. Friggeri et al., "Assessing fluid responsiveness in critically ill patients: false-positive pulse pressure variation is detected by Doppler echocardiographic evaluation of the right ventricle," *Critical Care Medicine*, vol. 37, no. 9, pp. 2570–2575, 2009.

[53] H. P. Wiedemann, A. P. Wheeler, G. R. Bernard et al., "Comparison of two fluid-management strategies in acute lung injury," *The New England Journal of Medicine*, vol. 354, no. 24, pp. 2564–2575, 2006.

[54] M. Feissel, J. Badie, P. G. Merlani, J. P. Faller, and K. Bendjelid, "Pre-ejection period variations predict the fluid

responsiveness of septic ventilated patients," *Critical Care Medicine*, vol. 33, no. 11, pp. E2534–E2534, 2005.

[55] S. Préau, F. Saulnier, F. Dewavrin, A. Durocher, and J. L. Chagnon, "Passive leg raising is predictive of fluid responsiveness in spontaneously breathing patients with severe sepsis or acute pancreatitis," *Critical Care Medicine*, vol. 38, no. 3, pp. 819–825, 2010.

[56] T. Boulain, J. M. Achard, J. L. Teboul, C. Richard, D. Perrotin, and G. Ginies, "Changes in BP induced by passive leg raising predict response to fluid loading in critically ill patients," *Chest*, vol. 121, no. 4, pp. 1245–1252, 2002.

[57] D. L. Rutlen, F. J. Wackers, and B. L. Zaret, "Radionuclide assessment of peripheral intravascular capacity: a technique to measure intravascular volume changes in the capacitance circulation in man," *Circulation*, vol. 64, no. 1, pp. 146–152, 1981.

[58] J. Maizel, N. Airapetian, E. Lorne, C. Tribouilloy, Z. Massy, and M. Slama, "Diagnosis of central hypovolemia by using passive leg raising," *Intensive Care Medicine*, vol. 33, no. 7, pp. 1133–1138, 2007.

[59] V. Caille, J. Jabot, G. Belliard, C. Charron, F. Jardin, and A. Vieillard-Baron, "Hemodynamic effects of passive leg raising: an echocardiographic study in patients with shock," *Intensive Care Medicine*, vol. 34, no. 7, pp. 1239–1245, 2008.

[60] X. Monnet, M. Rienzo, D. Osman et al., "Passive leg raising predicts fluid responsiveness in the critically ill," *Critical Care Medicine*, vol. 34, no. 5, pp. 1402–1407, 2006.

[61] A. Lafanechère, F. Pène, C. Goulenok et al., "Changes in aortic blood flow induced by passive leg raising predict fluid responsiveness in critically ill patients," *Critical Care*, vol. 10, no. 5, article R32, 2006.

[62] F. Cavallaro, C. Sandroni, C. Marano et al., "Diagnostic accuracy of passive leg raising for prediction of fluid responsiveness in adults: systematic review and meta-analysis of clinical studies," *Intensive Care Medicine*, vol. 36, no. 9, pp. 1475–1483, 2010.

[63] S. A. Landsverk, P. Kvandal, A. Bernjak, A. Stefanovska, and K. A. Kirkeboen, "The effects of general anesthesia on human skin microcirculation evaluated by wavelet transform," *Anesthesia and Analgesia*, vol. 105, no. 4, pp. 1012–1019, 2007.

[64] H. Dittmann, W. Voelker, K. R. Karsch, and L. Seipel, "Influence of sampling site and flow area on cardiac output measurements by Doppler echocardiography," *Journal of the American College of Cardiology*, vol. 10, no. 4, pp. 818–823, 1987.

[65] P. A. N. Chandraratna, R. Brar, S. Vijayasekaran et al., "Continuous recording of pulmonary artery diastolic pressure and cardiac output using a novel ultrasound transducer," *Journal of the American Society of Echocardiography*, vol. 15, no. 11, pp. 1381–1386, 2002.

[66] A. E. Jones, V. S. Tayal, and J. A. Kline, "Focused training of emergency medicine residents in goal-directed echocardiography: a prospective study," *Academic Emergency Medicine*, vol. 10, no. 10, pp. 1054–1058, 2003.

[67] R. Melamed, M. D. Sprenkle, V. K. Ulstad, C. A. Herzog, and J. W. Leatherman, "Assessment of left ventricular function by intensivists using hand-held echocardiography," *Chest*, vol. 135, no. 6, pp. 1416–1420, 2009.

[68] J. Pershad, S. Myers, C. Plouman et al., "Bedside limited echocardiography by the emergency physician is accurate during evaluation of the critically ill patient," *Pediatrics*, vol. 114, no. 6, pp. e667–e671, 2004.

[69] P. Vignon, F. Mücke, F. Bellec et al., "Basic critical care echocardiography: validation of a curriculum dedicated to noncardiologist residents," *Critical Care Medicine*, vol. 39, no. 4, pp. 636–642, 2011.

[70] E. Benjamin, K. Griffin, A. B. Leibowitz et al., "Goal-directed transesophageal echocardiography performed by intensivists to assess left ventricular function: comparison with pulmonary artery catheterization," *Journal of Cardiothoracic and Vascular Anesthesia*, vol. 12, no. 1, pp. 10–15, 1998.

[71] A. E. Jones, V. S. Tayal, D. M. Sullivan, and J. A. Kline, "Randomized, controlled trial of immediate versus delayed goal-directed ultrasound to identify the cause of nontraumatic hypotension in emergency department patients," *Critical Care Medicine*, vol. 32, no. 8, pp. 1703–1708, 2004.

[72] A. Vieillard-Baron, C. Charron, K. Chergui, O. Peyrouset, and F. Jardin, "Bedside echocardiographic evaluation of hemodynamics in sepsis: is a qualitative evaluation sufficient?" *Intensive Care Medicine*, vol. 32, no. 10, pp. 1547–1552, 2006.

[73] A. Vieillard-Baron and C. Charron, "Preload responsiveness or right ventricular dysfunction?" *Critical Care Medicine*, vol. 37, no. 9, pp. 2662–2663, 2009.

[74] A. Vieillard-Baron, "Assessment of right ventricular function," *Current Opinion in Critical Care*, vol. 15, no. 3, pp. 254–260, 2009.

[75] C. Charron, V. Caille, F. Jardin, and A. Vieillard-Baron, "Echocardiographic measurement of fluid responsiveness," *Current Opinion in Critical Care*, vol. 12, no. 3, pp. 249–254, 2006.

[76] A. Vieillard-Baron, K. Chergui, A. Rabiller et al., "Superior vena caval collapsibility as a gauge of volume status in ventilated septic patients," *Intensive Care Medicine*, vol. 30, no. 9, pp. 1734–1739, 2004.

[77] K. Knobloch, A. Lichtenberg, M. Winterhalter, D. Rossner, M. Pichlmaier, and R. Phillips, "Non-invasive cardiac output determination by two-dimensional independent Doppler during and after cardiac surgery," *Annals of Thoracic Surgery*, vol. 80, no. 4, pp. 1479–1483, 2005.

[78] R. Chand, Y. Mehta, and N. Trehan, "Cardiac output estimation with a new Doppler device after off-pump coronary artery bypass surgery," *Journal of Cardiothoracic and Vascular Anesthesia*, vol. 20, no. 3, pp. 315–319, 2006.

[79] H. B. Nguyen, T. Losey, J. Rasmussen et al., "Interrater reliability of cardiac output measurements by transcutaneous Doppler ultrasound: implications for noninvasive hemodynamic monitoring in the ED," *American Journal of Emergency Medicine*, vol. 24, no. 7, pp. 828–835, 2006.

[80] I. Dey and P. Sprivulis, "Emergency physicians can reliably assess emergency department patient cardiac output using the USCOM continuous wave Doppler cardiac output monitor," *Emergency Medicine Australasia*, vol. 17, no. 3, pp. 193–199, 2005.

[81] A. M. Napoli, C. Korl, and A. Forcada, "Assessing inter-rater reliability and agreement between two methods of noninvasive hemodynamic monitoring in clinically stable Emergency Department patients," *Annals of Emergency Medicine*, vol. 54, pp. S11–S12, 2009.

[82] D. J. Sturgess, R. L. S. Pascoe, G. Scalia, and B. Venkatesh, "A comparison of transcutaneous Doppler corrected flow time, b-type natriuretic peptide and central venous pressure as predictors of fluid responsiveness in septic shock: a preliminary evaluation," *Anaesthesia and Intensive Care*, vol. 38, no. 2, pp. 336–341, 2010.

[83] S. W. Thiel, M. H. Kollef, and W. Isakow, "Non-invasive stroke volume measurement and passive leg raising predict volume responsiveness in medical ICU patients: an

observational cohort study," *Critical Care*, vol. 13, no. 4, article R111, 2009.

[84] H. B. Nguyen, D. P. Banta, G. Stewart et al., "Cardiac index measurements by transcutaneous Doppler ultrasound and transthoracic echocardiography in adult and pediatric emergency patients," *Journal of Clinical Monitoring and Computing*, vol. 24, no. 3, pp. 237–247, 2010.

[85] R. L. Summers, W. C. Shoemaker, W. F. Peacock, D. S. Ander, and T. G. Coleman, "Bench to bedside: electrophysiologic and clinical principles of noninvasive hemodynamic monitoring using impedance cardiography," *Academic Emergency Medicine*, vol. 10, no. 6, pp. 669–680, 2003.

