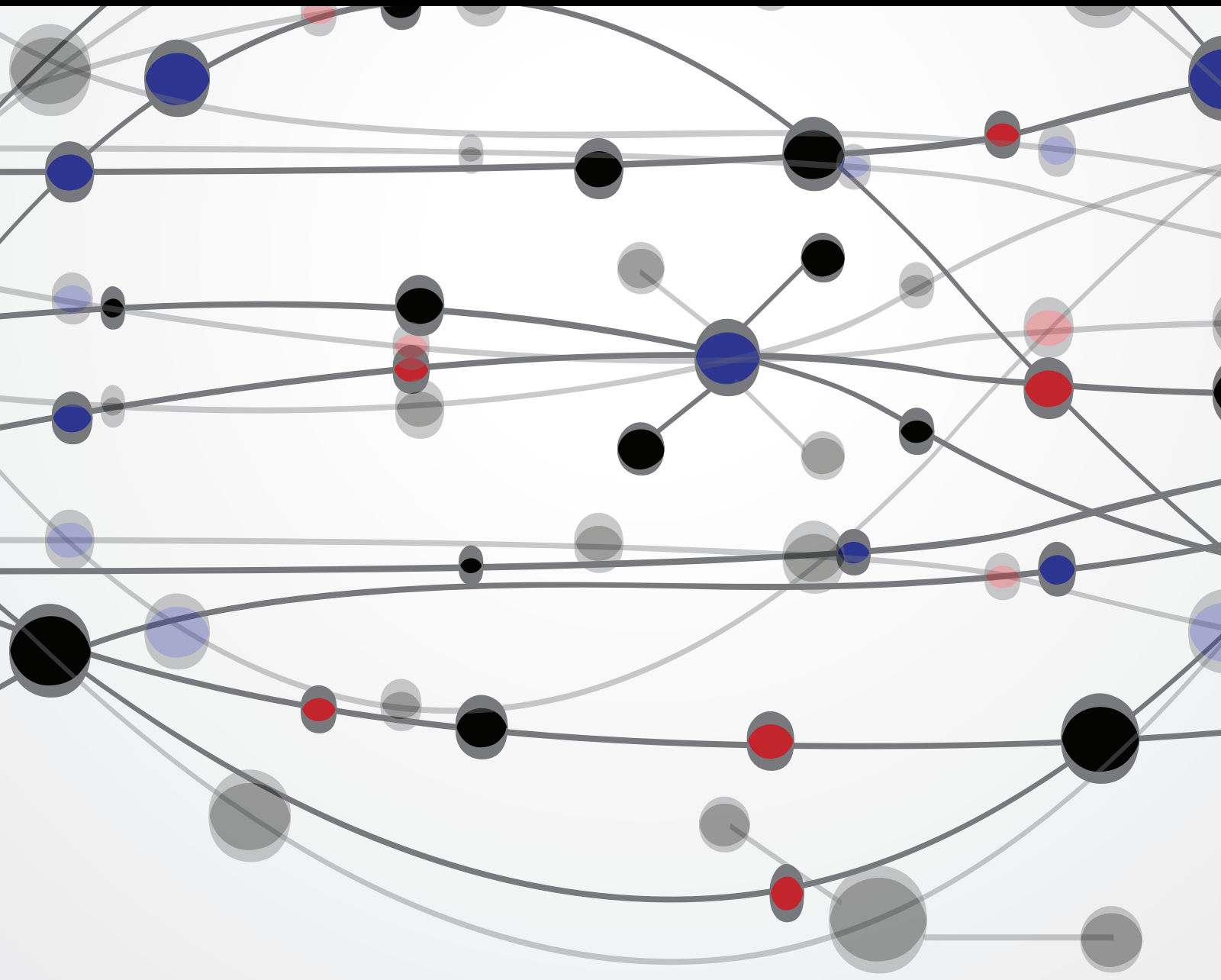
The Scientific World Journal

Heart Failure

Guest Editors: Yanggan Wang, Yanzong Yang, and Xun Ai



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Editorial

Heart Failure

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Received 8 December 2013; Accepted 8 December 2013; Published 12 February 2014

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Heart failure (HF) affects nearly 5 million people in the US and 15 million people worldwide [1, 2]. HF has a considerable impact on affected patients with a high mortality and reduced quality of life. There is also an economic burden to our society due to the huge health-care costs of HF management. To date, the effectiveness of HF diagnosis and management strategies still need to be improved.

When HF is advanced, malfunction of multiple organs is involved and the degree of organ damage is correlated with the progress of HF. Treatment of HF patients depends on the stage of HF. This special issue on HF introduces a new HF evaluation "HLM" system and reviews the role of natriuretic peptide in HF diagnosis and management.

At the end stage of HF, heart transplant often offers the best treatment option. Left ventricular assist devices (LVADs) are surgically implanted pumps that can be used as destination therapy and as a bridge to transplant. However, graft failure is a major cause of mortality among postheart transplant patients. Also, severe mitral regurgitation in HF patients has negative impact on left atrium, right heart, and lung function that ultimately impacts effectiveness of LVAD. The current issue reveals two new approaches, extracorporeal membrane oxygenation rescue and transapical concomitant mitral valve repair to improve the outcome of heart transplant and LVAD therapies. In addition, a review about interaction between renin and IGFII/M6P receptors in nonclassical renin effects and cardiac remodeling sheds light on manipulation of the IGFII/M6P receptor as a potential therapeutic approach to prevent cardiac remodeling in HF. We anticipate more progress in HF management in the near future.

