BioMed Research International

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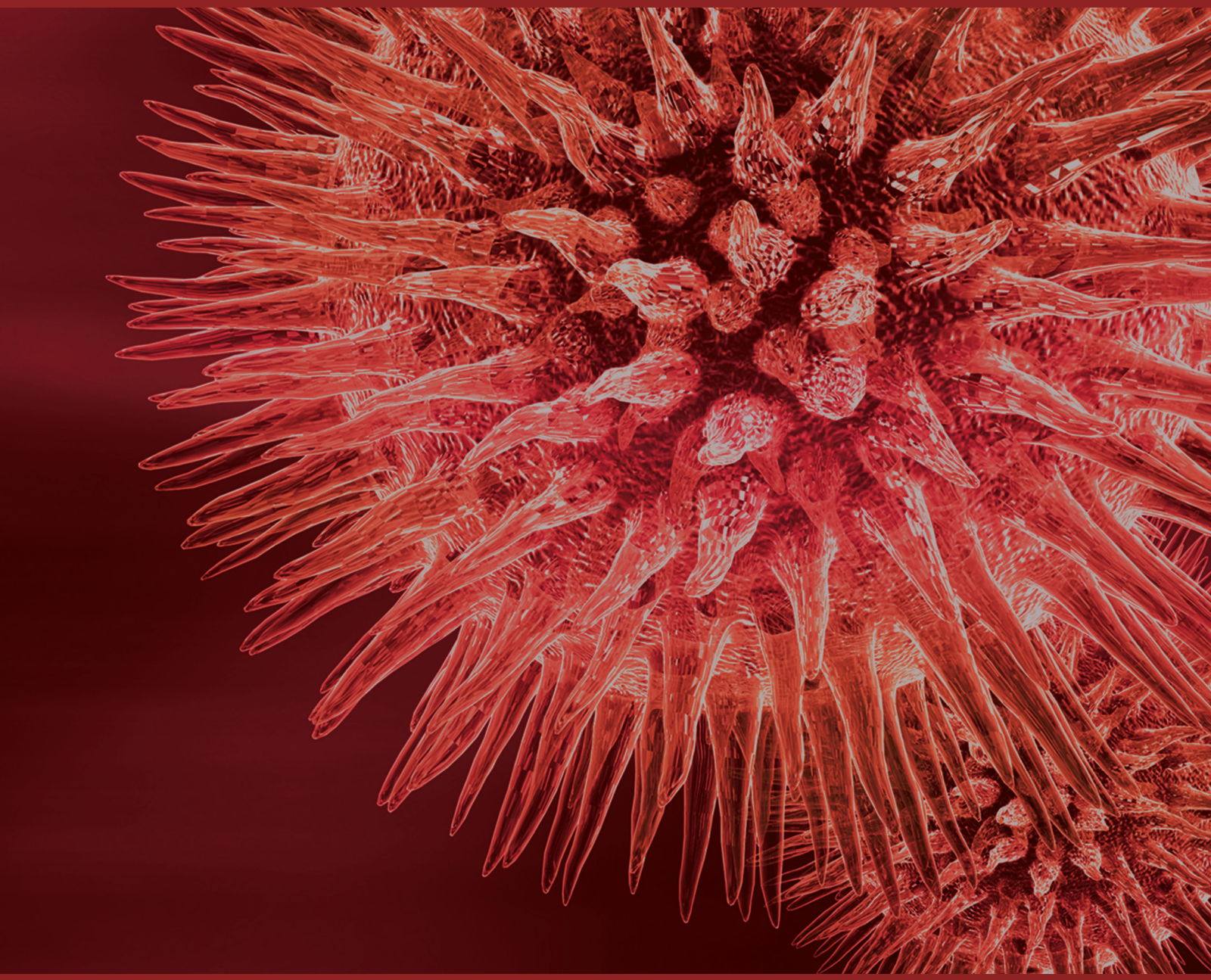
Guest Editors: Francesco Nicolini, Massimo F. Piepoli, Giulio Agnetti, and Giuseppe Siniscalchi



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Editorial

Alternatives to Transplantation in the Treatment of Heart Failure: New Diagnostic and Therapeutic Insights

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The aim of our current special issue was to present a series of original researches and reviews on recent advances in the diagnosis, medical therapy, and surgical approaches of heart failure.

As reported in the introductive review of Agnetti et al., cardiovascular disease is the leading cause of mortality in the US and in westernized countries with ischemic heart disease accounting for the majority of these deaths. Paradoxically, the improvements in the medical and surgical treatments of acute coronary syndromes are leading to an increasing number of "survivors" who are then developing heart failure. Despite considerable advances in its management, the gold standard for the treatment of end-stage heart failure patients remains heart transplantation. Nevertheless, this procedure can be offered only to a small percentage of patients who could benefit from a new heart due to the limited availability of donor organs. The authors reported in this comprehensive review the evaluation of the safety and efficacy of innovative approaches in the diagnosis and treatment of patients refractory to standard medical therapy and excluded from cardiac transplantation lists.

Among the studies included in this special issue, two of them investigated specific pathogenic aspects of heart failure. M. Kunin et al. studied the role of proinflammatory cytokines in congestive heart failure. In particular the authors evaluated the effect of peritoneal dialysis used in the long-term management of these patients on the peripheral-circulating levels of these cytokines. Interestingly, they found that peritoneal dialysis treatment caused a reduction in circulating inflammatory cytokines levels along with improvement in plasma markers of inflammation in patients with refractory chronic heart failure, concluding that this effect may be partly responsible for the efficacy of peritoneal dialysis for refractory heart failure.

It is described that heart failure is accompanied by the development of an imbalance between oxygen- and nitric oxide-derived free radical production leading to protein nitration. To cast further light on this issue, A. Cabassi et al. investigated the relationship between plasma myeloperoxidase-related chlorinating activity, ceruloplasmin, and ferroxidase I and nitrosative stress and inflammatory, neurohormonal, and nutritional biomarkers in heart failure patients. This elegant study supported the conclusions that plasma myeloperoxidase chlorinated activity is increased in elderly patients who suffer from chronic heart failure and positively associated with ceruloplasmin and inflammatory, neurohormonal, and nitrosative parameters, suggesting a key role in heart failure progression.

A major focus of studies on acute heart failure is the need for methods that allow the early detection of hemodynamic variables that can be a key prognostic role after cardiac surgery. F. Corradi et al. in their study investigated

the Renal Doppler Resistive Index as a marker of oxygen supply and demand mismatch in 61 postoperative cardiac surgery patients. Interestingly, by multivariate analysis, Renal Doppler Resistive Index was significantly correlated with mixed-venous oxygen saturation, suggesting that, in mechanically ventilated patients after cardiac surgery, it could be used as a marker of early vascular response to tissue hypoxia.

We must not forget that there are many patients suffering from heart failure secondary to extracardiac diseases. Among the causes of heart failure, an important place is held by cardiotoxicity due to antineoplastic treatments that has emerged as a clinically relevant problem as a consequence of the relevant improvement of survival after cancer. In the last decade recent advances have emerged in clinical and pathophysiological aspects of left ventricular dysfunction induced by the most widely used anticancer drugs. M. Molinaro et al., in their comprehensive review entitled "Recent Advances on Pathophysiology, Diagnostic and Therapeutic Insights in Cardiac Dysfunction Induced by Antineoplastic Drugs," have particularly examined the role of early, sensitive markers of cardiac dysfunction, in order to predict this form of cardiomyopathy before left ventricular ejection fraction is reduced. It seems actually that this is increasingly important issue, along with the evaluation of novel therapeutic and cardioprotective strategies, to protect cardiooncologic patients from the development of congestive heart failure. As reported by A. Adegunsoye et al., there are also a consistent number of patients who die due to right heart failure and pulmonary hypertension secondary to fibrotic lung diseases. Significant factors which appear to play a role in the mechanism of progression of right heart dysfunction include chronic hypoxia, defective calcium handling, hyperaldosteronism, pulmonary vascular alterations, cyclic strain of pressure and volume changes, elevation of circulating TGF-β, and elevated systemic NO levels. The authors have reported an exhaustive review of novel therapeutic strategies for reducing right heart failure associated mortality in fibrotic lung diseases, because only "an early, effective and individualized therapy may prevent overt right heart failure in fibrotic lung disease leading to improved outcomes and quality of life."

Another major focus of studies on acute heart failure is related to the evaluation of new surgical alternatives to transplantation or new systems or new materials available for future cardiac assist devices. In this special issue the review of J. Anand et al. explores the evolution of mechanical circulatory support and its potential for providing long-term therapy, which may address the limitations of cardiac transplantation. The innovation progresses have led to a solution of current challenges involving device complications. Moreover outcomes continue to improve and further data from both small and large registries help to advance evidence-based practices: thus patients in the most advanced stages of heart failure appear to have more hope than ever before. On the other hand the high costs, expanding indications, and rapidly increasing number of devices implanted will ultimately require important decisions to be made on the part of society, clinicians, and administrative agencies in order to establish the potential amount of economic resources to spend on this expensive, yet effective, therapy. Patient selection will remain paramount, although a very large population of patients will have the potential to benefit.

In particular, K. Unthan et al. reported a study on the design and evaluation of a fully implantable control unit for blood pumps. It is well known that pneumatic devices sufficiently supply the patients with blood flow, although the patient's quality of life is limited by the percutaneous pressure lines and the size of the external control unit. General requirements for any implantable control unit are defined from a technical and medical point of view: need for a Transcutaneous Energy Transmission, autonomous operation, safety, geometry, and efficiency. The authors described the development of the control unit of the ReinHeart, a fully implantable Total Artificial Heart that, in validation tests, is demonstrated to be a stable operation with a promising good efficiency. Finally P. Morillas-Sendín et al. assessed the effect of sevoflurane and propofol on organ blood flow in a porcine model with a left ventricular assist device. The authors demonstrated that, compared with propofol, sevoflurane increases blood flow in the brain, liver, and heart after implantation of a left ventricular assist device under conditions of partial support, giving interesting indications for the intensive pharmacological care of these high-risk patients.

The modern approach to the diagnosis and treatment of heart failure is multidisciplinary and should be based on a close collaboration among researchers, clinicians, and cardiac surgeons particularly given that mandatory multiorgan attention is required in these high-risk patients.

Future therapies for heart failure could include ventricular assist devices implantation or ventricular restoration techniques with the aim to obtain a reverse, positive remodeling in the unloaded heart. With an expanding "toolbox" of comprehensive basic, medical, surgical, and technological approaches, it is expected that these novel findings will soon be translated to the clinical practice. In fact, new therapeutic strategies are needed by the millions of patients suffering from heart failure. We hope that this special issue will help readers become familiarized with recent progress regarding the diagnosis and treatment of heart failure.

Acknowledgments

We want to give special thanks to all the authors who shared their excellent work to be included in our special issue and the reviewers whose criticisms and advices were fundamental for the selection of the best work.

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Massimo F. Piepoli
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Giuseppe Siniscalchi

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Research Article

Renal Doppler Resistive Index as a Marker of Oxygen Supply and Demand Mismatch in Postoperative Cardiac Surgery Patients

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Background and Objective. Renal Doppler resistive index (RDRI) is a noninvasive index considered to reflect renal vascular perfusion. The aim of this study was to identify the independent hemodynamic determinants of RDRI in mechanically ventilated patients after cardiac surgery. *Methods*. RDRI was determined in 61 patients by color and pulse Doppler ultrasonography of the interlobar renal arteries. Intermittent thermodilution cardiac output measurements were obtained and blood samples taken from the tip of pulmonary artery catheter to measure hemodynamics and mixed venous oxygen saturation (SvO_2). *Results*. By univariate analysis, RDRI was significantly correlated with SvO_2, oxygen extraction ratio, left ventricular stroke work index, and cardiac index, but not heart rate, central venous pressure, mean artery pressure, pulmonary capillary wedge pressure, systemic vascular resistance index, oxygen delivery index, oxygen consumption index, arterial lactate concentration, and age. However, by multivariate analysis RDRI was significantly correlated with SvO_2 only. *Conclusions*. The present data suggests that, in mechanically ventilated patients after cardiac surgery, RDRI increases proportionally to the decrease in SvO_2, thus reflecting an early vascular response to tissue hypoxia.

1. Introduction

In humans and animals, various quantitative and semiquantitative Doppler parameters have been proposed to quantify renal blood flow. Among these, renal Doppler resistive index (RDRI) measured from intrarenal arteries is the one most widely used for clinical investigations since it does not require estimations of Doppler angle or vessel cross-sectional area [1]. Moreover, animal studies have shown that RDRI is dependent on perfusion pressure [2] and is increased by hypotension in the presence of hypovolemic or normovolemic anemia [3].

During low-flow states, splanchnic hypoperfusion and blood flow-redistribution are part of the physiological response to oxygen supply and demand mismatch. In two previous studies, RDRI has been shown to be able to detect tissue hypoperfusion and oxygenation due to occult hemorrhagic shock in hemodynamically stable polytrauma patients [4] and to correlate with levels of arterial standard base excess and expression of tissue hypoxia [5]. Moreover, in patients with acute respiratory distress syndrome, high RDRI values were related to mild hypoxemia due to short-term low fraction of inspired oxygen (FiO_2) [6]. Based on the above

Table 1: Baseline characteristics of the population at inclusion.

Baseline characteristics at inclusion	All patients	RDRI > 0.7	RDRI ≤ 0.7	*P*
Age, years	70 ± 8	75 ± 6	70 ± 8	0.510
Sex, m/f	52/9	9/2	43/7	0.616
Simplified acute physiology score II	27 ± 11	27 ± 11	27 ± 11	0.940
EuroSCORE	6 ± 3	7 ± 2	6 ± 3	0.445
Ejection fraction, % (before surgery)	42 ± 13	50 ± 11	41 ± 12	0.580
Creatinine, mg/dL (before surgery)	1.1 ± 0.1	0.9 ± 0.2	1 ± 0.2	0.188
Vasoactive inotropic score	23 ± 15	22 ± 11	24 ± 16	0.909

findings, it can be hypothesized that changes in RDRI reflect a vascular response to tissue hypoxia in postoperative cardiac surgery patients with oxygen supply and demand mismatch.

This hypothesis was tested in the present study by searching for independent hemodynamic correlates of RDRI in mechanically ventilated patients after cardiac surgery.

2. Material and Methods

2.1. Patients. The study was approved by institutional review board of our university hospital (protocol number 812/2014). Study protocol and aim were explained to patients before surgery and each of them gave a written informed consent.

Sixty-one consecutive patients admitted to the intensive care unit after elective cardiac surgery were included in the study (Table 1). They were required to have a pulmonary artery catheter in place as per clinical indications and satisfy the following inclusion criteria: (1) age > 18 years; (2) absence of acute kidney injury or ongoing recovery from acute kidney injury; (3) no history of chronic renal failure; (4) absence of any condition known to modify renal Doppler resistive index, namely, suspected or confirmed obstructive renal failure, arrhythmia, renal artery stenosis, sepsis, mitral or tricuspid regurgitation, and intra-abdominal hypertension; (5) no renal replacement therapy; (6) no conditions making RDRI examination not reliable; and (7) no conditions needing mechanical ventilation with positive end-expiratory pressure > 5 cm H_2O or FiO_2 > 50%.

All patients were mechanically ventilated with tidal volume of 8–10 mL/kg of predicted body weight and positive end-expiratory pressure of 5 cm H_2O and FiO_2 50%. They were sedated by continuously infused propofol. At the time of inclusion, no patient was receiving renal replacement therapy or had overt acute renal failure. RDRI measurements were performed immediately before hemodynamic measurements, at admission in intensive care unit (ICU), and within the first 12 hrs whenever needed per clinical condition.

2.2. Measurements

2.2.1. Hemodynamic Monitoring. Patients were positioned 30° supine and all pressure transducers were referred to mid chest at the level of right atrium. All patients had a radial arterial catheter (*Arterial Leadercath 3F*, *Vygon*, *Ecouven, France*) and a pulmonary artery catheter (*141HF7*, *Edwards Lifesciences, Unterschleißheim*, *Germany*). Clinical data were collected from the bedside monitor (Drager Infinity Delta XL, Dräger Medical GmbH Lübeck, Germany). Intermittent thermodilution cardiac output (CO) measurements were performed using the pulmonary artery catheter by injecting 10 mL of normal saline into the superior vena cava at room temperature. Three consecutive injections were randomly made during the respiratory cycle. If measurements differed by >10%, the cardiac output was measured two more times and a mean was calculated after exclusion of the highest and lowest values. To avoid variation between operators, the injections were always performed by the same experienced operator. Washout curves were examined for stable baseline temperature, undisturbed rapid upstroke, and exponential decay without signs of early recirculation. Cardiac output was normalized for total body surface area to obtain the cardiac index (CI). Blood samples (2 mL per sample) were taken from the tip of pulmonary artery catheter to measure SvO_2. The correct positioning of the catheter was confirmed by the waveform of the pressure curve, catheter length, and chest X-ray. SvO_2 was measured (*ABL800 FLEX*, *Radiometer Medical ApS*, *2700 Brønshøj*, *Denmark*).

The following hemodynamic parameters were calculated: arterial oxygen saturation (SaO_2), mixed venous oxygen saturation (SvO_2), oxygen delivery index (DO_2I), oxygen consumption index (VO_2I), oxygen extraction ratio (O_2ER), central venous pressure (CVP), cardiac index (CI), left ventricular stroke work index (LVSWI), heart rate (HR), pulmonary capillary pressure (PCP), and mean arterial pressure (MAP).

2.2.2. Color and Pulse Doppler Ultrasonography. All ultrasonographic examinations were performed by a single expert operator using a Philips CX50 Echocardiography (*Philips Healthcare*, *Eindhoven*, *Netherlands*) with a S5-1 Sector Array transducer for kidney's examination with the patient in supine position. After a general preliminary examination of the abdominal cavity and organs, Doppler ultrasound measurements were obtained in the interlobar arteries of the renal cortex. The ultrasound examination was considered technically adequate if the following criteria were met: (a) a clear two-dimensional longitudinal scan with definition of renal parenchyma, (b) a good color Doppler image with representation of the intrarenal vascular blood flow, and (c) at least three consecutive Doppler time-velocity spectra for each renal area (upper, middle, and lower regions). Waveforms

Table 2: Hemodynamic data and oxygenation parameters.

	All	RDRI > 0.7	RDRI ≤ 0.7	P
Heart rate (bpm)	86 ± 12	94 ± 13	84 ± 12	0.028
MAP (mmHg)	76 ± 10	77 ± 10	76 ± 10	0.708
MPAP (mmHg)	24 ± 5	24 ± 4	24 ± 5	0.601
CI (L/min/m^2)	2.7 ± 0.6	2.5 ± 0.8	2.7 ± 0.6	0.466
LVSWI (Joule)	25 ± 8	24 ± 10	26 ± 7	0.412
CVP (mmHg)	12 ± 3	11 ± 4	12 ± 3	0.864
PCP (mmHg)	14 ± 5	14 ± 5	15 ± 5	0.523
SVRI (dynes s/cm^5/m^2)	2044 ± 558	2191 ± 687	2001 ± 517	0.434
PVRI (dynes s/cm^5/m^2)	300 ± 160	373 ± 205	277 ± 140	0.189
Hemoglobin (g/dL)	11 ± 2	11 ± 2	11 ± 2	0.539
Lactate concentration (mmol/L)	1.5 ± 1	1.5 ± 0.4	1.5 ± 0.9	0.925
SaO_2 (%)	98 ± 2	97 ± 2	99 ± 2	0.033
SvO_2 (%)	66 ± 6	57 ± 2	67 ± 6	<0.001
ΔCO_2 (mmHg)	5 ± 2	6 ± 2	5 ± 3	0.492
DO_2I (mL/m/m^2)	378 ± 93	355 ± 88	385 ± 94	0.361
VO_2I (mL/m/m^2)	128 ± 33	146 ± 40	122 ± 29	0.110
O_2ER (%)	35 ± 0.07	41 ± 0.04	32 ± 0.06	<0.001
RDRI	0.64 ± 0.06	0.74 ± 0.03	0.62 ± 0.04	<0.001

MAP: mean artery pressure; MPAP: mean pulmonary artery pressure; CI: cardiac index; LVSWI: left ventricular stroke work index $[(MAP_{(mmHg)} - PCWP_{(mmHg)}) \times SVI_{(mL)} \times 0{,}0133322]$; CVP: central venous pressure; PCP: pulmonary capillary pressure; SVRI: systemic vascular resistance index; PVRI: pulmonary vascular resistance index; SaO_2: arterial oxygen saturation; SvO_2: mixed venous oxygen saturation; ΔCO_2: venoarterial CO_2 gradient; DO_2I: oxygen delivery index $[CI \times Hb \times 1.34 \times SaO_2 + 0.003 \times PaO_2]$; VO_2I: oxygen consumption index $[CI \times Hb \times 1.34 \times SvO_2 + 0.003 \times PvO_2]$; O_2ER: oxygen extraction ratio $[VO_2I/DO_2I]$; RDRI: renal Doppler resistive index; Hb: hemoglobin (gr/mL); PaO_2: partial pressure of arterial oxygen (mmHg); PvO_2: partial pressure of mixed venous oxygen (mmHg).

were recorded and renal Doppler resistive index was calculated according to Planiol and Pourcelot protocol [7]. For each of the three renal areas, three Doppler measurements were taken, and the mean values were then averaged to derive an index for the whole organ in order to minimize sampling error. Pulsed wave Doppler spectrum was increased by using the lowest frequency shift range that did not cause aliasing and the wall filter was set at a low frequency (100 MHz). Values of renal Doppler resistive index > 0.70 were considered abnormal, with normal values ranging between 0.48 and 0.68 [8]. Renal venous flow was evaluated to exclude the presence of occlusion or thrombosis.

2.3. Statistical Analyses. Results were expressed as mean ± standard deviation or percentage. Categorical data were compared by Pearson's χ^2 test with Yates correction or Fisher's exact test when appropriate. Continuous variables were compared with Student t-test for unpaired data.

Relationships between RDRI and hemodynamic indexes were evaluated by Pearson's correlation coefficient. A power calculation for correlation test was performed as previously described [9]. Main hemodynamic and clinical continuous variables were entered into univariate linear regression models, in which RDRI was set as dependent variable. The variables that reached statistical significance at the univariate analysis, without violating the assumption of no multicollinearity, were then entered into a multivariate linear regression model.

A two-sided P value < 0.05 was assumed as statistically significant. Statistical analyses were performed using SPSS 20.0 (SPSS, Chicago, Ill), GraphPad Prism 6.00 (GraphPad Software, San Diego, CA), and the R software/environment (version 3.1.2; R Foundation for Statistical Computing, Vienna, Austria).

3. Results

A power calculation carried out for a linear correlation coefficient of 0.4 with type-I error probability of 0.05 returned a statistical power of 0.90 with a sample size of 61.

According to inclusion criteria, no patient had creatinine levels outside the normal range (0.50–1.20 mg/d). The creatinine mean value at admission was 1.1 ± 0.1 mg/dL. RDRI was adequately measureable from both kidneys in 56 patients and from the right kidney alone in the remaining 5 patients, because of suboptimal visualization of left kidney due to overlying bowel gas. Thus 117 measurements were obtained in the 61 patients. Eleven patients had RDRI >0.70. When subjects were grouped on the basis of this cutoff, those with RDRI >0.7 had higher heart rate, lower SaO_2 and SvO_2, and larger O_2 extraction ratio (Table 2). No other hemodynamic variable was significantly different between the two groups.

RDRI showed a significant inverse correlation with SvO_2 ($r = -0.605$; $P < 0.001$), O_2-ER ($r = -0.582$; $P < 0.001$), CI ($r = -0.294$; $P = 0.0265$), and LVSWI ($r = -0.322$; $P = 0.035$), but not with HR ($r = 0.205$; $P = 0.113$), CVP

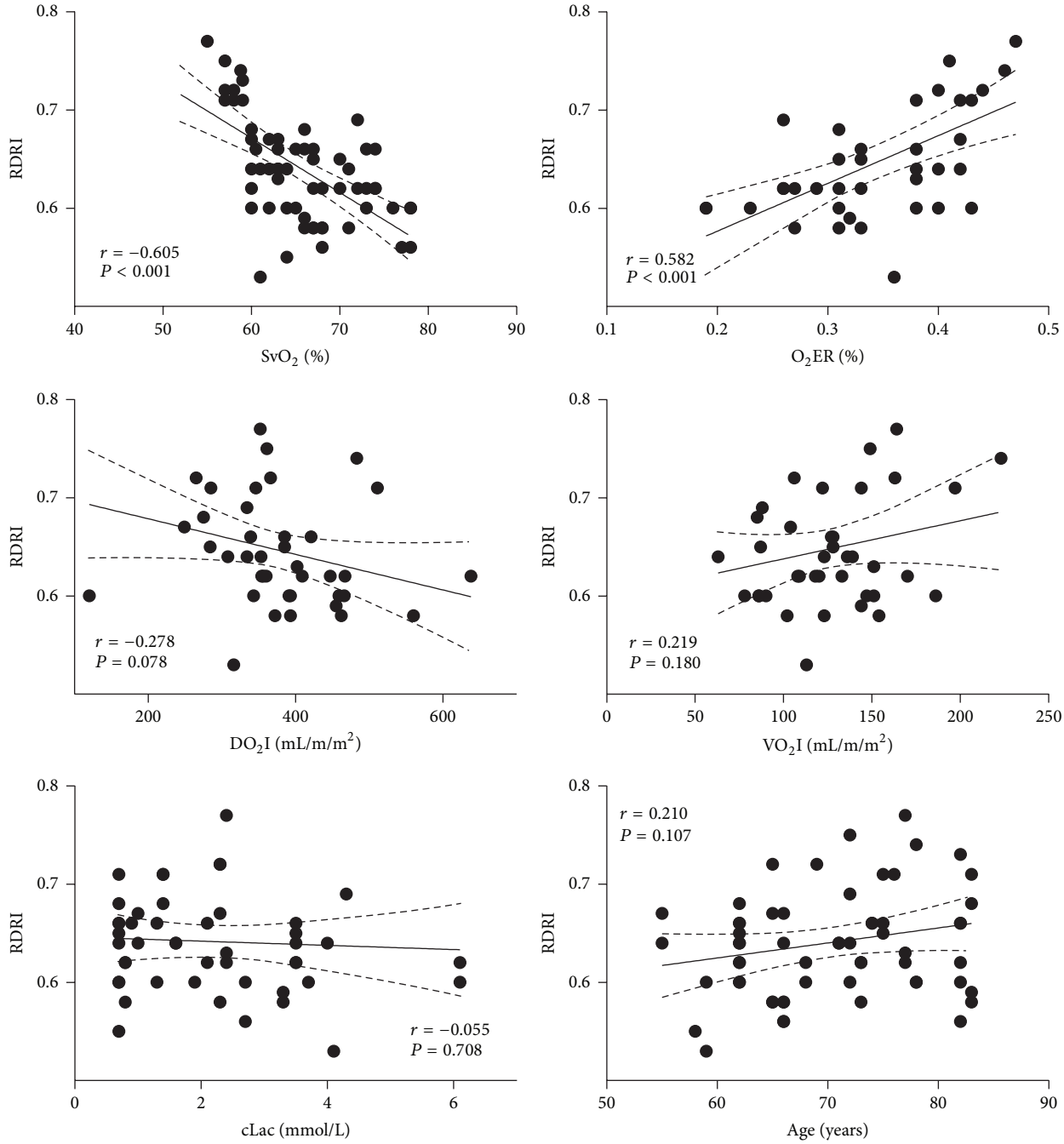

Figure 1: Correlations of renal Doppler resistive (RDRI) index with SvO_2: mixed venous oxygen saturation, O_2ER: oxygen extraction ratio [VO_2I/DO_2I], DO_2I: oxygen delivery index [$CI \times Hb \times 1.34 \times SaO_2 + 0.003 \times PaO_2$], VO_2I: oxygen consumption index [$CI \times Hb \times 1.34 \times SvO_2 + 0.003 \times PvO_2$], cLac: arterial lactate concentration, and age, in 61 patients admitted to the intensive care unit after elective cardiac surgery.

($r = 0.081$; $P = 0.532$), MAP ($r = -0.166$; $P = 0.201$), PCP ($r = 0.059$; $P = 0.650$), SVRI ($r = 0.260$; $P = 0.088$), DO_2I ($r = -0.278$; $P = 0.078$), VO_2I ($r = 0.219$; $P = 0.180$), arterial lactate concentration ($r = -0.055$; $P = 0.708$), and age ($r = 0.210$; $P = 0.107$) (Figures 1 and 2).

Potential predictive hemodynamic parameters for RDRI were entered into univariate linear regression models. A statistical significance was found for LVSWI ($P = 0.035$), CI ($P = 0.029$), O_2-ER ($P < 0.001$), and SvO_2 ($P < 0.001$) (Table 3). O_2-ER and LVSWI were not included in the multivariate analysis because they were highly correlated with SvO_2 and CI, respectively. The multivariate regression model including SvO_2 and CI as independent variables yielded an overall R^2 of 0.390 ($P < 0.045$), with SvO_2 being the major

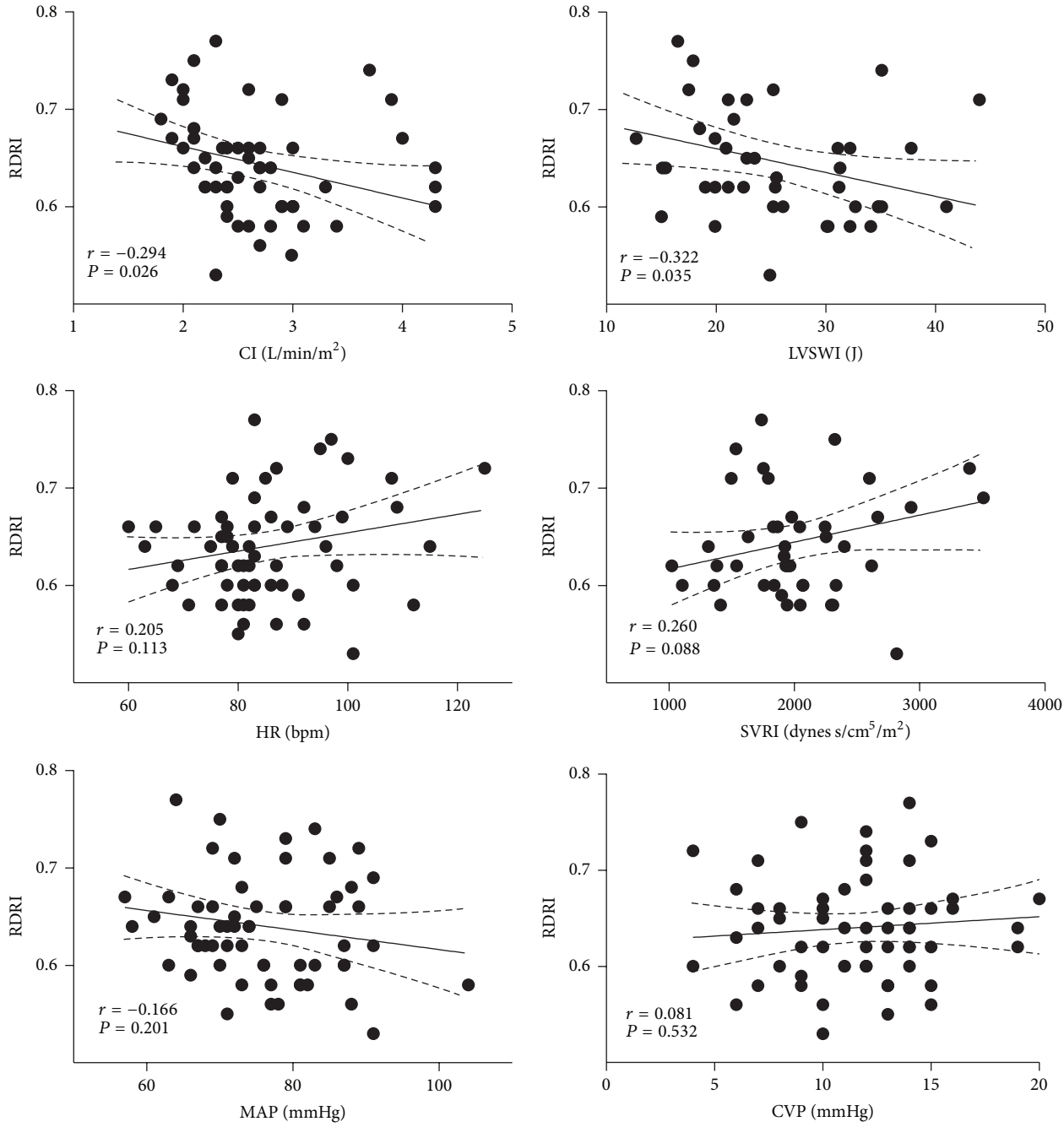

Figure 2: Correlations of renal Doppler resistive (RDRI) index with CI: cardiac index, LVSWI: left ventricular stroke work index [$(MAP_{(mmHg)} - PCWP_{(mmHg)}) \times SVI_{(mL)} \times 0{,}0133322$], HR: heart rate, SVRI: systemic vascular resistance index, MAP: mean artery pressure, and CVP: central venous pressure, in 61 patients admitted to the intensive care unit after elective cardiac surgery.

contributor ($P < 0.001$). Even when age was forced in the multivariate analysis the overall significance of the model did not change ($R^2 = 0.42$; $P < 0.045$), confirming SvO_2 as the major contributor (Table 3).

Patients with $SvO_2 < 55\%$ had a RDRI significantly higher than those with $SvO_2 \geq 55\%$ (0.73 ± 0.04 versus 0.63 ± 0.04; $P < 0.001$).

The evolution of patients with high RDRI did not differ from that observed in patients with normal values in terms of ICU length of stay (8 ± 6 versus 7 ± 6 days; $P = 0.763$), hospital length of stay (18 ± 10 versus 17 ± 10 days; $P = 0.857$), ICU mortality (0 versus 4 patients; $P = 0.459$), number of red blood cell transfusion requirements (4 ± 4 versus 5 ± 4; $P = 0.447$), time of mechanical ventilation (108 ± 126 versus

Table 3: Univariate and multivariate linear regression analysis of potential predictive hemodynamic parameters for renal Doppler resistive index.

Parameter	Univariate analysis			Multivariate analysis			Multivariate analysis		
	β	SE	P	β	SE	P	β	SE	P
Lactate	0.041	0.014	0.840			Not entered			
PCP	−0.059	0.001	0.650			Not entered			
CVP	0.082	0.002	0.531			Not entered			
MAP	−0.167	0.001	0.199			Not entered			
Heart rate	0.204	0.001	0.115			Not entered			
Age	0.211	0.001	0.106			Not entered	0.179	0.001	0.110
VO_2I	0.223	0.001	0.178			Not entered			
SVRI	0.259	0.001	0.090			Not entered			
DO_2I	−0.277	0.001	0.079			Not entered			
LVSWI*	−0.321	0.001	0.036			Not entered			
Cardiac index	−0.293	0.012	0.027	−0.226	0.010	0.039	−0.181	0.010	0.107
O_2ER*	0.581	0.114	<0.001			Not entered			
SvO_2	−0.604	0.001	<0.001	−0.555	0.001	<0.001	−0.573	0.001	<0.001

β: regression coefficient; SE: standard error. *Variables excluded from the multivariate analysis because of the violation of assumption of no multicollinearity.

84 ± 132 h; $P = 0.604$), intra-aortic counter pulsation (2 versus 4; $P = 0.247$), and number of patients requiring hemodialysis (0 versus 1; $P = 0.831$).

4. Discussion

High RDRI values were previously described to be a reliable predictor of occult or incipient hemorrhagic shock in hemodynamically stable polytrauma patients, with low arterial lactate levels and normal hemoglobin at admission [4]. Moreover, a significant correlation between RDRI and arterial standard base excess, as a marker of tissue hypoxia, was consistently found in polytrauma patients [5]. Also in patients with acute lung injury, RDRI has been described to increase during short-term low-FiO_2 titration, thus providing evidence of substantial renal effects due to hypoxemia [6].

The main finding of the present study is that RDRI was significantly correlated with SvO_2 and cardiac index, independent of the presence of other hemodynamic abnormalities. This supports the hypothesis of an early and significant response of the renal vasculature to an even mild oxygen supply and demand mismatch. To the best of our knowledge, this is the first study showing a correlation between RDRI and invasive hemodynamic measurements, particularly SvO_2. We observed a negative correlation between RDRI and SvO_2 but not an inverse correlation between RDRI and mean arterial pressure. This finding suggests that the renal vasoconstrictor response is likely to be modulated not only by a reduction in effective circulating volume, but also by mechanisms depending on oxygen supply and demand mismatch, as expressed by SvO_2. This pathophysiologic response may be triggered even in the presence of normal arterial oxygenation [10].

One possible explanation is that kidney is highly sensitive to ischemic injury, due to its complex microvascular structure coupled with high metabolic needs. Under normal steady-state conditions, the oxygen supply to the renal parenchyma is largely exceeding its oxygen demand [10–20]. However, under pathological conditions the delicate balance between oxygen supply and demand is commonly overturned. In this context, cellular hypoxia develops in response to the decreased availability of oxygen due to inadequate convective delivery from the microcirculation.

It has been previously shown that resistance index can exceed the threshold of 0.70 in elderly subjects without renal insufficiency [21, 22], due to age-related changes in vascular compliance, atherosclerosis, or presence of arterial hypertension-related vascular damage [23, 24]. In our study, age was not identified as an independent determinant of RDRI in both uni- and multivariate regression analysis probably due to the narrow age range of patients.

Most patients admitted to ICU after cardiac surgery need support by vasoactive drugs, which can modify the vascular tone of renal arteries, thus probably affecting RDRI measurements. In the present study the use of vasoactive drugs did not significantly differ between patients with RDRI above or below 0.7, as documented by the vasoactive-inotropic score (VIS) calculated for each patient at each measurement.

This study has some limitations. First, our critically ill patients were sedated and mechanically ventilated with standardized ventilation after cardiac surgery, and thus results cannot be extrapolated to either spontaneously breathing patients or other critical conditions requiring protective mechanical ventilation. Second, patients with increased creatinine levels were excluded from the study. Although this makes the results not applicable to patients with acute or chronic renal failure, it allowed us to avoid confounding factors influencing renal vasoconstriction. Third, the age and the use of vasoactive drugs were quite similar among patients, which may have prevented finding significant correlations. Nevertheless, the narrow range of age and the similar use of vasoactive drugs in all patients allowed us to describe the response of RDRI to tissue hypoxia independently of other

confounding factors. Fourth, the study was not potentiated to find differences in terms of clinical outcomes.

In conclusion, the results of the present study suggest that RDRI is sensitive to oxygen supply and changes in SvO_2, supposedly reflecting a vascular response to hypoxia.

Conflict of Interests

None of the authors have any financial interest in the manufactures cited in this paper.

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Review Article

New Insights in the Diagnosis and Treatment of Heart Failure

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Cardiovascular disease is the leading cause of mortality in the US and in westernized countries with ischemic heart disease accounting for the majority of these deaths. Paradoxically, the improvements in the medical and surgical treatments of acute coronary syndrome are leading to an increasing number of "survivors" who are then developing heart failure. Despite considerable advances in its management, the gold standard for the treatment of end-stage heart failure patients remains heart transplantation. Nevertheless, this procedure can be offered only to a small percentage of patients who could benefit from a new heart due to the limited availability of donor organs. The aim of this review is to evaluate the safety and efficacy of innovative approaches in the diagnosis and treatment of patients refractory to standard medical therapy and excluded from cardiac transplantation lists.

1. Introduction

Cardiovascular disease is the leading cause of mortality in USA and Western countries with ischemic heart disease accounting for the majority of these deaths. Paradoxically, the improvements in the medical and surgical treatment of acute coronary syndromes are leading to an increasing number of "survivors" who are then developing heart failure. Despite considerable advances in the management of heart failure, the gold standard for the treatment of end-stage heart failure patients remains heart transplantation. Nevertheless, this procedure can be offered only to a small percentage of patients who could benefit from a new heart due to the limited availability of donor organs. In fact, the number of heart transplants has remained static worldwide and the number of heart transplants performed each year in the US has plateaued at about 2100 for the past few years. Improving awareness of the very end stages of heart failure is emerging as a major need for the clinical community, and implementing best practices for palliative care is also imperative.

A number of innovative approaches are being investigated on the basis of improved survival and quality of life in patients refractory to medical therapy and excluded from cardiac transplantation lists. These procedures include the optimization of medical therapy, coronary artery bypass surgery and valve surgery in high risk patients, ventricular restoration techniques, and the implantation of ventricular assist devices as destination therapy or other approaches (such as cardiac resynchronization therapy) [1]. Future therapies for heart failure could include new approaches with stem cell therapy, associated with standard revascularization techniques or with other procedures such as the implantation of innovative ventricular assist devices, new ventricular restoration techniques, or new drugs.

The continuous innovations in proteomic technologies will help pinpoint protein posttranslational modifications that could help elucidate the transition to heart failure (HF). This link between biology and technology could greatly assist in identifying biomarkers with increased specificity as well as more effective therapies.

2. Proteomics to Understand Heart Failure

2.1. The Contribution of Proteomics to Our Understanding of Biological Systems. Nowadays, mass spectrometry (MS) is used to detect, identify, and quantify a wide array of compounds spanning from small molecules, pharmaceuticals, metabolites (hence metabolomics), lipids (hence lipidomics), and peptides and proteins (hence peptidomics and proteomics). In the last four, the "-omics" suffix implies that hundreds to thousands of compounds can be detected in a single analysis providing a snapshot of a given metabolome, lipidome, peptidome, or proteome, respectively. As it is easy to imagine this capability has enhanced tremendously our understanding of biological systems. For the sake of brevity we will address the contribution of proteomics to HF research in this section. For the same reason we cannot be exhaustive and defer to other comprehensive reviews on cardiovascular proteomics for the interested reader [2].

The proteome was first defined publicly a little over a decade ago as the "protein complement of the genome" or the protein make-up that can be identified and quantified from a given biological sample. As an axiom, proteomics is the complex of technologies (centered around MS) used to study the proteome. Perhaps the most important contribution of these technologies to modern medicine is the discovery of the dazzling diversity of protein posttranslational modifications (PTMs). There are over 400 PTMs, such as phosphorylation, nitrosylation, acetylation, and methylation, currently listed in protein databases [3]. The vast majority of PTMs have an effect on a protein's life may it be activity, localization, turnover, and so forth or in other words its function. Posttranslational modifications are the most likely integrators of the interactions between the phenotype and the environment due to their dynamic regulation and this new knowledge has profound implications for biomedicine. For instance, the sporadic nature of many diseases, such as HF, could be explained in the light of proteins and their PTMs rather than the genetic background. In fact, the prediction of a phenotype solely based on genes is inherently complicated by the exponential increase in complexity when moving genes through transcripts to modified proteins and their complexes. The realization that PTMs are so abundant in nature is daunting; however, the technological advances seen in the last decade let us hope that their mapping is within reach and that with this information we will have a high-resolution picture of the molecular phenotype of many diseases in the near future.

As technologies quickly develop, their potential clinical applications also multiply. Like the computer industry some of these technologies, and mainly MS, have now reached a point where performance has allowed targeting an intermediate segment of the users market. That is to say that high-performance MS instruments which were previously relegated to well-funded and highly specialized research groups are now slowly becoming accessible to smaller institutions, including hospitals and clinical labs. The great potentials for biomarkers discovery and clinical labs analyses are still largely unmet by the limited knowledge of the scientific and medical communities.