[86] D. P. Bernstein, "A new stroke volume equation for thoracic electrical bioimpedance: theory and rationale," *Critical Care Medicine*, vol. 14, no. 10, pp. 904–909, 1986.

[87] A. M. Napoli, J. T. Machan, K. Corl, and A. Forcada, "The use of impedance cardiography in predicting mortality in emergency department patients with severe sepsis and septic shock," *Academic Emergency Medicine*, vol. 17, no. 4, pp. 452–455, 2010.

[88] A. M. Napoli, K. Corl, F. Gardiner, and A. Forcada, "Prognostic value of noninvasive measures of contractility in emergency department patients with severe sepsis and septic shock undergoing early goal-directed therapy," *Journal of Critical Care*, vol. 26, no. 1, pp. 47–53, 2010.

[89] D. Milzman, A. Napoli, C. Hogan, A. Zlidenny, and T. Janchar, "Thoracic impedance vs chest radiograph to diagnose acute pulmonary edema in the ED," *American Journal of Emergency Medicine*, vol. 27, no. 7, pp. 770–775, 2009.

[90] L. A. H. Critchley and J. A. J. H. Critchley, "A meta-analysis of studies using bias and precision statistics to compare cardiac output measurement techniques," *Journal of Clinical Monitoring and Computing*, vol. 15, no. 2, pp. 85–91, 1999.

[91] W. C. Shoemaker, H. Belzberg, C. C. J. Wo et al., "Multicenter study of noninvasive monitoring systems as alternatives to invasive monitoring of acutely III emergency patients," *Chest*, vol. 114, no. 6, pp. 1643–1652, 1998.

[92] H. Keren, D. Burkhoff, and P. Squara, "Evaluation of a noninvasive continuous cardiac output monitoring system based on thoracic bioreactance," *American Journal of Physiology*, vol. 293, no. 1, pp. H583–H589, 2007.

[93] B. Sramek, *Systemic Hemodynamics and Hemodynamic Management*, BoMed Inc., Sedona, Ariz, USA, 4th edition, 2008.

[94] J. Weber, C.F. Heidelmeyer, E. Kubatz, and J. B. Bruckner, "Determination of cardiac output under PEEP-respiration with the "NCCOM 3" non-invasive bioimpedence monitor in comparison with the thermodilution method: a study in anesthetized dogs," *Anaesthesist*, vol. 35, no. 12, pp. 744–747, 1986.

[95] M. Genoni, P. Pelosi, J. A. Romand, A. Pedoto, T. Moccetti, and R. Malacrida, "Determination of cardiac output during mechanical ventilation by electrical bioimpedance or thermodilution in patients with acute lung injury: effects of positive end-expiratory pressure," *Critical Care Medicine*, vol. 26, no. 8, pp. 1441–1445, 1998.

[96] G. Castor, G. Molter, J. Helms, I. Niedermark, and P. Altmayer, "Determination of cardiac output during positive end-expiratory pressure—noninvasive electrical bioimpedance compared with standard thermodilution," *Critical Care Medicine*, vol. 18, no. 5, pp. 544–546, 1990.

[97] N. Y. Raval, P. Squara, M. Cleman, K. Yalamanchili, M. Winklmaier, and D. Burkhoff, "Multicenter evaluation of noninvasive cardiac output measurement by bioreactance technique," *Journal of Clinical Monitoring and Computing*, vol. 22, no. 2, pp. 113–119, 2008.

[98] P. Squara, D. Denjean, P. Estagnasie, A. Brusset, J. C. Dib, and C. Dubois, "Noninvasive cardiac output monitoring (NICOM): a clinical validation," *Intensive Care Medicine*, vol. 33, no. 7, pp. 1191–1194, 2007.

[99] D. L. Medin, D. T. Brown, R. Wesley, R. E. Cunnion, and F. P. Ognibene, "Validation of continuous thermodilution cardiac output in critically ill patients with analysis of systematic errors," *Journal of Critical Care*, vol. 13, no. 4, pp. 184–189, 1998.

[100] J. M. Monti, S. Weintraub, and T. Egner, "Differential age-related decline in conflict-driven task-set shielding from emotional versus non-emotional distracters," *Neuropsychologia*, vol. 48, no. 6, pp. 1697–1706, 2010.

[101] B. Sramek, J. A. Tichy, M. Hojerova, and V. Cervenka, "Normohemodynamic goal-oriented antihypertensive therapy improves the outcome," in *Proceedings of the 11th Scientific Meeting of the American Society of Hypertension*, American Society of Hypertension, New York, NY, USA, 1996.

[102] B. Sramek, E. Badila, D. Bartos, C. Tirziu, and S. Ghiorge, "Treating hypertension as a hemodynamic disorder results in three-fold improvement in outcomes," in *Proceedings of the 23rd Annual Scientific Meeting and Exposition*, American Society of Hypertension, New Orleans, La, USA, May 2008.

[103] C. M. Ferrario, J. M. Flack, J. E. Strobeck, G. Smits, and C. Peters, "Individualizing hypertension treatment with impedance cardiography: a meta-analysis of published trials," *Therapeutic Advances in Cardiovascular Disease*, vol. 4, no. 1, pp. 5–16, 2010.

[104] J. A. Clavijo-Alvarez, C. A. Sims, M. R. Pinsky, and J. C. Puyana, "Monitoring skeletal muscle and subcutaneous tissue acid-base status and oxygenation during hemorrhagic shock and resuscitation," *Shock*, vol. 24, no. 3, pp. 270–275, 2005.

[105] P. E. Marik and A. Bankov, "Sublingual capnometry versus traditional markers of tissue oxygenation in critically ill patients," *Critical Care Medicine*, vol. 31, no. 3, pp. 818–822, 2003.

[106] S. Trzeciak, R. P. Dellinger, J. E. Parrillo et al., "Early microcirculatory perfusion derangements in patients with severe sepsis and septic shock: relationship to hemodynamics, oxygen transport, and survival," *Annals of Emergency Medicine*, vol. 49, no. 1, pp. 88–e2, 2007.

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Review Article

Extravascular Lung Water and Acute Lung Injury

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Acute lung injury carries a high burden of morbidity and mortality and is characterised by nonhydrostatic pulmonary oedema. The aim of this paper is to highlight the role of accurate quantification of extravascular lung water in diagnosis, management, and prognosis in "acute lung injury" and "acute respiratory distress syndrome". Several studies have verified the accuracy of both the single and the double transpulmonary thermal indicator techniques. Both experimental and clinical studies were searched in PUBMED using the term "extravascular lung water" and "acute lung injury". Extravascular lung water measurement offers information not otherwise available by other methods such as chest radiography, arterial blood gas, and chest auscultation at the bedside. Recent data have highlighted the role of extravascular lung water in response to treatment to guide fluid therapy and ventilator strategies. The quantification of extravascular lung water may predict mortality and multiorgan dysfunction. The limitations of the dilution method are also discussed.

1. Introduction

In 1896, the physiologist Starling described the factors that influence fluid transport across semipermeable membranes like capillaries [1]. This description accounted for the net movement of fluids between compartments in relation to capillary and interstitial hydrostatic pressures, capillary and interstitial oncotic pressures, and coefficients of capillary permeability. Pulmonary oedema refers to the accumulation of fluid within the extravascular space of the lung and occurs when the Starling forces are unbalanced. This occurs most commonly from an increased pulmonary capillary hydrostatic pressure or an increased capillary permeability. The estimation of the severity of pulmonary oedema by chest auscultation, radiography, or arterial blood gas analysis is imprecise [2–4]. Chest auscultation may be altered by mechanical ventilation, and bedside chest radiographs in the critical care unit is subject to several technical limitations. There is poor correlation between the chest radiograph scores of pulmonary oedema and the actual amount of EVLW [5]. There is also high interobserver variability when applying the American-European Consensus Conference radiographic criteria for ARDS even amongst experts [6, 7]. Data from experimental studies suggest that EVLW on chest radiography may only be detectable when the lung water increases by more than 35% [8]. Experimental studies have also shown that arterial oxygenation decreased significantly only when the EVLW increases by more than 200% [4]. Hypoxaemia may be due to causes other than pulmonary oedema, and it is estimated that up to one-third of patients with ALI do not have any significant pulmonary oedema [9–11]. The ability to accurately measure EVLW within increments from 10 to 20% offers the potential to identify those patents that may benefit from fluid restriction, dieresis, or other therapies. The aims of this study are to critically analyze clinical studies investigating the prognostic and therapeutic values of EVLW measurement.

2. Materials and Methods

Studies were searched in PUBMED by using the terms "extravascular lung water" (EVLW) and "acute lung injury" (ALI) or "acute respiratory distress syndrome" (ARDS) as keywords. The search was further refined by selecting studies investigating the use of dilution methods to assess EVLW in ARDS or ALI. The authors used backward snowballing (i.e., scanning of references of retrieved articles and reviews).

Table 1: Different formulas for the calculations of ITBV reported in the current literature.