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Hindawi Publishing Corporation
The Scientific World Journal
Volume 2013, Article ID 175925, 8 pages
http://dx.doi.org/10.1155/2013/175925

Review Article

TNM-Like Classification: A New Proposed Method for Heart Failure Staging

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Received 10 July 2013; Accepted 29 September 2013

Academic Editors: X. Ai and Y. Yang

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Heart Failure (HF) is an acute or chronic syndrome, that causes a lot of damaging effects to every system. The involvement of different systems is variably related to age and others comorbidities. The severity of organ damage is often proportional to the duration of heart failure. The typology of HF and the duration determine which organs will be affected and vice versa the severity of organ damage supplies precious information about prognosis and outcome of patients with heart failure. Moreover, a classification based not only on symptomatic and syndromic typical features of heart failure, but also on functional data of each system, could allow us to apply the most appropriate therapies, to obtain a more accurate prognosis, and to employ necessary and not redundant human and financial resources. With an eye on the TNM staging used in oncology, we drawn up a classification that will consider the different involvement of organs such as lungs, kidneys, and liver in addition to psychological pattern and quality of life in HF patients. For all these reasons, it is our intention to propose a valid and more specific classification available for the clinical staging of HF that takes into account pathophysiological and structural changes that can remark prognosis and management of HF.

1. Introduction

Heart Failure (HF) is an acute or chronic unhealthy condition, characterized by the inability of the heart to warrant its pump function in terms of adequate oxygen supply to the body tissues. An enchanting explanation of the HF's condition was proposed by Neubauer who defined HF like an "engine out of fuel" [1]. Even though the pump's failure is common to both acute and chronic HF, these differ from one another in HF's duration and the kind of organ damage developed. The prevalence of HF is greater in the population over 50 years old and the incidence is directly correlated with age [2]. The incidence of HF is steadily increasing because the ageing of the population, especially in the occidental world. Moreover, hospitalization and domiciliary treatments for HF represent an important health care burden [3]. The incidence of HF is destined to increase substantially over the next decade [4]. Recent updates of AHA/ACC guidelines about HF focus on diagnosis and management of HF in adults [5]. The current methods for clinical assessment of HF subdivide patients with HF or with high risk for HF in four classes or stages. In the first two stages (A and B), the patients are asymptomatic, whereas in the last two stages, they have a clinically manifested HF (stage C) which becomes refractory to therapy (stage D). The current guidelines modulate therapeutic interventions on the basis of this classification.

In 2006, Senni et al. [6] claimed that the predictor parameters identified by clinical studies and trials may be often unrepresentative of HF in the community. Senni in his study highlights the importance of prognostic stratification in patients with HF and proposes the use of Cardiovascular Medicine Heart Failure (CVM-HF) index as a valuable tool for the prognosis of stable HF.

The authors focused not only on cardiac parameters but also on comorbidity of patients with HF and developed a model to evaluate the 1-year risk mortality at all stages of the disease. The CVM-HF index includes 13 variables: age, anemia, hypertension, chronic obstructive pulmonary disease, complicated diabetes mellitus, moderate to severe kidney dysfunction, metastatic cancer, absence of β blockers therapy,

absence of angiotensin-converting enzyme inhibitors/angiotensin receptor-antagonist, NYHA (New York Heart Association) class III/IV, left ventricular ejection fraction ≤20%, severe valvular heart disease, and atrial fibrillation. Depending on the score achieved, patients are considered in the low-, medium-, and high-risk group [6].

In 2009, Cygankiewicz et al. on Behalf of the MUSIC investigators, realized a study that proposed the evaluation of dynamic electrocardiographic measures to identify patients at risk of all-cause mortality and cardiac death [7].

In the same year, Vazquez et al. proposed the MUSIC Risk Score, a simple method that evaluates a limited number of variables tested with noninvasive methods. In the MUSIC Risk Score, demographic, clinical, echocardiographic, 12-lead ECG, and 24 h Holter monitoring and laboratory variables were taken into account to predict mortality in ambulatory patients with chronic HF [8].

Kalogeropoulos et al. in a recent study, tested the Seattle Heart Failure Model (SHFM) in patients with advanced HF. The study showed that this model overestimates survival, particularly in patients with implanted devices. On the contrary, in blacks, SHFM showed underestimation of the risk in patients with advanced HF [9].

Another risk score to assess in-hospital mortality in patients with HF was validated by Peterson et al. using American Heart Association Get With the Guidelines-Heart Failure (GWTG-HF) program data. This risk-score was established using variables identified in the multivariate model. The variables used were age, sex, race, atrial arrhythmia, diabetes, chronic obstructive pulmonary disease, peripheral vascular disease, coronary artery disease, cerebrovascular disease, ischemic etiology, depression, ejection fraction, blood urea nitrogen (BUN), sodium, hemoglobin, creatinine, heart rate, and systolic blood pressure [10].

More recently, Peterson et al. indicate a paradoxical inverse relationship between treatment and risk in HF. In practice, higher-risk patients are less likely to receive recommended therapy. This "mismatch treatment" is probably due to the fact that the patients with HF at high risk of mortality have more contraindications to drugs resulting in being ineligible to evidence-based therapy.

For all these reasons, one of the unmet needs in the field of HF is a clinical classification that accurately stratifies our patients in order to (a) make a more precise prognostic evaluation and (b) find the more appropriate treatment, not only in term of efficacy, but also in terms of cost-benefits [11]. A classification of this type, should enable the physician to better manage the patient's illness, but mainly the human and material resources available. In fact, a classification that takes into account comorbidities and their severity in patients with heart failure may also allow a different reimbursement of expenses incurred by national health systems and insurance. Only by framing the main organs involved in HF and their relationship, we can choose the most appropriate therapy to be adopted in a wide range of therapeutic tools available.

In this setting, we propose a staging system for HF similar to the TNM evaluation used in oncology [12]. The evaluation of myocardial damage is necessary, as well as the type of changes that can occur in the myocardial structure and function. This is the first step where "H"—for Heart—may be the analogue of "T" from the aforementioned TNM. The second step in this HF staging is the assessment of lungs involvement. For their functional and anatomical closeness to the heart, they may be indeed considered, continuing the analogy, as a lymph node station. Finally, remembering the etymological meaning of "metastasis," that in Ancient Greek signified "what is beyond there," similarly to the concept used in oncology for metastasization, the "Malfunction" of peripheral organs like kidney, liver, brain, and so forth may represent the final step "M."