2.2. A Brief Overview of the Technical Aspects of Proteomics. Mass spectrometers are classically named after their anatomy and are composed of a source, one or more analyzers, and a detector. For instance, a matrix assisted laser desorption ionization (MALDI) is a type of source, whereas time-of-flight (TOF) is one of the first used analyzers. The source is the part of the instrument where analytes (e.g., peptides and proteins in proteomics) are ionized so that they can be separated according to their mass (mass/charge or m/z) in the analyzer. Most commonly MS are coupled to liquid chromatography (LC, hence LC-MS). However, MS that are coupled with an LC typically have different sources than MALDI (such as Electron Spray Ionization or ESI) and analyzers (such as quadrupoles or "Q" and ion traps). To complicate things further, most modern instruments have multiple analyzers in series (hence Q-trap, Q-TOF, triple-Q, etc.). These last instruments are also referred to as tandem MS (or MS/MS) and the advantage of having multiple analyzers resides in the capability of sequencing a peptide (and often assigning PTMs unambiguously), with the cost being the time for acquisition (or analysis). The number of methodological approaches that have arisen in the last decade is also complex. They can be broadly divided into protein- and peptide-centric (or top-down and bottom-up to use a widespread nomenclature, resp.). The most common approaches are peptide-centric, which means that proteins are digested into peptides prior to MS analysis due to the increased stability of the latters and the fact that they can be measured more accurately. The separation of proteins prior to MS analysis can be achieved by polyacrylamide gel electrophoresis (PAGE) or LC (hence gel-based and gel-free approaches); however, LC is also used to inject proteins and peptides directly in the MS. Moreover, other separation techniques such as capillary electrophoresis (CE) can be also utilized [4]. One of the typical approaches based on the direct LC-MS analysis of digested proteomes is commonly known as "shotgun" [5], as peptides are digested, desalted, and injected into the MS. When it comes to quantification, two different schools of thought advocate for label and label-free approaches. In the former, peptides are chemically derived with various chemical "tags" prior to MS analysis. These are released in the MS to work as "reporters" for the quantity of a given peptide (and therefore protein) [6]. However, due to the increased reproducibility of separation and MS technologies, it is now possible to have an accurate quantification also in absence of reporters (label-free) [4]. Finally, the clinical relevance of top-down or protein-centric proteomics in HF research is also rapidly emerging [7]. Peptide-centric approaches can be utilized for both the "entire" proteome (proteome-wide) or fractions of it (subproteomes). Indeed the complexity of biological systems is such that it is hard to predict when full proteome-wide coverage will be achieved for complex samples. The detection of peptides in a MS is a competitive process; therefore the higher the complexity of the sample, the higher the chance that low-abundant peptides (proteins) may be missed. For this reason, the enrichment of specific PTMs (e.g., phosphoproteome [6]) or subproteomes (e.g., different organelles [8]) greatly enhances sensitivity. Targeted proteomics or the application of these technologies

to highly enriched subproteomes (e.g., individual proteins end, their PTMs, and their complexes) is arguably the best approach to gain the deepest level of detail. A successful example of this concept is the crossover of a MS technique known as multiple reaction monitoring (MRM) from the pharmaceutical industry to proteomics. Briefly MRM allows to precisely quantify proteins using the quantity of few peptide fragments in a tandem MS. The use of isotopically labeled internal standard enables absolute quantification. As an example, multiple reaction monitoring was recently used to accurately quantify the phosphorylation sites (known and new) of cardiac TnI, one of the gold standard markers to diagnose cardiac ischemia [9].

2.3. Proteomics to Tackle Emerging Concepts in HF Research. There has been an increasing consensus on the similarities between well-established organ proteinopathies (such as Alzheimer's and Parkinson's diseases) and HF [10]. This concept was pioneered a little over ten years ago by Robbins and colleagues who reported the presence of preamyloid oligomers (PAOs) similar to those observed in the brains of Alzheimer's patients, in cardiac specimens from HF patients [11]. In the last few years, this concept has been revamped by several studies. Few of the most recent ones have conveniently exploited proteomic technologies [12–14]. Indeed, it is not surprising that proteomic analysis will assist with elucidating new mechanisms of proteotoxicity as they happen not only in the brain but also in other organs, such as the heart. Of particular interest is the role of protein PTMs [15, 16]. These can be placed both enzymatically (such as phosphorylation) or occur as the result of environmental stress (such as oxidation). The latters are not regulated and therefore they can accumulate in a pathological fashion [12, 15]. If protein misfolding is a mechanism which can result in the uncontrolled accumulation of toxic species in the heart (such as PAOs), these technologies will greatly help in dissecting the relative contribution of different PTMs (chemical and enzymatic) to the etiology of several diseases, including HF.

2.4. What "Lies" Ahead. As new technologies and approaches become available to the medical community, it is challenging to remain up-to-date and pick those that will have a long-lasting impact. In this concluding paragraph three emerging methodologies which, in our opinion, are likely to play a major role in the future of clinical proteomics will be described briefly. The first is mass cytometry, made possible by the combination of flow cytometry and a TOF MS. In short this configuration enables to monitor several different antigens with little to no cross talk in a given cell subpopulation [17]. The second is MALDI imaging, combining the capabilities of MALDI-TOF MS with those of a microscope. Although its spatial resolution at this stage is limited, the distribution of a given peptide across a tissue section can be monitored with this approach [18]. Lastly, a new acquisition in the proteomic field is the possibility of accurately measuring the level of thousands of proteins at one time and retaining the capability of reinterrogating the obtained data with new questions that may arise even after the study is concluded. This novel approach has profound implications for clinical studies as it allows the creation of the *in silico* version of a proteome and its repeated interrogation. For example, this is particularly important for studies on HF due to the limited availability of (control) tissue [19]. The pioneering work of Aebersold and colleagues transferred the quantitative capability of MRM to proteome-wide approaches by using new acquisition methods. The increased speed of acquisition of certain MS configurations combined with "unbiased" detection approaches (Data Independent Acquisition or DIA) now permits "scanning" through a proteome by missing limited information. This information can be stored *in silico* and the resulting database can then be used as a reference to compare several different biological conditions and track back changes in a quantitative fashion. Several other applications are underway, including real-time diagnostics that could be particularly helpful in the operating room. With all these new technologies and knowledge there is an emerging need for technical expertise and education of the scientific community at large. The implementation of new software and algorithms to handle the amount of data that are being rapidly generated is an important task for the bioinformatic community. Lastly, local regulations will have to quickly adapt to allow the clinical community to translate efficiently the potential assays provided by these new tools into clinical practice.

3. Novel Medical Therapies in Heart Failure

3.1. Heart Failure with Reduced Ejection Fraction (HFrEF). In the past 25 years, there have been substantial improvements in the treatment of patients with chronic HFrEF. This is also due to the increased availability of drugs acting on the renin-angiotensin-aldosterone system (RAAS) and on the adrenergic systems, such as ACE inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), beta-blockers (BBs), and mineralocorticoid receptor antagonist (MRAs), proved by international randomized trials to be able to modify the natural history of this syndrome by prolonging survival [20].

Several demonstrations of a class effect of these drugs have been proven in the past years, and there is now a need for new drugs targeting different pathological pathways in order to further improve survival in HF patients. In a recent update from the European Society of Cardiology (ESC) guidelines on the management of acute and chronic HF, two major changes in the pharmacological treatment of patients with chronic HFrEF must be acknowledged:

(i) MRA treatment extension to patients with mild-to-moderate HFrEF as a consequence of the results of the EMPHASIS-HF trial (Eplerenone in Mild Patients Hospitalization and Survival Study in HF) [21], which enrolled 2737 patients aged ≥55 years with New York Heart Association (NYHA) functional class II symptoms and an ejection fraction (EF) <30% (<35% if the QRS duration was >130 ms). In this study, about 27% of relative risk reduction in cardiovascular death or HF hospitalization (primary outcome) was achieved with eplerenone treatment (up to 50 mg once daily).

Table 1: Recent studies in heart failure with reduced ejection fraction.

Study	Type	Drug/comp.	Number of pts/Age	Outcome	Results
ARS	PoC	Finerenone (BAY 94-8862) (nonsteroidal MRA)	458/72	Safety and tolerability in chronic kidney disease versus spironolactone	Significantly lower incidences of hyperkalemia than spironolactone
ATMOSPHERE	Outcome	Aliskiren (direct renin inhibitors)	7000	Cardiovascular death or HF hospitalization versus enalapril	Ongoing
LEPTH	Outcome	Riociguat (guanylate cyclase stimulator)	201/59	Change in mean pulmonary artery pressure	Not met but improved stroke volume and cardiac index and reduced pulmonary and systemic vascular resistance
SOCRATES-REDUCED	PoC	Vericiguat (guanylate cyclase stimulator)	410	Change in NT-proBNP	Ongoing
PARADIGM-HF	Outcome	LCZ696 (ARNI, angiotensin II receptor blocker and neprilysin inhibitor)	8442/63	Death from cardiovascular causes or a first hospitalization for heart failure	LCZ696 was superior to enalapril in reducing the risks of death and of hospitalization for heart failure
RED-HF	Outcome	Darbepoetin Alfa	2278/72	Death or hospitalization in patients with Hb (9.0–12.0 g/dL)	Not met but improved haemoglobin level
FAIR-HF	PoC	Intravenous iron (ferric carboxymaltose)	459/67	Self-reported Patient Global Assessment and NYHA functional class	Improvements in 6-minute walk test and quality of life assessment
ICHF	PoC	Intravenous iron (ferric carboxymaltose)		Improvement in LVEF	Ongoing
MOOD-HF	Outcome	Escitalopram (serotonin reuptake inhibitor)	700	Death or hospitalization	Ongoing

PoC, proof-of-concept.

These results led to a class IA recommendation for MRAs in these guidelines.

(ii) The SHIFT trial (Systolic Heart Failure Treatment with Ivabradine Compared with Placebo Trial) [22] has demonstrated that the use of ivabradine, a selective inhibitor of the If current in the sinoatrial node was associated with a significant reduction in the primary endpoint (cardiovascular disease related death or hospitalization for HF), mainly driven by a decrease in the rate of hospitalization in patients with NYHA class II or III HFrEF. This result is particularly relevant because it is the first drug to prove a clinically relevant result demonstrated in a randomized clinical trial in HFrEF patients by acting on pathophysiological systems different from the RAAS and the adrenergic system. Ivabradine was approved by the European Medicines Agency in 2012 for chronic HF in patients with elevated heart rates but at present it is not yet commercialized in the US.

Several new classes of drugs have been proposed or are under evaluation (Table 1):

(i) Finerenone (BAY 94-8862) is a next-generation nonsteroidal MRA that has shown improved selectivity for the mineralocorticoid receptor.

(ii) Aliskiren, a direct renin inhibitor, decreases PRA and thus may provide a greater RAAS blockade.

(iii) Omapatrilat is a molecule that was both a neprilysin and an ACE-I and whose development was terminated because of an unacceptable incidence of angioedema [23].

(iv) Angiotensin receptor neprilysin inhibitors (ARNIs) are a new class of drugs developed both to block the RAAS and augment natriuretic peptides by the combination of an angiotensin II type 1 receptor blocker and an inhibitor of neprilysin, also known as neutral endopeptidase, the enzyme which promotes breakdown of atrial and brain natriuretic peptides (ANP and BNP, resp.).

(v) Riociguat is a novel soluble guanylate cyclase stimulator, which produces cGMP, the second messenger of several biologically active molecules such as nitric

oxide or natriuretic peptides, and may improve central and peripheral hemodynamics.

(vi) Darbepoetin Alfa, an erythropoiesis stimulating agent, and intravenous iron may improve outcomes in patients with HF and anemia, a common comorbidity in HF. Patients experiencing both conditions have a lower functional capacity, worse quality of life, and higher rates of hospitalization and death than those without anemia [24].

(vii) Incretin based therapies have been developed in recent years to treat type 2 diabetes mellitus (DM). These agents include glucagon-like peptide-1 (GLP-1) agonists (exenatide and liraglutide) and dipeptidyl peptidase-4 inhibitors (sitagliptin, saxagliptin, and linagliptin). Animal and proof-of-concept clinical studies have shown cardioprotective effects of these drugs and potential benefits in patients with HF [25]. However, a large randomized clinical trial (SAVOR) testing the DPP4 saxagliptin showed a higher rate of occurrence of HF in patients with type 2 DM at high risk of CV events [26]. Another trial testing the DPP4 alogliptin (EXAMINE trial) showed no beneficial effect of the drug in patients with type 2 DM and a recent ACS [27]. With respect to GLP-1 agonist, large-scale clinical trials are still ongoing (EXCEL, ELIXA).

3.2. Heart Failure with Preserved Ejection Fraction (HFpEF). "No treatment has yet been shown, convincingly, to reduce morbidity and mortality in patients with HFpEF." This is the beginning of the very brief paragraph dedicated to pharmacological treatment of HFpEF in the ESC guidelines for the diagnosis and treatment of acute and chronic HF published in 2012. There is in fact substantial lack of evidence in the management of HFpEF patients: many of the treatments that have shown a benefit in HFrEF have failed to confirm their positive effects in patients with HFpEF. This is the case of *ad hoc* performed trials performed with ACE-I (PEPCHF) [28] and angiotensin receptor antagonists (CHARM-Preserved [29] and I-PRESERVE [30]).

Different reasons for the unsuccessful effects of these medications have been proposed: some were related to the patients (e.g., lack of specific symptoms with inappropriate enrollment and no agreement on the threshold of EF for definition of preserved systolic function), some were related to the trials (e.g., prolonged recruitment with a high rate of dropouts), some were related to the disease (e.g., different stages of disease), and some others were related to the tested drugs. For other classes of drugs such as BBs, we lack evidence from clinical trials (because no specific trial has ever been designed) and data derived from registries are quite controversial [31].

Since the publication of ESC guidelines, one large outcome trial (Treatment of Preserved Cardiac Function HF with an Aldosterone Antagonist, TOPCAT) and several proof-of-concept studies have been published where well accepted therapies in HFrEF and new therapeutic agents have been tested (Table 2).

The idea of evaluating the effect of drugs that have been proved to be of efficacy in patients with HFrEF in the setting of HFpEF has led to *TOPCAT*, the first international, multicenter, and randomized double-blind trial to assess the effect of spironolactone on clinical outcomes in the patients with HFpEF. It failed to demonstrate a significant improvement in the primary outcome, a composite outcome of cardiovascular mortality, aborted cardiac arrest, or HF hospitalization. These results were disappointing since the Aldosterone Receptor Blockade in Diastolic HF, *Aldo-DHF* trial had on the contrary given at least in part promising results. The substantially neutral results of TOPCAT may be explained by geographical differences in the characteristics of patients enrolled in some countries in which healthier patients were included (e.g., patients enrolled in the placebo group in Russia and Georgia experienced a significantly lower incidence of the primary endpoint compared to those in North or South America, 8.4 versus 31.8%) in which the treatment could not demonstrate a benefit, probably resulting in a dilution of the global effect.

These disappointing results have given the impulse for research in individualizing new therapeutic targets by exploring different pathophysiological pathways such as the nitric oxide (NO) myocardial cyclic guanosine $3',5'$-monophosphate-protein kinase-G pathway (NO-cGMP-PKG). At least some of the beneficial effects induced by NO and natriuretic peptides are in fact mediated by stimulation of soluble and membrane-bound guanylate cyclases, respectively, which produce the second messenger cGMP. Phosphodiesterase-5 (PDE-5) metabolizes cGMP and may limit beneficial NO and natriuretic peptide actions and reduce cGMP-mediated improvements in myocardial relaxation and hypertrophy reduction. The hypothesis that the PDE-5 inhibitor sildenafil might have some benefits in patients with HFpEF was tested in the *RELAX* trial.

The *PARAMOUNT* trial targeted this pathway from a different point of view and tested in patients with HFpEF LCZ696, a first-in-class ARNI that is a complex molecule from the combination of the neprilysin inhibitor prodrug AHU377 and the ARB valsartan. Neprilysin degrades biologically active natriuretic peptides which, as described above, stimulate the production of cGMP.

Inflammation seems to have an important role in the pathophysiology of HFpEF. The *D-HART* pilot study was a small double-blind, randomized, placebo-controlled, and crossover trial that tested anakinra, an interleukin-1 inhibitor, in patients with HFpEF. Anakinra led to a statistically significant improvement in the primary endpoint, which was peak oxygen consumption (+1.2 mL/kg/min, $p = 0.009$), and a significant reduction in plasma C-reactive protein (CRP) levels (−74%, $p = 0.006$). The reduction in CRP levels correlated with the improvement in peak oxygen consumption ($R = -0.60$, $p = 0.002$). Impaired relaxation is a fundamental component of HFpEF and for this reason there is a strong pathophysiological rationale for the utilization of a drug like ranolazine in this setting. The *RALI-DHF* (RAnoLazIne for the Treatment of Diastolic HF) study was a prospective, randomized, double-blind, placebo- controlled, small, and proof-of-concept study.

Table 2: Recent and ongoing studies in heart failure with preserved ejection fraction.

Study	Type	Drug/comp.	Number of pts/Age	Outcome	Results
TOP-CAT	Outcome	Spironolactone versus placebo	3445/69	Primary outcome: CV death/HF hospitalization/aborted cardiac arrest	In follow-up 3.3 years 18 versus 20 ($p = 0.14$)
Aldo-DHF	PoC	Spironolactone versus placebo	422/67	Coprimary outcomes: (i) Diastolic dysfunction (E/E′) (ii) Exercise capacity/peak VO2	In 12-month follow-up (i) 12.1 versus 13.6 ($p < 0.001$) (ii) 16.8 versus 16.9 (p = NS)
RELAX	PoC	Sildenafil versus placebo	216/69	Primary outcome: exercise capacity/peak VO2 Secondary outcome: (i) 6 min walk test (ii) Clinical outcome	In 24-week follow-up (i) −0.2 versus −0.2 (p = NS) (ii) 5.0 versus 15 m (p = NS) (iii) 94 versus 95 (p = NS)
PARAMOUNT	PoC	LCZ 696 angiotensin rec. + Neprilysin inhib. versus valsartan	266/71	Change NT-proBNP Side effects	Ratio LCZ696/valsartan 0.77 ($p = 0.005$) 22 patients (15%) on LCZ696 versus 30 (20%) on valsartan
DHART	PoC	Anakinra versus placebo	12/62	Exercise capacity/peak VO2	+1.2 mL/kg/min (+8%, $p = 0.009$)
RALI-DHF	PoC	Ranolazine (iv 24 h infusion followed by 13 days of oral treatment) versus placebo	20/73	Changes in hemodynamic parameters Changes in echocardiography, PeakVO2, and NT-proBNP parameters	LVEDP (mmHg) 23 versus 19 ($p = 0.04$); PCWP 18 versus 12 ($p = 0.04$) No changes (p = NS)
Kosmala	PoC	Ivabradine versus placebo	61/67	Exercise capacity (METS) Peak VO2	+1.5 versus +0.4 ($p = 0.001$) +3.0 versus +0.4 ($p = 0.003$)
PARAGON-HF	Outcome	LCZ956 versus valsartan		CV death and HF Hospitalization	Ongoing
SOCRATES-PRESERVED	PoC	Vericiguat (guanylate cyclase stimulator)		Change in NT-proBNP	Ongoing
EDIFY	Outcome	Ivabradine versus placebo	400	Diastolic dysfunction (E/E′, exercise capacity, NT-proBNP)	Ongoing

PoC, proof-of-concept.

4. Surgical Alternatives in the Therapy of Severe Left Ventricular Dysfunction

4.1. The Role of Coronary Revascularization. The most common cause of heart failure with severely depressed left ventricular ejection fraction (LVEF) is ischemic heart disease, accounting for more than 60% of cases [32]. Ischemic etiology of left ventricular (LV) systolic dysfunction leads to significantly higher mortality rates than other etiologies [33]. The explanation of this aggressive course is the well-known relationship among myocardial ischemia, interstitial fibrosis, and endothelial dysfunction, often with associated systemic comorbidities, such as diabetes, which worsen the natural history.

Observational studies comparing survival in patients treated surgically versus medically suggested that coronary artery bypass grafting (CABG) enhances survival in patients with ischemic cardiomyopathy [34–41]. Significant reductions from >50% to 10% in mortality have been demonstrated with surgery if compared with medical therapy.

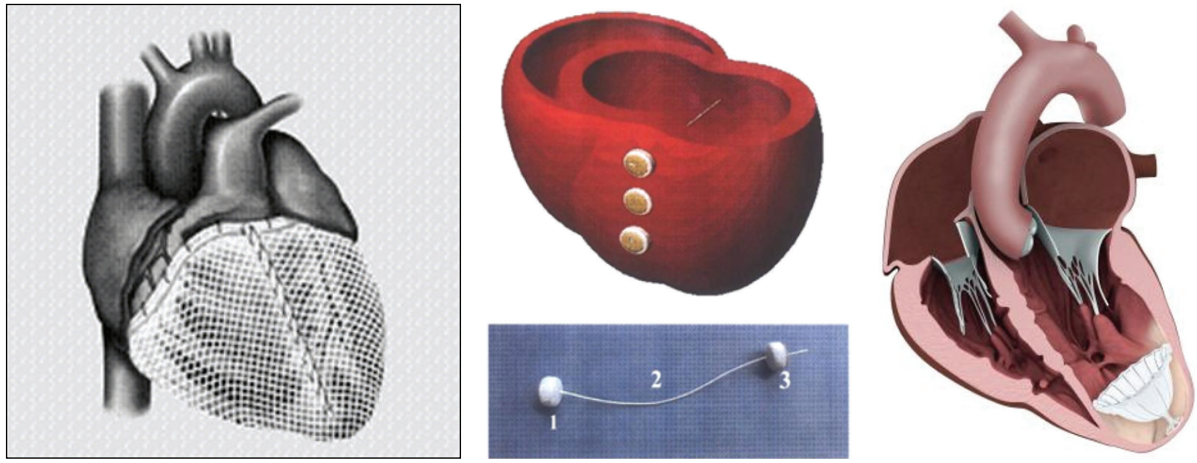
Results reported from early trials comparing medical therapy with CABG for the treatment of stable angina have a limited value in the current era because both surgical techniques and medical therapy have significantly and rapidly improved. Arterial grafts were rarely used in these trials, and medical therapy largely consisted of only nitrates and infrequent use of beta-blockers. Finally, patients with severe LV dysfunction were largely excluded from the enrollment. However, the Veteran Affairs Cooperative Study of Surgery [42] and the Coronary Artery Surgery Study [43] demonstrated a significantly higher survival rate in the patients with reduced LVEF after CABG in comparison with those who were randomized to medical therapy. Other studies confirmed that CABG in patients with severely depressed LVEF obtained a satisfactory survival rate similar to cardiac transplantation [44, 45].

Several contemporary trials studying treatments for ischemic coronary disease that included an intensive medical therapy, such as the MASS-II (Medicine, Angioplasty, or Surgery Study) trial and the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial, excluded patients with severe LV dysfunction [46, 47]. The BARI 2D (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes) trial included patients with LV dysfunction but only 17.5% of patients had LVEF <50% [48]. The ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial is currently enrolling patients but exclusion criteria include LVEF <35% [49].

Among 27 randomized controlled trials comparing CABG and percutaneous coronary intervention (PCI) [50], most of the patients had preserved LV systolic function (EF >50%). None of these trials specifically focused on patients affected by heart failure and/or LV systolic dysfunction. Two relatively large trials that included patients with depressed LVEF were BARI (Bypass Angioplasty Revascularization Investigation) [51], in which 22% of patients enrolled had LVEF <50%, and AWESOME (Angina with Extremely Serious Operative Mortality Evaluation) [52], in which 21% had LVEF <35%. Analyses of this subset of patients from these trials confirmed no differences in outcome between PCI and CABG [45, 53]. Moreover, the most recent trials comparing PCI with CABG failed to provide a clear superiority. The SYNTAX trial enrolled approximately 2% of patients with LVEF <30% [54]. The FREEDOM trial [55] reported similar outcomes with PCI with drug-eluting stents and CABG in patients with LVEF <40%, but only 2.5% of the patients were in this prespecified subgroup with depressed LVEF. Thus, the available data have insufficient statistical power to adequately compare PCI and CABG in patients with severe LV dysfunction.

The STICH trial is the only prospective, randomized, and controlled trial designed to study the role of CABG in patients with LVEF ≤35%. The aim of this trial was to test 2 hypotheses among patients with LVEF ≤35% and CAD amenable to CABG [56]: the comparison between CABG and medical therapy (MT) alone in 1,212 patients and the surgical ventricular restoration (SVR) hypothesis compared CABG with and without SVR in 1,000 patients. In the intention-to-treat analysis, no significant difference was observed in the primary outcome of all-cause mortality between patients randomized to CABG versus MT over a median follow-up period of 56 months. The CABG group reported improved rates of death from cardiovascular causes and lower rates of a combined endpoint of death from any cause and hospitalization for heart failure, which were secondary endpoints of the study [56]. Moreover, as-treated and adjusted analyses to consider patient crossovers suggested an overall favorable effect of CABG on primary and secondary outcomes [57, 58]. Final data derived from this trial suggest that the observed survival benefits of CABG in patients with severe LV dysfunction are related primarily to factors such as functional status assessed by a 6 min walk and/or the Kansas City Cardiomyopathy Questionnaire [59] and the interaction of angiographic severity of CAD, severity of LV systolic dysfunction, and severity of LV remodeling [60]. Patients with preserved effort tolerance but with multivessel CAD, lower EF, and higher end-systolic volume index were most likely to benefit from CABG, particularly with respect to long-term survival.

4.2. Surgical Ventricular Reconstruction. Changes in LV structure and function secondary to heart failure include remodeling of the LV from its normal elliptical shape to a more spherical shape. These modifications result in a dysfunctional, less efficient, and low contractile ventricle and are predictors of worse prognoses. Surgical ventricular reconstruction (SVR) may potentially reverse this process and partially restore functional capacity of LV [61–63]. Vincent Dor described in 1989 a technique of endoventricular circular patch plasty more commonly known as surgical ventricular restoration or Dor Procedure [64]. This technique consists of aneurysm resection with insertion of a circular Dacron or pericardial patch to reconstruct the ventricle. Surgical restoration therefore excludes akinetic septal regions of the LV and restores LV chamber size and shape to more physiologic conditions. Associated CABG showed significantly



(a) (b) (c)

Figure 1: (a) Acorn CorCap Cardiac Support Device. (b) Myosplint system. (c) Parachute ventricular partitioning device.

improved LV function and outcomes at 1 year [65]. The beneficial effects of SVR were further confirmed by the publication of outcomes of the Reconstructive Endoventricular Surgery returning Torsion Original Radius Elliptical shape to the LV (RESTORE) Group. In this study, 1,198 post-MI patients with HF were treated, showing an overall 30-day survival of 94% and 5-year survival of 69% [61].

However, it remained uncertain whether SVR combined with CABG would result in improved outcomes of patients with ischemic cardiomyopathy compared with CABG alone, particularly when associated with optimal medical therapy. This question led to the surgical ventricular reconstruction arm of the STICH trial [66]. In this arm, patients were enrolled if they had coronary disease amenable to surgical revascularization, severe systolic dysfunction with LVEF ≤35%, and significant LV anterior akinesia or dyskinesia that was amenable to SVR. A total of 1,000 patients were randomized to CABG alone versus CABG plus SVR. The primary outcome was a composite of all-cause mortality and cardiac hospitalization. The study showed no significant difference between the 2 therapies for the primary outcome with a median follow-up of 4 years. There were also no differences between the 2 groups in terms of secondary endpoints, including repeat hospitalizations, symptoms, or quality of life [66]. SVR associated with CABG does not appear to improve quality of life compared with CABG alone but does increase health care costs [67].

In the last years, several devices designed to restore LV geometry and decrease wall stress have been evaluated. The most tested has been the Acorn CorCap Cardiac Support Device (Acorn Cardiovascular, Inc). This device consists of a polyester mesh sutured circumferentially around the heart from the apex to the atrioventricular groove (Figure 1(a)). It provides circumferential support, decreases LV wall stress, and avoids progressive chamber dilatation [68]. The results of the pivotal Acorn clinical trial have been already published. Three hundred patients affected by HF were randomized to CorCap implantation with mitral surgery versus mitral surgery alone and to CorCap plus medical therapy versus medical therapy alone. Totally, 148 patients received CorCap: they demonstrated that they need less subsequent procedures (Cardiac Resynchronization Therapy or CRT, CABG, and repeat mitral surgery), an improvement in NYHA class and Minnesota Living with Heart Failure score (MLHF), and favorable echocardiographic reverse remodeling. However, no improvement in survival could be demonstrated at 1, 3, or 5 years [69–71].

The Myosplint system utilized three tensioning rods placed transversely through the left ventricle at the apex, mid, and base, respectively, secured and tensioned by epicardial pads. This device was designed to create a bilobular LV cross section with the aim of reducing the radius of the chamber of LV and consequently its wall stress (Figure 1(b)). The device was tested in 21 consecutive patients to demonstrate safety and feasibility. Whereas the original concept was proven safe and feasible, the authors concluded that the device did not address a satisfactory functional mitral regurgitation repair as the majority of patients who received the Myosplint also needed mitral valve surgery [72].

Coapsys device consisted of a similar tensioning device which bisected the heart and was connected by anterior and posterior epicardial pads. The aim of this device was to reposition the papillary muscles by being placed at the level of the mitral subvalvular apparatus and approximating the ventricular walls. It could be placed through sternotomy without cardiopulmonary bypass [73]. A large multicenter randomized study, the Randomized Evaluation of a Surgical Treatment for Off-Pump Repair of the Mitral Valve (Restor-MV trial), enrolled patients with CAD and functional MR to two arms: CABG with MV repair and CABG alone. The former arm was further randomized to CABG with traditional annuloplasty versus CABG with Coapsys. The latter arm, treated with CABG alone, was further randomized to CABG alone versus CABG with Coapsys.

The trial was stopped in advance because the researchers failed to secure funding for its continuation. Nevertheless, the

study demonstrated a survival advantage as well as decreased adverse events at 2 years in patients treated with CABG and Coapsys compared to those treated with CABG and standard annuloplasty [74].

The concept of a less invasive procedure to obtain LV restoration was exploited by the company BioVentrix, which developed the Less Invasive Ventricular Enhancement (LIVE) therapy utilizing the Revivent technology. The technique involves beating heart isolation of scarred and akinetic myocardium by using the Revivent Myocardial Anchoring System. This system is then placed by epicardial perforation of the myocardium and interventricular septum (IVS) at the borders of the scarred area. The internal anchor is then inserted inside the RV and anchored at the right ventricular surface of the IVS. Consequently, the LV lateral and IVS walls are slowly and completely apposed and the scar is isolated. Further investigations as to the role of this device are ongoing in a phase II study.

In 2006, Sharkey and colleagues described a left ventricular apex occluder, named ventricular partitioning device (VPD) [75]. The system components are three: an access system, a delivery system, and the VDP. The access system is comprised of a 14–16 F guide catheter and dilator which provide access to the apical LV. The catheter is used to deliver the collapsed VPD through the aortic valve to the apex of the LV. The delivery system has an inner lumen with a balloon just proximal to the engagement screw, which is used to inflate the VPD in order to achieve the anchoring of its struts against the ventricular walls, ensuring adequate isolation of the LV apex and stability of the device. The VPD consists of an expanded polytetrafluoroethylene (ePTFE) occlusive membrane associated with a self-expanding Nitinol frame shaped like an inverted umbrella or parachute with 16 struts. This device separates the enlarged and scarred left ventricle into two chambers: one dynamic and one static. The static chamber is the scarred or aneurysmal part of the LV that is distal to the device hemodynamically isolated by the occlusive device membrane; the dynamic chamber is the remaining normal LV (Figure 1(c)). This division causes regional hemodynamic unloading of the isolated dilated apical left ventricle, decreasing wall stress in that region. Moreover, the dynamic LV becomes less voluminous with partitioning, leading to volume/pressure unloading of the functioning myocardium [76]. The first human trial with the Parachute device (CardioKinetix Inc, Menlo Park, CA) was a single arm, prospective, and nonrandomized multicenter study that enrolled 39 patients. The primary end point was technical safety of the device as well as device-related complications within the first 6 months of follow-up. Inclusion criteria were anteroapical akinesis from an anterior myocardial infarction, LVEF of ≤40%, advanced NYHA class, and stable optimal medical therapy for at least 3 months before enrollment. Exclusion criteria were ischemic CAD requiring revascularization, previous revascularization, or CRT within 60 days and patients with significant valve disease. Of the 39 patients, five were thought to have unsuitable LV anatomy for VPD placement after enrollment. After this, the protocol was changed to include computed tomographic (CT) evaluation before enrollment to determine LV anatomical suitability. VPD was successfully delivered in 79% of patients initially enrolled and in 91% of patients in whom it was technically attempted. Overall 6-month success rate without events related to the device was 74%. Hemodynamically, despite significant reductions in LV volumes, LVEF and stroke volume index remained unchanged. Nevertheless, there was a significant decrease in NYHA class, and there were trends towards improvement in QOL measure and 6MWD, although they were not statistically significant [77].

Therefore, Parachute has encouraged with widespread enthusiasm the design of four trials in different stages of completion: the PARACHUTE Trial cohorts A and B following 89 patients enrolled, the PARACHUTE US trial enrolling 20 patients in 8 USA institutions, the PARACHUTE III postmarketing trial in 20 European centers to follow-up 100 patients, and the PARACHUTE IV trial that has begun patients enrollment in the second quarter of 2012 with the aim to enroll 478 patients across 65 USA institutions.

4.3. Mitral Valve Surgery. Functional mitral regurgitation (FMR) is a pathological condition resulting from geometrical distortion of the subvalvular apparatus secondary to LV enlargement and remodeling and due to idiopathic or ischemic cardiomyopathy [78]. Thus, FMR is not a primary mitral valve disease but the result of the previously mentioned complex remodeling processes of LV; however, its presence leads to further remodeling [78]. Surgeons have tried in the last decades to find the specific solutions to this topic with contradictory results and unresolved answers.

While some studies on FMR correction are ongoing, to date no data have clearly demonstrated the superiority of surgery versus optimal medical therapy [78–82]. Results from the Michigan University study showed that no evident advantage is obtained by mitral valve (MV) annuloplasty when compared to optimal medical therapy in terms of 5-year event-free survival in patients with mitral regurgitation and left ventricular systolic dysfunction of any origin; moreover, the same results were reached comparing optimal medical therapy to mitral valve annuloplasty for patients with non-ischemic etiology of FMR and LV dysfunction [83]. Another study by Kang et al. similarly showed that MV annuloplasty plus CABG in ischemic cardiomyopathy did not show any 5-year survival advantage when compared to isolated CABG alone but carried the weight of a higher operative mortality due to concomitant mitral surgery [84]. However, the same study showed a clear advantage by adding MV surgery in terms of residual mitral regurgitation in the follow-up of those patients suffering from severe grade of ischemic FMR [84]. Wong et al. [85] found that mitral annuloplasty in patients with moderate MR did not improve 1-, 5-, and 10-year survival but only the corresponding degrees of residual valvular regurgitation.

Other authors reported similar 5-year survival between isolated CABG and CABG plus MV surgery despite a significant lower mitral regurgitation (MR) grade at 1 year and a trend toward a lower MR grade at 5 years in the second group [86]. The same authors confirmed in a propensity-matched

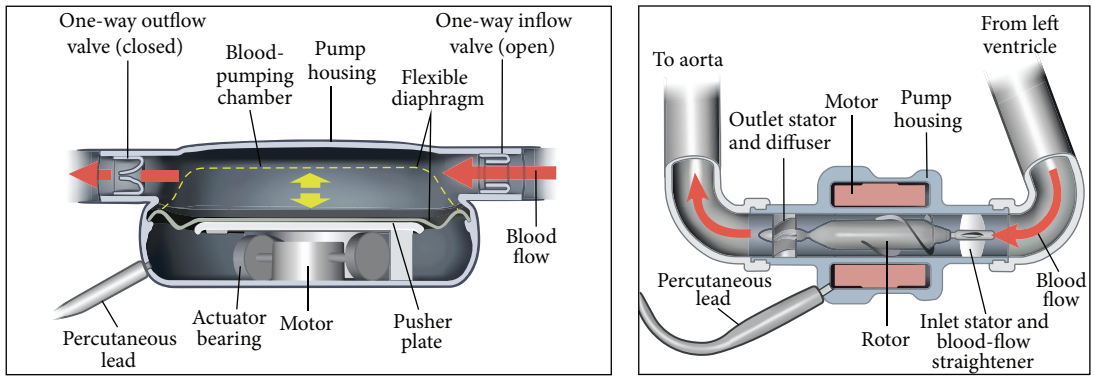


Figure 2: (a) Pulsatile pump. (b) Continuous flow pump.

analysis a similar 1- and 5-year survival and functional class with both surgical procedures (CABG versus CABG plus MV repair) but a significant reduction in MR grade at 1 year by adding MV repair [87].

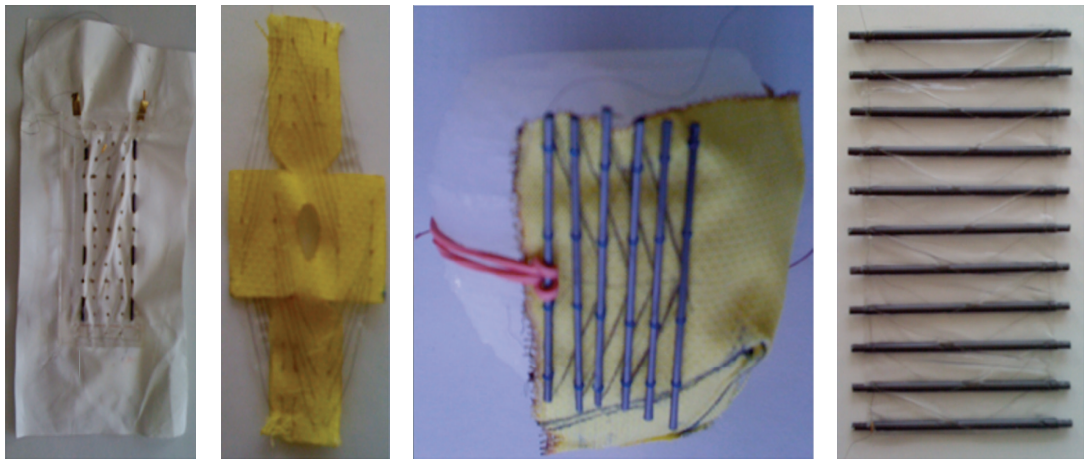
On the other hand, some literature data support the benefit of surgery for FMR. Trichon and coworkers analyzed a wide series of patients with ischemic FMR and found that PCI, CABG, and CABG plus MV repair all obtained a 3-year survival advantage compared to medical therapy in this subset of patients [88]. A retrospective study from the Brigham and Women's Hospital in Boston recently reported an improved survival of patients undergoing mitral valve repair for cardiomyopathy [89]. A recent analysis of more than 1,200 patients enrolled in the STICH Trial for ischemic cardiomyopathy demonstrated that concomitant MV repair in patients with moderate-to-severe FMR who underwent CABG reduces 30-day mortality compared to either patients undergoing isolated CABG or those medically treated [90]. Furthermore, these results were confirmed when 5-year survival was analyzed in the same subgroups of patients [90]. The recently published results from the RIME trial, a randomized controlled multicenter study from United Kingdom, showed that addition of MV surgery to CABG in the setting of ischemic cardiomyopathy resulted in similar 1-year survival, rate of hospital admission, and recurrence of atrial fibrillation; on the other hand, the study demonstrated greater 1-year improvement in the primary end point of peak oxygen consumption in the CABG plus MV repair group compared with the CABG group with a better LV reverse remodeling and a higher reduction in MR grade and in serum BNP values [91].

When nonischemic cardiomyopathy was considered, despite the absence of randomized controlled trials comparing surgery with optimal medical therapy and different techniques of surgery and despite the lack of data of a clear survival advantage potentially obtained with the correction of the functional incompetent mitral valve, recent literature studies all confirmed the beneficial impact of surgery [92–95].

Finally, percutaneous mitral valve therapies are of particular interest in patients at high risk for surgical intervention, including those with secondary MR related to CAD and heart failure. Promising results have been reported from Europe in such patients who remain symptomatic despite optimal medical therapy and CRT [96–98]. Two ongoing randomized trials of transcatheter valve repair versus medical management [99, 100] may clarify whether treating the mitral valve in addition to optimal medical therapy improves outcomes of patients with ischemic MR.

5. New System or New Materials Available for Future Cardiac Assist Devices

The expansion of cardiac transplant centers without any increase in donor supply led to longer waiting lists and longer time to transplantation, during which the prolonged benefit of the LVAD to provide support for over a year became apparent, although the majority of patients required support for shorter periods [101]. The overall survival to transplant after LVAD support has been around 65% during the past 5 years [102]. The next advance was the demonstration that the LVAD could also double survival as permanent "destination" therapy in patients not eligible for transplant. All these devices come hand in hand with a heavy medication, especially anticoagulants, creating a new weakness. The need of an external, anticoagulant-free, and ventricular assistance as a bridge to decision and/or permanent "destination" therapy is indubitable. A growing number of heart devices and machines are being used in heart failure treatment [103–107]. Ventricular assist devices (VADs) are machines that help improve pumping. They have gained well-known approval for use as a bridge to transplant in patients who are on medications but still have severe symptoms and are awaiting a donor heart. Nevertheless, more and more doctors are exploring the possibility that such devices may be adequate treatments themselves, preventing the need for a transplant in some patients. Therefore, they may be used as short-term (less than 1 week) or longer-term support [102, 108–114]. Most of the devices that we are using make an intrusion in the body and more critically in the heart (Figure 2). They are in direct contact with blood and need high doses of anticoagulants to function properly. Recently, we have studied a revolutionary system that seems to address all



(a) (b) (c) (d)

Figure 3: Four different methods to weave Nitinol. From left to right: (a) Nitinol woven on PTFE with a solid U-shaped structure; (b) Nitinol woven on Kevlar in a circular manner; (c) Nitinol woven around a carbon-tube structure fixed on a Kevlar envelope; (d) silicon matrix with carbon tubes and Nitinol weaning weaving.

these drawbacks. The key advantages of this new BiVAD are the biventricular assistance and its external positioning. This last point improves first of all the operative ease and security. Second, there is no direct contact with circulating blood getting rid of anticoagulants and furthermore it lowers the probability of rejection. An additional benefit is the possibility of differential assistance. In other words, this BiVAD is adjustable to any heart presenting left, right, or both sided dilatation [111, 112]. The tool mainly involved in the development of this new assist device is the metal alloy of nickel and titanium (Ni-Ti) Ninitol, where the two elements are present in roughly equal amount. Small changes in composition can significantly impact its properties. This alloy exhibits two closely related and unique properties: shape memory and superelasticity [115–118]. Shape Memory Alloys (SMAs) are a group of metallic materials that demonstrate the ability to return to some previously defined shape or size when subjected to the appropriate thermal procedure [118]. They have an austenitic ("hot") phase in which the material is generally stiffer and has a higher yield point, and a martensitic ("cool") phase which is less stiff and has a lower yield strength. In the low temperature, crystal phase they are generally superelastic. This means they can be deformed far more than other metals (approx. 10–20 times) of the same general family. They can be formed into a shape at higher temperature, cooled, and then formed to a different shape at room temperature. When heated, they return to the shape they had at the higher temperature. This may be repeated through several million cycles. There are several known metal combinations that have these properties. Nickel-Titanium (Ni-Ti or Nitinol) has proven to be the most flexible and useful SMA in engineering applications so far. It has greater ductability, more recoverable motion, excellent corrosion resistance, stable transition temperatures, high biocompatibility, and the ability to be electrically heated for shape memory recovery.

Several designs are under study [119–123]. One of them is based on a configuration where the Nitinol wires could be weaved on a tissue or a membrane that would be in direct contact with the heart walls. Besides, the wires deliver the highest force when weaved with an angle of 20° between each other. There are many ways to arrange a wire with this angle; one of those was an accordion like structure weaved on Kevlar or Teflon (polytetrafluoroethylene, PTFE). Another configuration is to realize a spiraling pattern keeping the idea of the 20° angle. Lastly, another solution is to use a solid structure surrounding the heart between each ventricle (Figure 2). Thanks to this carbon structure, the Nitinol wires can be attached and pulled until they are tightened around each ventricle. It is now possible to have different configurations surrounding each ventricle. In addition to that, two different wire lengths were tried. Either there was a unique wire going several times from one side of the structure to the other or there were many wires for each come and go (Figures 3–5).