PiCCO monitor	ITBV = 1.25 × GEDV
Sakka et al. [13]	ITBV = 1.25 × GEDV − 28
Reuter et al. [14]	ITBV = 1.16 × GEDV + 97
Michard et al. [15]	ITBV = 1.10 × GEDV + 180

3. Results and Discussion

The measurement of EVLW has been under investigation for about 40 years with the first report of the use of EVLW in the clinical management of critically ill patients by Eisenberg and colleagues more than 20 years ago [12]. The bedside method used to measure EVLW was the double-indicator technique. This method requires the simultaneous injection of an intravascular dye indicator and a diffusible (cold saline) indicator. It is assumed that the dye will remain in the intravascular space and the cold temperature will be distributed throughout the thoracic cavity. Differences in the dilution curves allow the calculation of EVLW. The difference in the mean transit time (MTt) multiplied by the cardiac output determine the extravascular thermal distribution volume, that is, intrathoracic thermal volume (ITTV) via cold saline − intrathoracic blood volume (ITBV) via dye dilution = EVLW. This technique is cumbersome, time consuming, and has not been widely used.

The single-indicator method uses a thermal indicator to calculate EVLW. Cold saline is injected through a central venous catheter, and the thermistor tip on a femoral arterial catheter, measures the downstream change in temperature in the abdominal aorta. The investigators Sakka et al. were able to quantify the relationship between the ITBV and the global end diastolic volume (GEDV), that is, that total volume and the end of diastole within all four chambers of the heart [13]. The equation is ITBV = 1.25 × GEDV − 28.4 mL. Other investigators have confirmed a similar relationship between ITBV and GEDV [14, 15]. The derivation of EVLW using a single-indicator technique is described in Figure 1 and a more detailed description is available elsewhere [15]. The EVLW represents both interstitial and alveolar fluid. The intrathoracic thermal volume (ITTV) is the product of cardiac output and the MTt. The pulmonary thermal volume is the product of the cardiac output and the exponential downslope time. The difference between the ITTV and the ITBV is an estimate of the EVLW. The accuracy of this technique compares favorably with the gravimetric method, the gold standard test for EVLW [16, 17]. Various formulas relating ITBV to GEDV are reported in Table 1. Importantly, there are no significant differences between the values for ITBV derived from these formulas [18].

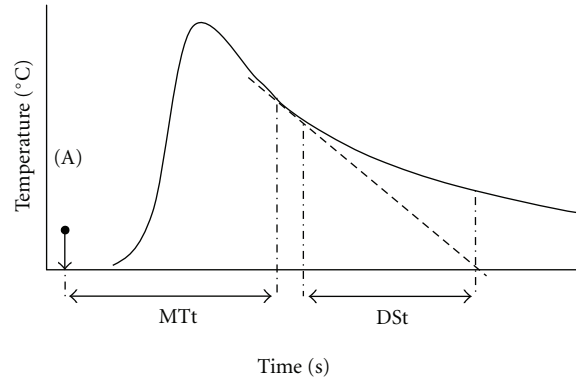

Figure 1: Thermodilution curves showing mean transit time (MTt) and downslope decay time (DSt) of the slope. The time point (A) represents the time of injection. The product of cardiac output and MTt equals the intrathoracic thermal volume. Multiplication of the cardiac output and the DSt equals the pulmonary thermal volume (PTV). The global end diastolic volume (GEDV) is equal to the ITTV − PTV. The intrathoracic blood volume = 1.25 × GEDV. The extravascular lung water (EVLW) is equal to the ITTV less the ITBV.

4. Distinguishing between Cardiogenic and Permeability Pulmonary Oedema

Evidence from several small studies suggests that the ratio of EVLW to ITBV may provide some clue to the cause of pulmonary oedema [19–21]. Early studies used the ratio of the EVLW and the volume of blood within the lungs, that is, the pulmonary blood volume to derive the pulmonary vascular permeability index [22–24]. More recently investigators have attempted to establish the diagnostic value of the EVLW/ITBV ratio [20, 25]. A high EVLW/ITBV ratio would support an increased permeability as the cause, whereas a low ratio would suggest hydrostatic pulmonary oedema. A small study of twenty mechanically ventilated patients by van der Heijden and Groeneveld explored the relationship between pulmonary leak index (PLI) for gallium labeled transferrin and EVLW/ITBV ratios before and after fluid loading in nonseptic patients [26]. The PLI refers to the transvascular transport rate of a protein bound radionuclide, such as ^{67}Ga-transferrin or ^{99m}technetium-albumin, measured by a bedside probe. A threshold EVLW/ITBV ratio of 0.23 had a positive predictive value of 39% and a negative predictive value of 82% for a high PLI. A similar study in sepsis-related ARDS/ALI found a statistically significant but weak relationship between EVLW and ITBV ($P = 0.045$, $r_s = 0.43$) [27]. These findings are unsurprising as the sensitivity and specificity of PLI in distinguishing cardiogenic and permeability pulmonary oedema is itself poor. The ITBV may be rapidly reduced when positive pressure ventilation is initiated limiting the interpretation of this ratio. These studies support earlier reports that highlight the potential value and some of the limitations of using EVLW/ITBV ration in trying to distinguish between hydrostatic and permeability pulmonary oedema. The EVLW/ITBV ratio remains an interesting physiologic concept and warrants further clinical enquiry.

5. Informing Fluid Therapy

Septic shock and ALI often coexist and require directed interventions. Fluid therapy is an intervention widely applied

to almost all critically ill patients and there is consensus that volume resuscitation should occur promptly [28, 29]. Concerns about restoring tissue perfusion must be balanced against the potential harms of volume excess. Simply, being volume responsive does not imply an improved outcome to the administration of volume, and there is some concern about the liberal use of fluids in critically ill patients [30]. A large randomized trial by the ARDS Clinical Trials Network compared liberal and conservative fluid strategies in patients with ALI/ARDS [31]. The 72-hour cumulative for the conservative group was 400 mL and 5100 mL in the liberal group. The study found no difference in mortality at 60 days (25.5% in the restrictive group versus 28.4 for the liberal group, $P = 0.3$). Patients in the conservative group showed an increase in ventilator-free days, reduced ICU stay, no increase in nonpulmonary organ failure, and a trend towards a reduced need for renal replacement therapy. A positive fluid balance in patients with ALI is associated with higher mortality in patients with ALI/ARDS [32]. While these studies did not measure EVLW, it may provide a rational way to monitor patients with ALI/ARDS. Indeed, more than 20 years ago, Eisenberg et al. compared protocol- (EVLW-) guided therapy to routine (pulmonary artery wedge pressure-guided) haemodynamic management in 48 critically ill patients [12]. The study reported a shorter time on mechanical ventilation as well as a lower mortality. The study also showed that restrictive fluid strategies could be safe and well tolerated in patients with ARDS. A follow-up study by Mitchell and colleagues enrolled 101 patients that to the EVLW- and wedge pressure-guided strategies [33]. The EVLW group had a lower positive fluid balance as well as less ventilator days and a shorter ICU stay.

EVLW has also been used to guide fluid therapy in a cohort of patients with subarachnoid haemorrhage and has been shown to be safe and reduced pulmonary complications [34].

ARDS is frequently associated with right heart dysfunction. It is estimated that up to 25% of patients with ARDS may develop acute cor pulmonale (ACP), the most severe form of right ventricular dysfunction [35]. In these patients, fluid administration may exacerbate right ventricular dilatation, worsening ACP. EVLW-guided therapy may offer a method to safely balance resuscitation against the potential harms of fluid excess.

6. Titrating PEEP

The consensus view about mechanical ventilation in patients with ALI is to use the appropriate level of PEEP to recruit collapsed lung while delivering small tidal volumes [36]. This simple intervention may have harmful effects on haemodynamic function and gas exchange, and the optimal PEEP has been the subject of substantial investigation [37]. Many techniques have been suggested to titrate the appropriate level of PEEP. These include increasing PEEP to achieve the maximum oxygenation, trading improvements in oxygen delivery against improvements in oxygenation, using pressure volume curves or dynamic stress indices or imaging techniques such as chest radiography and computed tomography [38]. The lack of effect of any of these techniques in large cohorts of patients may reflect the need for a more patient-centered approach. The application of PEEP may affect the measurement of EVLW by dilution methods as well as the actual amount of EVLW [39]. Increasing PEEP may reduce pulmonary vascular flow reducing the measured EVLW [39]. Increasing PEEP may also increase pulmonary flow to previously excluded areas, increasing the measured EVLW [40, 41]. Increasing PEEP may increase the actual EVLW by increasing central venous pressure, creating backward pressure on lymph flow [42]. A decreased pulmonary interstitial pressure may have a similar effect. Increasing PEEP may decrease actual EVLW by decreasing cardiac output, decreasing pulmonary capillary pressure. The application of PEEP may improve oxygenation without significantly changing EVLW. The mechanism in this situation is likely to be recruitment of atelectatic lung. The relationship between PEEP and EVLW remains unsettled and titrating PEEP to individual patients requires consideration of several variables. Comparing pre- and postintervention oxygenation, EVLW and EVLW/ITBV ratios may offer insight into whether the patient has recruited atelectatic lung, haemodynamic changes, pulmonary capillary permeability, and/or hydrostatic forces. This may help to individualize PEEP titration at the bedside.