2. Materials and Methods

2.1. "H" for Heart. To evaluate the extension of heart impairment, we propose to consider not only systolic and diastolic functions, in terms of ejection fraction and transmitral flow, but also other characteristical anatomo-functional conditions, as previous myocardial infarction and cardiac remodeling (hypertrophy and or dilatation). Previous myocardial infarction and its extension is a fundamental parameter to be considered in this staging process. Echocardiography is a valid tool to be used for the evaluation of the functional consequences of the ischemic-necrotic process. However, more recently, the magnetic resonance imaging has proved to add further information on tissue characterization, and precisely, on transmural extension of the infarct and myocardial viability [13, 14]. Left ventricular hypertrophy, well evaluable by echocardiography, is the consequence of a series of cardiac and vascular changes. Various etiologies, as hypertension or hypertrophic cardiomyopathies, account for left ventricular hypertrophy [15–17]. Left ventricular remodeling is easily evaluable by echocardiography, that allows the estimate of diameters (systolic and diastolic normal values: 50 ± 5 mm and 31 ± 5 mm, resp. [18]) volumes and shapes. The worst condition of heart in HF is represented by biventricular dysfunction that involves both the left and the right ventricles.

All these aforementioned parameters have a consolidated prognostic value. Matching in different ways these parameters, grading them from less to more severe conditions, we can obtain a staging of cardiac damage during HF (from H_1 to H_4: see scheme in Table 1).

2.2. "L" for Lung. The evaluation of grading and timing of pulmonary system's damage is necessary to give awareness of progress and severity of HF. The clinical manifestations of lungs' implication in HF are multifaceted. In this meaning, the relationship between heart and lungs is to be considered biunique. Even though, in a first moment, left ventricular dysfunction leads to pulmonary congestion, which reveals itself the pulmonary hypertension [19] occurrence, in second time, pulmonary hypertension and pulmonary volume overload precipitate right ventricular dysfunction [20]. Numerous evidences establish that the presence of pressure increment in pulmonary vasculature predicts a poor outcome in patients with HF [21]. Pulmonary hypertension also occurs in patients with HF and preserved ejection fraction [22]. Therefore, considering pulmonary involvement only in patients with

Table 1: (a) The parameters considered in the staging of the heart damage. (b) See text for the explanation (LV: left ventricle).

(a)

Cardiac damages
Hypertrophy
Transmitral flow
Previous N-STEMI
Previous STEMI
Ventricular remodeling
Ejection fraction < 35%

(b)

Staging
H_1: impaired systolic or diastolic function of LV without structural damage
H_2: LV with systolic or diastolic dysfunction and structural damage (hypertrophy previous myocardial infarction)
H_3: systolic and diastolic dysfunction (and/or EF < 35%) with left ventricular remodeling
H_4: biventricular systolic and diastolic dysfunction

HF and impaired ejection fraction would be incorrect [23]. Pulmonary hypertension, as well as HF, is also an age-related disease [24] and is tightly associated with increasing of left atrial diastolic pressures and increasing in systemic vascular resistances. Consequently, to better establish the severity of HF, the functional evaluation of the pulmonary circulation is necessary. Normal pulmonary arterial pressure has been defined with a value of mPAP (mean pulmonary arterial pressure) <25 mm Hg at rest and <30 mm Hg during exercise, while a normal pulmonary arterial wedge pressure (PAWP) has been defined as ≤15 mm Hg. In order to evaluate PAP, echo-Doppler is largely used, provided that the gold standard to evaluate the overall pulmonary hemodynamic is the right cardiac catheterization [25]. An increase in mPAP value > 25 mm Hg with a PAWP value ≤ 15 mm Hg is defined as precapillary pulmonary hypertension with negative influence on right ventricle that can lead to cor pulmonale. On the contrary, mPAP > 25 mm Hg and PAWP > 15 mm Hg, define a condition known as postcapillary pulmonary hypertension and it is characteristic of congestive pulmonary disease (Figure 1).

About congestive pulmonary disease, Gheorghiade [26] purposes a fine differentiation between hemodynamic congestion and clinical congestion, endorsing that the first one is a state of volume overload resulting in augmented left ventricular filling pressures, that precedes cardiopulmonary congestion by several days. Clinical congestion, is the combination of cardiopulmonary and systemic signs and symptoms that result from increased left ventricular filling pressures. The congestive state of pulmonary system occurs in HF when the mPAP and the PAWP are increased. It is also possible that this precarious condition lead to acute HF syndrome with pulmonary edema [27].

The early finding of "pulmonary involvement" and their treatment can reduce the progression towards HF. Gheorghiade still supports the usefulness of physical examination to evaluate hemodynamic congestion in the absence of cardiac catheterization. The physical bedside examination includes Valsalva maneuver [28], assessments of orthostatic blood pressure changes, and the heart rate and blood pressure response to sublingual nitroglycerin, in order to identify patients with high left ventricle filling pressures in the absence of signs and symptoms of clinical congestion. Moreover, about lung congestion, also pleural effusion should be considered in decompensated HF [29, 30]. In Table 2(a), we purpose the parameters that can supply a graduation of pulmonary involvement and in Table 2(b) is shown the Lung Staging in HF.

Obviously, a patient with pulmonary edema will be classified as Clinical Congestion L_2. The Cardiac Lung represents the arterialization of precapillary and postcapillary pulmonary vasculature and it is easy to imagine how this condition maximally compromises the respiratory function. In order to offer the best therapy for each patient, pulmonary parameters (L_n) have to be tightly considered in association with the estimation of cardiac damage expressed by H_n. For example, in treating a patient with pulmonary edema, L_2 would assume a different role if associated to a cardiac damage estimated as H_1 or H_4. In fact pulmonary edema could occur in patients with a preserved left ventricular systolic function, but also in patients with severe systolic disfunction (cardiogenic shock) and left ventricular remodeling (H_4L_2) or cardiogenic shock, two different conditions with different therapeutic approaches.