6. Conclusions

The modern approach to the diagnosis and treatment of heart failure is multidisciplinary and should be based on a close collaboration among researchers, clinicians, and cardiac surgeons, particularly given that mandatory multiorgan attention is required in these high risk patients.

Future therapies for heart failure could include ventricular assist devices implantation or ventricular restoration techniques with the aim to obtain a reverse, positive remodeling in the unloaded heart.

With an expanding "toolbox" of comprehensive basic, medical, surgical and technological approaches, it is expected that these novel findings will soon be translated to the clinical practice. In fact, new therapeutic strategies are desperately needed by the millions of patients suffering from heart failure.

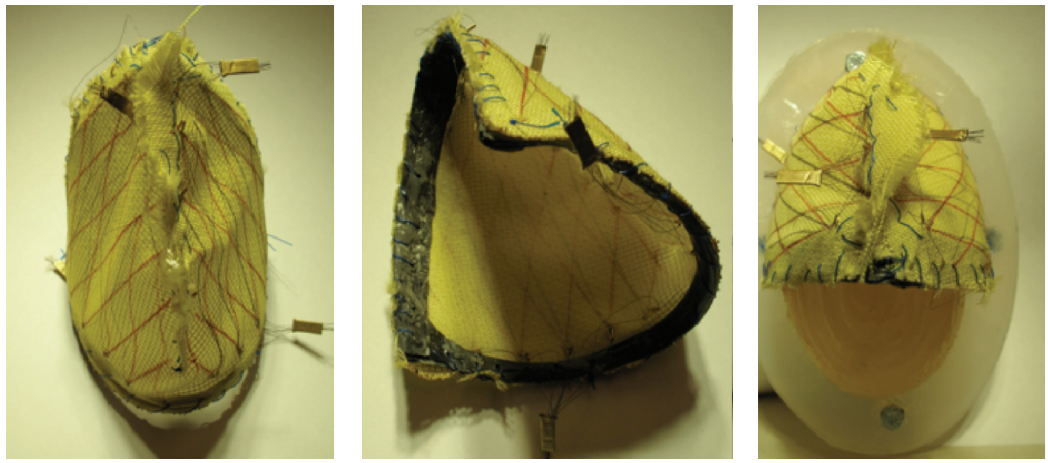


Figure 4: Ventricular "envelope" with a Nitinol woven structure on both sides.

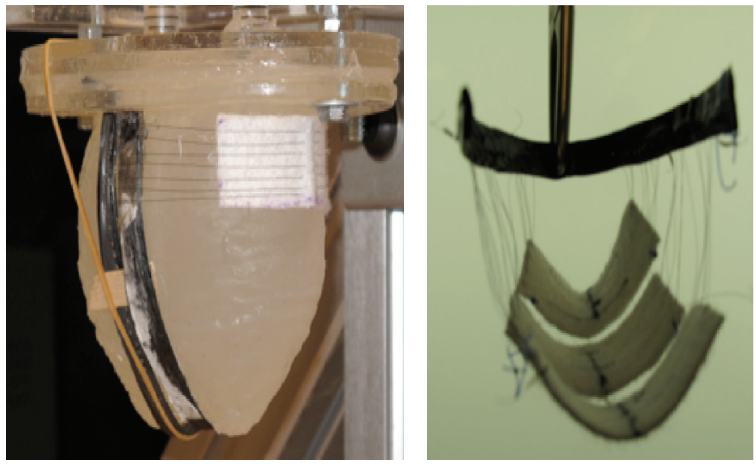


Figure 5: Wires around the ventricle with a slice of PTFE between the wall and the wires.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Recent Advances on Pathophysiology, Diagnostic and Therapeutic Insights in Cardiac Dysfunction Induced by Antineoplastic Drugs

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Along with the improvement of survival after cancer, cardiotoxicity due to antineoplastic treatments has emerged as a clinically relevant problem. Potential cardiovascular toxicities due to anticancer agents include QT prolongation and arrhythmias, myocardial ischemia and infarction, hypertension and/or thromboembolism, left ventricular (LV) dysfunction, and heart failure (HF). The latter is variable in severity, may be reversible or irreversible, and can occur soon after or as a delayed consequence of anticancer treatments. In the last decade recent advances have emerged in clinical and pathophysiological aspects of LV dysfunction induced by the most widely used anticancer drugs. In particular, early, sensitive markers of cardiac dysfunction that can predict this form of cardiomyopathy before ejection fraction (EF) is reduced are becoming increasingly important, along with novel therapeutic and cardioprotective strategies, in the attempt of protecting cardiooncologic patients from the development of congestive heart failure.

1. Introduction

The prognosis of cancer has dramatically improved in the last decades: several types of malignancies can be now cured or maintained in remission for a long time and patients can live the remainder of their lives free of disease. However, they are also exposed to chronic complications of antineoplastic treatments. Many classes of chemotherapeutic drugs can impair cardiovascular homeostasis and favor or even trigger cardiovascular disorders. The more the survival of oncological patients increases, the higher is the likelihood that cardiovascular consequences of cancer therapies become the major health problem after tumor elimination is achieved. The most common side effects of anticancer treatment include vasospastic and thromboembolic ischemia, arterial hypertension, arrhythmia, and cardiac dysfunction up to heart failure (HF) [1, 2]. The latter is an especially fearful long-term complication of chemotherapy because it remains a slowly progressing condition that ultimately can only be resolved by heart transplantation. Nevertheless, this procedure can be offered only to a small percentage of subjects due to the limited availability of donor organs. In fact, the number of heart transplants has remained static worldwide and the number of heart transplants performed each year in the United States has plateaued at about 2100 for the past few years (2001 Heart and stroke statistical update. Dallas: American Heart Association, 2000).

Here we first give an updated overview of the main characteristics and mechanisms of chemotherapy-associated cardiac toxicity, since a thorough knowledge of this

phenomenon can provide important hints to predict, treat, and prevent it. Special attention is paid for chemotherapy-related cardiac dysfunction, in the light of the clinical and social burden of heart failure that may ensue [3, 4]. Next, we examine the approaches that have already been implemented in clinical practice or are currently being investigated for the prompt diagnosis and effective management of chemotherapy cardiotoxicity.

2. Classification of Chemotherapy-Related Cardiotoxicity

Left ventricular (LV) dysfunction induced by *anthracyclines* has historically been the most relevant form of chemotherapy cardiotoxicity [7]. Nevertheless, new oncological drugs, such as intracellular signaling inhibitors, may be also cardiotoxic, as they target pathways that also play a major role in the maintenance of cardiac homeostasis, especially when during stressful conditions, such as hypertension or hypertrophy [1]. For instance, *human epidermal growth factor receptor 2 (HER/ErbB2)* and *angiogenesis inhibitors*, which have entered clinical practice in relatively recent years, profoundly affect cardiac metabolism and contractile proteins (for important reviews on such mechanisms, please refer to [2, 8–12]). This type of toxicity does not display cardiomyocyte disruption, is most often reversible with treatment discontinuation, and has been named type II LV dysfunction [13]. Conversely, cardiotoxicity produced by anthracyclines is typically irreversible, with marked ultrastructural myocardial derangements, and is referred to as type I [13]. However, these two paradigms of cardiotoxicity may overlap: for example, the anti-ErbB2 antibody, *trastuzumab*, can trigger irreversible cardiac damage in patients previously treated with anthracyclines [14].

3. Cardiotoxicity of Anthracyclines

Anthracyclines are antibiotics belonging to the family of rodomicine, originally isolated from *Streptomyces peucetius*, with very potent antineoplastic activity [15]. In particular, *doxorubicin* and *epirubicin* are currently the cornerstone of treatment of many malignancies, including breast cancer, lymphomas, and sarcomas. It has been estimated that approximately 10% of patients receiving doxorubicin or its derivatives will develop cardiac complications, even up to 10 years after the completion of chemotherapy [1]. However, endomyocardial biopsy studies and seriate measurements of troponin I have revealed that cardiac cell alterations already occur during or a few hours after exposure to anthracyclines, regardless of when clinical manifestations appear. Furthermore, an early and subclinical deterioration of systolic function can be detected in most patients exposed to anthracyclines with Tissue Doppler or Speckle Tracking echocardiography [16, 17]. The delay between cardiac injury and clinical presentation may be explained by the fact that anthracycline cardiotoxicity is temporarily compensated for by the activation of protective signaling pathways and by a myocardial functional reserve [18, 19].

The probability of developing anthracycline cardiomyopathy is primarily dose dependent [20]. Additional risk factors are genetic predisposition, very young or old age, female gender, intravenous bolus infusion, hypertension, diabetes mellitus, preexisting cardiac disease, previous or concurrent mediastinal radiation therapy, and combination with alkylating or antimicrotubule chemotherapeutics [1, 21–26]. Thus, accurate medical history may be helpful in identifying individuals susceptible to anthracycline cardiotoxicity. However, it should be noted that many of the aforementioned risk factors have been identified over relatively short follow-up periods and that long-term investigations are needed to confirm their relevance [1].

3.1. Molecular Mechanisms of Anthracycline Cardiotoxicity. *Anthracyclines* are DNA intercalating agents that form a ternary complex with topoisomerase 2. This enzyme transiently breaks the DNA backbone to untangle the supercoiled DNA complex in a process required for transcription, replication, and recombination [2, 27, 28]. Under physiological conditions topoisomerase 2 reanneals the cut strands. Conversely, when the complex with anthracyclines is formed, the relegation is inhibited resulting in an uncontrolled occurrence of DNA strand breaks. The resulting cascade of molecular events, referred to as DNA damage response, eventually leads to mitochondrial dysfunction and accumulation of reactive oxygen species (Figure 1) [27]. Consistent with this model, *doxorubicin* cardiotoxicity is prevented in mice knockout for the gene encoding the cardiac isoform of topoisomerase 2 [27]. Besides eliciting the DNA damage response, anthracyclines also cause the formation of reactive oxygen species by accepting and immediately releasing electrons onto the oxygen molecules present inside the cardiomyocyte, especially in mitochondria [15, 27–31]. Furthermore, anthracyclines induce the intracellular accumulation of iron and form complexes with it, further inducing the production of free oxygen radicals via metal-catalyzed oxidoreductions [15, 29–31]. The DNA damage response and oxidative stress initiate a number of secondary cellular alterations, such as changes in calcium homeostasis and abnormalities of the contractile apparatus [15, 29–31]. At the ultrastructural level loss of myofibrils, dilation of the sarcoplasmic reticulum and cytoplasmic vacuolization are observed [15, 29–31]. Eventually, cardiomyocytes may die or undergo senescence following exposure to anthracyclines [32]. This can be because of direct toxicity of anthracyclines or as a result of the impairment of antiapoptotic signaling axis. For instance, our recent work has pinpointed a state of resistance to insulin-like growth factor-1, a hormone fundamental for cardiomyocyte survival, as a mechanism of doxorubicin-triggered death of cardiac cells [33, 34]. It has been proposed that apoptosis and senescence of cardiac progenitor cells chiefly contribute to the pathogenesis of anthracycline cardiomyopathy, as depletion of these cell population hinders the ability of the heart to regenerate in response to minor injuries which, thereby, accumulate and affect cardiac structure and function [35, 36].

Moreover, it is conceivable that anthracyclines also alter the activity of cardiac fibroblasts and the turnover of the

myocardial extracellular matrix. Doxorubicin enhances the expression of MMP2 and MMP9, thus weakening the collagenous matrix and contributing to myocardial remodeling [15, 37, 38]. Indeed, fibrosis is observed in hearts that have been exposed to doxorubicin [36] and may impinge on both diastolic and—via misalignment of cardiomyocytes—systolic function.

Anthracyclines also induce a local immune response, with the involvement of dendritic cells and distinct subsets of T lymphocytes, which may underlie part of the antineoplastic effect [39]. However, immune activation and inflammation may be harmful to the heart. Since anthracycline-triggered inflammation is at least in part secondary to the activity of IL-1β, suppression of the latter might blunt some of the adverse inflammatory effects that complicate chemotherapy with anthracyclines [40].

3.2. Other Agents. *Mitoxantrone* is an anthracycline analog that can damage myocytes, resulting in LV dysfunction similarly to anthracycline [1, 41]. Large single doses of *cylophosphamide* are able to cause hemorrhagic cell necrosis, bringing to heart failure or even death. Such toxic effects are seen very rarely since lower doses are being used these days [1, 42]. Another drug that has been linked to late-onset LV dysfunction (milder than anthracyclines) is *cisplatin* [1, 43].

Also, *taxanes* such as *paclitaxel* and *docetaxel* are antimicrotubule agents that bind to tubulin, thus impairing the disassembly of microtubules and inhibiting cell division. They are widely used in the treatment of multiple malignancies. The incidence of HF associated with such drugs, according to retrospective analysis, is relatively low (1.6% among patients treated with docetaxel-doxorubicin-cyclophosphamide and 0.7% for those treated with 5-fluorouracil-doxorubicin-cyclophosphamide) [44, 45].

The antimetabolite *5-fluorouracil (5-FU)* has been shown to cause angina-like chest pain and, in rare cases, myocardial infarction, arrhythmias, LV dysfunction, and sudden death [46–48]. In animal models, direct toxicity on the myocardium has been postulated. This could be due to myocardial accumulation of citrate that has been attributed to generation of fluoroacetate (formed from the degradation of 5-FU parenteral preparation) and can interfere with the Krebs cycle [48–51]. Also 5-FU can induce dose- and time-dependent depletion of high energy phosphates, apoptosis [48, 51–53], autophagy, ROS elevation, and senescence of cardiomyocytes and endothelial cells [54].

4. Cardiotoxicity of Type II Agents

4.1. Anti-ErbB2 Agents. The first and most widely used type II cardiotoxic drug is *trastuzumab*, a humanized monoclonal antibody against the extracellular domain IV of HER/ErbB2 [8, 9].

ErbB2 (also called HER2) is a member of the epidermal growth factor receptor family. Upon ligand binding, these transmembrane receptors homo- or heterodimerize, undergo transphosphorylation, and initiate a number of cellular responses. As no specific ligand for ErbB2 has been identified so far, it is believed that it normally functions as a dimerization partner of the other ErbBs [9]. By contrast, ErbB2 is overexpressed in about 30% of breast cancers, in which it spontaneously interacts with the other ErbBs independent of ligand stimulation, and triggers signaling cascade promoting tumor growth and survival [55]. Trastuzumab is highly effective in treating ErbB2-positive breast and also gastric cancers. However, it also causes cardiac dysfunction in a substantial proportion of patients, which was found to peak to 28% when trastuzumab is coadministered with anthracyclines [56, 57]. In fact, this association is now avoided.

As a class II cardiac dysfunction [58], trastuzumab-induced cardiac dysfunction appears to arise from impairment of contractility rather than loss of myocytes, and the release of troponin shown in sequential treatment with anthracyclines + trastuzumab seems to be ascribed to the previous chemotherapy [59]. EF is likely to recover and there is evidence that it is relatively safe to readminister trastuzumab after it has been discontinued and myocardial function has returned to baseline [13].

Pertuzumab is another, more recent anti-HER2 antibody that binds to the domain II of the receptor. A third HER2-targeting agent is *lapatinib*, a small molecule inhibitor of the intracellular tyrosine kinase domain of HER2. Trastuzumab only disrupts ligand-independent HER2 signaling; conversely, pertuzumab interferes with the formation of ligand-induced HER2 heterodimers. Lapatinib affects both ligand-triggered and ligand-independent HER2 signaling [9]. Interestingly, lapatinib seems to be less toxic than trastuzumab. Data about the toxicity of pertuzumab are limited [57].

Cardiotoxicity of HER2-targeting drugs has been ascribed to the inhibition of fundamental actions of neuregulin-1 in the heart [57, 60]. Neuregulin-1 acts on cardiac cells via ErbB4/ErbB4 homodimers and ErbB4/ErbB2 heterodimers to elicit protective pathways in response to stress (Figure 1) [60]. By blocking neuregulin-1 effects in the heart, HER2 inhibitors may make it more vulnerable to noxious stimuli, among which anthracyclines. Consistent with this interpretation, mice with cardiac-specific deletion of ErbB2 show dilated cardiomyopathy, with increased susceptibility to cardiomyocyte death after anthracyclines [61]. The ErbB2 pathway is required for cell survival and continuing function and seems to be activated when the myocardium faces adverse hemodynamics or other stress, such as anthracycline therapies [62]. Upon withdrawal of trastuzumab, the normal ErbB2 pathway is reestablished, and the declined EF can return to normal, opposite to anthracyclines that produce a type I toxicity with permanent myocyte dysfunction. This is consistent with the increase in cardiotoxicity when trastuzumab is associated with anthracyclines: trastuzumab enhances or even uncovers the damage caused by anthracyclines. Once ErbB2 inhibitors block the ErbB2-triggered repair mechanisms, the oxidative damage induced by anthracyclines proceeds without control [59]. Indeed, experimental studies have shown that neuregulin 1 modulates doxorubicin damage in rat cardiomyocytes [14, 57, 63, 64].

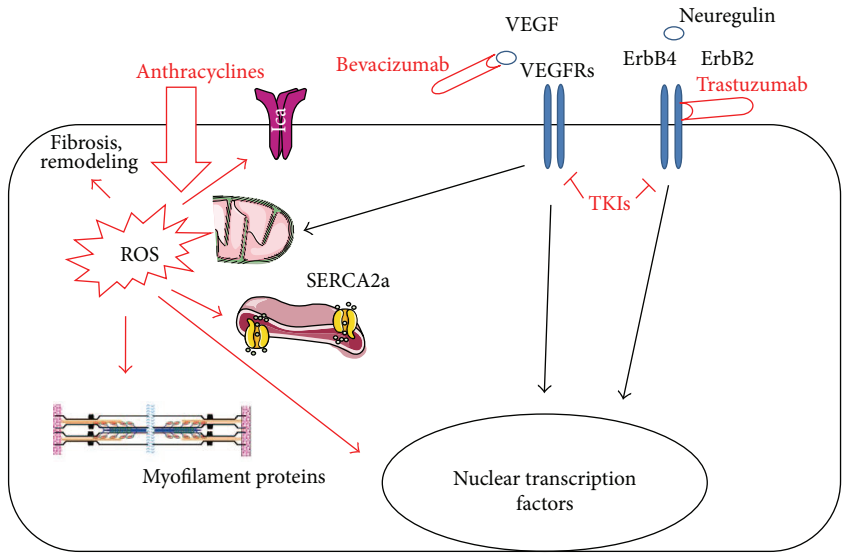

Figure 1: Schematic representation of the main mechanisms by which cardiomyocytes are damaged by the most cardiotoxic anticancer agents among those currently in use. Anthracyclines induce a DNA damage response and reactive oxygen species (ROS) production; these two initial events result in a cascade of secondary alterations affecting mitochondrial integrity and function, intracellular calcium dynamics, and contractile proteins. By blocking the activity of tyrosine kinase receptors, such as vascular endothelial growth factor receptor (VEGFR) or ErbB2/ErbB4, bevacizumab, trastuzumab, and tyrosine kinase inhibitors (TKIs) alter mitochondria and modulate gene expression. SERCA2a: sarcoendoplasmic reticulum calcium ATPase. Black arrows indicate physiologic, homeostatic effects. Red arrows indicate deleterious effects. Modified from [5, 6].

With its cardioprotective features, neuregulin is now being intensively studied in clinical trials as a therapeutic for heart failure [65].

4.2. Antiangiogenic Drugs. Among drugs that induce type II cardiotoxicity we have to acknowledge antiangiogenic drugs. In particular, *bevacizumab*, *sorafenib*, and *sunitinib* are now widely used in oncology; more recently, *pazopanib* and *vandetanib* have also been approved by the US Food and Drug Administration [1, 66, 67]. All these drugs interfere with vascular endothelial growth factor (VEGF) signaling (Figure 1). As VEGF contributes to cardiomyocyte function and growth on the one hand and to the integrity and expansion of the coronary and systemic circulation on the other one [8, 10, 11, 45, 67–70], it is not surprising that VEGF antagonism may lead to cardiovascular side effects, principally hypertension, thromboembolism, LV dysfunction, and HF [71–73]. Indeed, like cancer, the heart is highly dependent on adequate perfusion for its normal function [8, 10, 11, 45, 67–70], both relying on similar HIF-1 and VEGF pathways. Indeed, the inhibition of HIF-1 by p53 causes cardiac dysfunction during chronic pressure overload [74], and conditional expression of a VEGF scavenger caused microvessel rarefaction and myocardial hibernation which was fully reversible even months after switching off the expression of the scavenger [75, 76]. These data suggest that the heart is especially sensitive to antiangiogenic therapies in the setting of hypertension-related pressure overload.

Bevacizumab is an antibody, which binds specifically to circulating VEGF-A (that activates signaling in endothelial cells), and is currently approved for the treatment of advanced carcinoma of the lung, breast, and colon-rectum [77, 78]. Bevacizumab has been reported to induce LV dysfunction in 1% of chemotherapy-naïve patients and 3% of patients who have already received chemotherapy [79]. Instead, sunitinib and sorafenib, which are used in metastatic renal cancer and in imatinib-resistant gastrointestinal stromal tumors [72, 80], belong to the class of small molecule tyrosine kinase inhibitors. They are not very selective and also block signaling cascades other than the one of VEGF [10]. In particular, sunitinib inhibits more than 30 other receptor and nonreceptor tyrosine kinases, including c-Kit, platelet-derived growth factor receptor (PDGFR) alpha and beta, rearranged during transfection (RET), FMS-related tyrosine kinase 3 (FLT3), and colony-stimulating factor 1 receptor (CSF1R) [8, 10, 39, 81], which may be why it appears to be more cardiotoxic than other angiogenesis inhibitors, with a reported decrease in EF in up to 28% of treated patients [82–85]. Seminal studies [86–90] have proven the importance of these pathways in cardiovascular homeostasis. The higher incidence of sunitinib cardiotoxicity is also explained by inhibition of off-target kinases, such as ribosomal S6 kinase (RSK), with consequent activation of the intrinsic apoptotic pathway, and 5′ AMP-activated protein kinase (AMPK, important for the response to energy stress), with worsening of ATP depletion [8, 91]. Therefore, LV dysfunction would occur due to myocyte dysfunction. In mice treated with sunitinib and exposed to pressure load, Chu and colleagues [82] observed that cardiomyocytes exhibited opening of the mitochondrial permeability transition pore and marked mitochondrial swelling with destruction of the normal mitochondrial architecture. Moreover, direct administration of

sunitinib on different myocardial preparations results in a dose-dependent inotropic effect, accompanied by decline in intracellular Ca^{2+} and increased reactive oxygen species (ROS) production [67, 92].

At clinically relevant concentrations in *in vitro* kinase assay, sorafenib inhibits at least 15 kinases, including VEGF receptor, PDGFR, Raf-1/B-Raf, c-Kit, and FLT3 [8, 10, 67]. The rate of cardiotoxicity associated with sorafenib is not yet clear. Two meta-analysis, including almost 7000 patients treated with sunitinib and 900 patients treated with sorafenib, found a 4.1% rate of sunitinib-induced HF and 1% for sorafenib-associated cardiac dysfunction [93, 94], but most of these data are from retrospective analyses; only few trials have evaluated cardiac function and HF prospectively. Schmidinger and colleagues [71] reported that 3 out of 14 patients treated with sorafenib who experienced cardiac events showed abnormal EF.

Interestingly, a recent work from the Paolocci group [95] reported that a tyrosine kinase-receptor such as TrkB, with its endogenous ligand BDNF, is able to modulate the cardiac excitation-contraction coupling process directly, independently and in parallel to G protein-coupled receptor signaling. Such findings corroborate the concept that tyrosine kinase inhibition during anticancer therapies can disrupt important signaling, leading to consequent derangements in cardiac mechanical work that may largely contribute to loss in LV function [96].

Significant hypertension is seen with all three major antiangiogenic agents [97]. Bevacizumab results in a more serious form of hypertension that, at least in some instances, does not reverse with the removal of the offending agent. Remarkably, it has been suggested that drug-induced hypertension may be a biomarker of anticancer efficacy since patients who developed hypertension survived longer than those who did not [98]. In the work of Scartozzi and colleagues [99] on metastatic colorectal cancer patients, 20% of patients developed grade 2-3 hypertension. A partial remission was observed in 75 % of patients with bevacizumab-related hypertension and only in 32% of those without hypertension. Furthermore, patients who developed grade 2-3 hypertension had significantly longer progression-free survival than nonhypertensive patients [99].

4.3. Other Type 2 Agents. The BCR-ABL inhibitors, *imatinib* and *dasatinib*, are tyrosine kinase inhibitors used for treatment of chronic myelogenous leukemia and gastrointestinal stromal tumors. These two drugs were initially reported to induce HF, but large follow-up studies did not confirm such data [1, 100, 101].

5. Assessment and Treatment of Cardiac Damage during Cancer Treatment

Assessment of anticancer drug-related cardiotoxicity is an essential procedure before, during, and after treatment with these drugs. The majority of currently used methods used to assess cardiac function cannot differentiate between irreversible and reversible cardiotoxicity and may mislead physicians to stop potentially lifesaving cancer therapies. Cardiovascular side effects such as myocardial ischaemia, arterial hypertension, and dysrhythmia can be readily diagnosed, but detection of cardiac dysfunction is more challenging [1].

Preclinical screening for cardiotoxicity is fundamental for kinase inhibitors. Much preclinical screening focuses on the hERG (K^+ channel) assay because many drugs increase risk of arrhythmia. Primary cell cultures of human cardiomyocytes dedifferentiate and die quickly over time; therefore, they are not a good reflection of what happens *in vivo*. In the future, stem-cell-based assays and assays based on the use of engineered heart tissue could be used. These assays could integrate effects on membrane action potential, calcium handling, myofilament function, gene expression, and cell survival [1, 8, 9, 11, 66, 67, 103].

For initial screening and detection of cardiac dysfunction in oncologic patients, along with ECG and physical assessment, noninvasive imaging with echocardiography or MUGA (Multiple Gated Acquisition) scans are now commonly used in cancer patients [1, 45, 57, 104, 105]. These methods are useful for evaluating patients for cardiotoxicity but have limited accuracy for risk stratification [1]. Attention should be paid not only to systolic but also to diastolic cardiac function. It should be noted that patients with advanced cancer may already have cardiovascular abnormalities such as fatigue, dyspnea, malaise, and propensity to severe arrhythmia. Distinguishing these from side effects attributable to cancer therapies requires a specific expertise.

One important and very active field of research is the search of new indexes of cardiac function other than the ejection fraction [106, 107]. Although strong outcomes data support MUGA for estimation of LVEF, such methodology is limited by radiation exposure. On the other hand, echocardiographic EF measurement is to be preferred for its simplicity and availability, but has the downside of being variable and insensitive [108]. Indeed, the normal heart has a huge recruitable contractile potential; therefore it must have undergone a considerable damage and myocyte loss in order for EF to be decreased [109]. On such basis, it is important to use other markers for cardiac function in the diagnostic armamentarium [57, 59, 105, 109–116]. More sensitive techniques to be used in the cardiotoxicity settings could be contrast that increases border definitions, enhancing accuracy and limiting interobserver variability [117–119], while echo-stress could evidence undiagnosed functional changes [119–121]. Tissue Doppler and strain techniques have been shown to detect anthracycline-induced cardiac dysfunction earlier than conventional echocardiography, but it is not known if these methods have a higher specificity to detect type I cardiotoxicity [122]. Instead, other superior imaging methodologies such as cardiac magnetic resonance (CMR) look promising (Table 1). A downside of this methodology is its limited availability, but it can provide improved accuracy and reproducibility of EF measurements [108]. Also, it has the unique property of characterizing the myocardial tissue, identifying myocardial inflammation, edema, and strain [119]. Other explored modalities include the use of the uptake of iodine-123-metaiodobenzylguanidine (MIBG), a radiolabeled analogue of norepinephrine, which decreases

Table 1: Current insights in prevention, monitoring and treatment of cardiac dysfunction induced by anticancer drugs. Modified from [102].

Prevention	Monitoring	Treatment
Alternative anticancer strategies Reduced chemotherapeutic dose Liposomal formulations Less toxic alternatives (epirubicin, lapatinib) *Better patients selection* Age Cardiac risk Cardiac function *Use of cardioprotective drugs* β-blockers ACE inhibitors ARBs Dexrazoxane Statins	*Imaging* Assess the best modality Assess the best frequency *Biomarkers* BNP Troponins Novel markers (MPO?)	Hold or stop antineoplastic treatments Start HF therapies

following cardiac damage [119, 123, 124]. Additionally, actomyosin antibodies could be used to detect myosin exposed after myocardial injury [119, 125, 126]. Finally, a predictor of cardiotoxicity may also be the uptake of radiolabeled chemotherapeutics [119, 127, 128].

The use of cardiac biomarkers (Table 1) can solve the limitations of cardiac imaging to stratify the risk in cancer patients with cardiac dysfunction. Cardiac biomarkers such as troponins and natriuretic peptides may be expected to be elevated with significant cardiotoxicity. Patients treated with anthracyclines showed a transient increase in brain natriuretic peptide (BNP), but the predictive value for long-term cardiotoxicity may be limited when such marker is used alone [129, 130]. Instead, troponins I and T have been shown to predict late anthracycline cardiotoxicity in children [131], and in an adult population they can identify anthracyclines-treated patients that can benefit from ACE-inhibitors [132]. In spite of these promising results, the assessment of cardiac biomarkers is not being performed routinely in patients undergoing cancer treatment, and multicentre trials to evaluate the role of biomarkers in this population are a need [1]. A 2014 study from Ky et al., while confirming TnI to be associated with LV dysfunction in patients with breast cancer undergoing sequential therapy with doxorubicin and trastuzumab, also showed that a marker of oxidative stress such as myeloperoxidase (MPO) could be mechanistically relevant to cardiotoxicity with cancer therapy [133].

All things said, there is no current established algorithm for preoncologic treatments evaluation and follow-up of patients during and after cancer therapies. Nevertheless, we need to avoid that patients who survive cancer today develop cardiac dysfunction tomorrow. Therefore such patients should be strictly monitored by both cardiologists and oncologists [134]. In patients with indication for anticancer therapies, a first step would be to evaluate the cardiovascular risk (Table 1). This should be done on the basis of the identification of concomitant cardiovascular diseases and potential cardiovascular complications before anticancer treatments are started, keeping in mind that preexisting hypertension and heart diseases are common in oncologic patients. All in all, clinicians need to recognize and treat cardiovascular risk factors (hypertension, diabetes, current and previous cardiovascular disease, subclinical organ damage previously documented by ECG or echocardiography or carotid ultrasound study, established or subclinical renal disease, age, smoking, dyslipidemia, family history of premature cardiovascular disease, and abdominal obesity) in order to allow long-term continuous therapy with anticancer drugs [1, 45, 57, 67]. Age is indeed an important factor, with elderly patients being at higher risk of both type 1 and type 2 cardiotoxicity [1]. Interestingly, anthracyclines are used for cancer in children, too, and both elderly patients and children can develop LV dysfunction at lower cumulative doses [1, 22, 23]. Indeed the Childhood Cancer Survivor Study showed that, 30 years after anthracyclines, 73% of pediatric cancer survivors would develop at least 1 chronic condition, while 42% would develop a serious life threatening condition or even die of a chronic condition [48, 135]. Greater susceptibility to anthracycline cardiotoxicity has been associated also with female gender [26]. This may be due not only to differences in the pharmacokinetic of anthracyclines between the two sexes, but also because of protection conferred by androgens. Indeed, unpublished data from our laboratory show that testosterone reduces the toxicity of doxorubicin in cultured cardiomyocytes. Finally, it has to be acknowledged that, besides elderly and children, there is a certain risk of cardiotoxicity with occupational exposure to antineoplastic drugs in health care workers, through inhalation of vapors or skin contact with drops. This is particularly true for anthracyclines, while there is no clear evidence of 5-FU cytotoxicity, although there can be chest pain, aspecific ECG disorders, and induction of coronary disease [136].

A complete history and examination, with ECG and blood pressure measurement, are absolutely indicated. Careful monitoring and treatment of blood pressure throughout therapy with angiogenesis inhibitors is important [66, 103]. In such patients, ACE inhibitors, angiotensin receptor blockers (ARBs), and beta-blockers are to be preferred, especially considering that they are effective in preventing HF (Table 1) [67]. The US National Cancer Institute has recently published recommendations to maintain patients' blood pressure at lower than 140/90 mmHg [66, 103].

In spite of the above-mentioned limitations about EF monitoring, Suter and coworkers have proposed an EF based algorithm [1, 137] (EF decreases by 15% points or 10% points to a value below 50) which is easy to follow and can be combined with troponins and BNP. On such basis, when LV dysfunction is detected, systolic function should be reevaluated after 3 weeks, and eventual standard HF treatments can be started [1, 45, 57, 67]. If life expectancy is good, aggressive therapies with devices can also be considered [1, 138]. The priority for oncologic patients is reintroduction of anticancer treatments, even if cardiac therapies are concomitantly administered. Therefore strict monitoring of cardiac function is necessary. At the end of cancer treatments, EF should be monitored to check for late cardiotoxicity 6 months after the conclusion of the therapeutic regimen, then yearly for 2-3 years, and then every 3–5 years for life [1].

6. Novel Potential Perspectives in Prevention of LV Dysfunction Induced by Antineoplastic Drugs

According to the 2013 Focused Update of the AHA HF Guidelines, in order to prevent the onset of HF, patients on anticancer drugs should be considered as stage A HF patients [139]. This stage identifies patients at high risk of developing HF, but without structural heart disease or symptoms of HF yet. On such basis, patients on cardiotoxic agents should undergo noninvasive evaluation of LV function with imaging tests and biomarkers (Table 1). HF symptoms and signs should be monitored; cardiovascular risk factors should be addressed. Current strategies to prevent cardiotoxicity (Table 1) include regulation of infusion times to limit peak serum concentrations of anthracyclines, use of liposomal anthracyclines, use of chemotherapy regimens not containing anthracyclines, administering anthracyclines and trastuzumab sequentially rather than concurrently [44, 137, 140, 141], and implementing schemes of cardioprotection (Table 1) [102]. Although the use of preventive cardioprotective therapeutics has been proposed [142–144], most of the studies on HF induced by anticancer drugs have focused on early detection and attenuation or reversion of signs of LV dysfunction [102, 111, 145].

Until now, the vast majority of the studies on cardioprotection have been performed mostly on anthracyclines and, in the case of breast cancer, on anthracyclines + trastuzumab [30, 146] and have been proposing dexrazoxane [147], ACE inhibitors [148], and statins [149, 150] (Table 1). Interestingly, a recent study has evaluated the use of β-blockers (Table 1) to prevent anthracycline-induced cardiotoxicity. Concomitant β-blocker use may be cardioprotective in patients receiving trastuzumab, anthracyclines, or both [151]. Kalay and colleagues [152] observed that, in patients treated with carvedilol, LV ejection fraction and dimensions do not change with respect to control subject, while undergoing anthracycline chemotherapy. However several preclinical investigations suggest that all β-blockers may not be equally effective in preventing chemotherapy-induced cardiotoxicity [102]. Selectivity for β receptors seems important for cardiac protection from chemotherapy. In animal models of doxorubicin-induced cardiomyopathy, $\beta 2$ receptor-deficient mice develop severe and lethal acute cardiotoxicity, and the additional deletion of $\beta 1$ receptors rescues this completely [153]. Thus, in animals exposed to anthracyclines, $\beta 1$ activation seems to be cardiotoxic, whereas $\beta 2$ activation is cardioprotective. These data suggest that $\beta 1$ selective antagonist, rather than nonselective β blockers, may offer greater protection against anthracycline-induced cardiomyopathy. Molecular mechanisms of cardioprotection from $\beta 2$ receptors activation are activation of prosurvival kinases and decrease in the intracellular concentration of calcium, thus attenuating the mitochondrial dysfunction seen with anthracyclines [154].

Among β-blockers, carvedilol also has well-known antioxidant properties [155] and is able to protect cells against doxorubicin toxicity by reducing oxidative stress and apoptosis [156–158]. The same authors [159, 160] also showed the effects of ARBs in preventing oxidative stress and cardiotoxicity from anthracyclines. Nebivolol, a $\beta 1$ selective antagonist and $\beta 3$ agonist, has also been shown to reduce oxidative stress, decrease markers of myocardial injury, and improve LV function [161].

7. Conclusions

Cancer drugs currently in use and novel agents that target signaling pathways may all cause problems for the heart. Therefore, to prevent the development of heart failure, it is important that oncologic patients are strictly monitored from cardiologists. Indeed, a fundamental component of cardiooncologic strategies is to establish the vital balance of accepting temporary cardiovascular side effects so as not to impede a patient's ability to benefit from cancer treatment. In a patient with metastatic disease, risk of cardiotoxicity becomes a minor concern; instead, in a patient with a good prognosis, the risk of cardiotoxicity becomes more important [1, 57, 134]. Knowledge of the cardiac effects of anticancer agents balanced with knowledge regarding the natural history of the malignancy and the likelihood of tumor response offers such patients the greatest chance for long-term disease-free survival [1].

In the first place, it is important to recognize patients who are at increased risk for developing cardiac dysfunction associated with cancer treatments. The major mechanisms of left ventricular dysfunction are based on the development of oxidative stress [15, 27–31] and inhibition of cell signaling pathways, by new treatment modalities such as kinase inhibitors, that may also be important for the survival and homeostasis of cardiovascular tissue (Figure 1) [8, 10, 11, 67]. Through observation of side effects caused by new anticancer agents, some cardiovascular signaling pathways have become more clearly understood. Indeed, it is important to understand the relevance of such pathways in order to treat heart failure patients and improve longevity and quality of life for cancer patients. Currently, about 20% of all the investments on drug development is dedicated to small molecule kinase inhibitors, the majority of which (about 80%) being in cancer (with little component in inflammatory

and other diseases) [10]. This class is second only to research on drugs targeting G-protein-coupled receptors. Based on the number of kinase inhibitors currently in phase 1 or later clinical trials (about 150 [162]) there appears to be no slowing down in drug development in this area [10]. Beside the fact that this field of research is particularly lucrative, this means that in the next years we are likely going to see a huge increase in the market in the number of compounds which will produce more cardiac dysfunction [10]. In parallel to such increase in drug development, an extremely active field of research is the pursuit of novel strategies to face cardiotoxicity employing new therapeutic approaches or genetic manipulation, miRNAs, and gene transfer [4, 163–172].

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

Marilisa Molinaro and Pietro Ameri share first authorship.

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Review Article

Novel Therapeutic Strategies for Reducing Right Heart Failure Associated Mortality in Fibrotic Lung Diseases

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Fibrotic lung diseases carry a significant mortality burden worldwide. A large proportion of these deaths are due to right heart failure and pulmonary hypertension. Underlying contributory factors which appear to play a role in the mechanism of progression of right heart dysfunction include chronic hypoxia, defective calcium handling, hyperaldosteronism, pulmonary vascular alterations, cyclic strain of pressure and volume changes, elevation of circulating TGF-β, and elevated systemic NO levels. Specific therapies targeting pulmonary hypertension include calcium channel blockers, endothelin (ET-1) receptor antagonists, prostacyclin analogs, phosphodiesterase type 5 (PDE5) inhibitors, and rho-kinase (ROCK) inhibitors. Newer antifibrotic and anti-inflammatory agents may exert beneficial effects on heart failure in idiopathic pulmonary fibrosis. Furthermore, right ventricle-targeted therapies, aimed at mitigating the effects of functional right ventricular failure, include β-adrenoceptor (β-AR) blockers, angiotensin-converting enzyme (ACE) inhibitors, antioxidants, modulators of metabolism, and 5-hydroxytryptamine-2B (5-HT2B) receptor antagonists. Newer nonpharmacologic modalities for right ventricular support are increasingly being implemented. Early, effective, and individualized therapy may prevent overt right heart failure in fibrotic lung disease leading to improved outcomes and quality of life.

1. Introduction

The interstitial lung diseases (ILD) comprise a heterogeneous group of pulmonary disorders with similar clinical and radiographic characteristics. Etiologies range from identifiable environmental and medication exposures to connective tissue diseases. A significant portion of ILD remains idiopathic amongst which the progressive fibrotic lung diseases are the most clinically challenging and carry significant mortality burden [1]. This category includes idiopathic pulmonary fibrosis (IPF), fibrotic nonspecific interstitial pneumonia (FNSIP), chronic hypersensitivity pneumonitis (CHP), and connective tissue disease related ILD (CTD-ILD).

Treatment of ILD is usually targeted at avoiding potential etiologic factors, correction of hypoxemia, and blunting the inflammatory response that ultimately results in fibrosis. Despite advances in medicine, the incidence and mortality of IPF, one of the more common fibrotic lung diseases, continue to rise worldwide. Cardiovascular comorbidities like right heart failure (RHF) and pulmonary hypertension (PH) account for a large proportion of these deaths [2] and an effective approach to the management of these comorbid conditions constitutes an appealing target for improving outcomes and quality of life in this group of patients.

2. Pulmonary Hypertension and Right Ventricular Dysfunction in Fibrotic Lung Diseases

The development of PH in IPF patients has been associated with several mechanistic factors such as poor resting gas exchange, low diffusing capacity of the lungs for carbon monoxide (DLCO), increased desaturation with exercise, and

cardiovascular mediated exercise limitation [3–5]. Although the gold standard for the diagnosis of PH is right heart catheterization, PH can also be assessed with noninvasive modalities with prognostic implications.

More than 60% of patients with end-stage IPF demonstrate mean pulmonary artery pressure (mPAP) >25 mmHg [5–7]. Though the mPAP exceeds 40 mmHg in a fraction of these patients (~9%) [8], the extent of lung function impairment has not been shown to correlate significantly with severity of PH [8]. PH may rapidly progress in the later stages of IPF and other fibrotic lung diseases [4, 6]. The prognostic implications of PH in fibrotic lung disease have been demonstrated with mPAP, pulmonary vascular resistance (PVR), and cardiac index (CI). CI below 2.4 L/min/m^2 has been correlated with a limited life expectancy of several months [9–11]. Radiographic demonstration of right heart dilation and elevated serum levels of brain natriuretic peptide (BNP) also have prognostic significance with worsening PH in these patients [3–5]. Transthoracic echocardiogram (TTE) therefore remains a useful tool in the evaluation of PH and is currently the recommended method for early detection [12, 13]. Systolic PAP measurements by TTE are sensitive (79–100%) and specific (60–98%) for detection of PH especially in the presence of tricuspid regurgitation [14, 15]. Patients with chronic fibrotic lung disease may however experience wide variations in TTE estimations of sPAP necessitating the implementation of more accurate modalities in identification of patients at risk [16, 17]. The current guidelines for echocardiographic assessment of the right heart in adults also recommend the use of tricuspid annular plane systolic excursion (TAPSE) (reference range 1.5–2.0 cm) also referred to as tricuspid annular motion (TAM), a simple and easily reproducible technique which provides measurements of right ventricular annular systolic excursion in a longitudinal plane when evaluated in a standard apical 4-chamber view [18]. Stress echocardiography and newer techniques such as right ventricular function parameters as measured by tissue Doppler (e.g., RV E/Em index) or right ventricular isovolumic relaxation time (RV-IVRT) may yield better indices and improved correlation with survival [10, 19, 20]. The combination of more than one measure of right ventricular function may provide more reliable indices to detect abnormal function [18].

Cardiac MR is an increasingly attractive modality for assessing the pulmonary artery and right ventricle in patients with pulmonary fibrosis [21, 22]. Contrast-enhanced CT scans can also be used to assess right ventricular size; interventricular septal deviation and demonstration of contrast reflux into the inferior vena cava in individuals with PH are specific for the presence of tricuspid regurgitation [23].