7. Predicting Outcome

Prognostication is an important part of communicating with surrogates and in making decisions about treatment. Despite a wealth of knowledge about ALI and ARDS, prognostication remains difficult [43]. There is considerable overlap between the predictors of mortality in patients with ALI and the predictors of death in the general ICU patient [43]. Age, haematocrit, bilirubin, and 24-hour fluid balance have all been shown to useful clinical predictors from the ARDSNet study [43, 44]. More recently increased EVLW has been identified as a strong predictor or mortality in ALI. Sakka et al. performed retrospective analysis of 373 patients and showed that EVLW was higher in nonsurvivors compared with survivors (median: 14.3 mL/kg versus 10.2 mL/kg, resp., $P < 0.0001$) and predicted mortality independent of SAPS II or APACHE II score by regression modeling [45]. The study also identified a dose effect with mortality lowest in the group with EVLW < 7 mL/kg (<30%), intermediate in the groups <7–14 mL/kg (40%) and 15–20 mL/kg (60%), and highest in the group with EVLW > 20 mL/kg (80% mortality). A threshold of 15 mL/kg was able to discriminate survivors from nonsurvivors ($P = 0.002$). A small prospective study by Kuzkov and colleagues showed a significant correlation between increased EVLW and recognized markers of severity in ALI such as ling compliance, oxygenation ratio, and lung injury score [46]. A significant proportion of patients with ARDS are overweight and EVLW indexed to predicted body weight (PBW) compared with actual body weight (ABW) is higher (20.6 ± 4.6 versus 11.6 ± 1.9 mL/kg; $P = 0.002$) [47]. A 3-day mean EVLW > 16 mL/kg indexed to PBW

was found to predict death with 100% sensitivity and 86% specificity. A recent observational cohort study by Craig et al. showed that an elevated EVLW indexed to PBW measured within 48 hours of admission to ICU was significantly associated with mortality [48]. The median EVLW was 17.5 mL/kg (IQR 15.3–21.4) for non-ICU survivors and 10.6 mL/kg (IQR 9.5–15.4) for ICU survivors; $P < 0.0029$. The a odds ratio for death of EVLW indexed to PBW was 4.3 (confidence interval 1.5–2.9) per standard deviation increase, independent of oxygenation index, and APACHE II or SAPS II score. The argument has been that lung volumes are more closely correlated with height and gender than with actual body weight. Therefore, indexing EVLW to obese patients is likely to underestimate the severity of pulmonary oedema. An elevated EVLW indexed to PBW also predicts the development of multiorgan dysfunction syndrome (MODS) [49]. Data from small studies support the role of EVLW in predicting the clinical behavior during mechanical ventilation. High-frequency ventilation is better tolerated in patients with an EVLW > 15 mL/kg and pressure support better tolerated when the EVLW < 11 mL/kg [50, 51]. While the signal from these small, single center studies is encouraging, there is a lack of consensus about the definition of the normal values for EVLW or whether EWLV should be indexed to PBW or ABW.

8. Limitations of EVLW

It is estimated that up to one-third of patients with ALI/ARDS criteria do not have significant pulmonary oedema [9, 52, 53]. The mechanism for hypoxaemia in this group of patients may be due to atelectasis or consolidation in these patients. The diagnosis of ALI/ARDS on clinical criteria does not correlate well with autopsy findings [54]. EVLW may offer a reliable means of characterising ALI/ARDS by identifying those patients with increased pulmonary vascular permeability. This offers the prospect of a more homogenous group of patients that may benefit from interventions such as fluid restriction and diuresis and to recruit for further clinical trials. The measurement of EVLW may be altered by systematic or accidental errors of measurement. The single-indicator method relies on a predictable and constant relationship between the GEDV and the ITBV. Underperfusion that occurs pulmonary resection, pulmonary embolism, and pulmonary arterial occlusion may underestimate EVLW by about 10% [55, 56]. Experimental evidence suggests that this observation occurs only when vessels with a diameter >500 μm are occluded [57]. High cardiac output states may not allow sufficient time for equilibration with the extravascular distribution volume. Michard et al. studied the effect of cardiac index changes in critically ill patients in the range 1.9 L/min/m^2 to 7.1 L/min/m^2 as well as hyper- an hypovolaemic states but found no change in the relationship between GEDV and ITBV [15]. The presence of an intra-aortic balloon pump (IABP) renders continuous pulse contour analysis inaccurate but does not affect the accurate estimation of EVLW [58]. The same applies for the concomitant use of renal replacement therapy. EVLW calculation is accurate, provided that the vascular access catheter is not in the path of the indicator. A large aortic aneurysm may lead to underestimation of the EVLW and intracardiac shunts have unpredictable effects on the measured EVLW [59].

9. Conclusion

The use of thermodilution techniques to assess EVLW provides an accurate and readily accessible method at the bedside in critically ill patients. EVLW may have value in decision making about titrating PEEP, predicting clinical behavior during mechanical ventilation, guiding fluid therapy, and manipulating fluid balance and ultimately about prognostication.

References

[1] E. H. Starling, "On the absorption of fluids from the connective tissue spaces," *The Journal of Physiology*, vol. 19, no. 4, pp. 312–326, 1896.

[2] D. Lichtenstein, I. Goldstein, E. Mourgeon, P. Cluzel, P. Grenier, and J. J. Rouby, "Comparative diagnostic performances of auscultation, chest radiography, and lung ultrasonography in acute respiratory distress syndrome," *Anesthesiology*, vol. 100, no. 1, pp. 9–15, 2004.

[3] E. D. Sivak, B. J. Richmond, P. B. O'Donovan, and G. P. Borkowski, "Value of extravascular lung water measurement vs portable chest X-ray in the management of pulmonary edema," *Critical Care Medicine*, vol. 11, no. 7, pp. 498–501, 1983.

[4] P. Scillia, M. Delcroix, P. Lejeune et al., "Hydrostatic pulmonary edema: evaluation with thin-section CT in dogs," *Radiology*, vol. 211, no. 1, pp. 161–168, 1999.

[5] E. D. Sivak, B. J. Richmond, P. B. O'Donovan, and G. P. Borkowski, "Value of extravascular lung water measurement vs portable chest X-ray in the management of pulmonary edema," *Critical Care Medicine*, vol. 11, no. 7, pp. 498–501, 1983.

[6] M. O. Meade, R. J. Cook, G. H. Guyatt et al., "Interobserver variation in interpreting chest radiographs for the diagnosis of acute respiratory distress syndrome," *American Journal of Respiratory and Critical Care Medicine*, vol. 161, no. 1, pp. 85–90, 2000.

[7] G. D. Rubenfeld, E. Caldwell, J. Granton, L. D. Hudson, and M. A. Matthay, "Interobserver variability in applying a radiographic definition for ARDS," *Chest*, vol. 116, no. 5, pp. 1347–1353, 1999.

[8] P. D. Snashall, S. J. Keyes, B. M. Morgan et al., "The radiographic detection of acute pulmonary oedema. A comparison of radiographic appearances, densitometry and lung water in dogs," *The British Journal of Radiology*, vol. 54, no. 640, pp. 277–280, 1981.

[9] F. Michard, V. Zarka, S. Alaya, S. Sakka, and M. Klein, "Better characterization of acute lung injury/ARDS using lung water," *Chest*, vol. 125, no. 3, pp. 1166–1167, 2004.

[10] G. S. Martin, S. Eaton, M. Mealer, and M. Moss, "Extravascular lung water in patients with severe sepsis: a prospective cohort study," *Critical Care*, vol. 9, no. 2, pp. R74–82, 2005.

[11] A. B. J. Groeneveld and K. H. Polderman, "Acute lung injury, overhydration or both?" *Critical Care*, vol. 9, no. 2, pp. 136–137, 2005.

[12] P. R. Eisenberg, J. R. Hansbrough, D. Anderson, and D. P. Schuster, "A prospective study of lung water measurements during patient management in an intensive care unit," *American Review of Respiratory Disease*, vol. 136, no. 3, pp. 662–668, 1987.

[13] S. G. Sakka, C. C. Rühl, U. J. Pfeiffer et al., "Assessment of cardiac preload and extravascular lung water by single transpulmonary thermodilution," *Intensive Care Medicine*, vol. 26, no. 2, pp. 180–187, 2000.

[14] D. A. Reuter, T. W. Felbinger, K. Moerstedt et al., "Intrathoracic blood volume index measured by thermodilution for preload monitoring after cardiac surgery," *Journal of Cardiothoracic and Vascular Anesthesia*, vol. 16, no. 2, pp. 191–195, 2002.

[15] F. Michard, A. Schachtrupp, and C. Toens, "Factors influencing the estimation of extravascular lung water by transpulmonary thermodilution in critically ill patients," *Critical Care Medicine*, vol. 33, no. 6, pp. 1243–1247, 2005.

[16] J. C. Bock and F. R. Lewis, "Clinical relevance of lung water measurement with the thermal-dye dilution technique," *Journal of Surgical Research*, vol. 48, no. 3, pp. 254–265, 1990.

[17] T. Tagami, S. Kushimoto, Y. Yamamoto et al., "Validation of extravascular lung water measurement by single transpulmonary thermodilution: human autopsy study," *Critical Care*, vol. 14, no. 5, p. R162, 2010.

[18] F. Michard, "Bedside assessment of extravascular lung water by dilution methods: temptations and pitfalls," *Critical Care Medicine*, vol. 35, no. 4, pp. 1186–1192, 2007.

[19] X. Monnet, N. Anguel, D. Osman, O. Hamzaoui, C. Richard, and J. L. Teboul, "Assessing pulmonary permeability by transpulmonary thermodilution allows differentiation of hydrostatic pulmonary edema from ALI/ARDS," *Intensive Care Medicine*, vol. 33, no. 3, pp. 448–453, 2007.