2.3. Malfunction of Other Organs. HF brings countless peripheral systemic signs and symptoms and affects practically all the organs. First of all, there is a correlation between renal and cardiac function. Moreover, the incidence of chronic renal failure is increasing as well as that of HF [31]. Cardiorenal syndromes (CRS) indicate a pathological condition in which there is a tight relationship between cardiovascular system and renal function [32]. CRS is subclassified in five typologies depending on directional relation between kidney and heart. In the type one, a rapid worsening of cardiac function influences the renal function bringing an acute kidney injury (e.g., an acute HF could lead to a cardiogenic renal failure). CRS type two does not result in acute heart damage, but in chronically abnormal heart function that chronically affects the renal function, (e.g., patients with chronic HF often show chronic renal failure). CRS type three is characterized by a sudden worsening of the renal function that leads to acute cardiac injury. CRS type four is represented by a chronic primary renal disease that causes a chronic heart damage overtime. Finally, the CRS type five is characterized by a conjuncted cardiac and renal dysfunctions due to a chronic systemic disease. Figure 2 shows the graphical representation of cardio-renal syndrome and how the two organs can influence one another.

Renal function is an important parameter to consider in order to have an overall assessment of patient with HF. It is

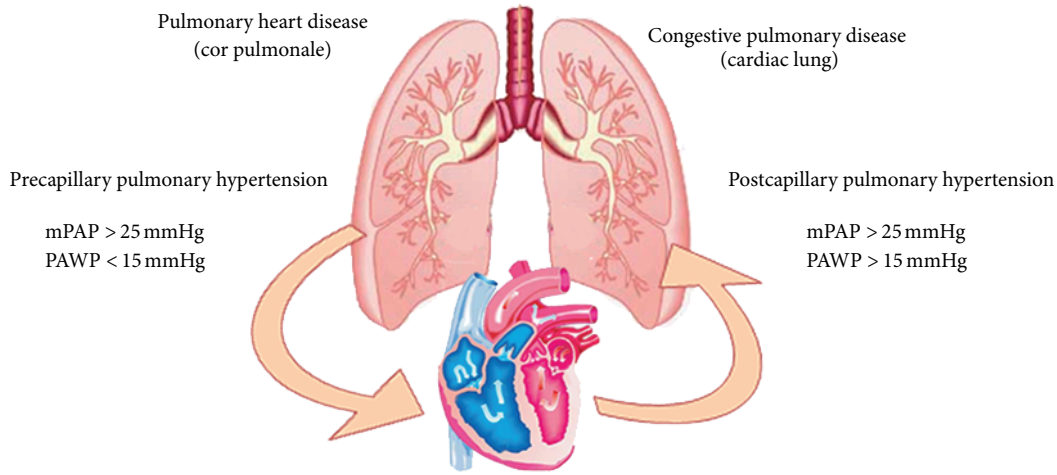

Figure 1: Physiopathology and reference range values in precapillary pulmonary hypertension and postcapillary pulmonary hypertension.

Table 2: (a) Schematic description of different pulmonary implications occurring in patients with HF. (b) Severity stages of lung involvement.

(a)

Parameters of pulmonary damage
Precapillary pulmonary hypertension (mPAP > 25 mmHg PAWP < 15 mmHg)
Postcapillary pulmonary hypertension (mPAP > 25 mmHg PAWP > 15 mmHg)
Pleural effusion
Pulmonary edema

(b)

	Staging
L_1	Hemodynamic congestion
L_2	Clinical congestion
L_3	Cardiac lung

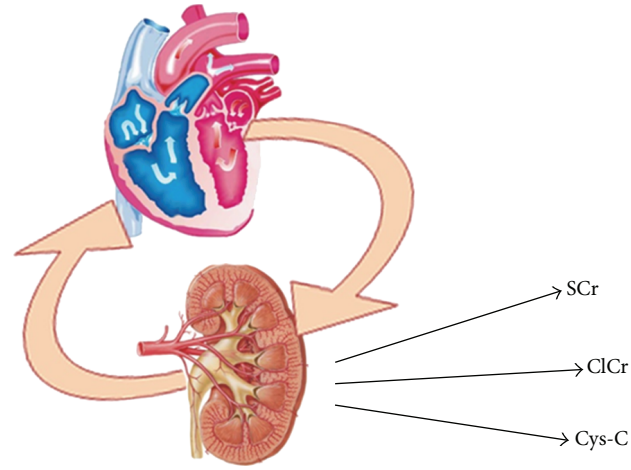

Figure 2: The concept of cardiorenal syndrome that often brings the insaturation of a vicious circle is graphically explicated. SCr: Serum Creatinine; ClCr: Clearance of Creatinine; Cys-C: Cystatine-C.

possible to investigate some parameters in order to define renal function and its impairment grade.

Creatinine (0.7 to 1.3 VN mg/dL) alone is not a reliable parameter for the measurement of renal function. Indeed, as produced by the muscles and eliminated by the kidney, it increases with muscle mass. Therefore, a value of 1.2 mg/dL is a normal expression of renal function in a patient with muscle mass particularly developed; on the contrary, the same value can "mask" a frank renal failure in a patient with low muscle mass. Furthermore, especially in the early stages of renal failure, small increases in the serum creatinine value indicate significant decreases in glomerular filtration rate (GFR). For these reasons, assessment of renal function cannot only be based on serum creatinine, but it is necessary to determine the GFR: the lower the creatinine clearance is, the lower the patients prognosis is [33]. In this context the evaluation of renal function, by calculating creatinine clearance [34], provides an optimal parameter to estimate peripheral signs of HF. The two main formulas for the calculation of GFR are the Cockroft-Gault and MDRD (Modification of Diet in Renal Disease), although currently the most widely used is a modification of the simplified MDRD formula (sMDRD or simplified MDRD).