3. Etiologic Factors in the Mechanism of Onset and Progression of Right Ventricular Dysfunction

Right ventricular failure commonly complicates chronic PH and is the strongest prognostic factor in this group of patients [24]. Right ventricular failure typically follows RV-PA uncoupling, which occurs when the elevated pulmonary vascular resistance exceeds the intrinsic contractility of the right ventricle. Unlike pulmonary arterial hypertension (PAH) in which disease severity of the distal pulmonary vasculature is thought to play key roles in occurrence of right ventricular hypertrophy and failure, the underlying mechanisms of right ventricular dysfunction in fibrotic lung diseases are not fully understood [25].

Experimental animal models of chronic PH have demonstrated the presence of diastolic dysfunction as an early marker for right ventricular remodeling and increased right ventricular fibrosis even in the absence of heart failure. Defective calcium handling, hyperaldosteronism, and RV-PA uncoupling herald the onset of overt right ventricular failure [26] (Figure 1). Other studies demonstrate that absence of caveolin-1, a structural protein predominantly expressed in fibroblast and endothelial cells, results in marked secondary right ventricular hypertrophy following significant pulmonary hypertension, with elevation of systemic NO levels [27]. This elevation in systemic NO levels which characterizes cardiomyopathy and PH in human and animal models may reduce myocardial contractility and mediate the deleterious effects of various cytokines on intrinsic myocardial inotropic activity [28, 29] (Figure 1).

Significantly elevated circulating levels of TGF-β, a profibrotic mediator that promotes aberrant gene expression and abnormal collagen deposition such as that occurring in pulmonary fibrosis, have been demonstrated in patients with dilated cardiomyopathy and worsening congestive heart failure [30]. TGF-β and IL-10 were also associated with increased pulmonary microvascular pressure and are thought to play key roles in cardiac and pulmonary fibrotic remodeling [30, 31]. TGF-β produced by cardiomyoblasts have been demonstrated to induce airway squamous metaplasia through Smad signaling, a mechanism that could worsen airflow obstruction in individuals with heart failure [32].

Chronic hypoxia appears to modify the response of the right ventricular to pressure overload by the uncoupling of endothelial nitric oxide synthase thereby resulting in an accelerated decline in right ventricular function [33] (Figure 1). Cyclic strain of pressure and volume changes on the right heart result in increased right ventricular wall tension promoting development of myocardial hypertrophy [34–36]. The increased stretch of the ventricular wall upregulates the transcription of the BNP gene thereby increasing cardiomyocyte secretion of BNP [37]. Its inactive metabolite NT-pro-BNP correlates with measures of right ventricular dysfunction as determined by CMR or echocardiography and elevated baseline values (>1,685 pg·mL^{-1}) predict poor prognosis [38–40].

Multiorgan fibrotic infiltration has also been described to result in right ventricular dysfunction. Alstrom syndrome, an autosomal recessive condition characterized by blindness, dilated cardiomyopathy, and metabolic abnormalities, is associated with fibrotic lung disease, glomerulofibrosis, and sensorineural hearing loss [41]. Myocardial evaluation of these patients with cardiac magnetic resonance imaging

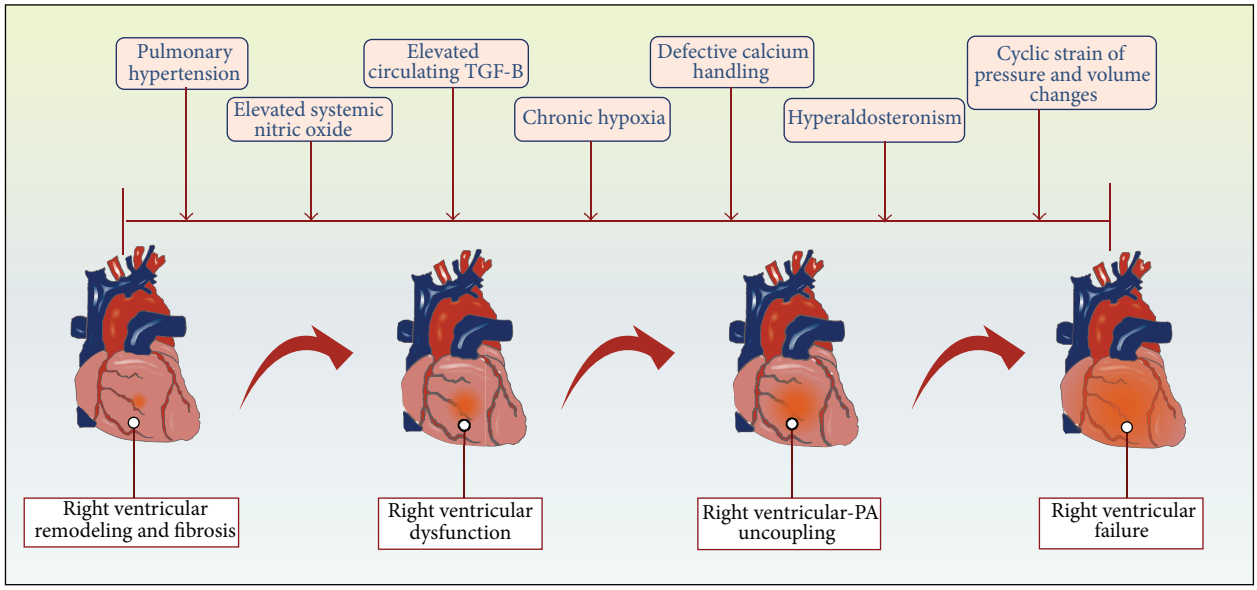

Figure 1: Factors associated with progression to right ventricular failure in fibrotic lung disease.

displays an absence of fluid or fatty infiltration. Instead all patients demonstrate a patchy distribution of myocardial fibrosis involving the left and right ventricles and concomitant impairment of biventricular function [41, 42].

4. Mortality from Right Heart Failure in Fibrotic Lung Disease

The interdependent physiologic mechanisms linking right heart failure to fibrotic lung disease reflect the anatomic proximity of these organs and the overall contribution to morbidity and mortality in patients with both conditions. As the worldwide aging population increased over the last few decades, hospitalizations for cardiovascular disease have also risen, a significant proportion of these due to heart failure [43–45]. The worldwide increase in the prevalence of heart failure and the 5-year mortality carried by this diagnosis exerts considerable socioeconomic impact on the affected individuals and the overall health care system [46]. Similarly, the occurrence of fibrotic lung disease may severely limit the life expectancy of affected patients such as the case in individuals with idiopathic pulmonary fibrosis where the median survival is 2-3 years rivaling that of several cancers [47]. A significant fraction of deaths in this subset of patients has been attributed to heart failure [48].

The contribution of right heart failure to mortality in fibrotic lung diseases involves a broad interplay of several pathophysiologic mechanisms such as structural alteration in the pulmonary vasculature with hemodynamic consequences, disequilibrium of pulmonary fluid homeostasis, occurrence of sleep disordered breathing, and distortion of pulmonary mechanics as evident on lung function testing.

4.1. Pulmonary Vascular Alterations. Despite high pulmonary pressures, which characterize right heart failure in fibrotic lung disease, these patients are less prone to developing pulmonary edema. Studies from autopsy findings and biopsy specimens suggest that the capillary bed undergoes several alterations including increased capillary dilation and thickness of the basement membrane, thickening of the tunica intima, and muscularization and circumferential fibrosis of the pulmonary vessels. These changes are accompanied by increased alveolar wall thickening following excessive collagen deposition, adjacent airway compression, and bronchial smooth muscle hypertrophy, processes amplified in the presence of underlying fibrotic lung disease [49–51]. These vascular alterations appear to decrease capillary filtration rate and increase the level at which hydrostatic pressure produces pulmonary edema [49, 51].

4.2. Impairment of Pulmonary Fluid Homeostasis and Acute Pulmonary Edema. Progressive left heart failure increases left atrial pressure transmitted via pulmonary veins and capillaries to the right heart manifesting as pulmonary hypertension and ultimately right heart failure. Long standing pulmonary hypertension increases tolerance of high pressures with a lower tendency to develop pulmonary edema. However a rapid rise in the capillary wedge pressure may result in pulmonary edema even at low pressures. Elevated hydrostatic forces may partially disrupt the alveolar-capillary unit resulting in pulmonary capillary stress fracture and eventual pulmonary edema [49, 52, 53].

4.3. Sleep Disordered Breathing. The presence of sleep disordered breathing commonly complicates heart failure and the associated sympathetic overactivity results in functional impairment and increased mortality [54, 55]. Up to a third of patients with advanced heart failure exhibit central sleep apnea with increased morbidity and mortality [56, 57]. Also,

the presence of obstructive sleep apnea is an independent risk factor for developing pulmonary hypertension and eventual cor pulmonale [36]. The importance of recognition of sleep-related breathing disorders in idiopathic pulmonary fibrosis has resulted in its categorization by the International Classification of Sleep Disorders (ICSD) to a unique group, "sleep disorders with sleep-related hypoventilation and hypoxemia in parenchymal or vascular lung diseases" [58] most recently reclassified in 2014 to the specific subgroup, "sleep-related hypoxemia disorder" [59]. This is a result of the peculiar pattern of oxygen desaturation that characterizes this group of patients. These individuals exhibit multiple phasic oxygen desaturations which occur frequently from hypoventilation and may eventually lead to sleep fragmentation and poor quality of sleep [60].

4.4. Impact of Heart Failure on Pulmonary Function Testing. Studies examining the altered lung function in patients with decompensated heart failure are few. Patients acutely hospitalized for heart failure appear to have increased pulmonary resistance and demonstrate reduction in lung compliance, total lung capacity, FEV1, and FVC with no change in DLCO when compared to subsequent follow-up testing [61]. FEV1 and FVC have been demonstrated to be independent predictors of mortality in this cohort [62, 63]. The restrictive physiology of pulmonary fibrosis may exacerbate these observed changes in the presence of concomitant heart failure. The contribution of heart failure to restrictive lung disease may be explained by the increased heart size in a fixed thoracic cavity thus reducing the functional lung volumes [64].

5. Heart Failure Exacerbating Fibrotic Interstitial Lung Diseases

Patients with fibrotic interstitial lung diseases often undergo acute respiratory decline, which may be due to the presence of congestive heart failure, venous thromboembolic disease, or infectious etiologies [65]. When careful exclusion of these causes has been performed, the acute respiratory deterioration is attributed to unexplained causes and is then termed acute exacerbation of interstitial lung disease (AE-ILD) such as acute exacerbations of idiopathic pulmonary fibrosis (AE-IPF) [66–71]. Because heart failure commonly complicates the clinical course of fibrotic lung disease, patients who present with rapidly worsening pulmonary symptoms, oxygen desaturation, and acute onset of radiographic infiltrates in the past month should undergo thorough detailed clinical and transthoracic echocardiographic assessment of ventricular function with exclusion of pulmonary hypertension and venous thromboembolic disease as part of their diagnostic workup [65, 72]. The therapeutic approach to management in these cases should target identifiable cardiac causes of respiratory decline in patients with fibrotic lung disease.

6. Treatment of Pulmonary Hypertension Associated with Right Ventricular Dysfunction

The sustained pulmonary vasoconstriction and progressive vascular remodeling that characterizes PH result in irreversible right heart dysfunction and ultimately acute decompensated right heart failure associated with high inhospital mortality [73–75]. The coexistence of chronic pulmonary disease and dysregulation of cellular proliferation may accelerate the World Health Organization (WHO) Functional Class (FC) decline of these patients into WHO-FC III or IV thus worsening survival outcomes [76–79].

The approach to treatment for these patients includes the use of oxygen and diuretics, as necessary, and anticoagulants in those individuals where specifically indicated [80, 81]. It should however be noted that the use of pulmonary vasodilators in lung fibrosis may contribute to worsening of gas exchange by inhibiting hypoxic pulmonary vasoconstriction [82].

6.1. Idiopathic Pulmonary Fibrosis and Pulmonary Hypertension. Multiple studies evaluating the utility of pulmonary vasoactive agents in patients with IPF and other fibrotic lung diseases have failed to demonstrate significant mortality benefits and in certain instances demonstrated harmful effects Table 2. This may be due to the absence of demonstrable vasoreactivity in PH-IPF patients thus limiting the utility of pulmonary vasodilators such as calcium channel blockers. Other limitations of these studies included a focus on short-term parameters, retrospective study design, and lack of randomization or inclusion of a placebo arm.

BUILD- (Bosentan Use in Interstitial Lung Disease-) 1 and BUILD-3 trials, which evaluated the effect of bosentan, a dual endothelin-1 receptor antagonist, in IPF failed to demonstrate a significant decrease in the time to IPF worsening [83, 84]. Macitentan, a novel dual endothelin receptor antagonist approved by the US FDA for treatment of PAH, was evaluated for the treatment of IPF in the MUSIC (Macitentan Use in an Idiopathic Pulmonary Fibrosis Clinical Study) trial [85]. Though this medication was well tolerated, the study revealed no significant difference in survival, lung function, or time to disease worsening.

In the ARTEMIS-IPF (Randomized, Placebo-Controlled Study to Evaluate Safety and Effectiveness of Ambrisentan in IPF) trial, subgroup analysis of patients treated with ambrisentan based on their PH status demonstrated no significant effect in those with mPAP >25 mmHg; rather they seemed to have disease progression and increased hospitalization for respiratory causes [86]. The more recent BPHIT (Bosentan in Pulmonary Hypertension Associated with Fibrotic Idiopathic Interstitial Pneumonia) trial which evaluated the safety and clinical efficacy of bosentan in patients with PH and fibrotic idiopathic interstitial pneumonia revealed no demonstrable difference in symptoms, functional capacity, or pulmonary hemodynamics over a 16-week period [87]. A subgroup analysis of patients enrolled in the STEP-IPF (Sildenafil Trial of Exercise Performance in

Idiopathic Pulmonary Fibrosis) evaluated those patients with right ventricular systolic dysfunction but not right ventricular hypertrophy and found that those who received sildenafil demonstrated some improvement in 6-minute-walk distance but no difference in mortality or rate of acute exacerbations [88]. Further, a small pilot trial examining the effect of Riociguat on pulmonary hemodynamics in patients with PH and ILD of any cause demonstrated an acceptable safety profile [89].

Subsequently, the 2015 ATS/ERS/JRS/ALAT clinical practice guidelines strongly recommend that ambrisentan should not be used in patients with IPF regardless of the presence or absence of PH [90]. Also given the lack of mortality benefits and likelihood of net harm with the use of sildenafil, current recommendations are that sildenafil should not be used for treatment of IPF. The variability in reported outcomes across trials, increased cost, and imprecise estimates of their effect led to a recommendation against the use of bosentan or macitentan for the treatment of IPF. However, the guidelines note that these medications may benefit patients with PH-IPF more than other IPF patients.

While the previous 2011 ATS/ERS/JRS/ALAT clinical practice guidelines argued against treatment of PH in patients with IPF, the most recent update in 2015 makes no specific recommendation regarding this cohort and notes the lack of sufficient evidence to guide the clinical decision making process [90, 91]. Well-designed clinical trials of novel PH agents with acceptable safety profiles would help to determine the differential effect of treating PH in patients with IPF.

6.2. Pulmonary Hypertension and Other Fibrotic Lung Diseases. Fibrotic lung disease often results in PH (WHO Group 3), which may rapidly progress in the advanced stages [82]. However, some studies have shown that a reduction in cardiac index <2.4 L/min/m^2 rather than mPAP predicts poor survival, thus indicating that coexisting ventricular dysfunction may be of prognostic significance [82]. The current guidelines recommend that, in addition to long-term oxygen therapy to keep arterial oxygen saturation above 90%, treatment of these patients should be focused on the underlying lung disease rather than the vascular component [82]. While it has been suggested that inhaled vasodilators may preferentially access those areas of the lungs with better ventilation and thereby improve oxygenation, supporting evidence in the form of large well-designed clinical trials is lacking.

Some patients with fibrotic lung disease may coincidentally develop PAH (WHO Group 1) as opposed to PH resulting from fibrotic lung disease (WHO Group 3) leading to uncertainty in patient classification [82, 92]. Occasionally patients with systemic sclerosis who develop pulmonary fibrosis and PH may demonstrate similar pulmonary hemodynamics to idiopathic PAH, thus making their classification of PH challenging. Such cases should prompt a referral to centers of expertise for appropriate management [82].

The benefit of PAH therapy in non-IPF fibrotic lung diseases remains unclear and is presently limited to retrospective studies [93]. Riociguat, a soluble guanylate cyclase stimulator, has demonstrated some efficacy in initial trials of patients with PAH (Group 1), PH associated with FLD (Group 3), or chronic thromboembolic pulmonary hypertension (Group 4) [89, 94–97]. However, larger well-designed clinical trials are needed before adaptation for widespread use [90].

6.3. Therapies for Pulmonary Arterial Hypertension

6.3.1. Calcium Channel Blockers. The dihydropyridine calcium channel blockers such as nifedipine and amlodipine appear to be safe and well tolerated in patients with a positive pulmonary vasoreactive test and may confer a survival benefit in these individuals. However they may exert potentially negative inotropic effects with long-term consequences that remain unclear [98].

6.3.2. Endothelin (ET-1) Receptor Antagonists (ERA). Endothelin-1, a potent vasoconstrictor produced by vascular endothelial cells and cardiomyocytes, also mediates the regulation of several biological processes in other tissues outside the cardiovascular system [99–102]. The effects of ET-1 are mediated via two different receptor subtypes, ET_A and ET_B. Endothelin (ET-1) receptor antagonists directly oppose its effects on cardiomyocyte contractility and the indirect effects on pulmonary vascular remodeling and vasoconstriction [103]. Bosentan, a nonselective receptor antagonist, was the first ERA to receive FDA approval for PAH in patients with WHO-FC III or IV. It has however been associated with sporadic increases in aminotransferases and anemia [104–107]. Ambrisentan, an ET_A selective antagonist, also improves exercise capacity with the added benefit of once daily dosing and a reduced tendency to cause aminotransferase abnormalities [108, 109]. Macitentan, the most recent oral ERA approved for use in these patients, was demonstrated to have a 45% reduction in morbidity and mortality and potential for use in patients with inoperable chronic thromboembolic pulmonary hypertension [110].

6.3.3. Prostacyclin Analogs. Prostacyclin (also called prostaglandin I_2 or PGI2), a molecule that mediates vasodilation, inhibits platelet aggregation and inflammation and vascular smooth muscle proliferation also has important direct cardiac effects [111, 112]. Synthetic PGI2 analogs such as epoprostenol (Flolan) improve right ventricular stroke work and have demonstrated survival, functional, and hemodynamic benefits in patients with PAH [113–116]. The significantly short half-life (3–5 min) and instability at room temperature presented practical challenges and more stable and convenient formulations (Veletri) have recently been made available with similar effects on pulmonary hemodynamics. Other PGI2 analogs such as treprostinil (which may be administered subcutaneously or intravenously or inhaled) and Iloprost (inhaled) may be used as alternative therapies [117–121]. Their direct effects on right ventricular function remain unclear and the initial improvement in exercise capacity observed with oral PGI2 analogs after 12 weeks has been reported to disappear after 1 year [122]. Furthermore, treatment with epoprostenol for 6 months has been reported to be associated with increased mortality, an effect that may be explained

by the detrimental consequences of increasing myocardial oxygen consumption when contractility increases [112, 123, 124].

6.3.4. Phosphodiesterase Type 5 (PDE5) Inhibitors. The formation of the intracellular messenger, cyclic guanosine monophosphate (cGMP), a potent smooth muscle relaxant and pulmonary vasodilator, is induced through activation of soluble guanylate cyclase (sGC) by nitric oxide (NO), a short-acting molecule produced by vascular endothelial cells [125]. The phosphodiesterase type 5 (PDE5) enzyme degrades cGMP; thus oral PDE5 inhibitors such as sildenafil and tadalafil result in significant vasodilatory and antiproliferative effects [126–128]. Sildenafil has been demonstrated in patients with idiopathic pulmonary fibrosis and right ventricular dysfunction to improve quality of life and preservation of exercise capacity [88].

6.3.5. Soluble Guanylate Cyclase (sGC) Stimulators. A recent sGC stimulator, Riociguat, independently increases cGMP levels and improves WHO functional class, pulmonary vascular resistance, and serum markers of right ventricular stress [129].

6.3.6. Rho-Kinase (ROCK) Inhibitors. These hold significant promise for treatment of RHF in severe PH and their acute administration results in modest pulmonary vasodilation [130, 131]. Their long-term effects on the right ventricular are unknown but a recent study of 74 patients who received fasudil, an intravenous rho-kinase inhibitor, demonstrated mortality benefits and reduced hospitalization and a favorable side effect profile [132]. The efficacy of statins and histone deacetylases in pulmonary hypertension has also been evaluated in multiple studies with limited success [133–136].

6.3.7. Other Connective Tissue Disease Specific Therapies. Inhaled nitric oxide (iNO) has been studied to examine its effect on pulmonary vasoreactivity in patients with systemic sclerosis (SSc) who demonstrate pulmonary hypertension and right ventricular failure [137]. A study of 60 patients found no response to iNO in diffuse SSc. Though 40% of patients with vasoreactivity to iNO had pulmonary fibrosis, patients with no vasoreactivity more commonly exhibited fibrosis typical of diffuse scleroderma [137]. Decreased pulmonary pressures after administration of iNO were associated with subsequent improvement in right ventricular systolic function [137].

In patients with systemic lupus erythematosus-associated pulmonary arterial hypertension (SLE-PAH), intensive immunosuppressive therapy with intravenous cyclophosphamide and oral glucocorticoids has been demonstrated to decrease mPAP and improve hemodynamic parameters, six-minute-walk distance, and survival [138–141].

6.3.8. Emerging Treatment Options. Oral prostanoids such as Beraprost (twice daily dosing) and treprostinil (thrice daily dosing) have been evaluated as monotherapy with mixed results but are currently under investigation in various trials for their utility as combination therapies [122, 142, 143]. Selexipag, an oral, nonprostanoid selective IP receptor agonist, demonstrated a 39% reduction in time to first morbidity or mortality over a 4-year period and is currently being evaluated for its safety profile [144, 145]. Vardenafil, an oral PDE5 inhibitor, has been demonstrated to improve pulmonary hemodynamics and exercise capacity at 12 weeks while reducing oxidative stress. It however remains under investigation for treatment efficacy in patients with PAH [146, 147]. Tyrosine kinase inhibitors such as imatinib have demonstrated treatment benefit in isolated cases, an effect that has not yet been replicated by several trials, some of which were discontinued due to severe side effects [148–155].

7. Effects of Antifibrotic and Anti-Inflammatory Agents on Heart Failure in Idiopathic Pulmonary Fibrosis

Two new agents have recently been approved for the treatment of patients with IPF. Pirfenidone is an oral antifibrotic agent with mechanisms of action that include the inhibition of key cytokines that mediate pathogenesis of inflammation and fibrosis [156]. Nintedanib is an oral intracellular inhibitor of tyrosine kinase that targets multiple growth factor receptors [157]. Both agents have been shown in multiple randomized controlled phase 3 trials to slow the rate of decline in lung function of patients with IPF [156, 157].

A multinational comprehensive evaluation of the long-term safety of pirfenidone in patients with idiopathic pulmonary fibrosis found no increased incidence in adverse cardiac events [158]. Interestingly, pirfenidone has been demonstrated in various animal models to attenuate myocardial fibrosis and left ventricular remodeling by inhibiting NLRP3-induced inflammation and subsequent fibrosis [159, 160], ultimately resulting in cardioprotective effects [161, 162]. However, these findings have not yet been demonstrated in human studies. Two large trials examining the efficacy and safety of nintedanib in patients with IPF did not demonstrate a significant increase in the incidence of cardiac adverse effects with the use of this medication [157].

8. Right Ventricle-Targeted Therapies

The initial cardiac hypertrophy, which occurs in response to the prolonged increase in pulmonary vascular pressure and altered hemodynamics, progressively becomes maladaptive and eventually results in decompensated ventricular function. As PH progresses, right ventricular dilation and fibrosis follow eventually resulting in functional right ventricular failure, the most common cause of death in patients with severe PH [24, 163, 164].

The persistently poor prognosis of patients with low right ventricular function despite therapies that effectively reduce the pulmonary vascular resistance highlights the crucial need for right ventricular-targeted therapies in these patients [165]. The underlying mechanisms of right ventricular failure are increasingly thought to differ from that of the left ventricle

Table 1: Effects of pharmacologic therapies in patients with right ventricular dysfunction*.

Medication	Route of administration	Mechanism of action	Right ventricular effect	Common side effects
Therapies targeting pulmonary hypertension				
Nifedipine and amlodipine	Oral	Calcium channel blockers	Reduce afterload	Headache, dizziness, and extremity edema
Bosentan, ambrisentan, and macitentan	Oral	Endothelin receptor antagonists	Reduce afterload	Headache, dizziness, and arrhythmias
Epoprostenol	IV	Prostacyclin analog	Reduces afterload	Nausea, vomiting, dizziness, and arrhythmias
Iloprost	Inhaled	Prostacyclin analog	Reduces afterload	Nausea, vomiting, headache, and diarrhea
Treprostinil	SC/IV/inhaled	Prostacyclin analog	Reduces afterload	Nausea, headache, cough, and dizziness
Sildenafil and tadalafil	Oral	Phosphodiesterase type 5 inhibitors	Reduce afterload	Nausea, vomiting, headache, and tritanopia
Riociguat	Oral	Soluble guanylate cyclase stimulator	Reduces hypertrophy	Headache, dizziness, gastritis, hypotension, and diarrhea
Imatinib	Oral	Tyrosine kinase inhibitor	Improves function	Nausea, vomiting, edema, diarrhea, rash, and pancytopenia
Fasudil	IV	Rho-kinase inhibitor	Reduces hypertrophy	Nausea, renal dysfunction, fever, and thrombocytopenia
Nitric oxide	Inhaled	Pulmonary vasodilator	Improves function	Hypotension and methemoglobinemia
Therapies targeting the right ventricle (RV)				
Carvedilol and bisoprolol	Oral	β-adrenergic receptor blockers	Decrease myocardial fibrosis	Dizziness, fatigue, diarrhea, and hyperglycemia
Ranolazine and trimetazidine	Oral	Modulators of metabolism	Decrease remodeling	Nausea, headache, dizziness, constipation, edema, and dyspnea
Ramipril	Oral	ACE inhibitor	Decreases myocardial fibrosis	Nausea, vomiting, cough, headache, and dizziness
Protandim	Oral	Antioxidant	Decreases myocardial fibrosis	Nausea, vomiting, rash, headache, and diarrhea
Therapies targeting pulmonary fibrosis**				
Pirfenidone	Oral	Antifibrotic agent	Decreases myocardial fibrosis	Nausea, vomiting, rash, headache, diarrhea, and dizziness
Nintedanib	Oral	Triple angiokinase inhibitor	Undetermined direct effect	Nausea, vomiting, headache, diarrhea, and anorexia

*None of these medications have been specifically approved for Group 3 pulmonary hypertension as these patients may have pulmonary fibrosis and may not demonstrate vasoreactivity. **Idiopathic pulmonary fibrosis, IV: intravenous, SC: subcutaneous.

and this may explain the variation in results across experimental therapies targeting both ventricles [166] (Table 1).

8.1. Pharmacologic Agents

8.1.1. β-Adrenoceptor (β-AR) Blockers. Though downregulated β-adrenergic receptors and increased sympathetic activity are typical features of pulmonary arterial hypertension, use of these medications may decrease heart rate and myocardial contractility and result in systemic vasodilation limiting their unrestricted utility in these patients [167, 168]. Patients with portopulmonary hypertension also demonstrate poor functional capacity and worse pulmonary hemodynamics with use of these medications [169]. Significant benefits such as reduction of myocardial oxygen consumption, restoration of effective Ca^{2+} transport, and prevention of arrhythmias

Table 2: Trials of pulmonary hypertension therapies in idiopathic pulmonary fibrosis.

Trial	Design	Medication/dose	Primary endpoint	Outcome
BUILD-1 (Bosentan Use in Interstitial Lung Disease)	Randomized, double-blind, placebo-controlled, multicenter study	Bosentan (oral) 62.5 mg b.i.d. × 4 wk., then 125 mg b.i.d. ≥ 12 mth.	6-minute-walk distance	Bosentan showed no superiority over placebo
STEP-IPF (Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis)	Randomized, double-blind, placebo-controlled trial	Sildenafil (oral) 20 mg t.i.d.	Proportion of patients with ≥20% increase in 6-minute-walk distance	Sildenafil showed no superiority over placebo in primary outcome
BUILD-3 (Bosentan Use in Interstitial Lung Disease)	Prospective, randomized, double-blind, placebo-controlled, event-driven, parallel-group trial	Bosentan (oral) 62.5 mg b.i.d. × 4 wk., then 125 mg b.i.d.,	Time to IPF worsening or death	No significant difference between treatment groups
ARTEMIS-IPF (Randomized, Placebo-Controlled Study to Evaluate Safety and Effectiveness of Ambrisentan in IPF)	Randomized, double-blind, placebo-controlled, event-driven phase 3 trial	Ambrisentan (oral) 10 mg daily	Reduction in rate of IPF progression	Early study termination due to worsening of lung function decline and increased respiratory hospitalizations in ambrisentan group
MUSIC (Macitentan Use in an Idiopathic Pulmonary Fibrosis Clinical Study)	Prospective, randomized, double-blind, multicenter, placebo-controlled, parallel-group phase 2 trial	Macitentan (oral) 10 mg daily	Effect on forced vital capacity	No differences in pulmonary function tests or time to disease progression or death
BPHIT (Bosentan in Pulmonary Hypertension Associated with Fibrotic Idiopathic Interstitial Pneumonia)	Randomized, double-blind, placebo-controlled phase 4 study	Bosentan (oral) 62.5 mg b.i.d. × 4 wk., then 125 mg b.i.d.	≥20% decrease from baseline of pulmonary vascular resistance index over 16 weeks	No difference in primary outcome

may be achieved with the careful use of these medications [170, 171]. Carvedilol, a selective β1-AR blocker, improves right ventricular function and exercise tolerance and is described to exert cardioprotective effects [172–174]. Use of carvedilol has also been described in experimental models to improve biventricular fibrosis [175]. Bisoprolol has been shown in animal studies to improve right ventricular-arterial uncoupling and survival [176]. The therapeutic benefits of inhibition of G protein-coupled receptor kinase-2 (GRK) mediated uncoupling of the β-adrenergic receptor have also been described with the use of Gallein, a novel small molecule that targets the G$\beta\gamma$ subunit of GRK2 [177, 178].

8.1.2. Angiotensin-Converting Enzyme (ACE) Inhibitors. The effect of ACE inhibitors on pulmonary hemodynamics and right ventricular function has not been evaluated by large studies. Limited data from case series yield conflicting results [179, 180]. Experimental animal models of ramipril describe an improvement in right ventricular systolic function [181].

8.1.3. Modulators of Metabolism. Progression of right ventricular failure is accompanied by downregulation of fatty acid oxidation, which may contribute to the mechanistic process [182, 183]. Metabolic modulators like ranolazine or trimetazidine have been demonstrated to mitigate the reduction in cardiac output with modest effects observed in right ventricular dysfunction [166, 183]. Use of etomoxir, an inhibitor of fatty acid oxidation, has been shown to have equivocal results in right ventricular failure [184].

8.1.4. Antioxidants. Administration of protandim in experimental PH models has been shown to upregulate the expression of HO-1 (hemoxygenase-1), an isoenzyme that facilitates

the production of antioxidant enzymes by promoting the expression of their genes [166, 185].

8.1.5. 5-Hydroxytryptamine-2B (5-HT2B) Receptor Antagonists. Murine models of pulmonary hypertension have demonstrated a significant role for 5-hydroxytryptamine (serotonin) in the development and progression of ventricular hypertrophy [186–188]. Terguride, a 5-HT2A and 5-HT2B receptor antagonist, and SB204741 (a 5-HT2B receptor antagonist) have been demonstrated to inhibit right ventricular fibrosis by reducing collagen deposition [189].

8.2. Nonpharmacologic Modalities. The efficacy of exercise rehabilitation and respiratory training in patients with pulmonary hypertension and heart failure has been studied and shown to improve exercise capacity, improve quality of life, and correct endothelial dysfunction [190, 191].

Cardiac resynchronization in PAH patients with ventricular dyssynchrony may correct the difference in duration of right ventricular contraction when compared to the left ventricle with subsequent improvement in right ventricular systolic function and diastolic relaxation [192–194]. Atrial septostomy may also be beneficial in severely ill patients with significantly elevated pressures by reducing the right ventricular preload [195, 196]; therapy should however be individualized to each patient and limited to centers with expertise at performing this procedure [166]. Mechanical right ventricular support with extracorporeal membrane oxygenation (ECMO) and ventricular assist devices (VAD) may also be necessary for temporary circulatory support [197–199]. The CentriMag (a short-term continuous-flow pump) and PVAD (a long-term pneumatic pulsatile pump) are circulatory assist devices recently approved by the FDA for right ventricular support [200, 201]. The Impella RP approved for use in Europe is being evaluated for its safety and efficacy in the USA for support of cardiac function in patients with right ventricular failure [202, 203].

9. Transplant for Treatment of Fibrotic Lung Disease

Progression of advanced pulmonary fibrosis that remains refractory to medical management may eventually require single- or double-lung transplantation. A study of 821 recipients of lung transplant for pulmonary fibrosis showed significantly better early and late survival in recipients aged < 60 years with single-lung transplant than bilateral lung transplant. Patients with IPF tend to be >60 years and in studies focused on IPF patients, double-lung transplant may be associated with equivalent or better long-term outcomes and graft survival than single-lung transplant [204, 205]; however unilateral transplant is an acceptable alternative and may affect the allocation process [206]. The preoperative mean PAP (<40 mmHg) has been demonstrated by multivariate analyses to be an independent risk factor for operative mortality (OR = 9.7; $p = 0.01$) [206]; younger patients with significant pulmonary hypertension may benefit from receiving bilateral lung transplant [206]. Patients with severe PAH and right ventricular dysfunction may be considered for combined heart-lung transplantation [166].

10. Conclusion and Future Directions

The rising prevalence and mortality from fibrotic lung diseases create an urgent need for improved therapeutic strategies in the management of right ventricular failure and PH in patients with fibrotic lung disease, as there is a significant limitation of organs available for transplant. The poor resting gas exchange, low diffusing capacity of the lungs for carbon monoxide (DLCO), and cardiovascular mediated exercise limitation that characterize this unique group of patients contribute to the mechanisms driving progression of right ventricular dysfunction to failure. Individualized therapy should be instituted early and target the underlying lung disease as well as those specific mechanisms leading to right ventricular failure. As new treatment options emerge, clinical trials should focus on development of therapies with the most efficacy and improvement in quality of life while considering the effects on right ventricular function.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Effects of Sevoflurane and Propofol on Organ Blood Flow in Left Ventricular Assist Devices in Pigs

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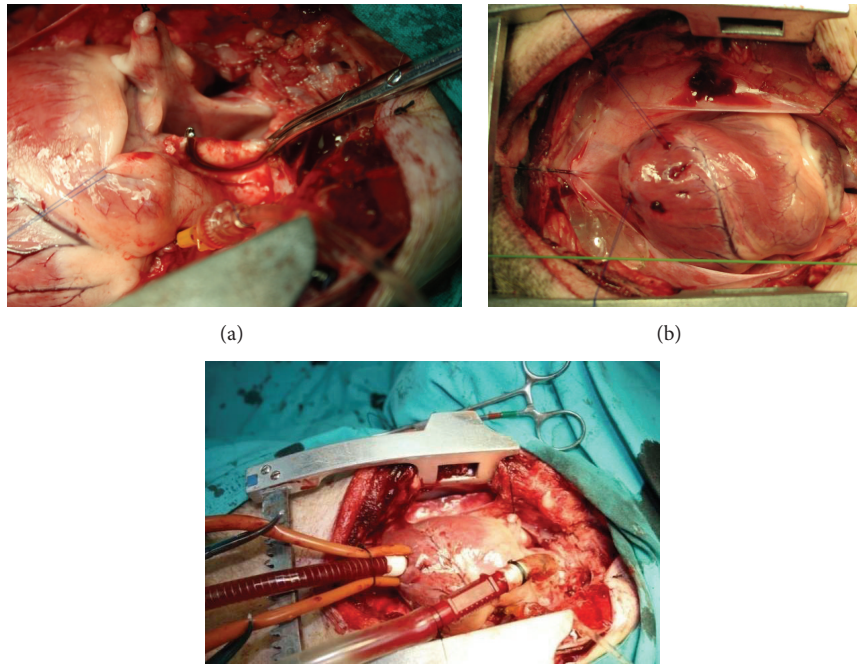
The aim of this study was to assess the effect of sevoflurane and propofol on organ blood flow in a porcine model with a left ventricular assist device (LVAD). Ten healthy minipigs were divided into 2 groups (5 per group) according to the anesthetic received (sevoflurane or propofol). A Biomedicus centrifugal pump was implanted. Organ blood flow (measured using colored microspheres), markers of tissue injury, and hemodynamic parameters were assessed at baseline (pump off) and after 30 minutes of partial support. Blood flow was significantly higher in the brain (both frontal lobes), heart (both ventricles), and liver after 30 minutes in the sevoflurane group, although no significant differences were recorded for the lung, kidney, or ileum. Serum levels of alanine aminotransferase and total bilirubin were significantly higher after 30 minutes in the propofol group, although no significant differences were detected between the groups for other parameters of liver function, kidney function, or lactic acid levels. The hemodynamic parameters were similar in both groups. We demonstrated that, compared with propofol, sevoflurane increases blood flow in the brain, liver, and heart after implantation of an LVAD under conditions of partial support.

1. Introduction

Ventricular assist devices (VADs) are a promising therapeutic option for patients with advanced heart failure. VADs can act as a bridge to transplantation, as a destination therapy for patients with contraindications to transplantation, or as a bridge to a future recovery [1–3]. In the last few decades, VADs have been increasingly used in patients with end-stage heart failure, because heart transplantation is limited by a marked lack of donors [4].

The main purpose of a VAD is to maintain perfusion of vital organs. To improve the clinical output of the VAD, it is necessary to optimize perioperative conditions (continuous-flow VAD, hemodynamic monitors, and anesthetic drugs) [5, 6]. Although several studies show the effects of the VAD on organ blood flow (heart, brain, liver, and kidney) [7–9], the effect of anesthetics on organ blood flow in patients with a VAD has not been analyzed to date. Several studies have reported data on the response of organ blood flow to the administration of various anesthetics [10–13], although this effect remains unclear for VADs.

Given the beneficial effects of volatile anesthetics (sevoflurane) compared with intravenous anesthesia (propofol) on organ blood flow during cardiovascular surgery [14–17], we hypothesized that, compared with propofol, sevoflurane would increase organ blood flow in patients with a left VAD (LVAD). The aim of this study was to investigate differences between the effect of sevoflurane-based volatile anesthetic and that of propofol-based intravenous anesthetics on organ blood flow (brain, liver, heart, kidney, lung, and intestine)



(a) (b)

(c)

Figure 1: LVAD placement. Aortic partial cross-clamp (a). Implant of the input cannula through the apex of the left ventricle (b and c).

and to assess markers of tissue injury after implantation of an LVAD (continuous centrifugal pump) under conditions of partial support in a porcine model.

2. Methods

The animals used in our experiment were from the farm of the Technological Institute of Agrarian Development (EX 013-C) (Community of Madrid, Spain). The pigs were moved from this farm to the Experimental Medicine and Surgery Unit, Gregorio Marañón University General Hospital (ES280790000087), where they remained under a controlled environment until the intervention (20–22°C and relative humidity of 55%). The study was performed in accordance with European Union guidelines on the protection of animals used for experimental and other scientific purposes (Directive 2010/63/EU and Spanish Royal Decree RD 53/2013 BOE) and was approved by the Ethics Committee, Gregorio Marañón University General Hospital, Madrid, Spain.

2.1. Experimental Design. The study was conducted with ten healthy minipigs. Animals were block-randomized (Microsoft Excel 2003) to receive either propofol in continuous perfusion as anesthetic maintenance (propofol group, $n = 5$) or sevoflurane (sevoflurane group, $n = 5$).

2.1.1. Anesthesia Protocol. The animals were simultaneously premedicated with intramuscular ketamine 20 mg/kg (Ketolar, Parke-Davis, Madrid, Spain) and atropine 0.04 mg/kg (Atropina Braun, Serra-Pamies, Reus, Spain). Pulse oximetry and electrocardiographic monitoring were performed in the operating room. The pigs were provided with oxygen 100% via a face mask, a 20 G cannula was inserted into an ear vein, and anesthesia was induced with intravenous fentanyl 2.5 μg/kg (Fentanest, Kern Pharma, Barcelona, Spain) and propofol 4 mg/kg (Diprivan 1%, AstraZeneca, Madrid, Spain). After intubation, the animal was connected to a volume-controlled ventilator (Dräger SA1, Dräger Medical AG, Lübeck, Germany) with FIO_2 of 1, an inspiratory : expiratory ratio of 1 : 2, a tidal volume of 12–15 mL/kg, and the respiratory rate adjusted to maintain normocapnia as previously described [18]. Anesthesia was maintained with intravenous fentanyl (2.5 μg/kg/30 min) in all animals and propofol in continuous infusion (11-12 mg/kg/h) (propofol group) or 2% sevoflurane (sevoflurane group). All animals received an infusion of saline solution (8 mL/kg/h). A 9 F arterial catheter was inserted into the right femoral artery and a pulmonary artery catheter (7.5 F Swan-Ganz CCOmbo catheter, Edwards Lifesciences, Irvine, CA, USA) connected to an oximetry monitor (Vigilance, Edwards Critical-Care Division, Irvine, CA, USA) was inserted into the right internal jugular vein.

2.1.2. Surgical Protocol. A Biomedicus 540 centrifugal pump was implanted in the minipigs undergoing continuous-flow support. After median sternotomy, the animal was heparinized at a dose of 4 mg/kg. An aortic partial cross-clamp was applied (just for anastomosing the output cannula of the LVAD to the aorta) and a 2 cm aortotomy performed (Figure 1(a)). The output cannula of the LVAD was anastomosed to the ascending aorta, and the input cannula

(23 F Medtronic Ultraflex, Metdtronic Inc., Minneapolis, USA) was placed through the apex of the left ventricle. The implant of the input cannula is practiced by placing two circular sutures (Figure 1(b)), and then the cannula was placed with two turnstiles around the cannula (Figure 1(c)). Finally, both cannulas were connected to the device. LVAD placement was without cardiopulmonary bypass and without cardioplegia. Console parameters were adjusted to obtain a pump flow of 50% (partial support) of the baseline cardiac output (cardiac output before LVAD is initiated) using the pulmonary artery catheter for 30 minutes. Input flow was measured using an ultrasound transducer (EMTEC, Germany) attached to the input cannula of the device.

2.2. Organ Blood Flow Measurements. Colored microspheres (Dye-Trak, Triton Technology Inc., San Diego, CA, USA) were used to measure organ blood flow. Once the LVAD was implanted (before the start of LVAD, baseline), yellow microspheres (diameter of 12 microns) were injected into the left atrium (1.5 million microspheres per injection). The LVAD was then initiated, and violet microspheres were injected after 30 minutes of partial support. After each experiment, the animal was sacrificed using potassium chloride, and tissue samples of both brain hemispheres (right and left frontal lobe), heart (right and left ventricles), liver, lung (middle lobe of right lung), kidney, and ileum were obtained to measure organ blood flow. The basic principle of all deposition techniques for regional flow measurement is that the deposition is proportional to the flow (per unit volume or mass of tissue). Due to the movement of microspheres out of the capillaries into the interstitium, retention of microspheres is excellent. The idea is that deposited markers give a measure of flow per unit volume of tissue at the level of the capillaries. The microspheres were isolated from tissue by digestion with potassium hydroxide, they were centrifugated, the dyes were extracted from the colored microspheres, and the separation of colors and measurement of their concentration was performed by spectrometry [19, 20].