[20] A. B. J. Groeneveld and J. Verheij, "Extravascular lung water to blood volume ratios as measures of permeability in sepsis-induced ALI/ARDS," *Intensive Care Medicine*, vol. 32, no. 9, pp. 1315–1321, 2006.

[21] J. Verheij, P. G. H. M. Raijmakers, A. Lingen, and A. B. J. Groeneveld, "Simple vs complex radionuclide methods of assessing capillary protein permeability for diagnosing acute respiratory distress syndrome," *Journal of Critical Care*, vol. 20, no. 2, pp. 162–171, 2005.

[22] A. B. J. Groeneveld, P. G. H. M. Raijmakers, G. J. J. Teule, and L. G. Thijs, "The 67Gallium pulmonary leak index in assessing the severity and course of the adult respiratory distress syndrome," *Critical Care Medicine*, vol. 24, no. 9, pp. 1467–1472, 1996.

[23] P. G. H. M. Raijmakers, A. B. J. Groeneveld, J. A. Rauwerda, G. J. J. Teule, and C. E. Hack, "Acute lung injury after aortic surgery: the relation between lung and leg microvascular permeability to 111indium-labelled transferrin and circulating mediators," *Thorax*, vol. 52, no. 10, pp. 866–871, 1997.

[24] P. G. H. M. Raijmakers, A. B. J. Groeneveld, G. J. J. Teule, and L. G. Thijs, "Diagnostic value of the gallium-67 pulmonary leak index in pulmonary edema," *Journal of Nuclear Medicine*, vol. 37, no. 8, pp. 1316–1322, 1996.

[25] A. B. J. Groeneveld, F. B. Plötz, and H. R. Van Genderingen, "Monitoring the permeability edema of ventilator-associated lung injury," *Critical Care Medicine*, vol. 33, no. 1, pp. 250–252, 2005.

[26] M. van der Heijden and A. B. J. Groeneveld, "Extravascular lung water to blood volume ratios as measures of pulmonary capillary permeability in nonseptic critically ill patients," *Journal of Critical Care*, vol. 25, no. 1, pp. 16–22, 2010.

[27] A. B. J. Groeneveld and J. Verheij, "Extravascular lung water to blood volume ratios as measures of permeability in sepsis-induced ALI/ARDS," *Intensive Care Medicine*, vol. 32, no. 9, pp. 1315–1321, 2006.

[28] E. Rivers, B. Nguyen, S. Havstad et al., "Early goal-directed therapy in the treatment of severe sepsis and septic shock," *The New England Journal of Medicine*, vol. 345, no. 19, pp. 1368–1377, 2001.

[29] S. M. Lin, C. D. Huang, H. C. Lin, C. Y. Liu, C. H. Wang, and H. P. Kuo, "A modified goal-directed protocol improves clinical outcomes in intensive care unit patients with septic shock: a randomized controlled trial," *Shock*, vol. 26, no. 6, pp. 551–557, 2006.

[30] F. Michard and J. L. Teboul, "Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence," *Chest*, vol. 121, no. 6, pp. 2000–2008, 2002.

[31] H. P. Wiedemann, A. P. Wheeler, G. R. Bernard et al., "Comparison of two fluid-management strategies in acute lung injury," *The New England Journal of Medicine*, vol. 354, no. 24, pp. 2564–2575, 2006.

[32] Y. Sakr, J. L. Vincent, and K. Reinhart, "High tidal volume and positive fluid balance are associated with worse outcome in acute lung injury," *Chest*, vol. 128, no. 5, pp. 3098–3108, 2005.

[33] J. P. Mitchell, D. Schuller, F. S. Calandrino, and D. P. Schuster, "Improved outcome based on fluid management in critically ill patients requiring pulmonary artery catheterization," *American Review of Respiratory Disease*, vol. 145, no. 5, pp. 990–998, 1992.

[34] T. Mutoh, K. Kazumata, M. Ajiki, S. Ushikoshi, and S. Terasaka, "Goal-directed fluid management by bedside transpulmonary hemodynamic monitoring after subarachnoid hemorrhage," *Stroke*, vol. 38, no. 12, pp. 3218–3224, 2007.

[35] A. Vieillard-Baron, J. M. Schmitt, R. Augarde et al., "Acute cor pulmonale in acute respiratory distress syndrome submitted to protective ventilation: incidence, clinical implications, and prognosis," *Critical Care Medicine*, vol. 29, no. 8, pp. 1551–1555, 2001.

[36] A. S. Slutsky, "Mechanical ventilation. American College of Chest Physicians' Consensus Conference," *Chest*, vol. 104, no. 6, pp. 1853–1859, 1993.

[37] G. D. Rubenfeld, "How much PEEP in acute lung injury," *Journal of the American Medical Association*, vol. 303, no. 9, pp. 883–884, 2010.

[38] L. Gattinoni, E. Carlesso, L. Brazzi, and P. Caironi, "Positive end-expiratory pressure," *Current Opinion in Critical Care*, vol. 16, no. 1, pp. 39–44, 2010.

[39] J. C. Myers, T. E. Reilley, and C. T. Cloutier, "Effect of positive end-expiratory pressure on extravascular lung water in porcine acute respiratory failure," *Critical Care Medicine*, vol. 16, no. 1, pp. 52–54, 1988.

[40] R. C. Allison, P. V. Carlile, and B. A. Gray, "Thermodilution measurement of lung water," *Clinics in Chest Medicine*, vol. 6, no. 3, pp. 439–457, 1985.

[41] P. V. Carlile, D. D. Lowery, and B. A. Gray, "Effect of PEEP and type of injury on thermal-dye estimation of pulmonary edema," *Journal of Applied Physiology*, vol. 60, no. 1, pp. 22–31, 1986.

[42] R. H. Demling, N. C. Staub, and L. H. Edmunds, "Effect of end expiratory airway pressure on accumulation of extravascular lung water," *Journal of Applied Physiology*, vol. 38, no. 5, pp. 907–912, 1975.

[43] C. R. Cooke, J. M. Kahn, E. Caldwell et al., "Predictors of hospital mortality in a population-based cohort of patients

with acute lung injury," *Critical Care Medicine*, vol. 36, no. 5, pp. 1412–1420, 2008.

[44] C. R. Cooke, C. V. Shah, R. Gallop et al., "A simple clinical predictive index for objective estimates of mortality in acute lung injury," *Critical Care Medicine*, vol. 37, no. 6, pp. 1913–1920, 2009.

[45] S. G. Sakka, M. Klein, K. Reinhart, and A. Meier-Hellmann, "Prognostic value of extravascular lung water in critically III patients," *Chest*, vol. 122, no. 6, pp. 2080–2086, 2002.

[46] V. V. Kuzkov, M. Y. Kirov, M. A. Sovershaev et al., "Extravascular lung water determined with single transpulmonary thermodilution correlates with the severity of sepsis-induced acute lung injury," *Critical Care Medicine*, vol. 34, no. 6, pp. 1647–1653, 2006.

[47] C. R. Phillips, M. S. Chesnutt, and S. M. Smith, "Extravascular lung water in sepsis-associated acute respiratory distress syndrome: indexing with predicted body weight improves correlation with severity of illness and survival," *Critical Care Medicine*, vol. 36, no. 1, pp. 69–73, 2008.

[48] T. R. Craig, M. J. Duffy, M. Shyamsundar et al., "Extravascular lung water indexed to predicted body weight is a novel predictor of intensive care unit mortality in patients with acute lung injury," *Critical Care Medicine*, vol. 38, no. 1, pp. 114–120, 2010.

[49] F. T. Chung, H. C. Lin, C. H. Kuo et al., "Extravascular lung water correlates multiorgan dysfunction syndrome and mortality in sepsis," *PLoS ONE*, vol. 5, no. 12, article e15265, 2010.

[50] J. Zeravik, U. Borg, and U. J. Pfeiffer, "Efficacy of pressure support ventilation dependent on extravascular lung water," *Chest*, vol. 97, no. 6, pp. 1412–1419, 1990.

[51] J. Zeravik and U. J. Pfeiffer, "Efficacy of high frequency ventilation combined with volume controlled ventilation in dependency of extravascular lung water," *Acta Anaesthesiologica Scandinavica*, vol. 33, no. 7, pp. 568–574, 1989.

[52] A. B. J. Groeneveld and K. H. Polderman, "Acute lung injury, overhydration or both?" *Critical Care*, vol. 9, no. 2, pp. 136–137, 2005.

[53] G. S. Martin, S. Eaton, M. Mealer, and M. Moss, "Extravascular lung water in patients with severe sepsis: a prospective cohort study," *Critical Care*, vol. 9, no. 2, pp. R74–82, 2005.

[54] A. Esteban, P. Fernández-Segoviano, F. Frutos-Vivar et al., "Comparison of clinical criteria for the acute respiratory distress syndrome with autopsy findings," *Annals of Internal Medicine*, vol. 141, no. 6, 2004.

[55] O. Godje, M. Peyerl, T. Seebauer, O. Dewald, and B. Reichart, "Reproducibility of double indicator dilution measurements of intrathoracic blood volume compartments, extravascular lung water, and liver function," *Chest*, vol. 113, no. 4, pp. 1070–1077, 1998.