Creatinine clearance, calculated by Cockroft-Gault formula, takes in consideration creatinine serum concentration (mg/dL), age (in years), weight (in Kg), and gender (multiplying the total score for 0.85 in female patients). The complete formula is [(140 − age) × weight]/72 × serum creatinine concentration; the value resulted is multiplied by 0.85 in female patients. The reference values are 57–115 in women and 95–145 in men [35].

Simplified MDRD formula, to calculate creatinine clearance, takes in consideration parameters as serum creatinine, ethnicity, and gender. The formula is GFR (mL/min/1.73 m^2) = 186 × serum creatinine − 1.154 (μmol/L) × age − 0.203 (×0.742 if the patient is a woman) (×1.21 if the patient is black) [36]. Moreover, cystatin C (Cys-c), an endogenous

marker of glomerular filtration rate (GFR), is another useful parameter to assess renal function also in patients with HF [37]. Cys-C is a part of the cysteine protease and its serum concentration increases when the GFR diminishes. Since creatinine concentration is influenced by muscle mass and growth and also by other pathological conditions as liver cirrhosis, anorexia nervosa, and so on, Cys-C has proved to be a more reliable parameter in assessing renal function [38]. The usefulness of Cys-C in HF has recently been confirmed by the study of Campbell et al. that demonstrated a poor outcome in patients with high level of Cys-C and impaired renal function [39].

It is possible to evaluate blood urea nitrogen (BUN) in order to complete the renal assessment, but it is necessary to consider that BUN is an ambiguous marker of renal impairment because it is strongly influenced by catabolism and catabolic alteration. The parameters to be considered for the evaluation of renal function are shown in Table 3(a).

In order to overview other possible damaged organs in HF, we report an interesting study that supports this concept: "heart disease affecting the liver and liver disease affecting the heart" [40]. HF brings liver complications like alterations of functional liver tests that recover to normal values with the compensation of HF. The study of Allen et al. brings forth that an increment in total bilirubin, alkaline phosphatase, and ALT (alanine transaminase), and a reduction in albumin, are reliable in patients with HF [41]. Moreover, the study proves that this kind of data variably influences the prognosis of patients with HF. To assess liver dysfunction some scores were structured, in particular Child-Pugh score and MELD (Model for End Stage Liver Disease) score. MELD score takes into account total bilirubin, serum creatinine, and INR; Child-Pugh evaluates total bilirubin, serum albumin, INR, ascites, and hepatic encephalopathy. Notice how in both scores created to evaluate liver function, INR and total bilirubin are considered [42]. The INR should be considered carefully since about 1/3 of HF patients is on anticoagulant therapy.

The etiology of liver congestion in HF depends on different variables [43]. When the pulmonary vascular resistance increases and the mPAP is over 25 mm Hg, the repercussion of high pressure induces a volume overload in portal circulation. It is well known that right HF causes liver congestion. For this clinical evidence, in staging HF, it is necessary to consider the hemodynamic and organic function of liver. To obtain an estimate of hemodynamic changes in hepatic district, we can measure the main portal vein flow velocity using duplex sonography [44, 45]. A reduced portal flow that can be detected is likely a consequence of HF. The increment of portal pressure due to right HF could remain silent for years before clinical manifestations occurrence. Another very important parameter that physicians may consider to estimate the congestion state of venous system is the collapse of the inferior vena cava measured with ultrasonography during maximum inspiration. In this regard, a study published by Blehar and coworkers, shows how the diameter variations of the inferior vena cava are related to volume overload in patients with HF [46]. Analogous to the events that occur in kidneys, what occurs in liver during HF ("liver impairment") is to be considered as a consequence of a more advanced disease. We must underline that, to give a careful estimate of liver damage in HF, it is necessary to evaluate all the parameters summarized in Figure 3 and Table 3(b). In fact, the staging of liver damage based on only one of these parameters is simplistic and misleading because it is known that liver function tests are aspecific indices of deterioration of liver and are therefore to be interpreted in order to make a differential diagnosis with other hepatic diseases. During the investigation of liver's impairment, we can face other clinical features as ascites. Cardiac ascites might indeed develop in patients with a right ventricular failure and systemic venous hypertension [47].

Finally, another organ that can be affected by HF is also central nervous system. In fact cerebral hypoperfusion and impaired cerebral function occur in HF [48, 49]. Cerebral vasoreactivity depends on cardiac functional variables. Cerebral complication that can occur in HF is also another consequence of progression of cardiac disease. Other important aspects of brain involvement in HF are psychological troubles. We mainly refer to the depression. In this regard, the research reported by Gottlieb et al. is very interesting [50]. This study demonstrated that a great part of enrolled patients with HF showed signs of depression and that the coexisting depression severely impacts on life's quality and prognosis. Finally, in a comprehensive assessment of the patient with HF it is important to remember a parameter that gives us an idea of the cachectic state of the subject and is representative of multiple organ failure. The most robust and studied marker that can do this is the BMI (mass (Kg)/height (m)^2) [51, 52].

Table 3: (a) Parameters of kidney damage. (b) Hepatic damage parameters.

(a)

Parameters of kidney damage
Glomerular filtration rate
Blood urea nitrogen
Serum creatinine
Clearance of creatinine
Cystatin C

(b)

Parameters of hepatic damage
γ-GT
Bilirubine (total) increased
ALT, AST
Alkaline phosphatase increased
Albumin decreased
Diminished INR value
Ascites
Impairment of portal blood flow
No changes of inferior vena cava diameter variation during inspiration

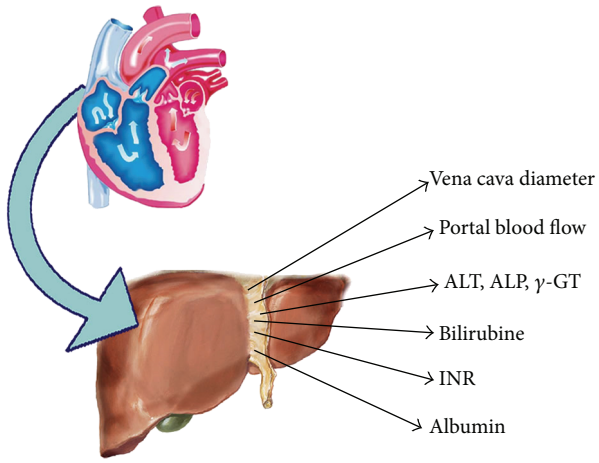

Figure 3: Shows the way of liver's impairment in HF. ALT: Alanine Transaminase; ALP: Alkaline Phosphatase; INR: International Normalized Ratio.