2.3. Markers of Tissue Injury. Serum levels of total bilirubin, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase, and alkaline phosphatase were evaluated as parameters of hepatobiliary function. Creatinine and urea were studied as parameters of renal function. Lactate dehydrogenase and lactate were measured as nonspecific indicators of tissue injury. All previously described markers of tissue injury and nitric oxide (NO) were studied at baseline (after implantation before turning it on) and 30 minutes after implantation of the LVAD.

2.4. Hemodynamic Measurements. The hemodynamic data included heart rate, mean arterial pressure, mean pulmonary arterial pressure, central venous pressure, pulmonary capillary wedge pressure, systemic vascular resistance index, pulmonary vascular resistance index, continuous cardiac output, and mixed venous oxygen saturation, all of which were recorded at baseline and 30 minutes after implantation of the LVAD. Body temperature was also studied.

2.5. Hematologic Parameters and Arterial Blood Gas Measurements. A femoral arterial catheter was used to perform the hematologic and blood gas analyses at baseline and 30 minutes after implantation of the LVAD.

2.6. Data Analysis and Statistics. The primary endpoint was organ blood flow in the LVAD, which was compared between the two groups. The variable was expressed as mean ± SEM. We used the Kolmogorov-Smirnov test to analyze the distribution of quantitative variables; between-group comparisons were based on the t-test for independent samples. Statistical significance was set at a P value of <0.05. The statistical analysis was performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp, Armonk, NY, USA) and S-PLUS 6.1.

3. Results

3.1. Physiological Parameters. No differences were detected between the groups (sevoflurane versus propofol) in terms of age (143 ± 7 versus 126 ± 10 days, $P = 0.28$), weight (34 ± 1 versus 25 ± 3 kg, $P = 0.052$), or height (93 ± 2 versus 87 ± 1 cm, $P = 0.07$).

3.2. Effect of Anesthetics on Organ Blood Flow. Blood flow was significantly higher in the brain (both frontal lobes) (Figures 2(a) and 2(b)), heart (both ventricles) (Figures 3(a) and 3(b)), and liver (Figure 4(a)) after 30 minutes of partial support in the sevoflurane group than in the propofol group, although no significant differences were recorded for the lung (Figure 4(b)), kidney (Figure 5(a)), or ileum (Figure 5(b)).

3.3. Effect of Anesthetics on Markers of Tissue Injury and Nitric Oxide. Serum levels of alanine aminotransferase and total bilirubin were significantly higher after 30 minutes of partial support in the group that received propofol. However, there were no significant differences between the groups in other parameters of liver function and kidney function or in lactic acid levels (Table 1). There were no differences between the groups in nitric oxide in plasma (Table 1).

3.4. Hemodynamic Parameters. No differences were found between the groups in pump flow of LVAD (propofol group 0.94 ± 0.09 L/min versus sevoflurane group 1.01 ± 0.09 L/min).

The hemodynamic parameters showed marked stability in both groups; there were no significant differences in either the sevoflurane group or the propofol group before implantation of the LVAD and after 30 minutes of partial support (Table 2).

3.5. Hematologic Parameters and Blood Gas Analysis. No statistically significant differences were found between the groups for hemoglobin and hematocrit after 30 minutes (Table 3). Arterial oxygenation, systemic arterial PCO_2, bicarbonate, and pH were similar in both groups before implantation and after 30 minutes of partial support (Table 3).

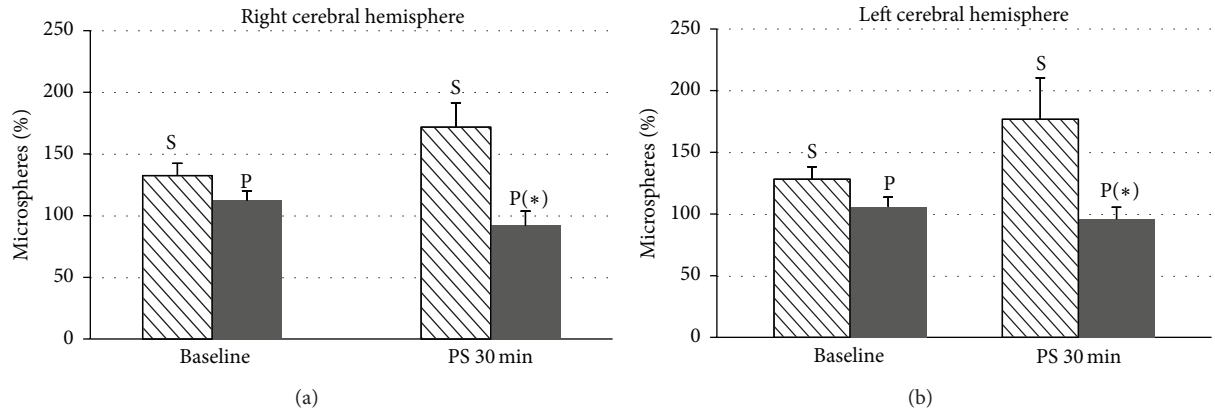


Figure 2: Date are expressed as the mean ± standard error of the mean. Cerebral blood flow in the right frontal lobe (a) and left frontal lobe (b) of pigs with a ventricular assist device in both groups, sevoflurane (S) and propofol (P), at baseline and after 30 minutes of partial support. Statistically significant differences are shown: $^{*}P < 0.05$ versus sevoflurane.

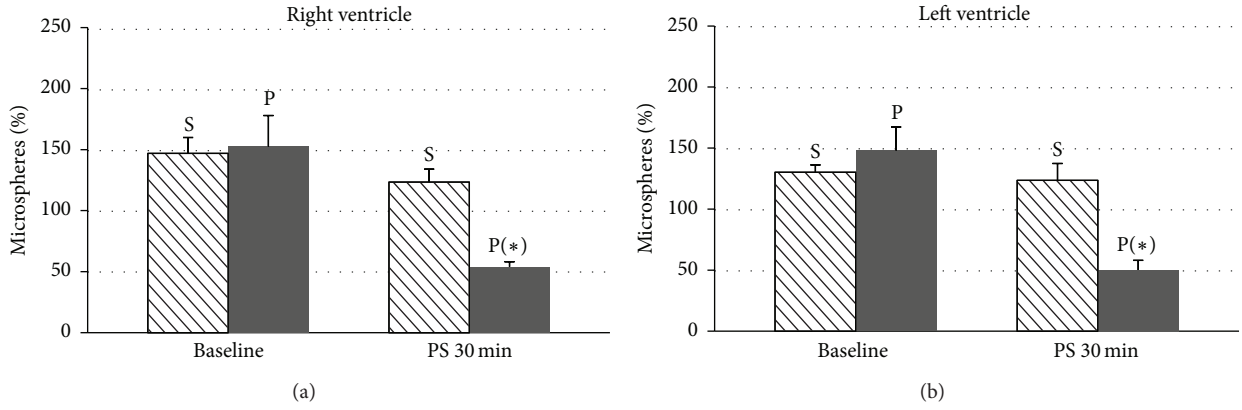


Figure 3: Date are expressed as the mean ± standard error of the mean. Blood flow in the right ventricle (a) and left ventricle (b) of pigs with a ventricular assist device in both groups, sevoflurane (S) and propofol (P), at baseline and after 30 minutes of partial support. Statistically significant differences are shown: $^{*}P < 0.05$ versus sevoflurane.

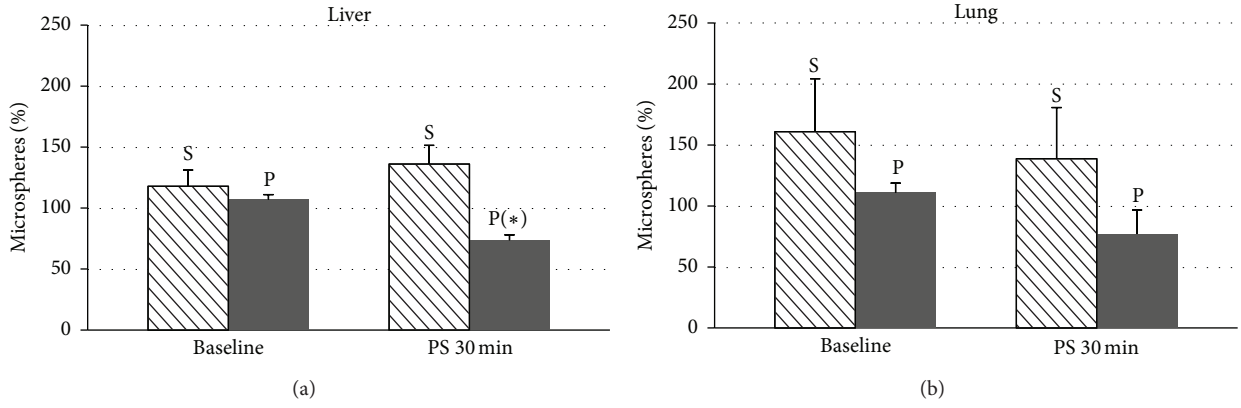


Figure 4: Date are expressed as the mean ± standard error of the mean. Blood flow in the liver (a) and lung (b) of pigs with a ventricular assist device in both groups, sevoflurane (S) and propofol (P), at baseline and after 30 minutes of partial support. Statistically significant differences are shown: $^{*}P < 0.05$ versus sevoflurane.

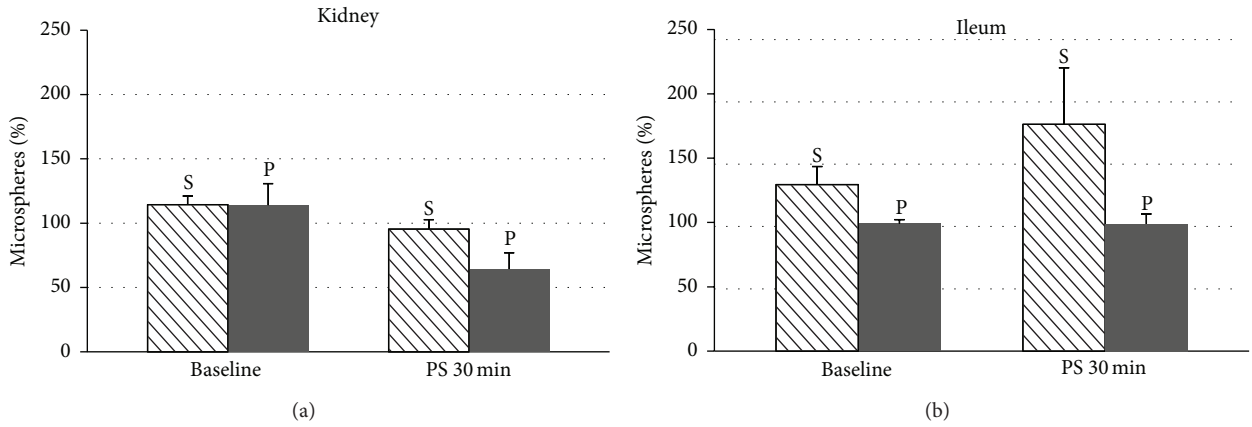


Figure 5: Date are expressed as the mean ± standard error of the mean. Blood flow in the kidney (a) and ileum (b) of pigs with a ventricular assist device in both groups, sevoflurane (S) and propofol (P), at baseline and after 30 minutes of partial support.

4. Discussion

The results obtained show that, compared with propofol, anesthesia with sevoflurane increases blood flow in the brain, liver, and heart tissue after implantation of an LVAD under conditions of partial support in a porcine model. In addition, increased levels of serum markers of cellular injury in LVAD were observed with propofol. To our knowledge, this is the first study to demonstrate a beneficial effect of sevoflurane compared with propofol on organ blood flow in a Biomedicus 540 centrifugal pump in a porcine model. These findings justify further investigation to determine whether sevoflurane modifies organ blood flow in clinical settings.

The number of patients diagnosed with advanced heart failure is increasing worldwide, and LVAD is a pivotal treatment option for end-stage heart failure [21]. Because complications in the use of LVAD (multiple organ failure, right ventricular failure, neurological dysfunction, and arrhythmias) have been reported [22, 23], anesthesia and perioperative management of these critically compromised patients requires extensive monitoring, special anesthetic management with appropriate drugs, and expert postoperative care [24, 25].

4.1. Effect of Anesthetics on Organ Blood Flow. Several studies have reported changes in organ blood flow in response to the administration of volatile anesthetics and propofol [11–13, 26–28], although this effect has not been analyzed during implantation of an LVAD. Sevoflurane and propofol are frequently used as maintenance anesthetics during placement of an LVAD [29]. Some authors have associated reduced cerebral blood flow with both drugs [12]; however, we only found greater cerebral blood flow in sevoflurane-anesthetized animals with an LVAD. Patients with LVAD are associated with neurologic events. The most common causes are thromboembolism and hemorrhagic stroke and less frequent causes are ischemia due to low perfusion and air embolism [30]. However, we are not sure that a higher flow reduces the occurrence of ischemia due to air embolism. According to our results, sevoflurane could be a good option to lower the incidence of ischemia due to low perfusion in LVAD-supported patients.

The results of some studies support cardiac and hepatic protective effects of sevoflurane with respect to propofol after coronary artery surgery in humans [14, 16]. Our results also support the beneficial effect of sevoflurane compared with propofol on the heart and liver in LVAD. However, no differences were observed with sevoflurane compared with propofol for blood flow in other organs (lung, kidney, and intestine). The different blood flow response to sevoflurane could be explained by its dose-dependent effect [26–28].

Propofol and sevoflurane are used during cardiac surgery. Propofol exerts cardioprotective effects by different mechanisms: in the isolated heart, it attenuates metabolic changes induced by exogenously applied hydrogen peroxide [31], reduces infarct size by inhibition of GSK-3β activity (propofol induces cardiac preconditioning) [32], and attenuates ischemia-reperfusion injury mediated through increase in nitric oxide synthase activity and NO production (cardiac function and coronary flow are improved with propofol) [33, 34]. In our study there were no differences in NO between both groups: sevoflurane and propofol. Propofol attenuates the changes in myocardial tissue levels of adenine nucleotides and lactate during ischemia, reduces troponin I release on reperfusion after cardioplegic arrest in cardiopulmonary bypass in a model porcine [35], and shows antiarrhythmic effect during myocardial ischemia in rats [36]. However, cardiopulmonary bypass (CPB) is known to alter the plasma propofol concentrations (hemodilution, hypotension, hypothermia, isolation of the lungs from the circulation, and possible sequestration of drugs in the bypass circuit affect drugs plasma concentrations) [37].

Sevoflurane also induces preconditioning and attenuates myocardial ischemia/reperfusion injury via caveolin-3-dependent cyclooxygenase-2 inhibition, AMP-activated protein kinase, and antioxidative effects in experimental studies [38–40]. Clinical studies show that sevoflurane provides cardioprotection in patients undergoing coronary artery bypass graft (CABG) [41], and there is some data that shows that troponin T levels after off-pump CABG were lower in

Table 1: Markers of tissue injury and nitric oxide in both groups (propofol and sevoflurane) at baseline and 30 minutes after implantation of a left ventricular assist device.

	Propofol $n = 5$	Sevoflurane $n = 5$	P values
ALT (U/L)			
Baseline	29 ± 2	25 ± 2	0.221
PS 30′	29 ± 2	23 ± 2	0.048*
AST (U/L)			
Baseline	50 ± 10	35 ± 3	0.116
PS 30′	94 ± 46	44 ± 3	0.358
Bilirubin (mg/dL)			
Baseline	0.25 ± 0.06	0.13 ± 0.02	0.081
PS 30′	0.24 ± 0.02	0.12 ± 0.04	0.028*
GGT (U/L)			
Baseline	63 ± 12	55 ± 8	0.584
PS 30′	62 ± 22	47 ± 8	0.496
AP (U/L)			
Baseline	82 ± 8	72 ± 8	0.428
PS 30′	89 ± 12	79 ± 7	0.507
LDH (U/L)			
Baseline	330 ± 19	331 ± 13	0.943
PS 30′	374 ± 18	347 ± 27	0.420
Creatinine (mg/dL)			
Baseline	0.44 ± 0.03	0.57 ± 0.06	0.085
PS 30′	0.45 ± 0.03	0.47 ± 0.03	0.596
Urea (mg/dL)			
Baseline	27.2 ± 2.2	22.2 ± 0.9	0.059
PS 30′	28.2 ± 2.6	22.2 ± 1.2	0.053
Lactic acid			
Baseline	1.5 ± 0.5	1.1 ± 0.2	0.453
PS 30′	1.5 ± 0.3	1.2 ± 0.2	0.434
NO (μM)			
Baseline	418 ± 47	691 ± 47	0.056
PS 30′	280 ± 92	478 ± 92	0.270

Data are expressed as the mean ± standard error of the mean. ALT: alanine transaminase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transpeptidase; AP: alkaline phosphatase (AP); LDH: lactate dehydrogenase; NO: nitric oxide; PS: partial support. Statistically significant differences are shown. *$P < 0.05$ propofol versus sevoflurane.

Table 2: Hemodynamic parameters in both groups (propofol and sevoflurane) at baseline and 30 minutes after implantation of a left ventricular assist device.

	Propofol $n = 5$	Sevoflurane $n = 5$	P values
HR (beats/min)			
Baseline	95 ± 4	89 ± 9	0.546
PS 30′	101 ± 6	101 ± 6	0.964
AP_m (mmHg)			
Baseline	70 ± 3	65 ± 5	0.384
PS 30′	65 ± 8	74 ± 7	0.404
PAP_m (mmHg)			
Baseline	23 ± 2	25 ± 2	0.506
PS 30′	27 ± 1	33 ± 3	0.083
CVP (mmHg)			
Baseline	15 ± 1	15 ± 1	0.856
PS 30′	14 ± 3	16 ± 2	0.584
CPP (mmHg)			
Baseline	18 ± 1	18 ± 1	0.471
PS 30′	15 ± 0.5	19 ± 1	0.052
SVRI			
Baseline	1583 ± 199	1368 ± 143	0.450
PS 30′	1128 ± 173	1433 ± 234	0.351
PVRI			
Baseline	171 ± 65	159 ± 32	0.877
PS 30′	217 ± 37	339 ± 85	0.269
CO (L/min)			
Baseline	2.4 ± 0.3	3 ± 0.3	0.185
PS 30′	2.5 ± 0.4	3.1 ± 0.4	0.347
SvO_2 (%)			
Baseline	77 ± 4	82 ± 3	0.429
PS 30′	82 ± 1	89 ± 3	0.150
T (°C)			
Baseline	35.1 ± 0.2	35.9 ± 0.3	0.080
PS 30′	33.9 ± 0.4	34.6 ± 0.4	0.332

Data are expressed as the mean ± standard error of the mean. HR: heart rate; AP_m: mean arterial blood pressure; PAP_m: pulmonary artery mean pressure; CVP: central venous pressure; CPP: pulmonary capillary wedge pressure; SVRI: systemic vascular resistance index; PVRI: pulmonary vascular resistance index; CO: continuous cardiac output; SvO_2: mixed venous oxygen saturation; T: temperature; PS: partial support.

patients receiving sevoflurane compared to propofol [42]. In this context, cardioprotection by sevoflurane compared to propofol could also be superior in patients undergoing noncardiac surgery [43]. However, troponin T increased in patients undergoing repair of congenital heart defect with cardiopulmonary bypass anesthetized with propofol and sevoflurane [44]. In our study we did not use cardiopulmonary bypass (there was no ischemia/reperfusion) in LVAD implantation.

It is known that sevoflurane tends to cause vasodilatation cerebral, increases cerebral blood flow (CBF), and decreases cerebrovascular resistance [45]. However, propofol produces cerebral vasoconstriction indirectly by reducing cerebral metabolism and causes a decrease in CBF that is well matched to cerebral metabolism [46]. Regarding why in our study sevoflurane increases CBF, Kaisti et al. [12] confirmed that CBF is lower with propofol than with sevoflurane.

4.2. Effect of Anesthetics on Markers of Tissue Injury. The objective of a VAD is to maintain adequate organ perfusion [2]. However, liver dysfunction has been observed despite adequate hemodynamic support with an LVAD [47]. Some

Table 3: Hematologic parameters and blood gas analysis in both groups (propofol and sevoflurane) at baseline and 30 minutes after implantation of a left ventricular assist device.

	Propofol $n = 5$	Sevoflurane $n = 5$	P values
pH			
Baseline	7.4 ± 0.03	7.4 ± 0.02	0.314
PS 30′	7.3 ± 0.03	7.4 ± 0.02	0.583
PO_2 (mmHg)			
Baseline	503 ± 24	425 ± 42	0.147
PS 30′	492 ± 43	483 ± 25	0.867
PCO_2 (mmHg)			
Baseline	35 ± 2	38 ± 2	0.428
PS 30′	38 ± 3	42 ± 3	0.322
HCO_3^- (mmol/L)			
Baseline	22 ± 1	26 ± 1	0.073
PS 30′	21 ± 1	24 ± 1	0.052
Hb (g/dL)			
Baseline	7.0 ± 0.1	7.4 ± 0.4	0.337
PS 30′	8.0 ± 0.5	8.3 ± 0.7	0.730
Hct (%)			
Baseline	19.7 ± 0.3	21.9 ± 1.2	0.148
PS 30′	22.5 ± 1.4	24.5 ± 2.0	0.452

Data are expressed as the mean ± standard error of the mean. PO_2: partial pressure of oxygen; PCO_2: partial pressure of carbon dioxide; HCO_3^-: bicarbonate; Hb: hemoglobin; Hcto: hematocrit; PS: partial support.

authors have reported hyperbilirubinemia in patients following implantation of an LVAD by hepatic sinusoid endothelial dysfunction [48] or cardiac congestion [49]. In our study, total bilirubin was higher in propofol-anesthetized animals than in sevoflurane-anesthetized animals; this finding was consistent with reduced blood flow in the liver and heart with respect to sevoflurane-anesthetized pigs.

Bernard et al. [50] found a portal blood flow decreased at both 1.2 and 2 MAC sevoflurane, whereas an increase in hepatic arterial blood flow was recorded at 2 MAC. These findings could explain why sevoflurane increases hepatic blood flow in our study.

4.3. Benefit of the Results for the Clinics. In our study, the use of sevoflurane leads to better outcomes after LVAD implantation by optimizing blood flow in the heart, brain, and liver. Although the necessary time to place an LVAD is short, the use of volatile anesthetic in cardiac surgery potentially reduces long-term cardiovascular complications and mortality [51]. Furthermore, intraoperative and postoperative sevoflurane administration in patients undergoing off-pump CABG could improve the cardioprotective effect compared with patients who received sevoflurane only in the intraoperative period [42]. It is possible because there is a disposable delivery system (AnaConDa) that is designed for halogenated sedation of patients in ICU [42]. LVAD, biventricular assist device (BIVAD), and extracorporeal membrane oxygenation (ECMO) are associated with a high incidence of complications (bleeding and tamponade requiring reexploration, right ventricular failure, respiratory failure, acute respiratory distress syndrome and pulmonary edema, neurologic complications, renal and hepatic failure, and infection) [5], and patients with complications are likely to require sedation and mechanical ventilation for a longer time period in ICU [52]. These patients could benefit from the sevoflurane effect over organs flow not only during the intraoperative, but also during the postoperative recovery period in the ICU.

4.4. Study Limitations. The present study is subject to a series of limitations. First, the LVAD is designed to be used in patients with heart failure; therefore, our results may not be directly applicable in clinical practice, because we used a healthy heart, as described elsewhere [53, 54]. This limitation should be addressed in an animal cardiogenic shock model. Second, since we studied the short-term effects of anesthetics (propofol and sevoflurane) in animals with an LVAD, the long-term effects of these drugs on organ blood flow warrant further investigation. Third, the effects of inhaled anesthetics [26–28, 55] and the intravenous anesthesia (propofol, opioids) [56, 57] may be dose-dependent. The concentration of sevoflurane we used represents approximately 1 minimum alveolar concentration, which is similar to the concentration used in other studies that show beneficial effects in a model of ischemia-reperfusion after thoracic-aortic occlusion in pigs [58].

We found that sevoflurane could be superior to propofol with respect to blood flow in the brain, liver, and heart tissue in a porcine model with LVAD. These findings may have significant clinical implications for anesthesiologists regarding the choice of sevoflurane in patients with an LVAD.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Design and Evaluation of a Fully Implantable Control Unit for Blood Pumps

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As the number of donor hearts is limited while more and more patients suffer from end stage biventricular heart failure, Total Artificial Hearts become a promising alternative to conventional treatment. While pneumatic devices sufficiently supply the patients with blood flow, the patient's quality of life is limited by the percutaneous pressure lines and the size of the external control unit. This paper describes the development of the control unit of the ReinHeart, a fully implantable Total Artificial Heart. General requirements for any implantable control unit are defined from a technical and medical point of view: necessity of a Transcutaneous Energy Transmission, autonomous operation, safety, geometry, and efficiency. Based on the requirements, a prototype is designed; it incorporates a $LiFePo_4$ battery pack with charger, a rectifier for transcutaneous energy transmission, the motor's driver electronics, and a microcontroller which monitors and controls all functions. In validation tests, the control unit demonstrated a stable operation on TET and battery supply and a safe switching from one supply to the other. The overall mean efficiency is 14% on TET and 22% on battery supply. The control unit is suitable for chronic animal trials of the ReinHeart.

1. Introduction

In some cases of heart failure, a heart transplant is the only therapy left for the patient. While donor hearts remain the gold standard of treatment, the number of patients greatly exceeds the limited number of donor organs. In cases where no allograft is available, Total Artificial Hearts (TAH) can provide an alternative. Pneumatic devices have successfully served as a bridge to transplant for the last 30 years [1]. However, these pneumatic systems require permanent percutaneous drivelines and a noisy compressor [2]. Thus, the improvement of the patient's quality of life becomes an increasingly significant consideration in the development of new devices, as TAH application is extended to the use as destination therapy.

Fully implantable devices renounce the percutaneous drivelines and transmit the energy into the body of the patient via two coils. Two coils of which one is subcutaneously implanted and the other is secured on the patient's skin are inductively coupled to transmit the energy wirelessly. This so-called Transcutaneous Energy Transmission (TET) evades the risk of driveline infection. Implanted backup batteries allow taking off all external gear for a limited time frame and thereby simplify body care and improve mobility. As a consequence, the patient's quality of life is highly improved by these fully implantable devices.

Up to now, only two devices have been fully implanted into patients: the AbioCor TAH and the Lion Heart Left Ventricular Assist Device (VAD) [3, 4]. Unfortunately both are no longer on the market and none of the recently available devices is fully implantable. Lately, the mayor VAD companies resumed TET system developments to enhance the patient's quality of life [1]. Whenever a TET system is used, a control unit which operates the pump also has to be implanted. This paper focuses on the configuration and design of such an implantable control unit. It provides an overview of the ReinHeart TAH, defines special requirements for implantable electronics, and describes the testing

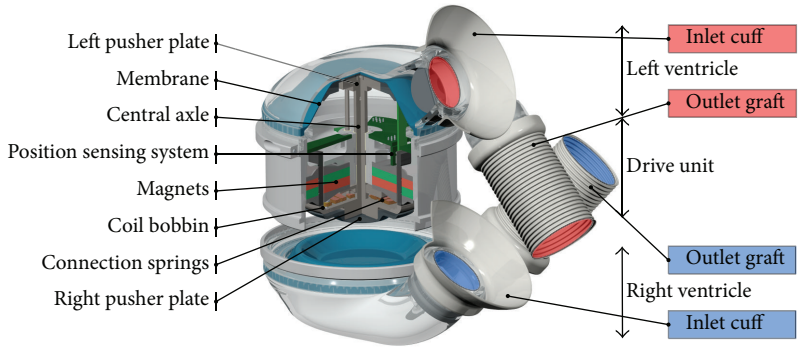

Figure 1: Detailed description of the TAH pump unit [5].

methodology for its evaluation. The validation of the prototype in a mock circulation loop is described and hydrodynamic and electric as well as mechanic attributes are presented. The paper closes with a conclusion and a preview of future work.

2. Material and Methods

In the following section, the general setup of the ReinHeart TAH, the control units target system, is briefly described. The requirements for adapting an extracorporeal control unit to an implantable control unit are listed and explained. Finally, the test setup for the validation of the prototype is described.

2.1. System Overview. The fully implantable Total Artificial Heart ReinHeart is currently being developed at the Institute for Applied Medical Engineering in Aachen, Germany. A detailed description of the ReinHeart can be found in [5]. Unlike a pneumatic drive, the electromagnetic driver of the ReinHeart enables the energy transmission through a TET system. It transmits energy into the body from an external coil to an implanted coil. An alternating current in the external coil induces an electrical voltage in the implantable coil via inductive coupling and supplies the driver with energy with no tissue defects and minimized risk of infection. A paper about the TET system is currently in preparation.

The general setup of the ReinHeart pump unit consists of a left and a right ventricle (Figure 1). The electromagnetic motor is arranged between the ventricles and separated from the blood by a polyurethane membrane. The motor moves two pusher plates which are connected on both sides of an axis. Thus, the pusher plates move simultaneously and alternately eject the left and right chambers. The left systole takes place during the right diastole and vice versa. Since the membranes are not attached to the pusher plates, the ventricles fill passively. The pressure in the compliance chamber is adjustable. Therefore the pressure gradient between the atrium and the motor unit can be increased to control the filling characteristics.

The movable part of the motor consists of the pusher plates on both sides of an axis and a coil bobbin. It is arranged in the magnetic field of the stator. Lorenz force is produced by current flow perpendicular to the magnetic field of the motor magnets and results in an upward motion. Inverting the current in the same magnetic field reverses the force and produces a downward motion. The magnitude of the force can be directly influenced by the amount of current in the coils. Therefore the control unit must provide time dependent current profiles to each coil to maintain the movement of the pusher plates. For a smoother and more efficient movement the motor of the ReinHeart TAH consists of four separate coils. Details about the drive unit are described in [6].

2.2. Requirements. When replacing a motor control unit from an external setup with a fully implantable control unit, additional functions must be added and novel requirements have to be taken into account. Those requirements are specified in the following.

2.2.1. Wireless Energy Transmission. All energy used by the pump unit and electronics must be induced into the body by inductive coupling. For energy transmission, a changing flux density is required. As such, alternating current is applied. The alternating current in the external coil induces alternating voltage in the implantable coil, which must be rectified to a stable direct current.

2.2.2. Safety. The driver electronics must be powered at all times after implantation. In the case of a sudden disconnection of the transmitting coil, the power demand of the electronics must be met by an implanted battery pack. In this scenario, the power supply must switch to battery support uninterruptedly. The battery must be charged whenever the TET System is reconnected. The internal battery is expected to supply the TAH for at least half an hour [7]. This will enable the patient to take off all external gear for a period of time which will offer improved quality of life. Finally, the battery has to be safe and durable despite the large number of charging cycles [8]. Consequently, the chemical type of the battery must be chosen accordingly.

Table 1: Influence of the different requirements on each part of the control unit.

	Input power	Driver electronics	Microcontroller
Wireless safety	Add rectifier Add battery	Adapted to wide voltage input range	Monitor TET voltage Monitor battery voltage
Autonomous	Automatic switching, recharging as soon as TET is connected	Provide coil currents	Control of the motor trajectory by control of the motor currents
Efficiency	Utilization of small number of efficient components with low heat production		
Geometry	Utilization of small packages and low number of electrical components		

2.2.3. Autonomous Pumping. Independent of the connection or disconnection of the external devices, the control unit has to assure a continuous pumping of the TAH, that is, a sinusoidal movement of the pusher plates at a preset beat rate. The movement has to be uniform regardless of varying input and output blood pressures.

2.2.4. Efficiency. The efficiency of the implanted electronics ultimately affects the amount of energy which has to be transmitted into the body. A good efficiency prolongs the time in which the system can support the patient without external components. Furthermore, a low energy consumption and a high efficiency reduce the internally generated heat to a minimum. For comparison, efficiencies reported by earlier developments varied between 6 and 39 % with most efficiencies in the range of 10 to 15% [4, 9, 10].

2.2.5. Geometry. Anatomical fitting studies, both virtual and cadaver studies, were conducted to determine the optimal size and location of the pump unit in a former study [11]. As a result, the TAH motor unit and ventricles have a diameter of 85 mm and a height of 90 mm. Because the space of the native heart is taken up completely by the pump unit, the electronics must be placed in a separate casing, which is located in the abdomen. To minimize the invasive approach, the electronics and the internal batteries must fit in the same casing. The resulting device configuration is displayed in Figure 2.

The housing volume documented by earlier developments is 277 cm^3 to 402 cm^3 [4, 12]. The material of the housing must be biocompatible and seals must protect the electronics from penetration of moisture. Finally, a convex shape, orientated on the shape of the abdominal wall, at the ventral side of the housing and rounded edges makes it more comfortable to wear.

Some of the above mentioned requirements compete against one another, especially at the interplay of efficiency and geometry, which must be considered throughout the whole design. As an example, additional functions like TET or battery support increase the size of the control unit's circuit board. Consequently, the higher number of electrical components, which are included for enhanced functionality, lower the efficiency. In the tradeoff between safety and geometry, not all batteries with a high energy to volume ratio are suitable for implant application. Shape and dimensions of the batteries limit the space available for electronics. Finally, produced waste heat could be spread more effectively by components in bigger packages with a larger surface area. Table 1 gives an overview of the tasks caused by the requirements. A balance between the different requirements was considered during the design of the control unit, which is described in the following section.

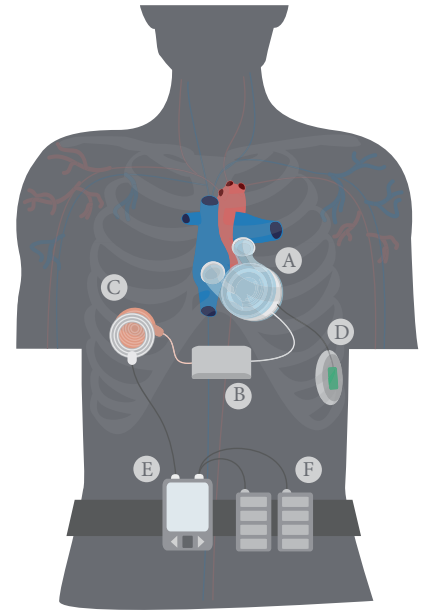

Figure 2: Assembly of the complete TAH system [5].

2.3. Validation. The designed prototype was validated in a mock circulation loop (MCL) described in detail elsewhere [13]. Systemic and pulmonary resistance, systemic arterial and pulmonary arterial compliance, and the venous volume of the MCL were controlled by a computer. The MCL was filled with a mixture of water (57.5%) and glycerin (42.5%); the resulting viscosity of 3.663 mPas was measured at room temperature. For this evaluation the pressure levels were fixed to the following values. The mean aortic pressure and the pulmonary artery pressure were set to 100 mmHg and 25 mmHg, respectively. The right and left atrium pressures were kept at 10 mmHg mean pressure. All pressures were registered by DPT-6000 (CODAN pvb Critical Care GmbH, Germany) sensors over fluid filled pressure lines. The beat rate was adjusted between 100 and 160 beats per minute. Ultrasound flowmeters (Transonic, USA) captured the resulting flow. All mentioned data was gathered by a dSpace Data

Acquisition System (dSpace, Germany). Additional electrical characteristics were recorded by a power meter WT1800 (Yokogawa, Japan) and a keysight oscilloscope (Agilent, USA).

3. Results and Discussion

A prototype based on the requirements for an implantable control unit was designed and evaluated. The requirements indicated that additional electronics besides the driver electronics have to be combined to one input power unit. Specifically, the rectifier for the TET, the battery, battery charger, and electronics for switching the input power from battery to TET. A microcontroller takes over the control and monitors functions of the system. Design and evaluation are described separately for each module in the following.

3.1. Design of the Prototype. The design of the electronics was realized with the software Altium Designer. It laid out on a six layer circuit board (Figure 3), because additional layers allow a more compact as well as noise optimized design. Table 1 summarizes the influence of each initially defined requirement on the different electronic units of the prototype. In the following, the resulting design of each unit is described.

3.1.1. Input Power. The control unit must be continuously powered after implantation.

Figure 4 documents the organization of the input power. The input switches between an alternating voltage received by the implanted TET coil and the direct voltage of the implanted batteries. Cells consisting of lithium-iron-phosphate ($LiFePo_4$) with a capacity of 1.1 Ah were chosen for the internal battery, as this type of a lithium ion battery combines a high power density, low self-discharge rate, a long cycle life, and a safe operation [14]. Since the electronics work with a minimum nominal voltage of 12 V, four cylindrical $LiFePo_4$ cells with a single nominal voltage of 3.3 V are used in series. Depending on the state of charge, the battery pack voltage, in the following named battery voltage, reaches 12 to 14.4 V. As this battery voltage can directly supply the power electronics without a voltage level shifter, accompanying power losses were minimized.

The AC voltage of the TET is rectified to a DC voltage, which is named TET voltage for further description. In order to charge the battery pack with a maximum voltage of 14.4 V, the TET minimum voltage is determined to be 15 V. Depending on the displacement of the external and implanted coil and the load, the voltage varies between 15 and 50 V.

TET voltage and battery voltage were connected in parallel. The power switch ensures current flow in the direction of the driver electronics by efficient, actively switching diodes. This prevents a short circuit to the battery voltage in the rectifier and vice versa. Whenever the external TET system is connected, its DC output voltage will exceed the battery voltage and therefore supply the driver electronics. The permanent supply voltage is labeled control unit voltage. TET

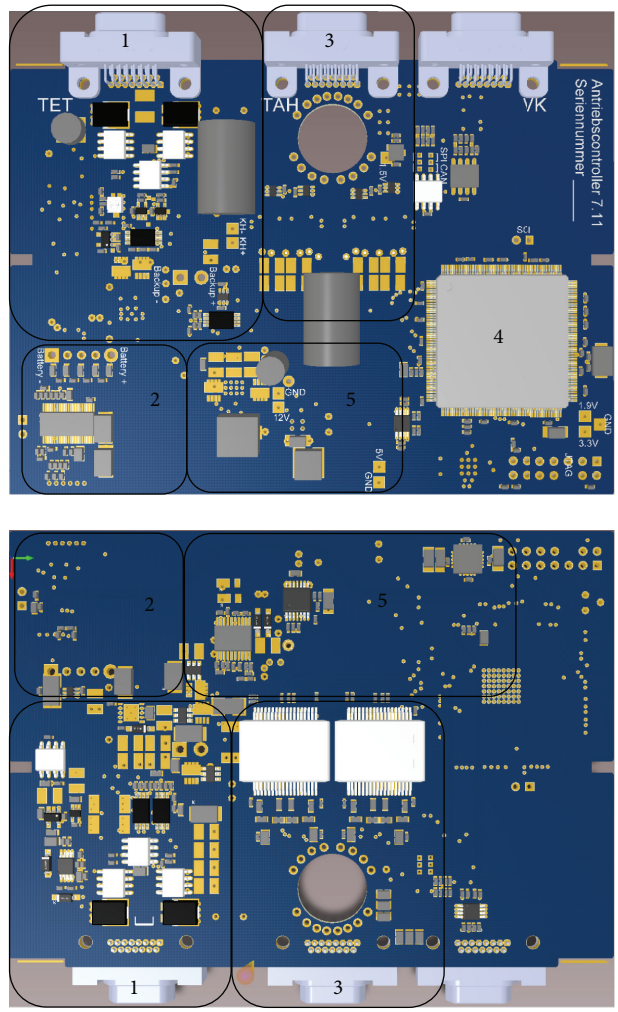

Figure 3: Circuit board of TAH control unit: 1-input power, 2-battery charger, 3-driver electronics, 4-microcontroller, and 5-voltage level shifter.

and battery voltage are constantly compared to each other to detect which input currently supplies the system.

To further improve the efficiency, no voltage converter is used to generate a constant control unit voltage. The power electronics of the motor driver, the battery, and the voltage level shifters, which create the operation voltages for sensors and microcontroller units, were configured to work with the input voltage range and regulate the output independent of the changing input. The resulting circuit is shown in area 1 of Figure 3.

Figure 4 illustrates how the TET voltage is connected to the charger of the battery pack. In order to assure supply of the control unit whenever the TET system is unable to deliver power, the battery will need to be charged as soon as the external TET System is connected. Constant-Current–Constant-Voltage charging is the optimum charging strategy for $LiFePo_4$ batteries. The charging process is controlled by the microcontroller. Until the battery pack voltage reaches 14.4 V the entire battery pack is charged with constant current. After the battery, voltage reaches 14.4 V, the voltage is

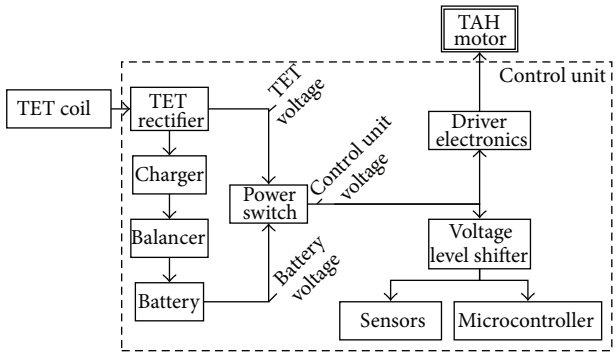

Figure 4: Organization of the input voltage.

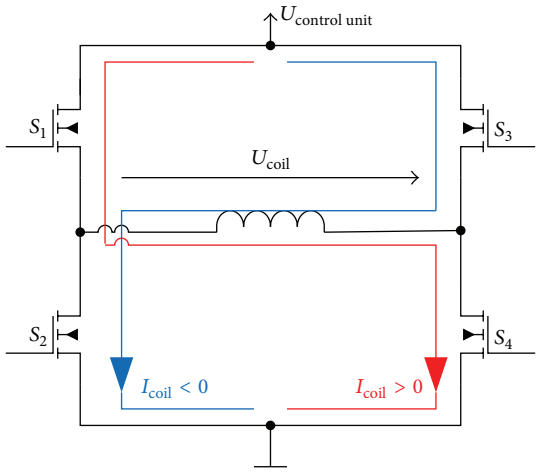

Figure 5: Schema of a full bridge circuit.

kept constant and the charging current slowly decreases. The battery is considered full when the charging current drops below 50 mA and the process is terminated by the software of the microcontroller. Over the charging period, the battery voltage increases continuously which roughly indicates the state of charge.

The sum of the cell voltages is not sufficient to ensure a safe charging process, since single cell voltages could exceed their end-of-charge voltage which could damage or even destroy the cell. Consequently, the voltages of all cells in the pack are balanced while charging to prevent overcharging of single battery cells and termination of the charging process when only one cell is fully charged. Through balancing, the maximum energy is saved in the battery pack. The cells are balanced passively by converting the excess charge to waste heat. The resulting charging and balancing circuit is presented in area 2 of Figure 3.

3.1.2. Driver Electronics. The moving part of the motor contains four coils. The current of each coil varies over time in sign and magnitude independent of the other coil currents. As such, each motor coil is driven by a separate electronic circuit, which is shown in Figure 5. The displayed full bridge allows the generation of positive or negative currents out of positive dc supply voltage.

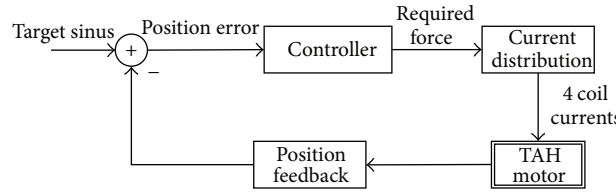

Figure 6: Position control schema.

Each of the full bridges for each coil is composed of four switches. If switches S1 and S4 are closed, positive current flows through the motor coil. On the contrary if switches S2 and S3 are closed, current flows in the opposite direction through the coil. Since the current in coils only changes slowly compared to the voltage across the coil, the desired magnitude of current can be created by fast chopping of the voltage across the coil. The time proportion in which the voltage is on, compared to the time period of a full cycle, determines the magnitude of the resulting current and should result in a linear relationship between "on" time and current.