[56] P. Rossi, M. Wanecek, A. Rudehill, D. Konrad, E. Weitzberg, and A. Oldner, "Comparison of a single indicator and gravimetric technique for estimation of extravascular lung water in endotoxemic pigs," *Critical Care Medicine*, vol. 34, no. 5, pp. 1437–1443, 2006.

[57] L. Oppenheimer, V. B. Elings, and F. R. Lewis, "Thermal-dye lung water measurements: effects of edema and embolization," *Journal of Surgical Research*, vol. 26, no. 5, pp. 504–512, 1979.

[58] M. Janda, T. W. L. Scheeren, J. Bajorat et al., "The Impact of intra-aortic balloon pumping on cardiac output determination by pulmonary arterial and transpulmonary thermodilution in pigs," *Journal of Cardiothoracic and Vascular Anesthesia*, vol. 20, no. 3, pp. 320–324, 2006.

[59] S. G. Sakka, C. C. Rühl, U. J. Pfeiffer et al., "Assessment of cardiac preload and extravascular lung water by single transpulmonary thermodilution," *Intensive Care Medicine*, vol. 26, no. 2, pp. 180–187, 2000.

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Review Article

Toward Intelligent Hemodynamic Monitoring: A Functional Approach

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Technology is now available to allow a complete haemodynamic analysis; however this is only used in a small proportion of patients and seems to occur when the medical staff have the time and inclination. As a result of this, significant delays occur between an event, its diagnosis and therefore, any treatment required. We can speculate that we should be able to collect enough real time information to make a complete, real time, haemodynamic diagnosis in all critically ill patients. This article advocates for "intelligent haemodynamic monitoring". Following the steps of a functional analysis, we answered six basic questions. (1) What is the actual best theoretical model for describing haemodynamic disorders? (2) What are the needed and necessary input/output data for describing this model? (3) What are the specific quality criteria and tolerances for collecting each input variable? (4) Based on these criteria, what are the validated available technologies for monitoring each input variable, continuously, real time, and if possible non-invasively? (5) How can we integrate all the needed reliably monitored input variables into the same system for continuously describing the global haemodynamic model? (6) Is it possible to implement this global model into intelligent programs that are able to differentiate clinically relevant changes as opposed to artificial changes and to display intelligent messages and/or diagnoses?

1. Introduction

Thirty years ago, tracking the heart rate (HR) was the only means of automatic, continuous, real-time and noninvasive, hemodynamic monitoring. A more elaborate level of monitoring was necessarily invasive and required a central venous catheter for continuous pressure (CVP) assessment. A third level was based on the placement of a pulmonary artery catheter (PAC) and of an arterial line for continuous pulmonary artery pressure (PAP) and systemic arterial pressure (SAP) curve recording.

From this traditional data monitoring, a complete haemodynamic diagnosis was obtained on demand by the measurement of a set of additional variables, such as cardiac output (CO), pulmonary wedge pressure (PWP), blood lactate, haemoglobin concentration (Hb), arterial haemoglobin oxygen saturation (SaO_2), and mixed venous haemoglobin oxygen saturation (SvO_2). From these elementary data, several other variables were derived such as pulmonary and systemic resistance to flow (PVR and SVR), right and left ventricles stoke work (RVSW and LVSW), and tissue oxygenation indices: oxygen arterial and venous content (CaO_2 and CvO_2), oxygen delivery (DO_2), arteriovenous oxygen differences (AVD), tissue oxygen extraction (EO_2), and oxygen consumption (VO_2).

Therefore a complete haemodynamic analysis was done only in a small proportion of patients, and when the medical staff had the time and inclination. This resulted sometimes in significant delays between an event and its diagnosis and therefore any treatment required.

Today, more haemodynamic variables are monitored continuously by less invasive means than before; for instance using pulse contour CO, as compared to traditional invasive discontinuous bolus thermodilution. We can speculate that we are now able to collect enough real-time information continuously in order to make a complete, real-time, haemodynamic diagnosis. It implies not only continuous data recording but also continuous analysis using artificial intelligence. This is what we call "intelligent haemodynamic monitoring". In the engineering industry, a functional analysis system

technique (FAST) is used in the conception and the development of a product. It would be helpful to clinicians if they share with engineers the same fundamental approach. This is a prerequisite for reinforcing the way industry and clinicians are collaborating for the benefit of our patients. Basically, we must answer three questions: when, why, how?

When is easy: continuously, real time.

Why? Because patients are in a severely compromised state, there is sudden and large variability in their cardiovascular status and we speculate that continuous, real-time, monitoring with appropriate alarm settings will minimize the delay between an event and its appropriate treatment, leading to better outcome.

How, is the most difficult question to answer. We suggest a functional analysis as follows.

(i) What is the actual best theoretical model for describing haemodynamic disorders?

(ii) What are the needed and necessary input/output variables for describing this model?

(iii) What are the specific quality criteria and tolerances for collecting each input variable?

(iv) Based on these criteria, what are the validated available technologies for monitoring each input variable, continuously, real time, and if possible non-invasively?

(v) How can we integrate all the needed reliably monitored input variables into the same system for continuously describing the global haemodynamic model?

(vi) Is it possible to implement this reliably described haemodynamic model into intelligent programs able to differentiate clinically relevant changes versus artificial changes and to display intelligent messages and/or diagnoses?

2. Functional Approach

2.1. What Is the Actual Best Model for Describing Hemodynamic Disorders. The semantic frames we are using today for classifying haemodynamic disorders are still derived from the discontinuous measurements available early in critical care medicine development. From normal or abnormal ranges of CVP, PCWP, CO, and SAP, we are still defining diagnostic terms such as hypovolaemic, cardiogenic, obstructive or hyperdynamic shock from which we infer specific therapeutic interventions. However, these diagnostic categories are simplistic, lead to a loss of information, and may not trigger all necessary treatment. Integrating new continuously monitored variables is an opportunity to update our reasoning processes, based on more robust models of haemodynamic disorders. Doing this, we must avoid falling from Charybdis into Scylla and distorting the haemodynamic reality in order to fit in with available electronic languages or with new artificial variables developed by the industry in their efforts to find complete solutions by the use of one single technology.

The best theoretical model of shock for monitoring purposes would be that one giving a complete and comprehensive description of all possible pathological processes observed in clinical practice and for which evidence is provided. At this level of our analysis, we must only consider the physiological principles. Practical limitations will be considered afterwards, in an appropriate step of the functional analysis.

Within this scope, a haemodynamic physiologic and pathologic model has been developed for a complete computerized haemodynamic diagnosis in the 1990's [1, 2]. In this model, all mechanisms of shock are supposed to stem from tissue oxygen demand outstripping oxygen supply. A global oxygen consumption (VO_2) below the needs ($^nVO_2$) is consequently the best way to describe a macrocirculation disorder [3, 4]. This model, established by a panel of experts [2] from basic physiology, has been validated by the evidence that modelled variables have the highest prognostic value as compared to other traditional elementary and derived variables [1]. In addition, the diagnostic categorizations based on this model have been shown to be at least equivalent to that of experienced intensivists [2, 5]. We can also consider that studies showing an improved outcome when DO_2 was rapidly increased to cover estimated needs is indirect proof of validity of this model [6]. The principles are as follows. Practical examples can be found and/or created online (http://www.hemodyn.com/).

As seen above, shock is defined by

$$VO_2 < {}^nVO_2 \text{ or } \frac{VO_2}{{}^nVO_2} < 1. \tag{1}$$

Since $VO_2 = CO \times AVD$, we can estimate the required values of CO and AVD for reaching a given value of $^nVO_2$, for each specific patient, at a specific moment in time. So now, we can express this as

$$^nVO_2 = {}^nCO \times {}^nAVD. \tag{2}$$

Then (1) can be reformulated as

$$\frac{VO_2}{{}^nVO_2} = \left\{\frac{CO}{{}^nCO}\right\} \times \left\{\frac{AVD}{{}^nAVD}\right\}. \tag{3}$$

Since $DO_2 = CO \times CaO_2$ and $EO_2 = AVD/CaO_2$, the formula (3) can also be formulated as

$$\frac{VO_2}{{}^nVO_2} = \left\{\frac{DO_2}{{}^nDO_2}\right\} \times \left\{\frac{EO_2}{{}^nEO_2}\right\}, \tag{2 bis}$$

where $^nDO_2$ and $^nEO_2$ are the needed values of DO_2 and EO_2 to reach $^nVO_2$

From (3) we can see that shock, defined by $VO_2 < {}^nVO_2$, can be the result of a circulatory disorder ($CO < {}^nCO$) or a tissue disorder ($AVD < {}^nAVD$), or both, or insufficient compensation of one arm by the other. Since CaO_2 is derived schematically by $Hb \times 1.34 \times SaO_2$, it is immediately clear from (2 bis) that tissue hypoxia may occur due to (1) excessive demand and/or (2) insufficient CO, (3) insufficient SaO_2, (4) insufficient Hb, and (5) insufficient EO_2 (Figure 1). Therefore, the traditional clinical diagnostic categorisation of

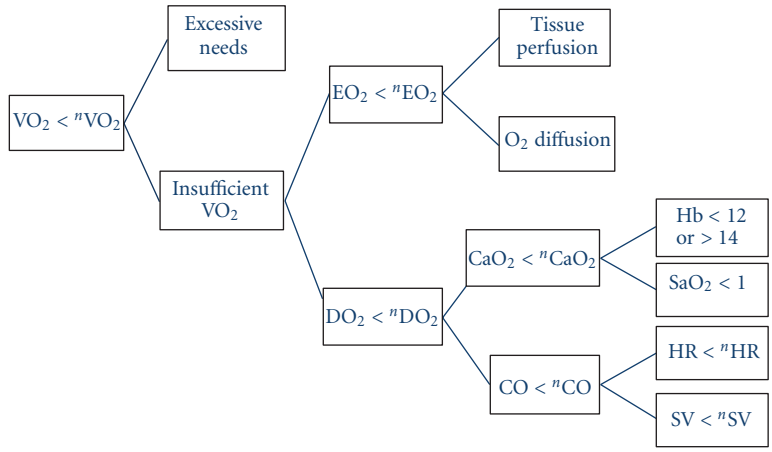

Figure 1: Root algorithm for representing the global hemodynamic model. The model gives priority to the higher box as compared to the lower. For example at the first step, the algorithm recommend decreasing excessive needs before looking at improving VO_2.

shock that referred mainly to mechanisms 2, 4, and 5, appear artificial and incomplete.