In conclusion, we would like to purpose this score to weight organ's malfunction that can occur in HF. Considering the presence and the number of malfunctioning organs in HF, we can have the M staging as represented in Table 4. The staging of HF influences the prognosis of patients more than their therapy, but, without any doubt, it is necessary to take into consideration any single "malfunction of other organs" in order to guarantee the best treatments and the best quality of life in patients with HF.

3. Conclusion

In our opinion it can be very useful to gain a classification of HF and its progression with a methodological scoring like the TNM evaluation used in oncology. The latest guidelines are mostly based on syndromic and symptomatic classification of HF that, in some cases, could be insufficient. Moreover, the NYHA classification has already been shown to be insubstantial in the evaluation of some kind of patients [53, 54]. We support this viewpoint because this symptomatic classification cannot give a real overview of general health state of the patients with HF. The progression of clinical research in the ambit of HF's classification is still open. What has been written in these pages is intended to provide a classification to proportion our interventions depending on the type of patients we face and to better consider their degree of disease.

With a TNM-like evaluation we do not risk to rely on single parameters, sometimes aspecific, but we have the opportunity to evaluate all the necessary parameters and enclose them in a single compressive classification representing the patient in that moment. This classification will allow us to use a traditional therapy for patients in initial stage of HF ($H_1L_1M_0$) and to apply second-tier line therapies in patients with $H_2L_2M_n$ stage. In fact, the presence of malfunction of other organs authorizes the physicians to employ type of therapies that will be not only cardioprotective, but also nephroprotective, hepatoprotective, and so on, justifying the increased cost of therapy in proportion to the benefits obtained. Besides, this type of classification can be very useful in assessing the true end-stage patients ($H_4L_3M_3$). In these cases, the classification HLM allows us to pursue the most appropriate therapy targeting the quality of life remained with palliative support.

Starting with a patients' followup, applying this new staging system, the future prospect is to stratify prognosis, consider the course of therapy, and evaluate cardiovascular events of patients affected by HF.

Table 4: Staging of malfunction of other organs.

Score	Staging
0	M_0: no malfunction of other organs
1	M_1: single organ damage due to HF
2	M_2: double organ damage due to HF
≥3	M_3: multiple organ damage

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Hindawi Publishing Corporation
The Scientific World Journal
Volume 2013, Article ID 260298, 10 pages
http://dx.doi.org/10.1155/2013/260298

Review Article

Renin and the IGFII/M6P Receptor System in Cardiac Biology

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Received 12 June 2013; Accepted 20 August 2013

Academic Editors: X. Ai and Y. Wang

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Nonenzymatic cardiac activities of renin are well described during the last years and contribute either to cardiac-specific effects of the renin-angiotensin-aldosterone-system (RAAS) or to the pharmacological effects of RAAS inhibition. The interaction of renin with insulin-like growth factor II/mannose-6-phosphate (IGFII/M6P) receptors participates in nonclassical renin effects and contributes to cardiac remodelling caused by RAAS activation. The current findings suggest an important role for renin IGFII/M6P receptor interaction in cardiac adaptation to stress and support the idea that excessive accumulation of renin during inhibition of RAAS directly contributes to blood pressure-independent effects of these pharmacological interventions. It becomes a challenge for future studies focussing on chronic hypertension or myocardial infarction to comprise regulatory adaptations of the kidney, the main source of plasma renin and prorenin, because they directly contribute to key steps in regulation of cardiac (mal)adaptation via IGFII/M6P receptors. This receptor system is part of peptide/receptor interactions that modifies and possibly limits adverse remodelling effects caused by angiotensin II. Evaluation of interactions of renin with other pro-hypertrophic agonists is required to decide whether this receptor may become a target of pharmacological intervention.

1. Introduction

The renin-angiotensin-aldosterone system (RAAS) has an outstanding position in cardiac adaptations that balance blood pressure and body requirement in response to orthostase reaction or physical stress. Although a quick and effective increase in blood pressure is required to withstand the challenge to physical stress, uncontrolled activation of this system leads to chronic hypertension. High blood pressure is a major risk factor for adverse cardiac events such as stroke, myocardial infarction, and chronic heart disease. Therefore RAAS which plays a major role in many types of chronic hypertension is a main target for antihypertensive treatment regimes. However, it has well been recognized that RAAS is a complex network of biologically active peptides and their corresponding receptors that go far beyond the proper control of blood pressure. It is also clear that not all side effects of peptides participating in this system and the activation of their corresponding receptors are necessarily inducing adverse effects on cardiac tissues. A nice example for this is the different role of angiotensin II type one and type two receptors in intracellular signalling (as reviewed in detail in [1]).

In recent years it has been noticed that the first step in the RAAS cascade, the release of renin from juxtaglomerular cells in response to an activation of the sympathetic nervous system, is far more than the release of an aspartyl protease required for converting angiotensinogen into angiotensin I. This review will focus on those effects of renin that are mediated by stimulation of cardiac-specific insulin-like growth factor II/mannose-6-phosphate receptors (IGFII/M6P) and will summarize our current understanding of how renin expression and posttranslational modification will lead to activation of this receptor. The central question is how this will influence the adaptation to chronic pressure overload and cardiac stress in general. Although we are far from a complete understanding of these basic questions, there are already enough data supporting the idea that renin-dependent IGFII/M6P receptor activation participates in structural remodelling of cardiomyocytes. Furthermore, it has anti-hypertrophic properties as well. Thereby it potentially counteracts an angiotensin II-dependent adverse remodelling.