3.1.3. Microcontroller. The microcontroller provides input signals to the driver electronics and the battery charger. It also collects additional information from the other units like the control unit and battery voltage as well as the driver electronics total current, battery, and motor coil currents. It is important to gather the information in a single microcontroller to guarantee that the system is never running low on energy and detect fault conditions in the electronics before they become an issue for the patient.

Table 1 illustrates that the microcontroller is responsible for autonomous pumping. The motor in the pump unit is supposed to follow a sine wave with amplitude up to 9 mm to alternatingly empty the left and right pump chamber. In Figure 6, the algorithm controlling the motor's position is described: a position sensor in the TAH monitors the actual position of the pusher plates. This monitoring is critical, as deviations between the target and the actual position of the pusher plates may occur, due to the changing blood pressure. The position error is used to adapt the required force and maintain a smooth sinus motion. The force depends on the in- and outlet pressures of the ventricles as well as the pump speed. Since Lorenz force is directly proportional to the current flow through the motor coils and the fraction of the magnetic flux available in the coil's position, the current is distributed according to the strength of the magnetic field. This way no current is wasted into heat, in positions where no magnetic flux is available to create a force.

3.2. Validation of the Prototype. As described in Section 2, the pump unit was connected into the mock circulation loop and operated by the developed control unit for testing.

3.2.1. Input Power. In a first trail, the uninterruptedly switching from TET to battery and back to TET was tested by continuous monitoring of the control unit voltage. The distance between the external and the implantable coil was set

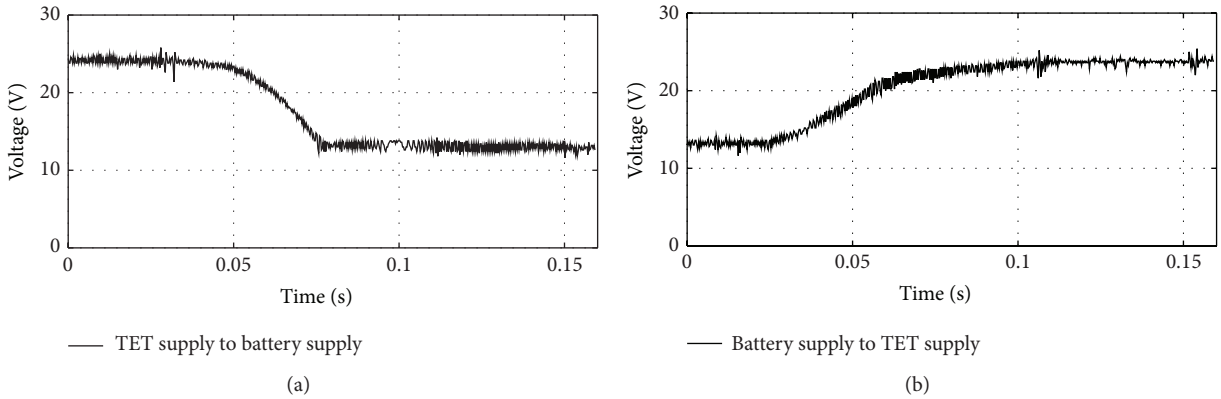

Figure 7: (a) Switching from TET supply to battery supply and (b) switching from battery supply to TET supply.

Table 2: Differences in cell voltages for balanced and unbalanced charging.

	Unbalanced voltage [V]	Balanced voltage [V]
Battery cell 1	3.584	3.441
Battery cell 2	3.588	3.442
Battery cell 3	3.595	3.443
Battery cell 4	3.552	3.442

to 16 mm, which resulted in a 24 V TET voltage. The battery voltage was measured at 13 V. The control unit voltage at the transition from one input to another is shown in Figure 7.

When switching the TET system off, the control unit voltage dropped to the battery voltage within 30 ms. If the external coil is removed, the transition time highly depends on how fast the coil is moved. On battery support, no setback in performance was noticed and all pressures were kept at stable level. When the TET system was reconnected, the control unit voltage was constant at TET voltage level after about 50 ms. In summary, a smooth and fast transition between TET and battery voltage could be verified in both directions.

In another experiment, a battery pack was charged without balancing and the resulting cell voltages are detailed in the first column of Table 2. The maximum difference between two cells was found at 43 mV. In contrast, when integrating a balancer, voltages between any of the different battery packs were nearly identical. The absolute voltages in balanced state were smaller than the unbalanced values since no further charging took place during the balancing process. Conclusively, the implemented balancer assures that all cells of the battery pack are charged equally and therefore guarantees the maximum energy storage in the battery pack.

3.2.2. Driver Electronics. The suitability of the full bridge circuits to regulate the coil currents was tested in another study. In general, the "on" time of a chopped voltage across a motor coil determines the magnitude of the resulting current. This linear relationship was evaluated as displayed in Figure 8. For positive and negative voltage, 15 different

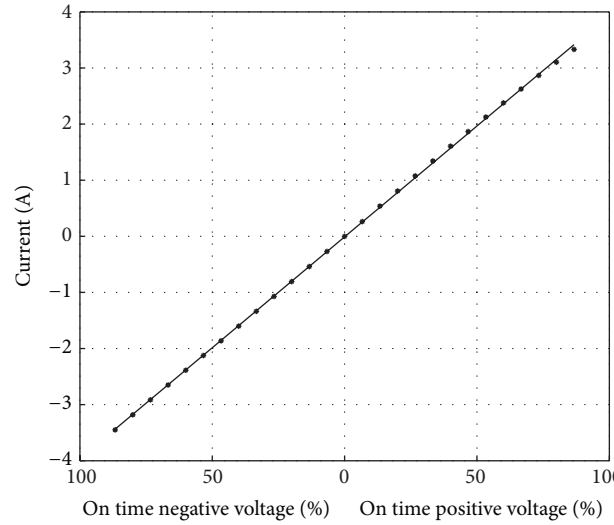

Figure 8: Current over "on" time of the voltage.

percentages of on time were applied to the first coil of the motor and the resulting current through the coil was measured. The straight line represents a linear interpolation of the individual current measurements.

In short, all measured currents match the interpolation, which proves the linear relationship between "on" time of the chopped voltage and current in the motor coil. Consequently, the full bridges circuit is suitable to gradually control the coil current and ultimately control the motor movement.

3.2.3. Microcontroller. The position control was tested by comparing the target pusher plate position with the positions measured by the microcontroller (Figure 9). The first half of the pump cycle corresponds to the right systole and left diastole, while the second half corresponds to the left systole and right diastole. The actual position follows the target position with an error of up to 7.5%. Although the error is visible in the middle of the curve, the motor reaches the peak values at the end of the left and right systole and thereby guarantees the complete ejection of the ventricle volume into the arteries.

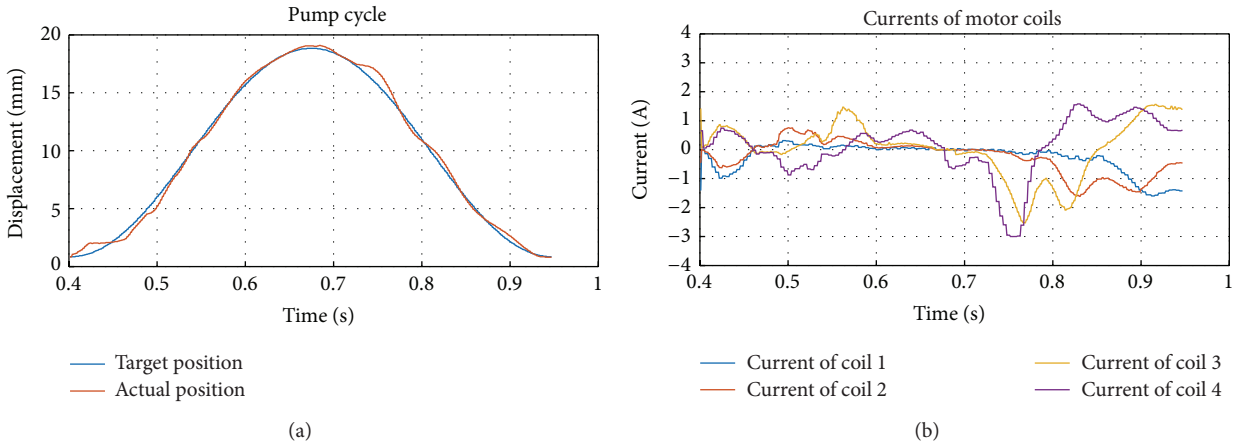

FIGURE 9: (a) Actual and target position among one pumping cycle and (b) current distribution in the four motor coils.

Figure 9 shows the four coil currents over one pumping cycle. As an illustrative case, coil 4 is observed during the left systole from 0.7 till 1 s. It starts with a high negative current at the beginning of the left systole. As the actuator with the attached coils moves through the magnetic field, the magnetic flux through coil 4 decreases, until it switches polarity at 0.71 s and continues to decrease. To maintain a force in the same direction, the current in coil 4 changes the polarity according to the change in the magnetic flux. It ends the left systole with a high positive current. Due to the higher pressure levels the currents during the left systole are generally higher than the currents during right systole. In summary, Figure 9 documents how the microcontroller successfully regulates the currents through all four coils depending on the magnetic field.

3.3. Overall Results of the Control Unit. The implemented control unit is shown in Figure 10. Its outer dimensions are 125 mm length, 86 mm depths, and height between 25 and 37.5 mm due to the convex shape. The volume measures 360 cm^3 and is comparable with the volume of earlier developments. The front panel holds three microjacks for connecting the implantable coil, the compliance chamber, and the pump unit. The jacks are sealed up to the front panel, which can be sealed to the housing itself.

In Figure 11, the inside of an opened control unit is displayed. The battery pack is fixed to the curved side of the case while the straight circuit board is mounted on the flat side of the case. In general, the size of the circuit board was adjusted to the length and width of the battery pack. However, some electrical components were too high to be mounted under the battery pack. Thus, the circuit board was extended in length to place higher electrical components aside from the battery pack. This size and shape of the control unit were validated positively in a cadaver study in a 75 kg male patient. Prototypes of the internal TET coil, the compliance chamber, and the control unit were positioned according to Figure 2. In comparison to a smaller dummy control unit with an additional battery pack in a second case, the one case prototype's fitting was satisfying, but allowed an easier implantation which is less traumatizing for the patient.

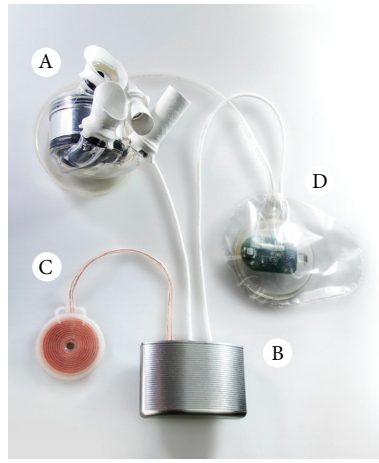

FIGURE 10: Figure 10: TAH implantable components: A-pump unit, B-first prototype of control unit, C-implanted TET coil, D-compliance chamber [5].

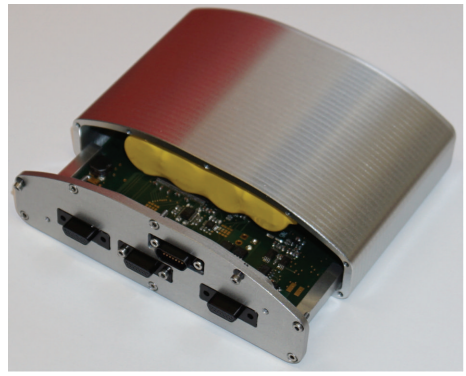

FIGURE 11: Front panel removed, view into the control unit.

Finally, hydrodynamic performance and efficiency of the complete TAH was investigated. The pressure in the compliance chamber was set up to a level which results in full fill, full ejection of the left and partial fill, and full ejection

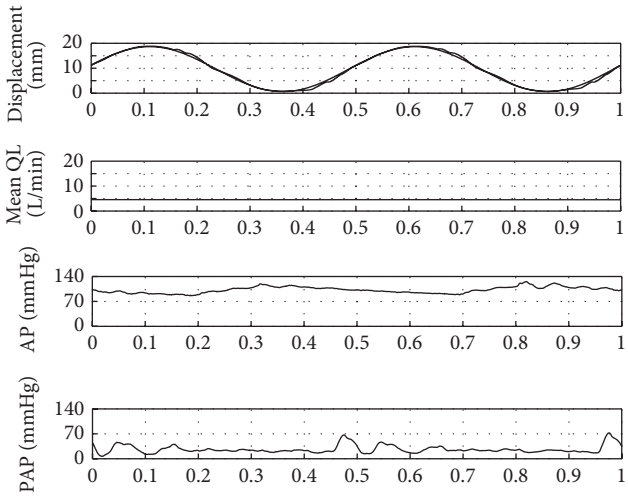

Figure 12: Hydraulic performance of the TAH.

of the right pump chamber. This assures left right balance of the TAH flow and best hydraulic efficiency. Figure 12 shows the flow and pressure curves captured by the DAQ for a beat rate of 120 bpm. The mean aortic flow was 5 L/min, which is comparable to blood flow of a healthy human. Mean aortic pressure and mean pulmonary artery pressure were 100 mmHg and 25 mmHg, respectively. The required mean power was 20 W.

Efficiencies for the various components were measured to evaluate how the losses are spread among the system. The efficiency of the control unit was calculated by the sum of the power dissipated in the four motor coils divided by the input electrical power drawn from the battery; the result was 83.5 % for the operating point. The efficiency of the hydraulic output power divided by the power drawn from the battery amounted to 22.6%. The hydraulic power was calculated by means of the mean flow rate and pressure levels. The average dc to dc efficiency of the TET system was evaluated and was determined to 62%. The peak efficiency at 45 W was 74%. Thereby the average efficiency of the control unit when supplied by the TET system would be 14%.

Further beat rates were investigated and pump and control unit performed in the full operating range up to 160 bpm and provided a maximum mean flow over 7.5 L/min.

4. Conclusion

A control unit which satisfies the requirements for a fully implantable TAH was designed and validated. It allows a safe and efficient operation of the designated pump unit of the ReinHeart TAH. The control unit successfully operated the pump unit without interruption during switchover between battery and TET in in vitro tests. The microcontroller software achieved autonomous pumping by controlling the motors motion on a sinusoidal trajectory. The utilized state of the art microcontroller technology enables modifications of the target trajectory to improve the interaction with the patient's physiology. It collects data from all modules which offers the implementation of safety queries and complex control algorithms. This variety of software adjustments was not implemented in earlier devices. Although a prototype for animal trails was accomplished, the efficiency and geometric dimensions were kept in a range acceptable for human implantation as experience with earlier devices indicate. The electronics for the TET system, the battery, and the motor control were inserted in one case. Compared to AbioCor TAH which used separate casing for the battery, the implantation expense was reduced. A cadaver study in a 75 kg male patient proved good fitting of the control unit prototype.

Some parts of the control unit already performed in animal trials and durability tests. Since all implantable components are designed for a lifetime of five years to bridge a reasonable timeframe, further in vitro and in vivo studies, especially long term trials, are necessary to confirm the performance of the entire control unit.

After long term validation of the TAH control unit additional improvements should be aimed for. The efficiency of the system can be improved by improving the control loop. This issue will be addressed in near future.

A wireless communication would allow forwarding the data collected by the microcontroller to an external user interface. Thereby the physician in charge could control the TAH operation. An ultimate goal would be physiological control of the pump rate according to the patient's blood pressures.

In a next integration step, the size of the control unit will be further reduced by applying state of the art micro technologies for circuit boards. Future battery technology will increase the support time of the internal batteries.

The implemented prototype was especially designed for the specific motor of the ReinHeart TAH. The same setup could be used to control active magnetic bearings of fully implantable blood pumps. Alternatively, the driver electronics of the setup could be easily adapted to drive a three phase rotatory device. In, the input power organization described in this paper is suitable for all fully implantable pumps.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Durable Mechanical Circulatory Support versus Organ Transplantation: Past, Present, and Future

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For more than 30 years, heart transplantation has been a successful therapy for patients with terminal heart failure. Mechanical circulatory support (MCS) was developed as a therapy for end-stage heart failure at a time when cardiac transplantation was not yet a useful treatment modality. With the more successful outcomes of cardiac transplantation in the 1980s, MCS was applied as a bridge to transplantation. Because of donor scarcity and limited long-term survival, heart transplantation has had a trivial impact on the epidemiology of heart failure. Surgical implementation of MCS, both for short- and long-term treatment, affords physicians an opportunity for dramatic expansion of a meaningful therapy for these otherwise mortally ill patients. This review explores the evolution of mechanical circulatory support and its potential for providing long-term therapy, which may address the limitations of cardiac transplantation.

1. Introduction

More than 5,000 heart transplants are performed each year worldwide, yet up to 50,000 people are candidates for this procedure [1]. For those who do undergo heart transplantation (HT), the current unadjusted 1-year survival rate is approximately 85%, with a median survival period ranging from 11 to 14 years [2]. Despite these promising outcomes, the unfortunate reality is that only about 2,000 donor hearts are available in the United States each year, and this severe limitation has not changed over time. Developed in the 1970s as a long-term sole therapy for heart failure, ventricular assist devices (VADs) antedate HT. However, with the introduction of cyclosporine and the increasing success of cardiac transplantation in the 1980s, the use of VADs expanded. Today there are 3 main indications for implantation of a VAD: bridging to transplantation, bridging to recovery, and destination therapy (DT). This review focuses on the subgroup of HF patients who may benefit from DT versus HT.

2. History of Mechanical Circulatory Support

On May 6, 1953, Gibbon, Jr. performed the first successful open heart procedure using a heart-lung machine of his own design. The device supported the young patient for 26 minutes while Gibbon closed an atrial septal defect [3]. Although the surgery was successful in this 1 case, all of Gibbon's subsequent patients died, and the mortality rate was high at other centers where the heart-lung machine was applied. In fact, 17 of the first 18 patients to undergo open heart operations died [4]. However, the dramatic success of C. Walton Lillehei's cross-circulation technique and Denton Cooley's bubble oxygenator [5] led to the rapid expansion of this technology. Although more surgeons began performing open heart surgery, it still involved a high mortality rate. Early observations by Frank Spencer and Michael DeBakey indicated that some patients who could not initially be weaned from the heart-lung machine would eventually recover if the support was prolonged. This experience stimulated an effort to develop more prolonged methods of cardiac support,

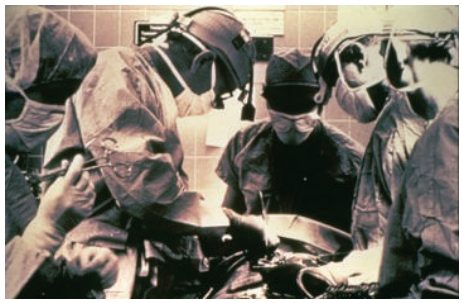

Figure 1: Dr. Cooley performing the first successful heart transplant in the United States—this figure illustrates Dr. Denton Cooley at Texas Heart Institute in May 1968, performing the first successful heart transplantation in the United States. (Photo courtesy of the Texas Heart Institute.)

allowing the patient to be spared from the damaging long-term effects of the heart-lung machine with the hope that, by prolonging cardiac assistance, recovery of the ventricle would ensue. There was a need for mechanical circulatory support (MCS) systems that could offer prolonged support—for days to weeks—and allow the heart time to recover.

Several early researchers made significant progress in the field of MCS, laying the groundwork for modern total artificial hearts (TAHs) and VADs. In 1963, Liotta et al. [6] reported the successful use of an implantable artificial ventricle in a patient who was in cardiogenic shock after a valve replacement procedure. Several years later, DeBakey [7] utilized a pneumatically driven VAD to bridge a young woman to myocardial recovery after cardiac surgery. The development and success of these MCS devices fueled the hope that such systems could be used to treat not only postcardiotomy cardiogenic shock but also HF.

Before the advent of clinical HT, mechanical heart replacement was pursued as the solution for advanced HF. In 1958, Akutsu and Kolff [8] became the first surgeons to implant a TAH into a dog, which was supported by the device for 90 minutes. In 1963, DeBakey urged a United States senate subcommittee to establish federal funding for TAH development. One year later, the National Institutes of Health established the Artificial Heart Program, providing 5 million dollars to support the creation of a mechanical heart.

While research involving both MCS and organ transplantation continued in the United States, Dr. Christiaan Barnard, of Cape Town, South Africa, astounded the world by performing the first human heart transplant in December 1967. Five months later, in Houston, Texas, Denton Cooley performed the first successful heart transplant in the United States (Figure 1) [9].

Other surgeons followed suit, and approximately 50 transplant centers were established worldwide. At that time, however, optimal immunosuppressive agents were not available, and tissue rejection proved to be an insurmountable problem. For this reason, the focus shifted away from HT and was redirected toward MCS.

In the 1970s, the National Heart, Lung, and Blood Institute was established by the National Institutes of Health, which again called for the development of long-term MCS devices. In 1969, Cooley became the first surgeon to implant a TAH clinically. It kept the patient alive for 65 hours until a suitable donor heart could be found, thus being the first device ever used as a bridge to transplantation [10]. Two years later, DeBakey reported 2 cases in which he had used an extracorporeal pneumatic left ventricular assist device (LVAD) to bridge postcardiotomy patients to recovery [7]. In 1978, Norman implanted the first LVAD to be used as a bridge to transplantation [11]. This was followed by Akutsu's second implantation of an LVAD in 1981, again as a bridge to transplantation [12]. In 1982, DeVries and colleagues implanted the first TAH intended for permanent cardiac support in Dr. Barney Clarke, a dental surgeon, who survived for 112 days [13].

The clinical advent of the improved immunosuppressant cyclosporine in the early 1980s allowed the meaningful clinical use of MCS as a bridge to transplantation. Ongoing advancements in immunosuppression have continued to demonstrate markedly improved cardiac transplant outcomes in the treatment of advanced HF. Unfortunately, because of severe limitations in the availability of donor allografts, nearly 10% to 15% of patients awaiting transplantation die before a suitable organ can be found. Another 10% to 15% lose their eligibility for a transplant, ultimately being dropped from the waiting list [14].

According to recent data, the expected mean survival period for patients with end-stage heart disease is only 3.4 months. Once a patient is dependent on inotropic agents, the 1-year survival rate decreases to only 6% [15]. The outlook is even more dismal for patients who are ineligible for HT. The lives of patients with advanced HF may frequently be saved, however, by the timely implantation of an MCS device. Although the majority of these patients can potentially become transplant candidates, the dependence on donor availability makes this therapy epidemiologically trivial.

3. Destination Therapy

By the end of the 20th century, many centers were actively involved in clinical investigations using the first generation of LVADs, which were positive displacement pumps. The results of the landmark Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial published in 2001 [16] set the stage for many future accomplishments. In this multicenter study, 129 patients with severe HF were randomized to receive either maximal medical treatment or an implantable, pulsatile-flow HeartMate Vented Electric (XVE) LVAD (Thoratec Corporation, Pleasanton, California, USA). All patients were ineligible for HT, had an estimated life expectancy of less than 2 years, and had received optimal medical therapy before enrollment. All patients also had New York Heart Association (NYHA) class-IV status, a left ventricular ejection fraction of less than 25%, and dependency on intravenous inotropic therapy or a peak oxygen consumption of less than 12 mL/kg/min.

These were among the sickest HF patients ever to have undergone a randomized prospective trial, and the results were extremely encouraging (Figure 2). One-year survival

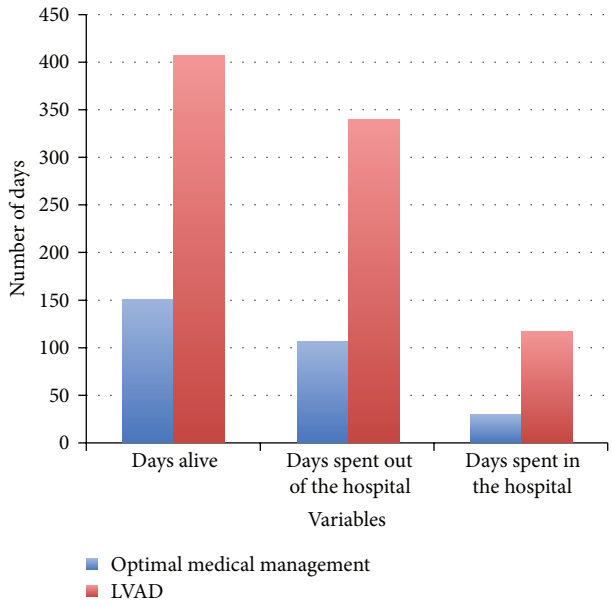

Figure 2: The hospitalization experience of the REMATCH trial—this figure illustrates the stark contrast in survival and hospital days between REMATCH trial patients who received optimal medical management versus LVAD therapy with a HeartMate XVE [16].

improved from 25% for patients receiving optimal medical therapy to 52% for those supported by an LVAD. The 2-year survival rates were 8% and 23%, respectively. Quality of life also significantly improved in the LVAD patients, as documented by better NYHA functional status and questionnaire-based assessment of general health perception. However, the patients with LVADs had a nearly 2-fold increase in their risk for adverse events, including infection, hemorrhage, and device malfunction.

Although the REMATCH trial did show improved success for the device-treated patients, it also raised ethical and medical questions regarding the need for the implementation of MCS. The goal of these original pulsatile LVAD devices was to support patients for 2 years. These data were becoming available for the bridge-to-transplantation population. In addition, the drug-therapy patients had already received optimal medical treatment for their advanced HF. At the time, they were randomized to LVAD implantation or to ongoing therapy that was deemed to be failing. Obviously, the high mortality rate of the medical arm of this trial was the main factor in the LVAD's success. The trial really emphasized the need for improved development in the field of long-term LVAD use as a sole therapy.

The Clinical Utility Baseline Study [17] was the first European investigation of DT. In this nonrandomized, observational study, the investigators evaluated the LionHeart LVD-2000 fully implantable, pulsatile LVAD (Arrow International, Reading, Pennsylvania, USA) in 23 patients. All had NYHA class-IV HF and were deemed ineligible for a transplant. The LionHeart LVD-2000 LVAD was uniquely powered by a transcutaneous energy transfer system, which eliminated the need for a percutaneous driveline and, therefore, was expected to have significantly fewer infectious complications. Compared to the REMATCH data, the rate of infections was in fact decreased, but there was a remarkable inferiority in the survival benefit. The 1- and 2-year survival rates were only 39% and 22%, respectively.

The Investigation of Nontransplant-Eligible Patients Who Are Inotrope Dependent [18] evaluated the Novacor LVAD (Novacor Corporation, Oakland, California, USA) in a multicenter, nonrandomized, prospective study. Fifty-five patients with inclusion criteria similar to those in the REMATCH study, including NYHA class-IV symptoms, ineligibility for HT, and failure to wean from inotropic therapy, were offered this device. Thirty-seven patients received an LVAD, and the other 18 patients (the control group) continued to receive optimal medical therapy. Compared to the control group, the LVAD recipients had a significant improvement in HF symptoms, and their survival was significantly higher at both 6 months (46% versus 22%, resp.) and 12 months (27% versus 11%, resp.). However, the LVAD group had a remarkably high rate of cerebrovascular events: 62% of all LVAD recipients had a stroke or transient ischemic attack during the study.

After the REMATCH trial results were published in 2001; the United States Food and Drug Administration approved the HeartMate XVE for DT. Medicare approval followed in 2003. The Novacor and LionHeart LVD-2000 devices showed inferior results and were not approved for this indication. As described above, first-generation devices were fraught with complications, which limited the long-term utility of these devices for DT. They were also too large and bulky to use in patients with a smaller body habitus, including women and children.

Another leap forward in the evolution of MCS devices was realized with the introduction of second-generation, continuous-flow (CF) LVADs. In contrast to their predecessors, CF pumps are smaller and simpler, with few moving parts. These pumps have an internal rotor suspended by contact bearings that provide continuous, axial flow. They also have smaller blood-contacting surfaces, an absence of valves, and decreased energy requirements. These characteristics have resulted in remarkably improved outcomes, increased durability, and broadened applicability.

The first clinical application of a durable CF-LVAD occurred in Berlin, Germany, in 1998 using a MicroMed DeBakey VAD (MicroMed Cardiovascular, Inc., Houston, Texas, USA), which was developed by Drs. DeBakey and George Noon in collaboration with the National Aeronautics and Space Administration [19]. The basis for this axial-flow LVAD technology came from the pioneering work of Drs. Richard Wampler and Robert Jarvik in collaboration with Dr. O.H. Frazier at the Texas Heart Institute (THI) [20]. Wampler developed the Hemopump Cardiac Assist System (Nimbus, Rancho Cordova, California), a catheter-mounted, intra-aortic axial-flow pump modeled after the 3rd century Archimedes screw. This pump, which was designed in the 1980s, demonstrated that temporary support could be provided using a high-speed impeller (25,000 rpm) with minimal hemolysis. After successful animal experiments at THI, Frazier implanted the Hemopump in 1998, marking the first temporary CF device implant [21].

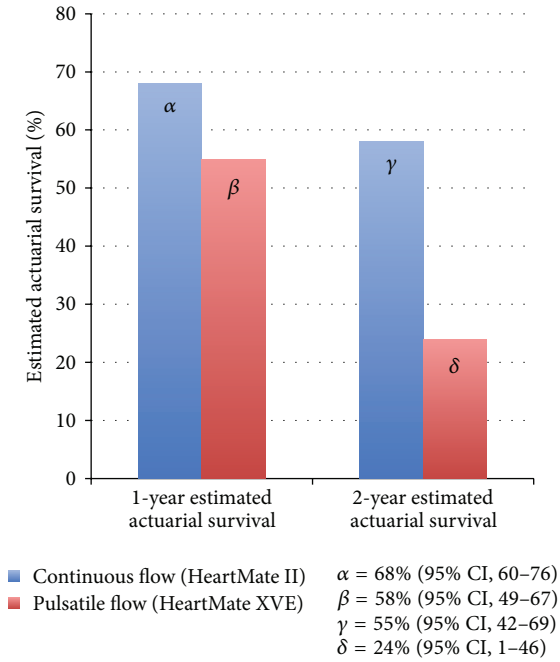

Figure 3: Estimated one-year actuarial survival for continuous-flow versus pulsatile flow LVAD therapy—this figure illustrates the one- and two-year actuarial survival for continuous-flow (HeartMate II) and pulsatile-flow (HeartMate XVE) LVADs. The results demonstrate the superiority of continuous-flow support [22].

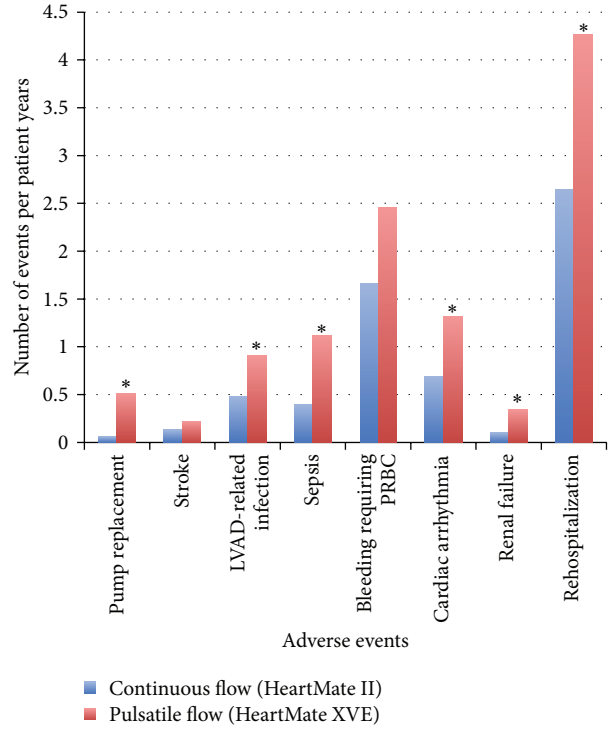

Figure 4: Adverse events associated with continuous- and pulsatile-flow LVADs—this chart illustrates a comparison of adverse events between continuous-flow and pulsatile-flow support listed as events per patient years. Those differences with a significant P value (<0.05) are indicated by an "∗" [22].

The next important milestone came with Jarvik's development of blood-immersed (nonlubricated) bearings, which allowed for long-term, implantable axial-flow pump designs. These two important events allowed for the development of future CF-LVADs and set the stage for a revolution in heart failure treatment [20]. Clinical trials utilizing newer, second-generation CF-LVADs, including the Jarvik 2000 (Jarvik Heart, Inc., New York, NY, USA), MicroMed DeBakey, and HeartMate II (Thoratec) pumps, would continue for nearly a decade, and the results would introduce a lasting and important change in the field of MCS.

In 2009, the results of a landmark trial [22] were reported, comparing the pulsatile, first-generation HeartMate XVE with the CF HeartMate II device. The study included 200 patients with a left ventricular ejection fraction of less than 25%, peak oxygen consumption of less than 14 mL/kg/min, NYHA class IIIB or IV symptoms, or the need for an intra-aortic balloon pump or inotropic therapy. Actuarial survival was significantly improved in the HeartMate II group compared to the HeartMate XVE group (68% versus 55%, resp., at 1 year and 58% versus 24% at 2 years; Figure 3). Adverse event rates were also significantly reduced with the HeartMate II (Figure 4).

In a later study [23], the HeartMate II investigators evaluated a cohort of 281 patients with similar inclusion criteria and compared these patients to the initial group. The later HeartMate II recipients had even lower rates of adverse events—including bleeding, infections, sepsis, and stroke—as well as a trend towards improved survival. This study showed that increased center experience and better patient selection could lead to further improvement in outcomes. In 2010, the Food and Drug Administration officially approved the HeartMate II for DT.

To ensure high-quality data collection across all centers that implant MCS devices, the National Heart, Lung, and Blood Institute issued a request for proposals to create a national database. In 2005, the University of Alabama was awarded a 5-year contract, which led to the formation of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) [24]. This registry was created with the goals of refining patient selection to maximize outcomes with MCS devices, identifying risk factors and predictors of outcomes, developing best-practice guidelines to reduce complications, guiding improvements in technology, and guiding clinical testing and approval of new devices.

Because NYHA class IV was too broad to allow physicians to distinguish between the preoperative clinical statuses of patients who require MCS, seven INTERMACS subclassifications were created. These ranged from profile 7 (advanced NYHA class-III symptoms) to profile 1 (critical cardiogenic shock) (Table 1). Moreover, 17 adverse events were outlined and defined. Designated DT therapy centers accepting payment from the Centers for Medicare and Medicaid Services were mandated to report scientific information to INTERMACS, and, as a result, the registry has received large volumes of patient data.

Table 1: INTERMACS profiles: profile descriptions for the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) classification system [47, 48].

Profile	Definition	Description
1	Critical cardiogenic shock (crash and burn)	Patients with life-threatening hypotension despite rapidly escalating inotropic support, critical organ hypoperfusion, often confirmed by worsening acidosis.
2	Progressive decline (sliding on inotropes)	Patient with declining function despite intravenous inotropic support may be manifest by worsening renal function, nutritional depletion, and inability to restore volume balance. Also it describes declining status in patients unable to tolerate inotropic therapy.
3	Stable but inotrope dependent (dependent stability)	Patient with stable blood pressure, organ function, nutrition, and symptoms on continuous intravenous inotropic support (or a temporary circulatory support device or both), but demonstrating repeated failure to wean from support due to recurrent symptomatic hypotension or renal dysfunction.
4	Resting symptoms	Patient can be stabilized close to normal volume status but experiences daily symptoms of congestion at rest or during ADL. Doses of diuretics generally fluctuate at very high levels. More intensive management and surveillance strategies should be considered, which may in some cases reveal poor compliance that would compromise outcomes with any therapy. Some patients may shuttle between 4 and 5.
5	Exertion intolerant	Comfortable at rest and with ADL but unable to engage in any other activity, living predominantly within the house. Patients are comfortable at rest without congestive symptoms but may have underlying refractory elevated volume status, often with renal dysfunction. If underlying nutritional status and organ function are marginal, patient may be more at risk than INTERMACS 4 and require definitive intervention.
6	Exertion limited (walking wounded)	Patient without evidence of fluid overload is comfortable at rest and with activities of daily living and minor activities outside the home but fatigue after the first few minutes of any meaningful activity. Attribution to cardiac limitation requires careful measurement of peak oxygen consumption, in some cases with hemodynamic monitoring to confirm severity of cardiac impairment.
7	Advanced NYHA III	A placeholder for more precise specification in future; this level includes patients who are without current or recent episodes of unstable fluid balance, living comfortably with meaningful activity limited to mild physical exertion.

Recently, Kirklin and associates [25] published the sixth annual INTERMACS report, which provides an analysis of over 12,000 patients who received MCS devices between June 2006 and June 2013 at 158 participating US hospitals, including 141 centers approved for DT. The authors note that CF devices have continued to yield good overall outcomes, with an actuarial survival rate of 80% at 1 year and 70% at 2 years. Furthermore, a significant increase in device implantation for DT is evident, with more than 40% of pumps having been implanted for this indication in 2011–2013.

Since the approval of VAD implantation for DT, there has been a dramatic increase in MCS device utilization. As of March 9, 2015, 159 active participating sites have enrolled over 14,000 patients into INTERMACS [26]. More patients with advanced HF are now potential candidates for surgical therapy, and outcomes are extremely encouraging (Figure 5). As DT outcomes approach those of HT, the question arises: When will we reach the point at which a patient who is eligible for HT may, instead, be provided with a VAD for DT?

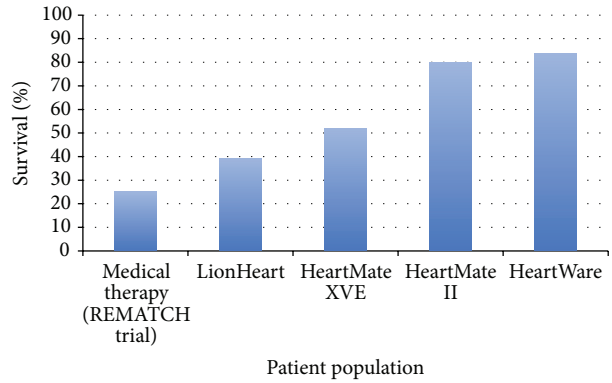

Figure 5: A comparison of 1-year survival with optimal medical therapy (REMATCH), pulsatile-flow VADs (LionHeart; XVE), and continuous-flow VADs (HMII; HVAD). The rise in survival echoes that newer technology along with improved management of VAD patients has led to an increased overall survival [17, 22, 49, 50].

4. Heart Transplantation versus Ventricular Assistance

With the availability of an alternative treatment that yields consistently acceptable and rapidly improving results, we are approaching the realization of a long-sought dream, to routinely augment the cardiac function of end-stage HF patients with permanent MCS.

For DT to be allowed in lieu of HT, many factors must be considered. Each modality comes with its own profile

of risks and benefits, and there is much to be clarified in regard to which patients may experience the greatest benefit from which intervention. It is important to weigh the adverse events associated with HT (allograft vasculopathy, immunosuppression, cancer, rejection, and drug toxicity) against those associated with MCS (thrombosis, hemorrhage, stroke, and infection) on an individualized basis. In addition, VAD recipients must cope with a battery holster and percutaneous driveline.

In regard to infection, the percutaneous driveline is an ongoing issue with current VAD designs. Its existence predisposes patients to an ongoing risk of infection. Avoiding the infectious risk associated with posttransplant immunosuppression may not be possible any time in the near future, though it may be possible to diminish the infectious risk of MCS. Methods for overcoming driveline-related infections include aggressive wound care [27], transcutaneous energy-transfer technology [28], and a smaller lead diameter for reducing trauma [29], as well as tunneling of the driveline to distant sites, such as the highly vascular postauricular region of the head, using a skull-mounted pedestal [30]. The original proposals for LVAD development excluded skin penetration. Considerable advances in transcutaneous powering of LVADs were made during the 1970s and early 1980s. In addition, transcutaneous power has already been successfully used in trials of the Arrow LionHeart and the AbioCor TAH (ABIOMED, Danvers, Massachusetts, USA). This technology can be applied to the currently used continuous-flow LVADs as well.

Given the severe shortage of cardiac allografts, the ongoing improvements in DT outcomes, and the increasing overall costs, proper patient selection for each modality will be of great importance. At what point would it be ethical to randomize patients to DT versus HT? Among patients currently listed for HT, are there any for whom DT might be more beneficial? Although no clinical trials have directly addressed these questions, information from the United Network for Organ Sharing, International Society for Heart and Lung Transplantation, and INTERMACS databases may help provide some insights.

To determine the characteristics of patients demonstrating the greatest benefit from HT, Kilic and colleagues [31] evaluated 22,385 patients in the United Network for Organ Sharing database and found a 10-year or greater posttransplant survival rate of 42%. Predictors of such longevity included a younger recipient age (less than 55 years), younger donor age, short ischemic time, Caucasian race, and an annual volume of nine or more heart transplants at the treatment center.

To demonstrate risk factors associated with suboptimal posttransplant outcomes, the same authors also evaluated the data for all patients who did not survive to 10 years [31]. The average number of years gained after HT was significantly lower in this group (3.7 ± 3.3 years). Predictors against long-term survival included diabetes mellitus and the need for preoperative mechanical ventilation. In another study, Stehlik and colleagues evaluated the International Society for Heart and Lung Transplantation database to elucidate risk factors for 1- and 5-year posttransplant mortality [32]. The following variables were risk factors for faster mortality after HT: increased donor age, ischemic time greater than 200 minutes, extremes of recipient age, renal dysfunction, congenital etiology of heart disease, and the need for extracorporeal membrane oxygenation and temporary pulsatile support.

To assess patients having yet to receive a transplant, Lietz and Miller [33] analyzed more than 48,000 patients in the United Network for Organ Sharing database. They reported the following independent predictors of death within 2 months of listing: status 1A listing, elevated creatinine level, previously failed HT, valvular cardiomyopathy, congenital heart disease, Caucasian ethnicity, low body weight, age greater than 60 years, elevated pulmonary capillary wedge pressure, and the need for mechanical ventilation, intravenous inotropic agents, or an intra-aortic balloon pump.

In evaluating more than 10,000 CF-LVAD recipients in the INTERMACS database, Kirklin and colleagues [25] found the following risk factors for increased mortality: elder age, female gender, elevated body mass index, history of stroke, renal dysfunction, right heart dysfunction, surgical complexity, implantation for DT, and INTERMACS profile level 1 or 2 status.

Because the limiting factor in HT versus MCS is organ availability, many argue that transplantation should be prioritized in favor of patients expected to incur the greatest survival benefit; other patients may continue receiving optimal medical management or be offered mechanical support. Taken together, previous studies imply that patients who preferentially undergo a transplant with nearby organs (involving a shorter ischemic time) from younger donors should be nondiabetic recipients with good renal function who are younger than age 55 do not require mechanical ventilation or extracorporeal membrane oxygenation, and are able to undergo transplantation at a high-volume center. In contrast, VAD support could preferentially be provided to patients who have a higher waiting-list mortality, such as elderly persons with low body weight, elevated pulmonary capillary wedge pressure, or previously failed HT who do not yet have critical INTERMACS profile 1 or 2 status.

Risk factor and survival analyses such as those reviewed here will become increasingly important in future algorithms. Challenges to current practices are already emerging from such reports. For example, several studies of outcomes in United Network for Organ Sharing status 2 patients have led investigators to question the need for transplantation in this population [34–36]. Because 1-year survival is nearly equivalent to that of transplantation and early listing has the lowest benefit without an urgent upgrade in status [36], some authors propose delaying status 2 listing and diverting organs to sicker patients. This is a controversial subject because many status 2 patients have excellent 1- and 3-year survival rates, yet a significant number require an urgent upgrade to status 1 and have a high mortality rate without transplantation [37].