From this initial root, the model may be enriched as seen in Figure 2, based on the same principles, by comparing an actual value with a needed or minimum value for reaching adequate VO_2 to cover needs.

In this model, there is no normal or abnormal variable range. An adequate value is that one that allows compensation for the insufficiency of one or several other variables. Adequate limits can be eventually introduced into the model if other pathophysiological processes are involved. For example, there is no theoretical risk in decreasing EO_2 until needed EO_2 is reached while increasing CO or Hb up to very high values may be limited by myocardial ischemia or rheological impairment.

Following the initial root (Figure 1), the various mechanisms of shock may be subsequently analysed. Figure 2 continues the root algorithm when $SV < {}^nSV$ (bottom right box of the Figure 1). Similarly an algorithm is described for each box of Figure 1. The basic principles are maintained in the secondary algorithms.

In Figure 2 we can see that the priority (higher lines) is still given to metabolic equilibrium at lower cost. First by restoring the coronary flow if necessary, then by decreasing the metabolic demand, finally by increasing the cardiac power first by filling, then if really necessary by inotropic support.

At each step (boxes in the figures), the best variables for answering the question and reaching the objective can be updated according to any recent developments and to the state of the art. For example, in Figure 1, tissue perfusion can be analysed from diuresis, brain activity, the StO_2, the local capillary flow, or nay other indicator to be invented. In Figure 2, right ventricle (RV) filling may be analysed by monitoring and targeting adequate values of right atrial pressure (RAP), RV end diastolic volume, pulmonary pulse pressure variation, or any other validated variable. Therefore, at each step of the model, we can choose between different variables assessing the same physiologic concept, according to the specific monitoring tools used for a given patient. Nevertheless, this implies knowing exactly which amount of uncertainty each variable introduces into the model.

This model is limited by two mechanisms. First, conformance, a self-limiting oxygen requirement in case of tissue hypoxia may lead to a perception of an acceptable VO_2 that may in fact be insufficient. Second, this model investigates only the macrocirculation. An acceptable global VO_2 may hide important tissue heterogeneity. However, a conformance can be suspected by repeated measurements which is the purpose of a continuous monitoring and even though stabilizing the macro circulation is not the last word in haemodynamics, it is a prerequisite. Microcirculation cannot be optimized without stabilizing the macro circulation first. Therefore a model based on global tissue hypoxia is a sound basis for macrohemodynamic monitoring.

Other decision trees have been suggested that may be considered as suitable models for haemodynamic monitoring. However, none of them have been clinically validated and most of them have been developed from one or several variables proposed by industry to optimise the usefulness of a specific device [7]. A validated model strictly based on physiological knowledge, independent of actual technical issues, like the one we developed, is more likely to highlight the actual limitations and to help instigate the appropriate research.

2.2. What Are the Needed and Necessary Input/Output Variables for Describing This Model and Detecting Deterioration? Once a global model has been described, the input and output variables are then clearly identified. Consensus on the definition of these terms is vital, otherwise, the reproducibility of the therapeutic actions based on the model would be poor.

However, due to various reasons, including the choice of monitoring and/or actual technological limitations, one or several needed input variables may be unknown, or lacking, or assessed discontinuously. In these situations, it is important to still fit as closely as possible with the model despite

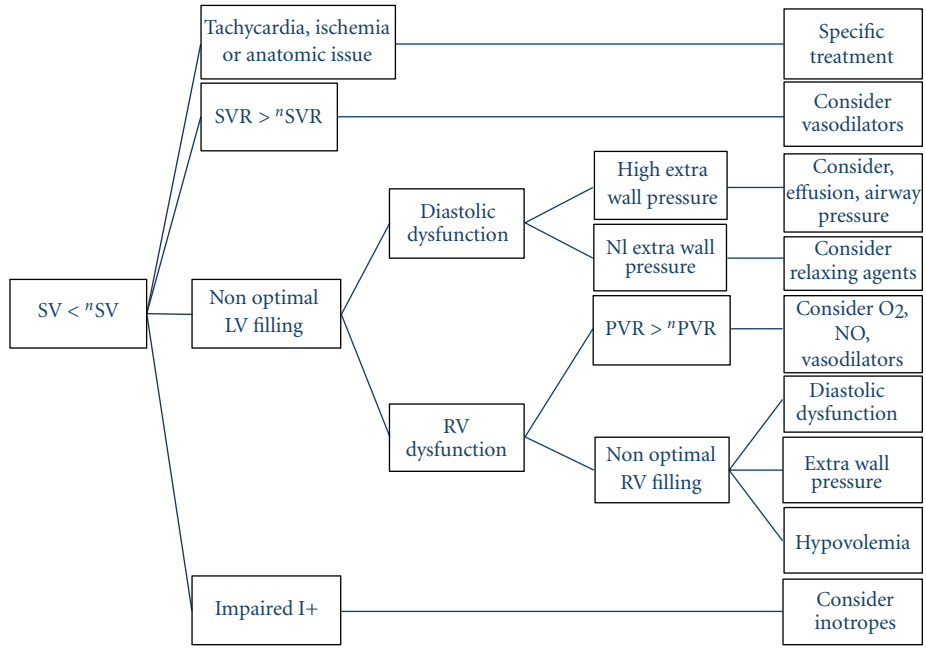

Figure 2: Subsequent algorithm dedicated to SV analysis. The needed SVR is that specific value of SVR allowing the generation of the minimum blood pressure (usually set at a mean value of 65 mmHg) with the needed CO. Similarly for needed PVR.

the bias introduced by the missing input data. There are theoretically three solutions. First, it is sometimes possible to find a surrogate of a given input variable assuming that the information provided is close. This is the case for example replacing SvO_2 by the central venous O_2 saturation ($ScVO_2$) or SaO_2 by the pulse oximetry (SpO_2) or total peripheral resistance instead of SVR when right aerial pressure is missing. Second, it is possible to give a fixed value to a given variable. For example, we may enter in the model directly at the level shown in Figure 2, assuming that the needed SV is the normal SV as a function of age and gender since the adaptative mechanisms of CO to needs are mostly resulting from a regulation of the heart rate. Third, it is possible to estimate a continuous variable from discontinuous clinical or paraclinical analysis. For example, VO_2 is often not monitored and VO_2 needs unknown. Consequently $VO_2/{}^nVO_2$ ratio <1 is suspected by the presence of clinical signs of shock or by an increase in blood lactate over time. Alternatively, a change in VO_2 needs (therefore translated to CO and EO_2 needs) can, be estimated by age, gender, body size, body temperature and/or empiric estimation of the change in metabolic needs due to underlying or associated pathologies. In any case, if we restrict our analysis to a part of the global model, we must assume that the blind part is fixed and given an approximate value. The reliability of the model is therefore reduced.

2.3. What Are the Specific Quality Criteria and Tolerance for Each Input Variable? The quality criteria and tolerance for the CO monitoring have been reviewed recently. [8, 9] The same effort must be done for each input variable of the model. Basically these criteria are very similar for all quantitative variables.

(1) The accuracy is how close the value is to a gold standard. It is estimated by the mean difference (bias) with the true value given by the gold standard.

(2) The linearity is the capability of maintaining constant the ratio between the physiologic signal and the electric output signal. Therefore the bias is constant. It can be verified by comparing the regression curve of the bias with the identity line.

(3) The precision is the ability to indicate the same value when the physiologic signal is stable. In other words, it is the variation due to random error in the signal processing. It can be estimated by the standard deviation/mean value when the physiologic signal is stable. The least minimum significant change (smallest change indicating a real change) is a direct consequence of precision.

(4) The resolution is the smallest change that the device can detect.

(5) The stability is the capability of maintaining the preceding quality criteria unchanged during time (without drift).

(6) The measuring range is the boundaries of value where the preceding quality criteria are found acceptable

(7) The responsiveness is the delay between a real change in the physiologic signal and a change greater than the least minimum significant change in the observed value. Coupled with the linearity, it determines the accuracy of the amplitude response.

The six first quality criteria are common to all measurement and monitoring tools. The seventh, time-dependent quality criteria, is specific to monitoring devices.