Table 1: Selected examples of the effect of pharmacological intervention at various sites of the RAAS on plasma renin concentration.

Species	Site of inhibition	Renin concentration		References
		Basal	Treatment	
Human	Renin (aliskiren)	14.9 mU/L	48.4 mU/L	[5]
Human	ACE (ramipril)	14.4 mU/L	35.2 mU/L	[5]
Human	AT1 (irbesartan)	17 mU/L	56 mU/L	[6]
Human	Renin (aliskiren)	5.6 pg/mL	34.9 pg/mL*	[7]
Human	AT1 (irbesartan)	5.6 pg/mL	11.3 pg/mL	[7]
Rat (SHR)	Renin (aliskiren)	9.3 ± 0.9 mg/kg	11.3 ± 1.9 mg/kg	[8]
Rat (SHR)	ACE (captopril)	9.3 ± 0.9 mg/kg	87.1 ± 61.0 mg/kg*	[8]
Rat (SHR)	ACE (captopril)	6.3 ± 1.6 ng/mL	27.4 ± 6.7 ng/mL*	[9]
Rat (SHR)	AT1 (irbesartan)	9.3 ± 0.9 mg/kg	143.0 ± 33.5 mg/kg*	[8]
Mouse ($ApoE^{-/-}$)	Renin (aliskiren)	755 ± 90 ng/mL	3760 ± 567 mg/mL	[10]
Mouse ($ApoE^{-/-}$)	AT1 (irbesartan)	755 ng/mL	11235 ± 3001 ng/mL	[10]

2. The Role of Renin in the Renin-Angiotensin-Aldosterone System (RAAS) in Cardiac Adaptation to Pressure Overload

RAAS is one of the major systems involved in proper blood pressure control and it is causally involved in various cardiac-specific adaptations of the heart either to chronic pressure overload or to the consequences of myocardial infarction. In general two steps of proteolytic activation contribute to the effect. The first step converts angiotensinogen to angiotensin I and the second step converts angiotensin I into angiotensin II. Angiotensin II is considered as the most important molecule of this pathway. Renin, released from juxtaglomerular cells, causes the proteolytic cleavage of angiotensinogen to angiotensin I which is also a target of proteolytic cleavage. Angiotensin-converting enzyme (ACE) cleaves angiotensin 1 into angiotensin II. Finally angiotensin II acts on angiotensin receptors of which two types have been described, named type one and type two. Type 1 receptors are G-protein coupled receptors triggering most of the well described effects of angiotensin II on cardiac and vascular cells whereas type 2 receptors seem to be less prevalent and antagonize the action of type 1 receptors. There are important extensions to this system that have been described in greater detail before (see [2] for details). First, various site products such as angiotensin IV can be formed specifically in the presence of ACE inhibition or angiotensin receptor blockade and they activate mas receptors. Second, inhibition of angiotensin II by ACE blockade can be bypassed by chymases. Third, in addition to the classical angiotensin II-dependent effects on natrium retention, blood pressure, induction of thirst, and others, angiotensin II also acts on the release mechanisms of renin, thereby forming a feedback inhibition of the system (Figure 1). As a consequence of this any pharmacological inhibition within this cascade, such as ACE inhibition or receptor blockade, attenuates this feedback inhibition leading to an enhanced release of renin and increased plasma renin concentration (Table 1). It has been speculated that this increased renin release may hamper the beneficial effect of RAAS inhibition [3]. This has been a matter of debate since the direct renin inhibitor aliskiren may increase renin plasma concentration more effectively than ACE or AT1 receptor inhibition [4].

However, it may also be true that renin acts in nonenzymatic ways and improves cardiac remodelling and function and that the increase in renin plasma concentration offers the possibility that renin participates in anti-remodelling and anti-hypertrophic effects. Such nonenzymatic effects may be generated by binding to and activation of IGFII/M6P receptors. Here we discuss possible pathways by which such effects may be performed. These effects of renin require mannose-6-phosphate transfer to renin and prorenin but no aspartyl proteolytic activity of renin. In other words, antagonizing parts of RAAS either by direct inhibition of renin activity by aliskiren, by inhibition of ACE, or by angiotensin receptor blockade enhances plasma levels of renin and prorenin. This increases the ability of both molecules to activate IGFII/M6P receptors. Last but not least, the enzymatic activity of renin can be enhanced by binding to and activating prorenin receptors in cardiac tissues.

3. Renin: Transcription, Translation, and Regulation of Its Release

An extended review about the molecular understanding of the regulation of renin transcription, translation, and release has recently been published in a review article covering the physiology of kidney renin [11]. We will address only those topics of this area that are of specific interest for the role of renin in cardiac effects triggered by IGFII/M6P receptors. The renin gene was mapped to chromosome I and represents a protein with high interspecies homology, that is, 73% sequence homology between sheep and human renin, 85% sequence homology between rat and mouse DNA, and 68% sequence homology between rat and human renin [12–15]. Its 5′ flanking region has a classical promoter function and the transcriptional regulation is further modified by a renal enhancer. The promoter region covers 123 bp from −117 to +6 (positions relative to the transcriptional start site).