Stratifying which patients should receive HT versus DT is an important and intriguing question that currently has no clear answer. Many factors will have to be considered, and further analysis of risk factors and survival data may help to guide such decisions. Future randomized clinical trials

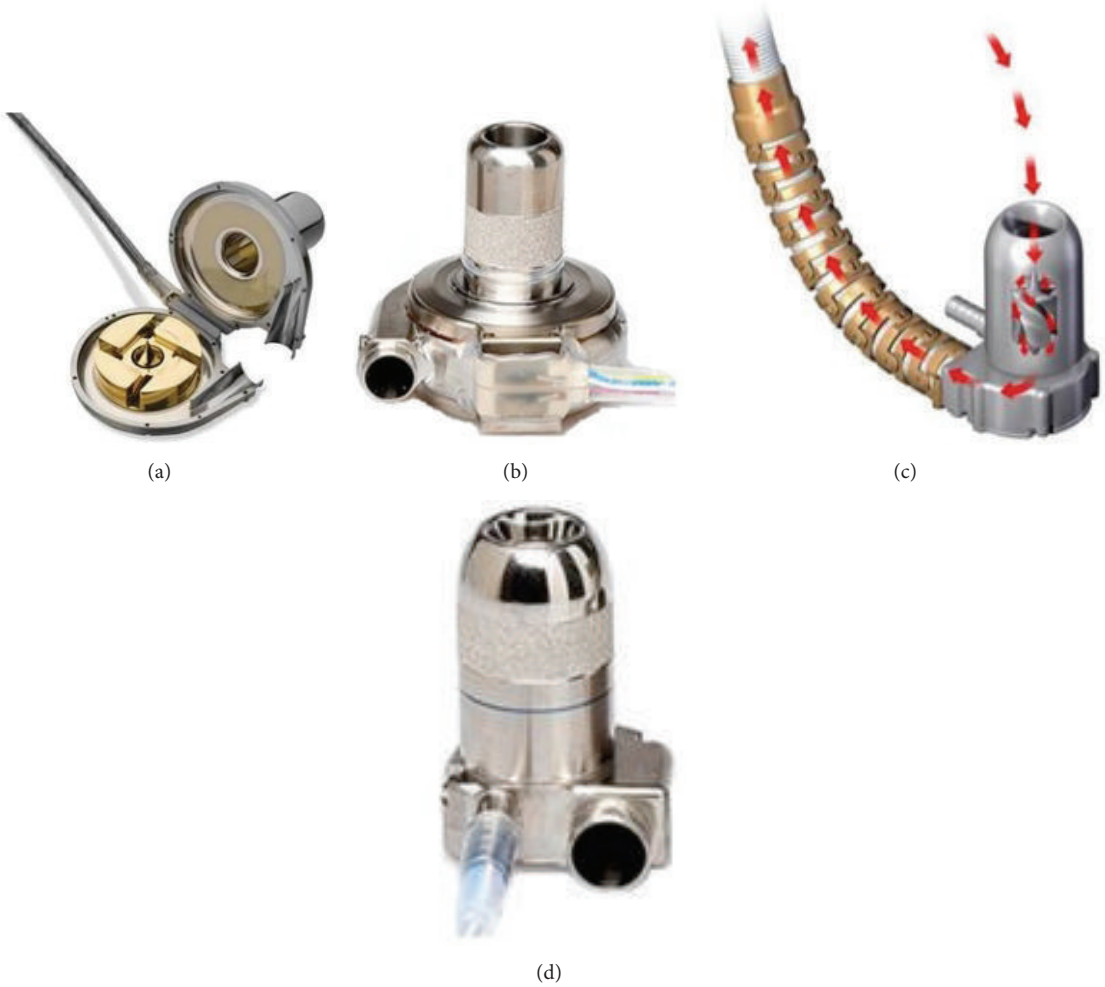

Figure 6: HeartWare devices: the HeartWare ventricular assist device (HVAD) ((a)/(b)) is currently approved as a bridge to transplantation and is undergoing clinical trials for destination therapy. The HeartWare miniaturized ventricular assist device (MVAD) ((c)/(d)) is the latest design expected to undergo human clinical trials. Images adopted from HeartWare website.

addressing this issue would be of tremendous benefit and are greatly anticipated.

5. Future Perspectives

Recent progress in MCS therapy has permanently changed the prevailing strategies for managing advanced HF. Outcomes of MCS therapy are rapidly approaching those of HT. For the subset of patients with severe HF who are not candidates for HT, DT has been shown to be superior to maximal medical management. Among developing technologies, new devices continue to emerge into clinical practice.

Most recently, the Food and Drug Administration approved the HeartWare ventricular assist device (HVAD) (HeartWare, Inc., Framingham, Massachusetts, USA), a newer, third-generation LVAD. This miniaturized centrifugal pump uses a hybrid magnetic suspension with one moving part and no mechanical bearings. The HVAD is implanted into the intrapericardial space, abolishing the previous pump pocket, which was a problematic region for infection. The pump's small size also allows implantation into patients with a smaller body habitus (Figure 6). A multicenter evaluation of this device revealed actuarial survival rates of 90%, 84%, and 79% at 6, 12, and 24 months, respectively [38]. In November 2012, the HVAD received approval from the Food and Drug Administration for use in HF patients awaiting HT.

Two more devices are on the horizon, the HeartWare Miniaturized Ventricular Assist Device (MVAD) (Figure 6) and the HeartMate III (Thoratec Corporation, Pleasanton, California, USA) LVAD (Figure 7). The HeartWare MVAD is unique in that the pump itself resides within the inflow cannula. The magnetically suspended rotor has a wide-bladed design for reduced cellular trauma and provides up to 10 liters per minute of axial blood flow [39]. The MVAdvantage study, A Clinical Trial to Evaluate the HeartWare MVAD System, was recently announced [40].

The HeartMate III LVAD, unlike its axial flow predecessor (Figure 7), is a third-generation centrifugal flow pump. Unique in its three-dimensional, magnetically levitated rotor, it is capable of sharp alterations in speed allowing for an

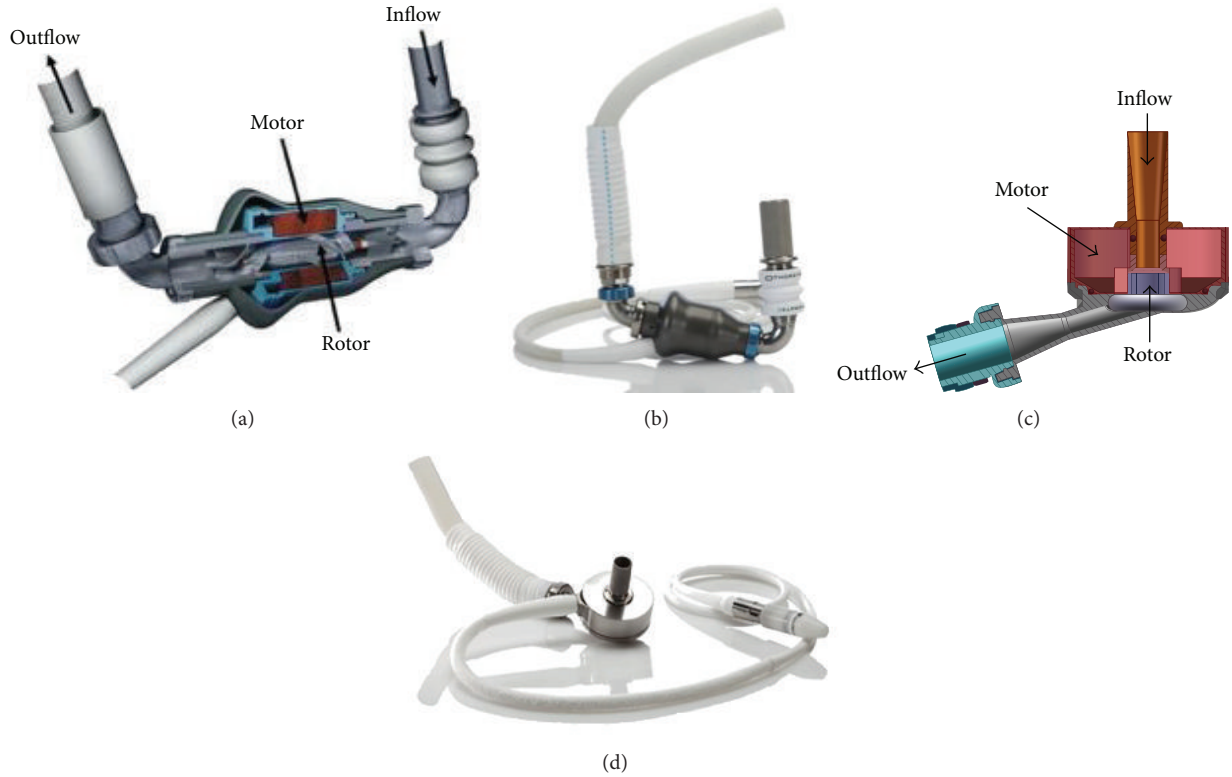

Figure 7: HeartMate devices: the HeartMate II LVAD ((a)/(b)) is currently approved as a bridge to transplantation and as a destination therapy. The HeartMate III LVAD ((c)/(d)) is a new, third-generation centrifugal pump expected to undergo clinical trials in the near future. Images adopted from [51].

induced pulsatile flow [41]. As long-term anatomic and physiologic effects to human vasculature and end-organ systems from reduced pulsatility are not known; speed modulation may prove beneficial. Future outcomes data will help to define the role of these new devices and techniques in flow modulation.

Another area of ongoing advancement is in the treatment of biventricular HF. Several MCS options exist and can be broadly divided into those that support the existing ventricles and those that require excision and mechanical replacement of the heart. Durable biventricular assist device (BiVAD) support using two intrapericardially placed VADs has been increasingly utilized, particularly since the introduction of third-generation centrifugal pumps. However, the need to balance pulmonary and systemic flows and the requirement of two controllers for separate right and left devices adds to complexity and is not ideal for long-term management.

The only currently approved device for total cardiac replacement is the SynCardia TAH. Having been implanted in more than 1,400 patients, a broad worldwide experience has supported the ongoing use of this device when necessary [42]. However, much like first-generation LVADs, the long-term endurance of its flexible membranes, valves, and many moving parts imposes barriers to prolonged, uncomplicated support. Furthermore, the currently approved device is quite large, having a 70-cc stroke volume and is approved for use only in larger patients (body surface area, $\geq 1.79\,m^2$). On the horizon, however, is a smaller (50-cc) device that will be suitable for adolescents and children and is currently undergoing clinical validation.

Attempts to improve TAH technology such that long-term total cardiac replacement can be performed safely and routinely continues to define the Holy Grail in the search for an alternative to HT, and significant progress is being made. At THI, there has been a large experience with experimental total cardiac replacement using dual CF-LVADs in large animals [43], as well as the world's first clinical application in March 2011 [44]. These experiments have provided surgical experience and important insights to the novel concept of pulseless physiology.

Another exciting technology currently under development at THI is the BiVACOR TAH, which holds potential for another leap forward in the field of MCS. The authors anticipate that this device will be the first practical, long-term mechanical replacement for the failing human heart. Expected benefits are similar to those realized in the evolution from pulsatile LVADs to CF technology. The BiVACOR moves away from archaic, complex, pulsatile designs with many moving parts, and a high probability for device failure to a more elegant, simplified, and durable design. The implantable device has a zero-power magnetic suspension system used to levitate and automatically balance the pulmonary and systemic blood flows created by the double-sided impeller, which is the singular moving part. The impeller's

position adjusts in response to differences in atrial pressures, which determine the relative efficiency of the pulmonary and systemic pumps. Large animal experiments continue to prove its utility and elegance. The BiVACOR project, headed by engineer Dr. Daniel Timms in collaboration with Drs William E. Cohn and O. H. Frazier, has great potential to fulfill the search for a durable and dependable TAH.

As more devices and newer technologies are introduced, patient selection remains of great importance to ensure optimal outcomes. In this respect, INTERMACS has announced the creation of MedaMACS (Medical Arm of Mechanically Assisted Circulatory Support), a new medical arm of the database. MedaMACS will assess patients whose HF is currently being medically managed (e.g., INTERMACS profiles 4 to 6) but who may derive benefit from early referral for MCS implantation. Another highly anticipated event has been the start of the Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management (ROADMAP) clinical trial [45]. This prospective, nonrandomized, multicenter trial will compare the impact of the CF HeartMate II LVAD to optimal medical management in non-inotrope-dependent, ambulatory patients with moderately advanced "stable" HF. The information revealed by MedaMACS and the ROADMAP trial will help to fill major gaps in our knowledge and may bring us closer to the day when we can appropriately stratify transplant-eligible patients for permanent mechanical support.

Finally, the expansion of current technology to allow for improved MCS options in children is an area of intense investigation. At the present time, the only approved device for pediatric support is the Berlin Heart, an extracorporeal, pulsatile pump that has saved many lives yet remains an outdated technology with the same limitations as first-generation adult LVADs. Current CF devices are too large for small infants and children, although ongoing developments in the miniaturization of durable pumps are underway. The NHLBI Funded Pumps for Kids, Infants, and Neonates (PumpKIN) trial is expected to begin soon, with the aim of comparing the Infant Jarvik 2000 and the Berlin Heart in a prospective, randomized study [46]. Furthermore, in an attempt to monitor the usage and characteristics of temporary and durable devices as well as patient characteristics and outcomes, the INTERMACS registry began PEDIMACS, the pediatric arm that began collecting pediatric data in September of 2012 [25]. The future advancements in pediatric MCS are both exciting and, to some, long overdue.

6. Conclusion

Since its inception, MCS has continued to evolve. From the intra-aortic balloon pump to the TAH, MCS provides better outcomes for patients with the worst prognoses. As innovation progresses to solve current challenges involving device complications, as outcomes continue to improve, and as further data from both small and large registries help to advance evidence-based practices, patients in the most advanced stages of HF appear to have more hope than ever before. No longer is MCS an experimental therapy, and no longer does HT offer the only chance at a cure. Mechanical support therapy—whether in the form of bridging to transplantation, DT, or even bridging to recovery—has become an important aspect of HF treatment. The high costs, expanding indications, and rapidly increasing number of devices implanted will ultimately require important decisions to be made on the part of society, medical practitioners, and administrative agencies regarding how much we are willing to spend and for whom this expensive, yet effective, therapy should be provided. Patient selection will remain paramount, but tremendous numbers of patients will have the potential to benefit.

Abbreviations

HT:	Heart transplantation
VAD:	Ventricular assist device
DT:	Destination therapy
MCS:	Mechanical circulatory support
TAH:	Total artificial heart
LVAD:	Left ventricular assist device
REMATCH:	Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure
NYHA:	New York Heart Association
CF:	Continuous flow
INTERMACS:	Interagency Registry for Mechanically Assisted Circulatory Support
THI:	Texas Heart Institute
BiVAD:	Biventricular assist device
PumpKIN:	Pumps for Kids, Infants, and Neonates
MedaMACS:	Medical Arm of Mechanically Assisted Circulatory Support
ROADMAP:	Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Clinical Study

Inflammatory Biomarkers in Refractory Congestive Heart Failure Patients Treated with Peritoneal Dialysis

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Proinflammatory cytokines play a pathogenic role in congestive heart failure. In this study, the effect of peritoneal dialysis treatment on inflammatory cytokines levels in refractory congestive heart failure patients was investigated. During the treatment, the patients reached a well-tolerated edema-free state and demonstrated significant improvement in NYHA functional class. Brain natriuretic peptide decreased significantly after 3 months of treatment and remained stable at 6 months. C-reactive protein, a plasma marker of inflammation, decreased significantly following the treatment. Circulating inflammatory cytokines TNF-α and IL-6 decreased significantly after 3 months of peritoneal dialysis treatment and remained low at 6 months. The reduction in circulating inflammatory cytokines levels may be partly responsible for the efficacy of peritoneal dialysis for refractory congestive heart failure.

1. Introduction

Removal of extensive fluid overload is one of the most difficult challenges in the management of severe congestive heart failure (CHF), particularly in patients who are refractory to diuretic therapy. Peritoneal ultrafiltration (UF) is a simple choice for daily fluid removal. Today, peritoneal dialysis (PD) is increasingly used to treat hypervolemic CHF patients who are resistant to conventional therapies, in particular when complicated by renal insufficiency (reviewed in [1, 2]). It was demonstrated that PD improves the functional status, reduces hospitalization rate, and even may decrease mortality rate [3–6].

The link between HF and inflammation was recognized and reported in 1990 by Levine et al. [7], who noted that levels of an inflammatory cytokine, tumor necrosis factor (TNF), were elevated in the setting of HF. Since this report, a number of studies have shown that, in addition to TNF, other proinflammatory cytokines and chemokines are also involved in cardiac function depression and progression of HF (reviewed in [8, 9]). It has been identified that biologically active molecules such as the cytokines are expressed in the setting of heart failure [10–13]. In many forms of cardiomyopathic left ventricular (LV) dysfunction, there is a rapid myocardial expression of proinflammatory cytokines such as interleukin-1 (IL-1), interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNF-α), which mediate, via specific receptors, various processes as gene expression, cell growth, or apoptosis [14–16].

Myocardial expression of cytokines contributes to depression of contractile performance and adverse LV remodelling. Cytokine-induced decreased contractile performance appears to result from sphingosine production, which interferes with myocardial calcium handling [15]. The activity of inflammatory cytokines is also influenced by anti-inflammatory cytokines such as transforming growth factor (TGF-β) and interleukin-10 (IL-10), which can downregulate the production of several inflammatory cytokines from macrophages and other cells [17, 18]. Peripheral-circulating levels of these cytokines are elevated in patients with heart failure and correlate with disease severity [8]. Several studies have shown that haemodiafiltration (HDF) using porous

synthetic membranes removes a wide range of circulating inflammation mediators [19–22] and can also influence circulating plasma concentrations of various mediators such as cytokines.

While emerging as an effective treatment option for refractory heart failure, peritoneal dialysis may by itself contribute to systemic inflammation (reviewed in [23]). The continuous presence of dialysis fluid with a high glucose concentration and glucose degradation products (GDPs), prolonged exposure to conventional bioincompatible glucose-based PD solutions, loss of residual renal function, and increased body fat mass all contribute to systemic inflammation in PD patients [23].

This study was designed to evaluate the net effect of peritoneal dialysis on circulating inflammatory and anti-inflammatory cytokine levels in patients with refractory CHF and fluid overload.

2. Subjects and Methods

2.1. Subjects. Patients with refractory CHF who were referred by their cardiologists to our PD unit between March 2012 and July 2014 and completed at least 3-month period of follow-up were enrolled into this study. The study protocol was approved by the Sheba Medical Center Institutional Human Research Board. All patients were in NYHA functional class IIIb or IV and showed symptoms and signs of severe cardiac failure with volume excess. They were receiving maximal therapy according to the heart failure guidelines including dietary fluid and salt restriction and maximal tolerable drug treatment, including diuretics, loop and distal tubule (metolazone), angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin II receptor blockers (ARB), beta-blockers, and digoxin. Some patients were also treated with intravenous furosemide and vasoactive agents in a CHF day care center. The inclusion criteria for PD were all of the following: (1) NYHA functional class IIIb or IV; (2) an echocardiographic evidence of significant left or right ventricular dysfunction, valvular heart disease, or pulmonary hypertension; (3) significant volume overload despite maximal doses of diuretics or repeated episodes of deteriorating kidney function (defined as a 50% increase in serum creatinine from basal concentration) during the intensification of diuretics treatment or recurrent hospitalization for volume overload in the preceding 3 months. Patients with contraindication for PD (such as severe lung disease, extensive abdominal scars, and abdominal aortic aneurism) or those incapable of learning and complying with the procedure of PD were excluded from the study. PD catheter was implanted by surgical dissection under local anesthesia in the operating room. In patients with ascites, peritoneal centesis was started by a specially trained PD nurse a day after Tenckhoff catheter insertion. In patients with significant volume overload, small volume exchanges (around 1,500 mL) were performed in the recumbent position by dialysis nurse starting the day after catheter placement. Until the patient and/or family member have learnt the dialysis technique (which usually takes 2-3 weeks), UF was performed by a PD nurse in the PD unit every day or every other day.

2.2. Clinical Evaluation. The following clinical parameters were collected: disease etiology and functional status (NYHA), preserved/reduced LV function, comorbidities and medications, body weight, and mean arterial blood pressure. Assessment of fluid status was based on clinical examination. Laboratory investigations included serum hemoglobin and leukocyte count, serum albumin, sodium, urea, creatinine, uric acid, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). Primary kidney disease was defined as urine protein >0.5 g/24 h, abnormal urine microscopy, and/or abnormal renal sonography (e.g., unequal kidney sizes or reduced kidney parenchyma). Patients with urine protein <0.5 g/24 h, normal urine microscopy, and normal kidneys per sonography were classified as having cardiorenal syndrome. Echocardiographic parameters used in the study included LVEF and RVEF and systolic pulmonary artery pressure (SPAP). Glucose- and non-glucose-containing (icodextrin) dialysis solutions (Teva Medical, Israel, and Cure Medical and Technical Supply, Fresenius, Germany) were used in the study. Data on the type and volume of PD solutions used by the patient and daily peritoneal UF volume were gathered.

2.3. Cytokine ELISA Assays. Plasma levels of TNF-α, IL-6, and IL-10 were assessed by enzyme-linked immunosorbent assay (ELISA) according to supplier protocols (R&D systems). This assay employed the quantitative sandwich enzyme immunoassay technique. The cut-off or lower limit of sensitivity was 0.106 pg/mL for TNF-α, 0.039 pg/mL for IL-6, and 0.09 pg/mL for IL-10.

2.4. BNP Assay. BNP was measured using the Alere Triage BNP Test, a rapid fluorescence immunoassay kit.

2.5. Statistical Analysis. The data are presented as median and range for continuous variables and as absolute numbers and percentages for categorical variables. Data presented in Table 2 were compared by two-tailed Student's t-test. Data in Figures 1 and 2 were compared by two-tailed paired Student's t-test. Differences were considered significant for $P < 0.05$.

3. Results

3.1. Clinical Outcome. The clinical, biochemical, and echocardiographic characteristics of the patients at baseline, prior to beginning of PD, are presented in Table 1. During the follow-up period, 3 patients died. Two died from CHF exacerbation and one diabetic patient died from septic foot complications. All patients continued treatment with oral furosemide. The median dose of oral furosemide the patients received did not change during follow-up: it was 160 mg per day (range 120–240 mg). Four patients were treated with metolazone regularly; another 4 were instructed to add metolazone when their body weight went up. The usual dose of metolazone was 2.5 mg twice a week. Patients who were treated in CHF day care center intravenous furosemide and vasoactive agents (8 out of 13 patients) continued the treatment while on PD.

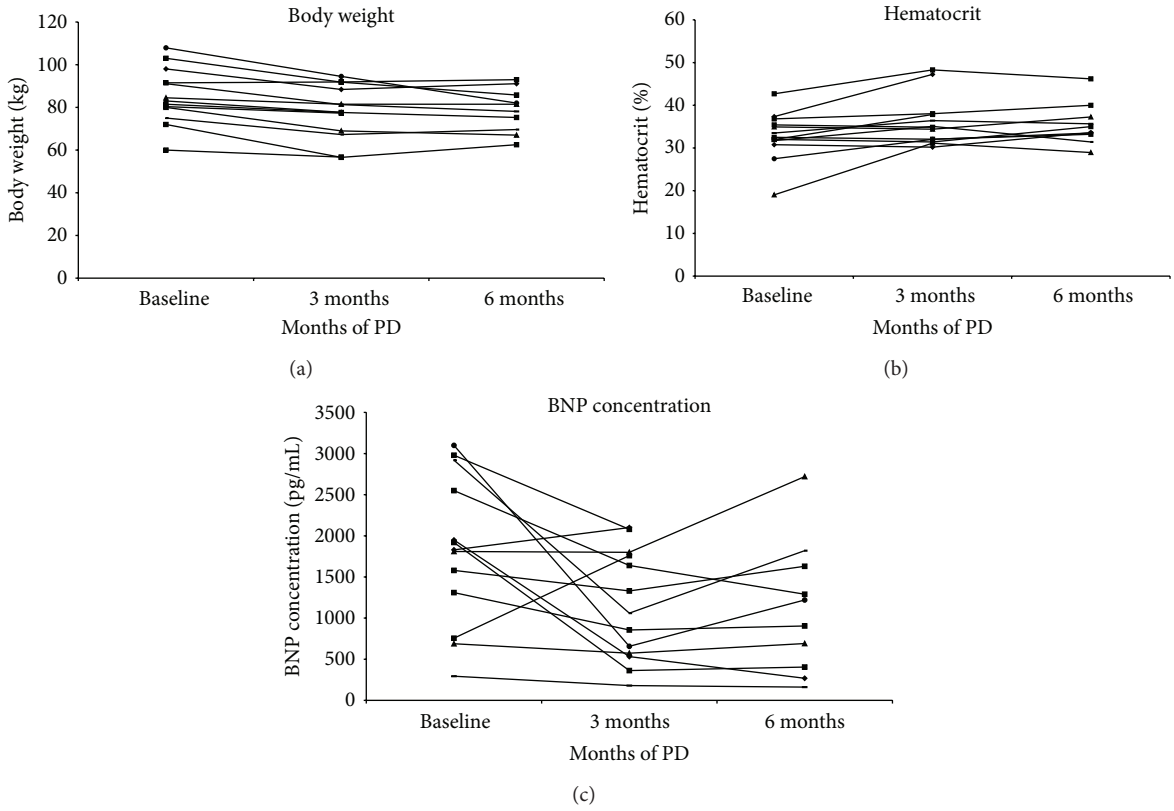

Figure 1: Selected clinical and biochemical variables of patients with refractory CHF treated with PD. Individual patient trajectories are shown. $n = 13$. (a) Changes in body weight. (b) Changes in blood hematocrit. (c) Changes in circulating BNP levels.

The median amount of PD solutions used per patient was 2 liters per day (range 2–12 liters). All patients reached a well-tolerated edema-free state during the first months after starting PD. By the end of the first 3 months of treatment, body weight of CHF patients decreased significantly due to fluid loss (Figure 1(a)). The median weight loss was 5.3 kg ($P = 0.0001$). Table 2 presented selected clinical and biochemical characteristics during patients' follow-up. The clinical benefit of PD manifested by improved NYHA functional class by a median of one class, from NYHA IV to III, which remained stable at 6 months of treatment ($P = 0.0035$). Blood hematocrit increased significantly during the treatment from median of 32.51 (19.03–42.68) to 34.84 (30.19–48.28) at 3 months ($P = 0.0156$) and to 34.29 (28.94–46.19) at 6 months ($P = 0.0051$, Figure 1(b)).

3.2. Circulating BNP Levels. Elevated pretreatment circulating BNP levels were found in all patients (Figure 1(c)). BNP levels decreased significantly from a median of 1830 (294–3100) to 1060 (180–2100) pg/mL ($P = 0.0259$) at 3 months and measured 1062 (161–2720) pg/mL ($P = 0.0385$) at 6 months.

3.3. C-Reactive Protein and Circulating Cytokine Levels. Baseline C-reactive protein (Figure 2(a)) was approximately 6-fold above the upper level of normal. There was a substantial drop in serum C-reactive protein concentration during the treatment. Median serum CRP decreased from 15.07 (5.09–108.3) at baseline to 5.81 (0.63–35.94) mg/L ($P = 0.0139$) at 3 months and was 5.78 (0.74–55.09) mg/L ($P = 0.0375$) after 6 months of PD.

Circulating TNF-α level (Figure 2(b)) decreased significantly from 4.81 (2.94–7.17) pg/mL at baseline to 4.29 (2.48–7.5) pg/mL ($P = 0.0313$) at 3 months and measured 4.02 (2.52–7.01) pg/mL ($P = 0.0028$) after 6 months of PD.

Circulating level of IL-6 (Figure 2(c)) decreased from median of 22.57 (5.74–52.46) pg/mL at baseline to 9.53 (3.34–43.29) pg/mL ($P = 0.0004$) at 3 months and was 11.68 (2.22–24.43) pg/mL ($P = 0.0133$) after 6 months of PD.

Median serum anti-inflammatory cytokine IL-10 levels (Figure 2(d)) decreased from 0.75 (0–3.29) pg/mL at baseline to 0 (0–1.93) pg/mL ($P = 0.056$) at 3 months and remained undetectable (range 0–2.6) pg/mL ($P = 0.0974$) at 6 months.

3.4. Preserved LV and RV Function. Inside the subgroups of patients, it was found that circulating TNF-α and IL-6 decreased unsignificantly in patients with preserved LV function. Circulating TNF-α level decreased from median of 5.97 (3.9–7.17) pg/mL at baseline to 4.28 (3.38–7.5) pg/mL ($P = 0.31$; $n = 4$) at 3 months and to 4.78 (3.4–7.01) pg/mL ($P = 0.1715$; $n = 4$) after 6 months of PD in patients with preserved LV function compared to TNF-α drop from 4.79 (2.94–6.53) pg/mL at baseline to 4.29 (2.48–5.51) pg/mL ($P = 0.055$; $n = 9$) at 3 months and to 3.91 (2.52–6.26) pg/mL ($P = 0.012$; $n = 9$) after 6 months in patients with low LV function.

Table 1: Selected clinical, biochemical, and echocardiographic characteristics of the patients at baseline.

Age, years	64 (52–82)
Females	4 (31%)
Ischemic cardiomyopathy	8 (61%)
NYHA class III/IV	4/9
Diabetes mellitus	8 (62%)
History of hypertension	8 (62%)
Primary kidney disease	8 (62%)
Body weight, kg	83 (60–107.9)
Mean arterial blood pressure, mm Hg	85.3 (67–108.7)
LVEF, %	20 (7–60)
Preserved LV function	4 (31%)
RV dysfunction	8 (62%)
Estimated SPAP, mm Hg	56 (38–92)
CHF day care treatment	8 (62%)
Medications	
Loop diuretic	13 (100%)
Thiazide and thiazide-like diuretics, metolazone	4 (31%)
Spironolactone	4 (31%)
Beta-blockers	12 (92%)
Digoxin	6 (46%)
ACEI or ARB	5 (39%)

Values are expressed as median and range for continuous variables and as absolute numbers and percentages for categorical variables.

Circulating level of IL-6 decreased from median of 15.83 (9.11–27.83) pg/mL at baseline to 9.98 (8.58–13.13) pg/mL ($P = 0.2102$; $n = 4$) at 3 months and to 8.75 (2.22–17.55) pg/mL ($P = 0.3915$; $n = 4$) after 6 months of PD in patients with preserved LV function compared to IL-6 drop from 28.55 (5.74–52.46) pg/mL at baseline to 6.49 (3.34–43.29) pg/mL ($P = 0.0009$; $n = 9$) at 3 months and to 14.6 (3.3–24.43) pg/mL ($P = 0.029$; $n = 9$) after 6 months in patients with low LV function. In patients with preserved LV function, the cause of CHF was nonischemic. Two patients had diastolic heart failure, one patient had restrictive cardiomyopathy with severe pulmonary hypertension of unknown cause, and one had primary pulmonary hypertension with right heart failure.

In patients with preserved RV function, circulating IL-6 levels decreased insignificantly following PD treatment from median of 13.4 (5.74–52.46) pg/mL at baseline to 8.58 (3.34–43.29) pg/mL ($P = 0.1323$; $n = 5$) at 3 months and was 16.95 (2.22–21.56) pg/mL ($P = 0.3466$; $n = 5$) after 6 months of PD in patients with preserved RV function compared to IL-6 fall from 28.19 (11.6–52.46) pg/mL at baseline to 9.56 (5.02–26.42) pg/mL ($P = 0.0003$; $n = 8$) at 3 months and to 8.75 (4.87–24.43) pg/mL ($P = 0.0094$; $n = 8$) after 6 months in patients with decreased RV function.

3.5. Treatment with ACE-I/ARBs and Spironolactone. Inside the subgroups of patients treated with ACE-I/ARBs or spironolactone, it was found that patients treated with ACE-I/ARBs demonstrated more significant decrease in inflammatory cytokines compared to the group without those drugs: TNF-α at 3 months and IL-6 at 3 and 6 months decreased significantly in treated group compared to significant decrease at 6 months for TNF-α and at 3 months for IL-6 in patients without those drugs. The differences between treated and nontreated groups were less consistent for spironolactone.

Circulating TNF-α level decreased from median of 4.93 (2.94–6.53) pg/mL at baseline to 4.29 (2.48–5.51) pg/mL ($P = 0.0403$; $n = 5$) at 3 months and to 3.98 (2.59–6.26) pg/mL ($P = 0.1618$; $n = 5$) after 6 months of PD in patients treated with ACE-I or ARBs compared to TNF-α drop from 4.8 (3.24–7.17) pg/mL at baseline to 4.28 (3.25–7.5) pg/mL ($P = 0.2027$; $n = 8$) at 3 months and to 4.12 (2.52–7.01) pg/mL ($P = 0.014$; $n = 8$) after 6 months in patients without ACE-I or ARBs. Circulating level of IL-6 decreased from median of 28.55 (11.6–52.46) pg/mL at baseline to 6.49 (5.02–26.42) pg/mL ($P = 0.006$; $n = 5$) at 3 months and to 11.35 (4.87–24.43) pg/mL ($P = 0.038$, $n = 5$) after 6 months of PD in patients treated with ACE-I or ARBs compared to IL-6 drop from 16.44 (5.74–52.46) pg/mL at baseline to 9.56 (3.34–43.29) pg/mL ($P = 0.0241$; $n = 8$) at 3 months and to 12.85 (2.22–21.56) pg/mL ($P = 0.1745$; $n = 8$) after 6 months in patients without ACE-I or ARBs.

Circulating TNF-α level decreased from median of 4.87 (2.94–5.43) pg/mL at baseline to 3.49 (2.48–4.29) pg/mL ($P = 0.0177$; $n = 4$) at 3 months and to 3.54 (2.59–3.91) pg/mL ($P = 0.987$; $n = 4$) after 6 months of PD in patients treated with spironolactone compared to TNF-α drop from 4.79 (3.24–7.17) pg/mL at baseline to 4.78 (3.3–7.5) pg/mL ($P = 0.2457$; $n = 9$) at 3 months and to 4.26 (2.52–7.01) pg/mL ($P = 0.0289$; $n = 9$) after 6 months in patients without spironolactone. Circulating level of IL-6 decreased from median of 26.61 (5.74–52.46) pg/mL at baseline to 6.26 (4.61–26.42) pg/mL ($P = 0.0589$; $n = 4$) at 3 months and to 8.1 (3.3–24.43) pg/mL ($P = 0.1799$; $n = 4$) after 6 months of PD in patients treated with spironolactone compared to IL-6 drop from 18.25 (9.11–52.46) pg/mL at baseline to 9.58 (3.34–43.29) pg/mL ($P = 0.0051$; $n = 9$) at 3 months and to 14.6 (2.22–21.56) pg/mL ($P = 0.0716$; $n = 9$) after 6 months in patients without spironolactone.

4. Discussion

Our study confirmed that PD treatment effectively removes fluid overload in patients with refractory CHF. Brain natriuretic peptide (BNP) levels measured 18-fold normal before the treatment, decreased significantly after 3 months of treatment, and remained stable at 6 months. Secretion of natriuretic peptides, BNP and amino-terminal pro-B-type natriuretic peptide (NTpro-BNP), is stimulated by ventricular stretch and wall tension in CHF. Both BNP and NT-pro-BNP plasma concentration have been shown to be useful in the diagnosis [24] and risk stratification [25, 26] of HF. It was demonstrated that conventional therapies for heart failure including diuretics, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and β-blockers lower natriuretic peptide values [27]. Patients referred by cardiologists to PD in our study already received maximal tolerable drug treatment. It seems that peritoneal dialysis

Table 2: Selected clinical and biochemical characteristics during patients' follow-up.

	Baseline	3 months	6 months	*P* value
NYHA class	4.0 (3.0–4.0)	3.0 (3.0–4.0)	3.0 (3.0–4.0)	0.0035
Serum creatinine, mg/dL	2.64 (1.54–5.89)	2.55 (1.36–6.27)	2.28 (1.32–8.11)	0.9907
Serum urea, mg/dL	210 (83–287)	135 (79–194)	143.5 (66–176)	0.0012
Serum sodium, mEq/L	135 (127–142)	134 (125–143)	138 (136–139)	0.1843
Serum uric acid, mg/dL	11.6 (4.5–14)	7.7 (6.3–13.7)	8.7 (7.3–11.6)	0.0585
Serum albumin, g/dL	3.2 (2.8–3.6)	3 (2.5–4.1)	3.3 (2.5–4.0)	0.1148
Serum WBC, 1,000/μL	5.91 (3.36–13.18)	7.05 (3.92–13.7)	7.005 (4.59–11.05)	0.4014
ESR	30 (5–80)	40 (2–75)	30 (2–80)	0.7183

Values are expressed as median and range.

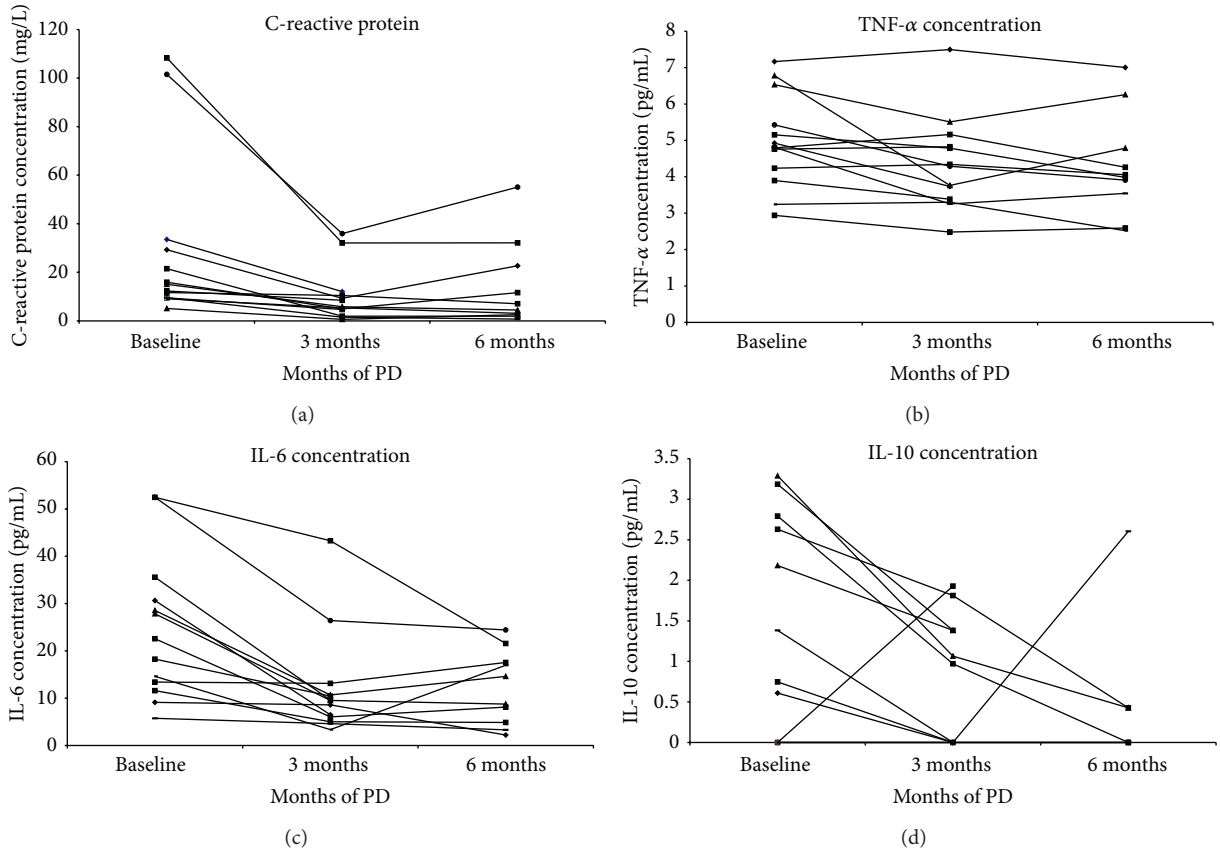

Figure 2: Circulating cytokine and C-reactive protein levels in patients with refractory CHF treated with PD. Individual patient trajectories are shown. $n = 13$. (a) Changes in serum C-reactive protein. (b) Changes in circulating TNF-α levels. (c) Changes in circulating IL-6 levels. (d) Changes in circulating IL-10 levels.

provided additional benefit and caused decrease of BNP levels in those patients.

CRP is liver-derived protein that is regulated by interleukin-6 [28]. CRP has been described to correlate with disease severity and prognosis in HF [29–33]. The role of CRP in the prediction of development of HF was also reported [34]. Use of ACE inhibitors and beta-blockers has been associated with lower levels of CRP in HF patients [35]. At the present time, despite its clear associations with HF disease severity and outcomes, it is not clear whether CRP is merely a marker of inflammation with no particular role in the development of HF or whether it is involved in the pathogenesis and progression of HF. CRP levels were elevated 6-fold upper normal limit in our patients. PD treatment led to significant decrease in CRP. Two other routine laboratory tests, erythrocyte sedimentation rate and white blood cell count, did not change significantly during the treatment.

Accumulating evidence indicates that proinflammatory cytokines play a pathogenic role in CHF. Inflammatory cytokines may modulate myocardial functions by a variety of mechanisms including stimulation of hypertrophy and fibrosis through direct effects on cardiomyocytes and fibroblasts,

impairment of myocardial contractile function through direct effects on intracellular calcium transport, and signal transduction through β-adrenergic receptors, induction of apoptosis, and stimulation of genes involved in myocardial remodeling [8]. Inflammatory mediators could also contribute more indirectly to the progression of HF through impairment of bone marrow function with secondary anemia and inappropriate endothelial cell activation and impairment of peripheral muscle with secondary induction of systemic inflammation and reflex abnormalities in HF [8]. Peripheral-circulating as well as intracardiac levels of these cytokines are elevated in patients with HF [7, 10, 12, 13, 36]. TNF-α and IL-6 circulating levels are elevated and correlate with disease severity in heart failure (reviewed in [9]). Proinflammatory molecules are activated starting at earlier phases of HF asymptomatic left ventricular dysfunction and continue to rise in direct relation to worsening NYHA functional class regardless of the etiology of HF [9, 34]. Circulating levels of TNF, IL-6, and TNF soluble receptors (sTNFR1 and sTNFR2) have been reported to predict poorer survival [9]. Most studies have evaluated patients with HF and depressed ejection, but it was demonstrated that higher TNF levels were independently associated with a greater risk of mortality even in patients with HF and preserved ejection fraction [37].

Clinical studies have shown that treatment with angiotensin receptor antagonists can lead to significant reductions in circulating levels of TNF in patients with HF [38]. β-adrenergic blockade has also been shown to result in significant reductions in proinflammatory cytokine levels in clinical studies with HF patients [39–44]. Treatment with the long-acting dihydropyridine calcium antagonist, amlodipine, for a period of 26 weeks lowered plasma IL-6 levels in patients with HF [45]. Other studies have noted that optimization of background standard therapy of HF with diuretics, ACE inhibitors, beta-blockers, and digoxin can result in significant reductions in circulating levels of TNF and IL-6 [46]. Our findings indicate that peritoneal dialysis markedly reduced circulating proinflammatory cytokine TNF-α and IL-6 levels showing additional benefit to already maximally tolerate traditional drug regiments. The interesting finding was an insignificant effect of PD treatment on TNF and IL-6 levels in patients with preserved LV function and on IL-6 level in patients with preserved RV function. This result needs further confirmation on large sample size. Larger patient's group size is also needed to separate the effect of PD on inflammatory cytokines from the effects of such standard drugs as ACE-I, previously shown to reduce circulating proinflammatory cytokines [38].