For each quality criteria, it is important to determine the tolerance, that is, what is the allowed amount of variation from the exact value. Ideally, tolerance must be determined from clinical requirements, dependent on the way the variable is implemented in the model. However, we are obliged to consider the actual technological issues. Thus a 20% tolerance is seen as actually acceptable for CO while it is 4% for the haemoglobin concentration and 2% for the haemoglobin saturation. However, the accumulated effect of different tolerances may lead to poor performance. For example, a tolerance of 20% in accuracy for CO monitoring plus a tolerance of 5 minutes in time response, plus a tolerance of 10% in the linearity plus a tolerance of 10% in stability may result in the absence of detection of a transient 30% CO decrease. To study the impact of cumulated tolerances on a monitored variable, it can be useful to determine what is a clinically relevant change of this variable and to measure the sensitivity and the specificity of a given device to detect these clinically relevant changes.

2.4. Based on These Criteria, What Are the Validated Available Technologies for Monitoring Each Input Variable, Continuously, Real time, and If Possible NonInvasively? Full validation of quality criteria below entails several considerations.

Choice of the Patient Population. A validation study must be applicable to all ICU patients. The haemodynamic profiles of sepsis and cardiac surgery are very different A useful device must provide accurate and precise data in all of these circumstances or extremes and this must be taken into account during the design of the validation studies. A monitoring device is also designed to detect and track changes in a variable over time. This can best be performed by building into the protocol an intervention that should on its own change the monitored variable.

Choice of the Reference Method. A monitoring system is typically a real-time, automatic, and continuous analyzer. An ideal device should provide good data from both snapshot measurements and continuous monitoring. Any validation study therefore needs to incorporate both of these factors into its design, especially with respect to its choice of a gold standard. A gold standard is most often lacking in clinical practice and we are obliged to consider simply a reference technology. However, few technologies even when they are considered as a reference method have fulfilled all the quality criteria listed above. Therefore, It may be necessary to choose a different reference method for studying separately each quality criteria.

Data Acquisition Method. A completely automatic continuous data recording technique should be preferably utilized for both the reference method and the studied technology in order to avoid errors when collecting large numbers of data points and also to limit any interobserver variability. It is preferable to collect raw data that has not been time-averaged by the device, in order to minimize the smart averaging and the smoothing effect used in many modern technologies. The rationale behind this is that the better the raw signal, the better the result will be after final averaging. As mathematically predicted, averaging more data decreases the variability but not the accuracy [10]. It must not be forgotten, however, that the devices will be ultimately used according to the data that they display, which quite often will be different to the raw numbers. How it affects the validation in the subsequent analysis must be explained and described in detail.

Data Acceptability. Before analysing the data collected in the fashion described above, it is important to validate the data. This requires an independent assessor who is blind to the choice of monitoring technology assessing the data. Periods of time when the patients are agitated, when one or both systems became disconnected, or periods of time where there is clear evidence of a situation leading to artefact can be deleted. This is a critical step of the validation that can be altered by subjective choices.

Data Segmentation. The monitoring trend line of a given variable can be schematically divided into periods of unchanged, increasing, or decreasing value. Fulfilling the criteria of quality determined above requires studying these different periods of time separately in order to minimize the physiological variability. Easy database segmentation can be performed using the trend line slope of the monitored variable. The inflexion point between two consecutive slopes may be automatically determined using the minimum sum of residuals for the two segments proposed by John-Alder [11].

Few technologies have been extensively studied using the quality criteria listed above [12]. We can consider that this has been achieved satisfactorily only for temperature and HR monitoring and for Hb, SaO_2, SvO_2, fand lactate measurements. Blood pressure monitoring (RAP, PAP, SAP) with actual transducers, appropriate lines, and filtering may be considered acceptable if properly maintained and positioned. SvO_2 and $ScvO_2$ monitoring using infrared spectroscopy may also be considered acceptable if properly positioned, flushed, and recalibrated.

All other monitoring variables have various degrees of limitations regarding the listed quality criteria, especially CO, SaO_2, Hb, lactate, ventricle filling and contractility indices, tissue perfusion indices. However, a complete analysis of these imitations is a prerequisite before using these variables in intelligent hemodynamic monitoring. The cumulative effects of these limitations may lead to poor results.

2.5. How Can We Integrate All of the Needed Reliably Monitored Input Variables on the Same System for Continuously Describing the Hemodynamic Model? Different companies currently develop integrating systems. But the reliability of the different variables provided by the same company may not be optimal. The best chance would be given by integrating a maximum number of reliable variables coming from different devices manufactured by different companies.

It is a challenge for scientific societies such as the ESICM to encourage such developments.

2.6. Is It Possible to Implement This Reliably Described Haemodynamic Model into Intelligent Programs Able to Differentiate Significant Changes versus Artifactual Changes and to Display Intelligent Messages and/or Diagnosis? This still requires a proper solution. An available intelligent program developed for analysing snapshot measurements [1, 2, 5] can be a basis for comparing trends. Including automatic trend lines in a reasoning process instead of validated measurements requires that artefacts be filtered out. It is also necessary to determine the time sampling to avoid continuous instantaneous diagnostic changes with no practical use. Once this will have been done, we will be ready to check if this type of monitoring is likely to increase the speed and appropriateness of therapeutic interventions and to improve outcome.

3. Conclusion

No matter how sophisticated and advanced the integrated monitoring system is in an intensive care unit, its ability to detect that a patient is deteriorating will still depend on the quality of the staff in the critical care unit and their ability to work as a team. More sophisticated monitoring should not be used at the expense of reducing staff/patient ratios but rather to enhance the ability of the staff to manage patients. The procurement of an appropriate clinical information system where there is none should also be high on the wish list to help collect the many direct and indirect variables of patient data and allow clinical decision support analysis. It is the task of industry to maximise the information provided by their technology. It is the task of the medical community to describe the ideal tool they need.

References

[1] P. Squara, D. Journois, J. F. Formela, B. Schremmer, J. F. Dhainaut, and G. Bleichner, "Value of elementary, combined, and modeled hemodynamic variables," *Journal of Critical Care*, vol. 9, no. 4, pp. 223–235, 1994.

[2] P. Squara, J. F. Dhainaut, M. Lamy et al., "Computer assistance for hemodynamic evaluation," *Journal of Critical Care*, vol. 4, no. 4, pp. 273–282, 1989.

[3] P. Squara, "Matching total body oxygen consumption and delivery: a crucial objective?" *Intensive Care Medicine*, vol. 30, no. 12, pp. 2170–2179, 2004.

[4] J. Vincent, "The VO_2/DO_2 relationship," in *Functional Hemodynamic Monitoring*, M. Pinsky and D. Payen, Eds., pp. 251–258, Springer, Berlin, Germany, 2005.

[5] P. Squara, E. Fourquet, L. Jacquet et al., "A computer program for interpreting pulmonary artery catheterization data: results of the European HEMODYN resident study," *Intensive Care Medicine*, vol. 29, no. 5, pp. 735–741, 2003.

[6] J. W. Kern and W. C. Shoemaker, "Meta-analysis of hemodynamic optimization in high-risk patients," *Critical Care Medicine*, vol. 30, no. 8, pp. 1686–1692, 2002.

[7] B. Vallet, E. Futier, and E. Robin, "Tissue oxygenation parameters to guide fluid therapy," *Transfusion Alternatives in Transfusion Medicine*, vol. 11, no. 3, pp. 113–117, 2010.

[8] P. Squara, M. Cecconi, A. Rhodes, M. Singer, and J. D. Chiche, "Tracking changes in cardiac output: methodological considerations for the validation of monitoring devices," *Intensive Care Medicine*, vol. 35, no. 10, pp. 1801–1808, 2009.

[9] P. Squara and J. D. Chiche, "Note technique: la validaion des outils de monitorage du débit cardiaque," *Reanimaton*, vol. 20, pp. 129–137, 2011.

[10] A. Singh, R. Juneja, Y. Mehta, and N. Trehan, "Comparison of continuous, stat, and intermittent cardiac output measurements in patients undergoing minimally invasive direct coronary artery bypass surgery," *Journal of Cardiothoracic and Vascular Anesthesia*, vol. 16, no. 2, pp. 186–190, 2002.

[11] H. B. John-Alder and A. F. Bennett, "Thermal dependence of endurance and locomotory energetics in a lizard," *The American journal of physiology*, vol. 241, no. 5, pp. R342–R349, 1981.

[12] P. Squara, D. Denjean, P. Estagnasie, A. Brusset, J. C. Dib, and C. Dubois, "Noninvasive cardiac output monitoring (NICOM): a clinical validation," *Intensive Care Medicine*, vol. 33, no. 7, pp. 1191–1194, 2007.

[13] PACT module ESICM on Technology Assessment updated 2010 by Cockings, Jonas, Waldmann (ESCIM website).

[14] M. Jonas and C. S. Waldmann, "Health technology assessment," *Oxford Desk Reference Critical Care*, pp. 574–575, 2008.

[15] M. Jonas, C. Waldmann, and M. Imhoff, "Technology assessment and procurement: "monitoring the monitor"," in *Controversies in Intensive Care Medicine*, Kuhlen, Moreno, Ranieri, and Rhodes, Eds., pp. 463–471, Medizinish Wissenschaftliche Verlagsgesellschaft, 2008.

[16] Computer assistance for hemodynamic evaluation, http://www.hemodyn.com/.