The proinflammatory cytokine response is controlled by a series of immunoregulatory molecules, termed the "anti-inflammatory" cytokines. These cytokines act in concert with specific cytokine inhibitors and soluble cytokine receptors to regulate the human immune response. Their physiologic role in inflammation and pathologic role in HF are being increasingly recognized [47]. In several inflammatory disorders, the potential pathogenic effect of inflammatory cytokines will depend on the balance in the cytokine network, particularly on the levels of counteracting anti-inflammatory mediators. Patients with severe HF were found to have decreased levels of TGF-β1 and inadequately raised levels of IL-10 in relation to the elevated TNF concentrations, and these abnormalities in the cytokine network were most pronounced in patients with the most severe HF [48]. Although HF patients have enhanced expression of anti-inflammatory cytokine IL-10 compared to the normal population [39], in patients with severe HF, IL-10 levels in relation to the elevated TNF concentrations are considered inadequately raised [34]. Therefore, the balance is tipped toward enhanced expression of proinflammatory cytokines relative to anti-inflammatory cytokines in the HF population. IL-10 downregulates the production of inflammatory cytokines in a variety of cell types and enhances the release of sTNF receptors; thus, it is known that IL-10 has potential beneficial effects in terms of its cardioprotective properties in CHF [49, 50]. It was demonstrated that circulating levels of IL-10 increased in relation to elevated TNF-α levels in patients with dilated cardiomyopathy and may support the concept that the increase of IL-10 levels enhances the release of sTNFR2 [43]. Moreover, elevated levels of IL-10 were markedly decreased, in accordance with the reduction of TNF-α levels, due to beta-blocker therapy [43]. Therefore, IL-10 may be a potential therapeutic agent, as an immunoregulatory factor, in CHF [43]. We demonstrated that IL-10 levels also tended to decrease (albeit not significantly) during PD treatment and this decrease was accompanied by TNF-α reduction.

We do not think that removal of proinflammatory cytokines by peritoneal membrane had a significant impact on cytokine plasma levels. Most of our patients were treated with one or two dialysis exchanges per day; therefore, significant removal is unlikely. It was also demonstrated that clearances of high molecular weight compounds such as b2-microglobulin by PD are significantly lower as compared to the clearances of the uremic retention solutes urea nitrogen and creatinine because high molecular weight hampers their diffusive and convective transport through the pores of the peritoneal membrane [51]. It was proposed that UF in general cannot be expected to remove high molecular weight substances such as cytokines in clinically relevant amounts owing to its operative characteristics [52]. Neurohumoral activation reset towards a more physiological condition after fluid removal during PD treatment is probably responsible for proinflammatory cytokines reduction. It was proposed that there are important interactions between the renin-angiotensin, adrenergic systems, and proinflammatory cytokines and many of the conventional therapies for HF may work, at least in part through the modulation of proinflammatory cytokines.

We assume that PD treatment can lower the circulating level of proinflammatory TNF-α and IL-6 in patients with refractory CHF and fluid overload showing additional benefit to already maximally tolerated traditional drug regiments. The limitations of the present study include its small number of patients and the lack of control group. In this regard, we cannot rule out that the observed decrease in inflammatory biomarkers was due to regression to the mean, more careful clinical follow-up compared with routine standards of care, or Hawthorne's effect rather than PD for itself.

In this group of advanced CHF patients refractory to traditional drug therapy with extremely high BNP levels, the effect of PD treatment on circulating IL-6 was the most prominent finding. In this regard, IL-6 can serve as biomarker to guide therapy in those patients. It appears that CRP in which liver production is regulated by IL-6 could also be used as a reliable marker for therapy response, taking into account the fact that its role in pathogenesis and progression of HF is less clear. Large-scale trials are needed to check whether the changes in inflammatory biomarkers over time correlate with morbidity and mortality in HF patients.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Myeloperoxidase-Related Chlorination Activity Is Positively Associated with Circulating Ceruloplasmin in Chronic Heart Failure Patients: Relationship with Neurohormonal, Inflammatory, and Nutritional Parameters

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Rationale. Heart failure (HF) is accompanied by the development of an imbalance between oxygen- and nitric oxide-derived free radical production leading to protein nitration. Both chlorinating and peroxidase cycle of Myeloperoxidase (MPO) contribute to oxidative and nitrosative stress and are involved in tyrosine nitration of protein. Ceruloplasmin (Cp) has antioxidant function through its ferroxidase I (FeO_xI) activity and has recently been proposed as a physiological defense mechanism against MPO inappropriate actions. *Objective*. We investigated the relationship between plasma MPO-related chlorinating activity, Cp and FeO_xI, and nitrosative stress, inflammatory, neurohormonal, and nutritional biomarkers in HF patients. *Methods and Results*. In chronic HF patients ($n = 81$, 76 ± 9 years, NYHA Class II (26); Class III (29); Class IV (26)) and age-matched controls ($n = 17$, 75 ± 11 years, CTR), plasma MPO chlorinating activity, Cp, FeO_xI, nitrated protein, free Malondialdehyde, BNP, norepinephrine, hsCRP, albumin, and prealbumin were measured. Plasma MPO chlorinating activity, Cp, BNP, norepinephrine, and hsCRP were increased in HF versus CTR. FeO_xI, albumin, and prealbumin were decreased in HF. MPO-related chlorinating activity was positively related to Cp ($r = 0.363$, $P < 0.001$), nitrated protein, hsCRP, and BNP and inversely to albumin. *Conclusions*. Plasma MPO chlorinated activity is increased in elderly chronic HF patients and positively associated with Cp, inflammatory, neurohormonal, and nitrosative parameters suggesting a role in HF progression.

1. Introduction

Heart failure (HF) disease is accompanied by the development of an imbalance between oxygen- and nitric oxide-derived free radical production and the ability of the protective shield represented by a series of antioxidant enzymes to scavenge and buffer the overwhelming quantity of radical species generated [1]. Myeloperoxidase (MPO) is a glycosylated heme-enzyme, mainly stored in the primary azurophilic granules of polymorphonuclear neutrophils and macrophages, which owns a potent bactericidal action that is mediated by production of hypochlorous acid from hydrogen peroxide and chloride ions [2, 3]. Generation of hypochlorous acid has been related to MPO and to this enzyme among the other animal hemoperoxidases [4]. MPO is also secreted in the extracellular space and increased plasma levels of MPO are promoted by inflammatory conditions in acute and chronic settings of cardiovascular patients [2]. A prognostic role of MPO has been reported in acute myocardial infarction, acute and chronic heart failure, and also healthy middle age or elderly subjects [5–8]. MPO contributes to the effects of oxidation and alterations of lipids and propagation of oxidative stress through chlorinating (halogenating) and peroxidase cycle activities [3]. MPO is also involved in the generation of nitrating species. In experimental and human HF, increased peroxynitrite ($ONOO^-$) generation, which leads to extensive tyrosine protein nitration, derives from nitric oxide and superoxide or from MPO among the known animal hemoperoxidases [9, 10]. Tyrosine nitration along with cysteine oxidation may affect protein structure with a loss of function as we demonstrated in HF patients where Ceruloplasmin (Cp) showed a reduced FeO_xI activity [11]. It has recently proposed that the physiological defense against the inappropriate action of MPO could be ascribed to Cp binding [12]. Cp, an alpha2-glycoprotein mainly synthesized by hepatocytes, whose functions include the transport of serum copper [13] and the acute phase inflammation reactant, is also involved in iron metabolism through its ferroxidase activity (FeO_x) [14]. Cp is the main contributor of FeO_x activity in human plasma and is called FeO_xI [15]. Cp has been suggested to be also a potent inhibitor of purified MPO, thus inhibiting production of hypochlorous acid even at low concentrations [16]. It has been demonstrated that, in plasma from Cp knock-out mice, MPO was able to act as a potent oxidizing enzyme, but no significant oxidation was observed in plasma from wild type animals where Cp was present [12, 16]. Cp and MPO binding has been suggested to be related to an electrostatic interaction between the cationic nature of MPO and the anionic charges of Cp [17]. It appears that Cp should provide a protective hedge against inadvertent oxidant production by MPO during inflammatory conditions (Figure 1). In the HF population, no data are available on the relationship between plasma MPO-related chlorinating activity and Cp and its FeO_xI activity. Also even less known are the relationships between plasma chlorinating activity related to MPO and different parameters, expression of neurohormonal (BNP, norepinephrine, plasma renin activity, and aldosterone), inflammatory (high-sensitivity C-reactive protein (hs-CRP)), metabolic-nutritional (albumin and prealbumin), and oxidative (nitrated proteins, free malondialdehyde, and 15-F2t-isoprostane) domains. Based on these premises, we undertook a study on a cohort of stable chronic elderly HF of different severity compared to age-matched Controls, to investigate the above relationships and focusing in particular on the interaction of plasma MPO-related chlorinating activity with Cp-mediated FeO_xI activity and with the other parameters linked to neurohormonal, inflammatory, nutritional, and oxidative/nitrosative domains.

2. Methods

2.1. Study Cohort and Follow-Up of Patients. Eighty-one consecutive stable chronic HF patients referred to the heart failure outpatient Clinic of the Cardiorenal Research Unit of the Department of Clinical and Experimental Medicine of the University Hospital of Parma were included in the present study. This group was a part of an original cohort of patients (81 of the 96 patients) already evaluated for nitrosative and oxidative stress in heart failure [11]. The diagnosis of HF was based on symptoms and clinical signs according to guidelines issued by the European Society of Cardiology [17] and by the American College of Cardiology [18]. The patients were free from clinical or laboratory signs of acute infection, rheumatoid or other autoimmune diseases, primary cachectic states (cancer, thyroid disease, severe liver disease, and severe chronic lung disease), neuromuscular disorders, myocardial infarction within the previous 20 weeks, diabetes mellitus, or severe chronic renal failure (serum creatinine level >2.0 mg/dL, >177 μmol/L). Patients were clinically stable and on constant therapy at least 8 weeks prior to entering the study. The study was approved by the University of Parma Ethics Committee and complied with the Declaration of Helsinki, and all participants provided written informed consent.

Seventeen age-matched healthy subjects were recruited as Controls (CTR) from healthy subjects reporting for a periodical check-up at the cardiovascular prevention clinic of the same department. On study entry, a complete medical history, a physical examination, basal laboratory tests (serum creatinine, electrolytes, and lipid profile), plasma neurohormonal and inflammatory markers determination, an electrocardiogram, and an echocardiogram were obtained from all patients. Estimated glomerular filtration rate (eGFR) was calculated from the four-component Model of Disease in Renal Disease (MDRD) equation incorporating age, race, sex, and serum creatinine level: estimated eGFR = $186 * (\text{serum creatinine [in milligrams per deciliter]})^{-1.154} * (\text{age [in years]})^{-0.203}$. For women, the product of the equation was multiplied by a correction factor of 0.742 [19].

2.2. Venous Blood Sampling Procedure and Biochemical Assays. Venous samples were collected as previously indicated [11, 20]. After at least 30 minutes of supine rest, blood was obtained from an indwelling catheter and collected in polypropylene tubes containing an EDTA (ethylenediamine tetraacetic acid) buffer (1.5 mg/mL), except for BNP where a mix of protease inhibitors (phenylmethylsulfonyl fluoride,

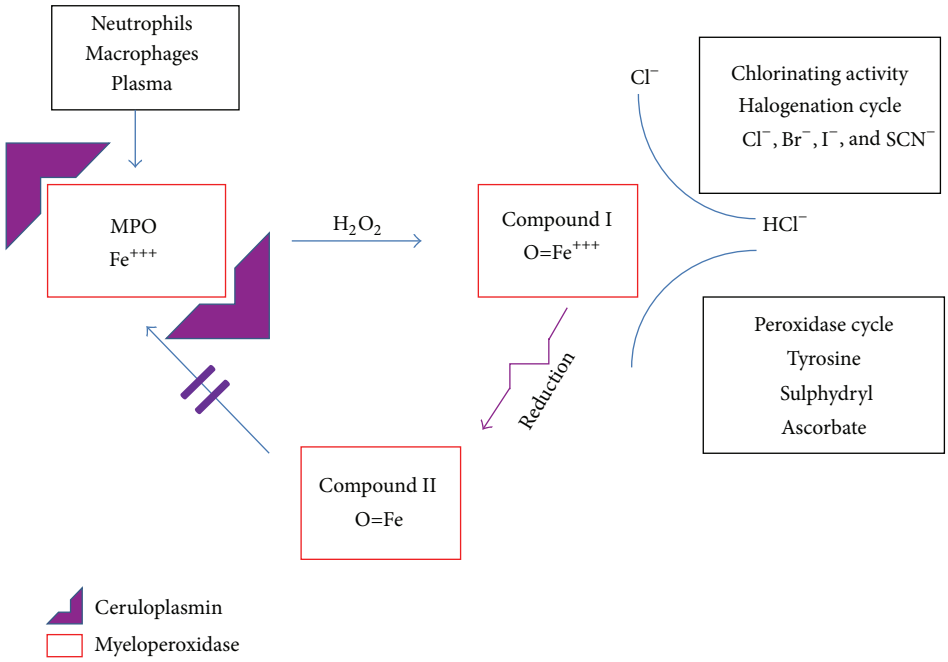

Figure 1: Schematic diagram indicating the relationship between Myeloperoxidase-related chlorinating activity and Ceruloplasmin (Cp). Ceruloplasmin binding to MPO determines reduction of the active Compound I to Compound II and prevents the recycling of Compound II back to the active enzyme.

trypsin inhibitor, and aprotinin 500 units/mL) was added. Except for FeO_xI activity measurement, where fresh serum samples were used, multiple aliquots of plasma samples were stored at −80°C until assay time for norepinephrine, BNP, free malondialdehyde (MAD), total nitrated proteins, and Cp. All laboratory measurements were performed without any freeze-thaw cycles of the samples and by investigators blind to the clinical data.

Plasma chlorination activity, related to MPO, was measured in EDTA plasma samples by a colorimetric assay (OxiSelect Myeloperoxidase Chlorination Activity Assay Kit, Cell Biolabs, Inc., San Diego, CA, USA) evaluating hypochlorous acid generation by monitoring Cl-tau generation as previously described [21, 22]. Each sample from patients and Controls has been tested for 2 time points' determination (30 and 60 minutes of hydrogen peroxide incubation). Twenty-five μL plasma sample from patients and Controls was mixed with 1 mM hydrogen peroxide solution according to the manufacturer instructions. After the generation of hypochlorous acid, the rapid reaction with taurine produced the stable taurine chloramine product. After adding a catalase-containing stop solution to block MPO catalysis by eliminating hydrogen peroxide, taurine chloramine reaction with TNB chromogen probe allowed measurement of MPO activity (absorbance at 405–412 nm). Data related to 60-minute incubation has been reported in the paper. The intra-assay and interassay coefficients of variation were 12% and 17% and the analytical sensitivity was 2.8 mU/mL. This assay measures plasma chlorinating activity that is related to MPO. Plasma samples from a subgroup of patients and CTR (one out of five patients) underwent MPO immunoprecipitation procedure to evaluate the contribution of MPO to plasma chlorinating activity. In the present study, chlorinating activity was found almost abolished in the supernatant after immunoprecipitation of MPO suggesting that chlorinating activity in plasma is mainly due to MPO (data not shown). A monoclonal anti-human anti-MPO antibody (Myeloperoxidase Antibody (1A1), Thermo Scientific Pierce Antibodies, Waltham, MA, USA) was cross-linked to Dynabeads protein G (Dynal Biotech, Oslo, Norway). Anti-MPO antibody was prepared from a stock solution of 1 mg/mL. After washing, 50 μL of Dynabeads (1.5 mg) was resuspended after magnetic separation (Dynal MPC) in 0.1 M Na_2HPO_4 pH 8.0 and transferred to a polypropylene test tube. The solution was incubated with rotation (Dynal MX1-Mixer) for 20 minutes at room temperature with 200 μL of phosphate buffer saline (pH 7.4) containing 6.5 μg of antibody. After magnetic removal of supernatant, the beads-Ab complex was resuspended with phosphate buffer saline (pH 7.4) with 0.02% Tween 20. Two hundred and fifty μL of diluted samples (1 : 25) from the patients and CTR was incubated with tilting and rotation for 60 minutes at room temperature. Test tubes were then placed on the magnet for 3 min to separate beads beads-Ab complex on the tube wall and the supernatant. Chlorinating activity was then measured in the supernatant.

FeO_xI was measured by ferrous ion as substrate (Fe(II); ferrous ammonium) according to the method of Erel [23]. Norepinephrine, BNP, plasma renin activity, aldosterone, free MAD, high sensitivity C-reactive protein (hsCRP), Cp, albumin, and prealbumin were determined as previously described [11, 19]. Total nitrated proteins levels were assessed using a sandwich ELISA assay kit (Oxis Research

Table 1: Clinical characteristics of heart failure patients and healthy Controls.

	Controls ($n = 17$)	NYHA Class II ($n = 26$)	NYHA Class III ($n = 29$)	NYHA Class IV ($n = 26$)
Age, years	76 ± 11	76 ± 7	77 ± 10	75 ± 9
Gender, male	7	13	9	20
BMI (kg/m^2)	23.7 ± 4.0	25.7 ± 2.9	23.8 ± 3.7	23.5 ± 3.6
Systolic BP (mm Hg)	135 ± 23	138 ± 19	136 ± 17	113 ± 19$^{*\dagger\#}$
Diastolic BP (mm Hg)	73 ± 8	80 ± 14	79 ± 12	64 ± 12$^{\dagger\#}$
Heart rate (bpm)	81 ± 13	78 ± 11	72 ± 11	80 ± 11
Ischemia/hypertense/idiopathic	—	20/13/0	24/14/0	22/6/2
Current smoker (%)	47	35	14	35
Ejection fraction (%)	66 ± 6	51 ± 6*	41 ± 7*†	29 ± 7$^{*\dagger\#}$
Haemoglobin (g/dL)	13.2 ± 1.0	12.9 ± 0.9	13.0 ± 1.4	12.6 ± 1.1
Neutrophils (10^3 cell/μL)	2.70 ± 0.92	3.73 ± 1.43*	3.51 ± 1.27*	3.66 ± 1.21*
Sodium (mEq/L)	141 ± 4	141 ± 4	138 ± 3	135 ± 5*†
eGFR (mL/min)	60 ± 22	49 ± 15	45 ± 18*	41 ± 14*

Data are reported as mean ± SD; eGFR: estimated glomerular filtration rate; ∗ indicates P less than 0.05 versus Controls, † versus NYHA II, and # versus NYHA III.

International Inc., Foster City, CA USA). The intra-assay and interassay coefficients of variation were 4% and 14% and the analytical sensitivity was 2 nmol/L.

The test analytical sensitivity was 0.15 ng/mL for PRA, 7.6 pg/mL for aldosterone, and 3.0 pg/mL for BNP. hs-CRP was measured using the Dade Behring N Highly Sensitive CRP assay (Dade Behring Diagnostics) on the BN 100 Nephelometer. Plasma-free malondialdehyde, a marker of lipid peroxidation, was measured together with 15-F2t-isoprostane as oxidative pathway markers.

Plasma-free malondialdehyde was determined by HPLC-based thiobarbituric acid separation and spectrophotometric [11]. The intra-assay and interassay coefficients of variation were less than 10%. Plasma 15-F2t-ISO, after the extraction procedure, was measured by an enzyme immunoassay kit (Cayman Chemical, USA). Intra- and interassay coefficients of variation were 6 and 9%, respectively.

2.3. Data Analysis. Values are presented as mean ± SD or as median (range). Comparisons of the baseline characteristic variables among Controls and HF patients in NYHA Classes II, III, and IV were made with one-way analysis of variance or nonparametric equivalent Kruskal-Wallis one-way analysis of variance by ranks (depending on the parametric or non-parametric distribution) followed by Bonferroni *post hoc* or Dunn's test. Relations between parameters, including MPO-related chlorinating activity, FeO_xI, Cp, nitrated protein, hsCRP, BNP, free MAD, albumin, prealbumin, and eGFR, were analyzed by linear regression analysis using Pearson or Spearman correlation coefficients. Lin-log plots are used to describe a semilog plot with a logarithmic scale on the x-axis and a linear scale on the y-axis or log-log plots to describe the relationship according to the distribution of the parameters. The D'Agostino-Pearson normality test was passed for all parameters, except for hsCRP, MPO-related chlorinating activity, and BNP that were log transformed to create a normal distribution. All statistical analyses were performed using SPSS for Windows 18.0 (SPSS Inc.). $P < 0.05$ was considered statistically significant.

3. Results

Eighty-one HF patients were included and agreed to participate in the study (40 females and 41 males). Their mean age was 76 ± 9 years and their New York Heart Association (NYHA) functional class was separated in Class II/III/IV: 26/29/26, respectively. The clinical characteristics are indicated in Table 1 and clinical parameters were compared to age-matched CTR subjects ($n = 17$). Setting at 45%, the cut-off for EF, 52 (64%) HF patients had a reduced EF and 29 (36%) had a preserved EF. HF cause was ischemic in origin in about 81% of the patients, and 43% of them suffered from hypertension. Systolic and diastolic blood pressure were significantly lower in NYHA Class IV patients versus the other groups of patients (Table 1). Estimated GFR was reduced in the advanced HF Class (III and IV) compared to Controls and NYHA Class II patients. HF patients showed higher plasma levels of MPO-related chlorinating activity, Cp, BNP, norepinephrine, hsCRP, free MAD, nitrated protein, and 15-F2t-isoprostane as compared to CTR subjects, whereas FeO_xI activity, albumin, and prealbumin were significantly reduced in HF versus CTR subjects (Table 2). A significant difference in MPO-related chlorinating activity was observed between HF patients and CTR, with an incremental trend from NYHA II to NYHA class IV (Figure 2(a) and Table 2). No differences were observed in MPO-related chlorinating activity between HF patients with reduced or preserved EF. Cp levels were higher in NYHA Classes III (+16%) and IV (+24%) as compared to NYHA Class II ($P < 0.05$) (Figure 2(b)). FeO_xI activity was reduced in Class IV HF patients compared to NYHA Class II patients (−23%) and Controls (−24%) as indicated in Table 2.

In HF patients, a close correlation was found between plasma MPO-related chlorinating activity and CP levels ($r =$

Table 2: Oxidative, neurohormonal, inflammatory, and nutritional parameters of heart failure patients and healthy Controls.

	Controls ($n = 17$)	NYHA Class II ($n = 26$)	NYHA Class III ($n = 29$)	NYHA Class IV ($n = 26$)
Oxidative				
MPO activity (mU/min)	10.5 (2.5–26.4)	21.9 (4.8–83.1)*	23.5 (2.5–102.5)*	30.1 (12.2–85.2)*
Ceruloplasmin (nmol/L)	2176 ± 453	2153 ± 426	2508 ± 489†	2662 ± 560*†
FeO_xI activity (UI/L)	442 ± 128	437 ± 142	367 ± 151	336 ± 110*†
Nitrated proteins (nmol/L)	274 ± 69	314 ± 75	402 ± 97*†	428 ± 85*†
Malondialdehyde (umol/L)	0.25 ± 0.09	0.32 ± 0.09	0.43 ± 0.13*†	0.47 ± 0.12*†
15-F2t-isoprostane, pg/mL	56 ± 30	91 ± 30	128 ± 48*†	140 ± 46*†
Neurohormonal				
Norepinephrine (pg/mL)	256 ± 76	266 ± 70	363 ± 101*†	621 ± 220*†#
BNP (pg/mL)	37 (11–62)	48 (12–196)	183 (19–459)*†	283 (105–620)*†
PRA, ng/mL/hr	1.12 ± 0.86	1.58 ± 0.81	2.41 ± 1.24*	4.69 ± 2.22*†#
Aldosterone, pg/mL	169 ± 79	177 ± 94	247 ± 135	295 ± 110*†
Inflammatory and nutritional				
hsCRP (mg/dL)	0.78 (0.12–4.56)	0.82 (0.17–9.30)	1.90 (0.66–36.16)*†	7.22 (1.49–44.31)*†#
Albumin (g/dL)	3.9 ± 0.5	3.9 ± 0.5	3.7 ± 0.6	3.1 ± 0.7*†#
Prealbumin, mg/dL	29.5 ± 5.3	29.8 ± 6.3	26.5 ± 7.7	20.2 ± 8.1*†
Total cholesterol (mg/dL)	194 ± 20	216 ± 34	210 ± 42	202 ± 36

Data are reported as mean ± SD or median (range) depending on the distribution of data; BNP: B type natriuretic peptide; hsCRP: high sensitivity C-reactive protein; PRA: plasma renin activity; MPO: Myeloperoxidase-related chlorinating activity; FeO_xI: ferroxidase I activity; ∗ indicates P less than 0.05 versus Controls, † versus NYHA II, and # versus NYHA III.

0.363, $P < 0.001$, and $n = 81$) whereas no correlation was found between plasma MPO chlorinating activity and FeO_xI activity ($r = 0.129$ and $P = 0.190$, Figure 3(a)). A positive linear relationship was observed between MPO-related chlorinating activity and nitrated protein ($r = 0.365$ and $P < 0.001$, Figure 3(b)), hsCRP ($r = 0.351$ and $P < 0.001$, Figure 3(c)). The strongest positive relationship was found between chlorinating activity and BNP ($r = 0.496$ and $P < 0.001$, Figure 4(a)), and no correlation was observed between MPO-related chlorinating activity and eGRF ($r = 0.149$ and $P = 0.123$, Figure 4(b)). A borderline negative correlation was found between MPO-related chlorinating activity and albumin ($r = -0.201$ and $P = 0.047$, Figure 4(c)).

4. Discussion

There are several results arising from this study on a cohort of chronic HF patients with both reduced and preserved EF. First plasma MPO-related chlorinating activity is elevated in elderly HF patients, with increasing levels linked to the worsening of NYHA class, compared with age-matched Controls. We measured plasma MPO-related chlorinating activity and not MPO mass and we observed that no differences were evident between reduced and preserved EF HF patients. Second, we reported a positive correlation between plasma MPO-related chlorinating activity and Cp levels in HF patients. This finding in part contrasts with what was expected. Cp binding to MPO should represent a protective shield against increased oxidant production by MPO, also in HF patients. Third, plasma MPO-related chlorinating activity is positively associated with several systemic inflammatory, neurohormonal, and oxidative/nitrosative parameters expressing the activation of these pathways in HF patients while progressing the disease. Fourth, a negative relationship has been found between with the MPO-related chlorinating activity and nutritional parameters. All these findings deserve specific comments.

First, we confirm what is already known that MPO-related chlorinating activity in HF patients is increased even if we do not have information on MPO enzyme mass levels. Circulating MPO enzyme levels are largely derived from the secretion of this enzyme from leukocytes in the blood stream after inflammatory activation. The process that leads to hypochlorous acid from hydrogen peroxide and chloride ions was always thought to be a unique characteristic of MPO excluding from this the other mammalian hemoperoxidases (eosinophil peroxidase, lactoperoxidase, and thyroid peroxidase) [4]. However, in a recent study, Li et al. identified the vascular peroxidase 1 as a new member of the family of heme peroxidase capable of producing small amounts of hypochlorous acid starting from chloride and hydrogen peroxide [22]. The majority of commercially available assays do not directly measure MPO enzymatic activity in plasma but the amount of the enzyme mass by enzyme-linked immunosorbent or chemiluminescent automated assay [24]. In the present study, we report the MPO-related chlorination activity of plasma from HF patients and found its activity increased while the severity of HF progresses.

We also investigated the relationship between MPO-related chlorinating activity and Cp levels and found a close positive association (Spearman's r 0.363, $P < 0.001$). As recently shown, Cp is considered a strong inhibitor of MPO activity, with a marked reduction of chlorination activity even at low concentration [12]. In our study, we were expecting a possible inverse association between MPO chlorinating activity and Cp circulating levels but the opposite was

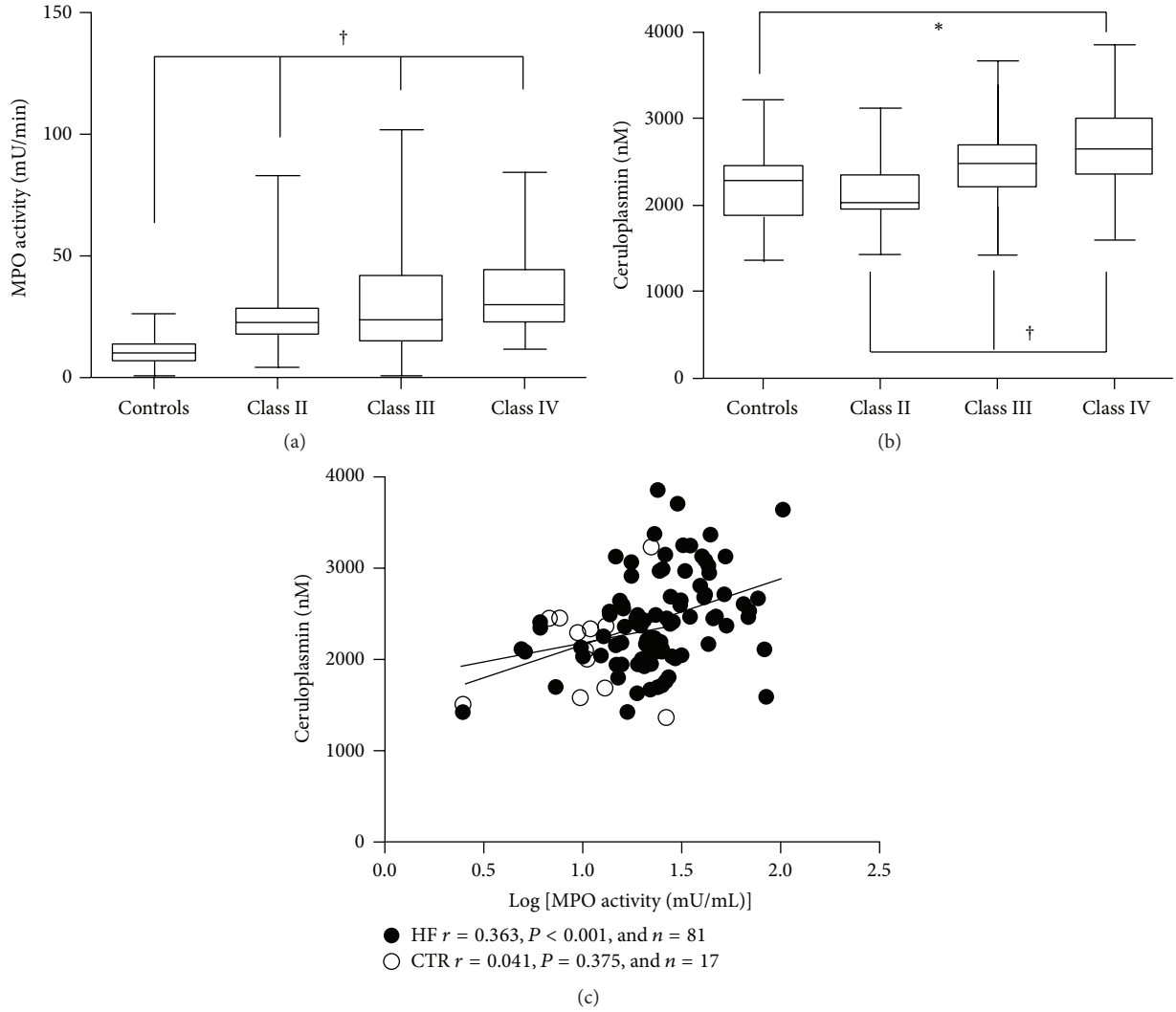

Figure 2: (a) Boxplots of serum MPO activity in Controls ($n = 17$) and heart failure patients (NYHA class II $n = 26$, III $n = 29$, and IV $n = 26$). One way ANOVA ($P < 0.001$) showed a significant difference among the groups (Classes II, II, and IV versus Controls, $^{\dagger}P < 0.01$). (b) Boxplots of serum Ceruloplasmin in Controls ($n = 17$) and heart failure patients (NYHA Classes II $n = 26$, III $n = 29$, and IV $n = 26$). One way ANOVA ($P < 0.001$) showed a significant difference among the groups (Classes IV and III versus Controls, $^{\dagger}P < 0.01$; Class IV versus Class II, $^{*}P < 0.05$). (c) Scatterplots of Myeloperoxidase chlorinating activity against Ceruloplasmin in HF patients and age-matched Controls. r = Spearman correlation coefficient.

observed in HF patients. In addition, no correlation was found between Cp-related FeO_xI activity and MPO-related chlorinating activity. It has recently been reported in literature that Cp levels are increased while increasing the severity of HF and probably reflecting the inflammatory status of these patients. Some evidences have also shown a strong independent prognostic value of high Cp circulating levels in stable patients undergoing elective coronarography and in a group of patients without HF or cardiovascular disease taken from the Atherosclerosis Risk in Communities Study [25, 26]. In our recent study, Cp circulating levels were not able to predict mortality, while it was Cp-related FeO_xI activity [11].

In the present paper, we showed the increased levels of circulating nitrated proteins in HF patients compared to Controls. A close positive association has been found between MPO-related chlorinating activity and circulating nitrated proteins. Our results agree with other studies reporting that severely diseased HF patients express the highest levels of plasma nitrated proteins [11, 27]. Protein nitrotyrosine formation has been claimed as a "footprint" for $ONOO^-$ generation [1, 28–31] but recently alternative mechanisms of nitration have been shown to take place *in vivo*, involving the generation of the $NO_2^{\bullet}$ radical by MPO and also eosinophil peroxidase [10, 13, 27, 30].

In our study, we reported a strong association between MPO-related chlorinating activity and hsCRP. This finding underlines the participation of a systemic inflammatory process in HF progression. Such observation agrees with a series of studies in different cohorts of patients where the associations between MPO and inflammation in acute and

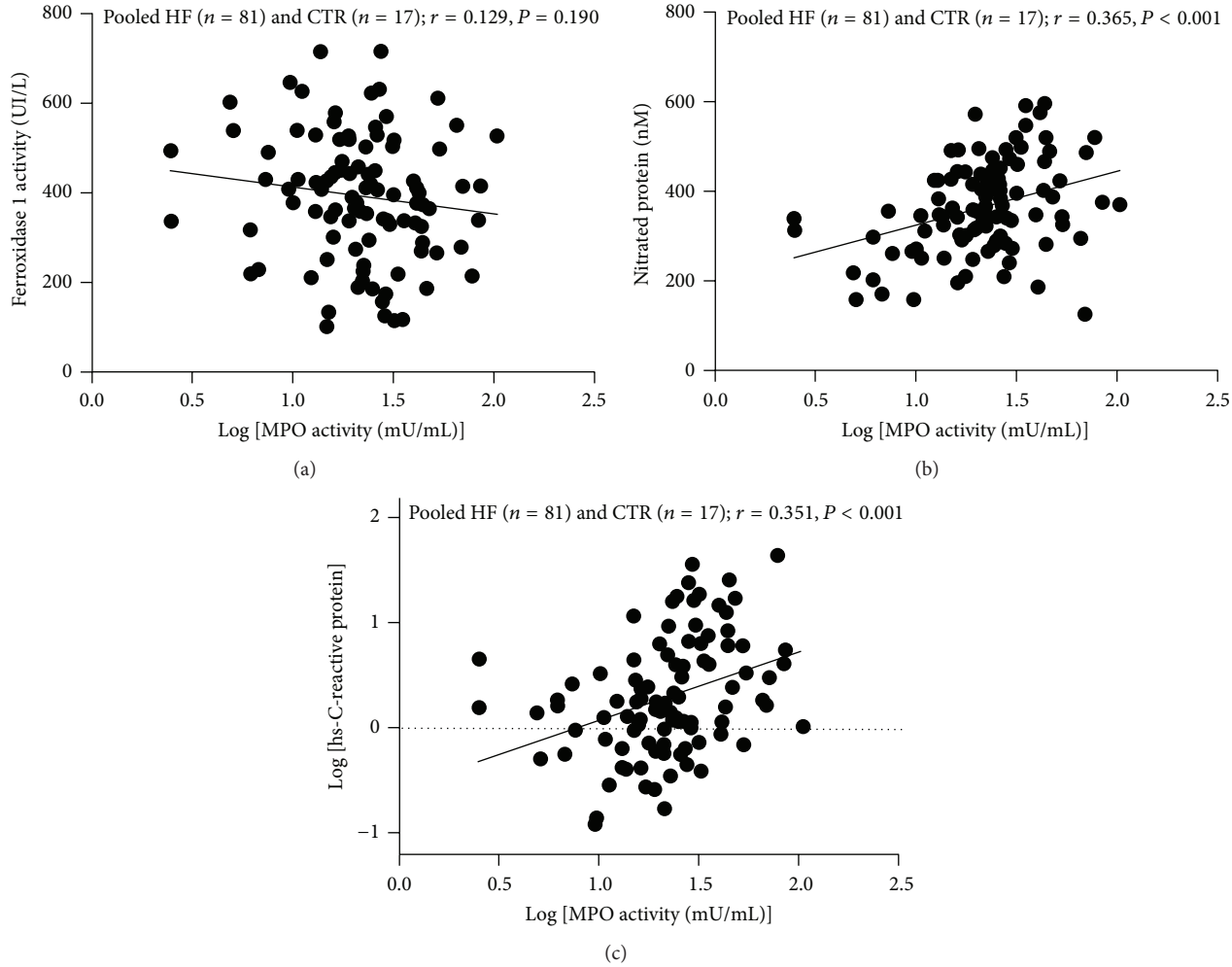

Figure 3: Scatterplots of Myeloperoxidase chlorinating activity against Ferroxidase I Activity (a), nitrated protein (b), and high sensitivity C-reactive protein (c) in pooled subjects patients (pooled HF patients (n = 81) and age-matched Controls (n = 17)). r = Spearman correlation coefficient.

chronic setting of coronary heart disease and in chronic systolic HF patients as well in other populations of patients such as hemodialysis patients were demonstrated [32–35].

However, in a recent and well-performed study in chronic systolic heart failure patients, Wilson Tang et al. did not observe the association between MPO (measured as mass and not chlorinating activity) and hsCRP [36]. The lack of association was somewhat unexpected and the authors suggested that MPO levels allow the differentiation of the leukocyte-based pathophysiologic contribution to cardiovascular disease from a generalized systemic inflammatory process that was more mirrored with hsCRP [36]. Some differences were detectable in their cohort of patients from the patients included in our study: their patients were younger (mean 57 years) and had systolic HF whereas in our group also preserved HF patients were included and they have better renal function.

In our study, we also showed a direct relationship between chlorinating activity and neurohormonal activation parameters, in particular BNP and norepinephrine. The closest association was with BNP in a Spearman coefficient r close to 0.5. In our study, renal function does not correlate with plasma MPO-related chlorinating activity in patients with HF: patients in NYHA Classes III and IV showed a reduction of 25–30% of the eGFR compared to Controls.

An interesting finding of our study is the observation of reduced levels of albumin and prealbumin in the advanced HF patients (Class NYHA IV versus the other Class and Controls) suggesting a poorer nutritional status. It has never been reported before in HF patients of an inverse relationship between MPO-related chlorinating activity and circulating levels of albumin. Protein malnutrition is a phenomenon that could be observed in HF when patients develop a state of cachexia and represents a serious negative prognostic factor. Both albumin and prealbumin values could be lowered while aging. In addition, albumin that can reflect the nutritional status can also be influenced by the chronic low inflammatory status accompanying the time course of HF disease.

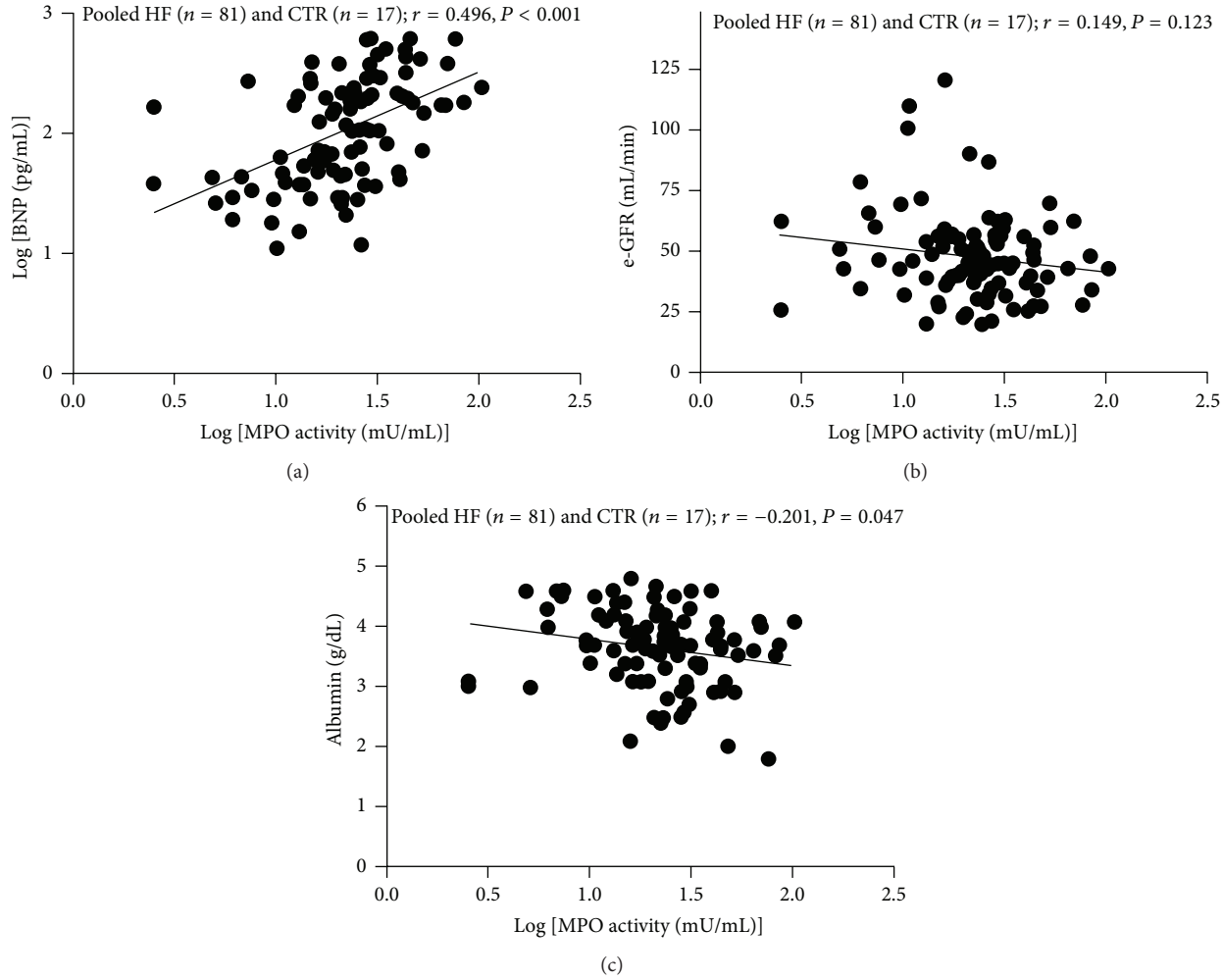

Figure 4: Scatterplots of Myeloperoxidase chlorinating activity against BNP (a), eGFR estimated glomerular filtration rate (b), and albumin (c) in pooled subjects patients (pooled HF patients (n = 81) and age-matched Controls (n = 17)). r = Spearman correlation coefficient.

The present study did not investigate the prognostic role of MPO-related chlorinating activity, which has already been suggested in various clinical cardiovascular conditions to identify patients at increased risk for progressive cardiac deterioration [32–36], but we explore the association with known mechanisms of progression of disease severity. Our cross-sectional study limits the interpretation of our findings. Although the association between increasing plasma MPO-related chlorinating activity and increasing HF severity does not prove a cause-and-effect relation, thinking of chlorinating activity as a disease marker without pathophysiological properties is reductive and it is still intriguing to note that MPO chlorinating activity appears to be involved in the increased nitration observed in HF patients and therefore an active contributor to disease progression. In conclusion, our findings provide insight into the interaction between MPO-related chlorinating activity, Cp, and other biomarkers, expressing different domains such as neurohormonal, inflammatory, metabolic-nutritional, and oxidative domains, all potentially involved in the prognosis of HF patients.

Conflict of Interests

The authors declare no conflict of interests regarding the publication of this paper.

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