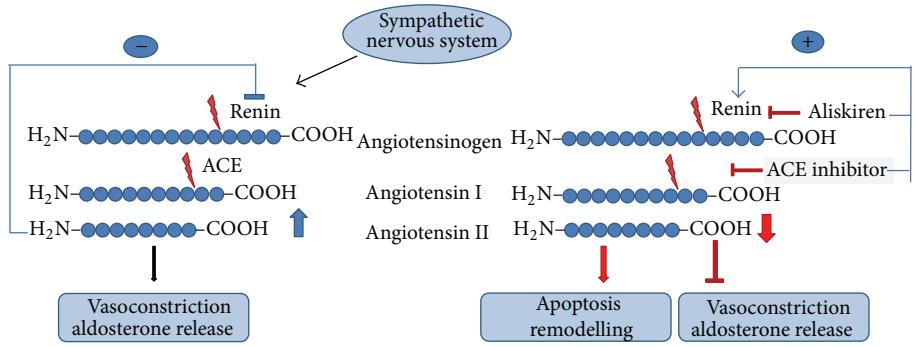

Figure 1: Coupling of sympathetic nervous system (SNS) to the renin-angiotensin system. Activation of the SNS increases the release of renin that forms angiotensin I from angiotensinogen. Angiotensin I is further converted to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II is the effector molecule triggering the known effects of angiotensin II aimed to increase blood pressure. Via its inhibition on renin release it also possesses a feedback loop (left side). Inhibition of the RAAS by either ACE inhibition, AT receptor antagonism, or direct renin inhibition increases the release of renin but lowers the concentration of angiotensin II. Thereby, it reduces AT receptor-dependent effects but exerts new effects linked to remodelling (right side).

It contains a classical TATA box [16]. A row of important cis-regulatory elements is located downstream of −200 which are also important in transcriptional regulation [17]. Renin is a cAMP-inducible gene that contains a classical cAMP response element (CRE) in the promoters of its human and mouse gene. Subtle distinctions may be seen with respect to differences in the response between these species [18–20]. In addition, the renin gene is also sensitive to PPARγ [2] which may be of particular interest in the context of cardiac effects of renin as some angiotensin receptor antagonists have PPARγ activating properties [21]. PPARγ activation downregulates angiotensin type 1 receptor expression but enhances renin expression. Thus the effect of PPARγ activation is rather complex but again directs RAAS to non-classical plasma renin effects via IGFII/M6P receptors [22]. However PPARγ is less relevant in rodents in this context [23]. During embryonic development, HOX and NOTCH pathways control the expression of renin [24]. In addition to its tight transcriptional control renin mRNA can also be stabilized, that is, by Y-Box protein-1 (YB-1), or destabilized, that is, by hydroxyacyl-CoA-dehydrogenase/3 ketoacyl-CoA thiolase/enoyl CoA hydratase beta subunit (HADHB) [25, 26]. The steady state mRNA expression of renin is increased by activation of the cAMP/PKA pathway via two different mechanisms: (a) an increase of its transcription and (b) stabilizing its mRNA. It is suppressed by activation of the PKC/calcium pathway that reduces the expression of renin and destabilizes its mRNA. In principle, catecholamines increase renin expression (and release, see later), whereas angiotensin II, activating phospholipase C (PLC), suppresses its expression and forms a feedback inhibition [27]. It is generally accepted that the majority of circulating renin originates from the kidney (mainly from juxtaglomerular cells). Renin is translated into protein in juxtaglomerular cells as a preprorenin protein. After cleavage of its presequence, it is directed into the Golgi apparatus. Here renin undergoes posttranslational modification and this step seems to be required for renin trafficking into dense-core secretory vesicles from which renin can be released by regulated exocytosis [28]. Moreover, this glycosylation is also a prerequisite for renin uptake from circulation in other tissues such as the heart [29, 30]. Renin is glycosylated like a typical lysosomal protein. In a first step N-acetylglucosamine-1-phosphate is transferred to selected mannose residues on lysosomal proteins. This reaction is catalyzed by UDP-GlcNAc : lysosomal enzyme N-acetylglucosaminylphosphotransferase [31, 32]. N-acetylglucosamine is removed in a second step leading to the typical Man-6-P monoester signal required for binding to IGFII/M6P receptors. Nowadays, it is well accepted that any cardiac stress will also interfere with renal physiology, leading to the cardiorenal syndrome. It will be necessary to investigate the expression and regulation of the enzymes involved in M6P labelling of renin in future. Without these N-glycosylation sites, renin cannot be packed into dense-core secretory granules for regulated exocytosis and will be released in a rather constitutive way. Renin can be released as prorenin and renin. Although prorenin has no enzymatic activity it cannot be considered as an inactive molecule because it interferes with IGFII/M6P receptors due to its glycosylation and thus it can be activated by prorenin receptors [6, 29, 33]. The analysis of the exact mechanism by which renin secretion is controlled is hampered by the fact that renin-producing cell lines as well as cultured juxtaglomerular cells secrete renin in a constitutive way. In culture the cells lose the ability to direct renin into secretory granules [11]. In situ approximately 75% of all renin is released as prorenin in a constitutive form, whereas renin is released by only 25% in a regulated manner [34]. The extent of prorenin release by the constitutive pathway simply depends on the regulation of renin transcription (see above). If necessary, that is, under conditions of chronic salt depletion, the amount of renin release is increased by altering the number of renin-producing cells. The regulation of renin secretion is performed by changes of the membrane potential of juxtaglomerular cells. Angiotensin II depolarizes these cells and it suppresses renin release whereas cAMP-dependent pathways hyperpolarize these cells and increase their release [35, 36]. Pharmacological inhibition of the Na^+,

K^+, $2Cl^-$ cotransporter activity by furosemide leads to hyperpolarization and release of renin [37]. Interestingly, myocardial infarction increases the renal expression of this cotransporter that results in depolarization of renin-secreting cells and reduction of renin release [38]. This already suggests renal side effects caused by myocardial infarction leading to dysregulation of renin release. This interaction requires future attention. Inhibition of renin release also depends on intracellular calcium levels. Plasma free calcium concentrations directly affect renin release probably by inhibition of calcium-dependent adenylyl cyclase isoforms [39, 40]. Furthermore, the cells also express calcium sensing receptors [41]. Stimulation of calcium sensing receptors by calcimimetics inhibits renin secretion [42]. In addition intracellular calcium is the trigger of angiotensin II-dependent feedback inhibition on renin release [43]. As expected, any interference with angiotensin II activity (ACE inhibition, direct renin inhibition, or angiotensin receptor inhibition) blocks this feedback and increases plasma levels of renin thereby increasing nonenzymatic effects of renin that depend on interaction with IGFII/M6P receptors.

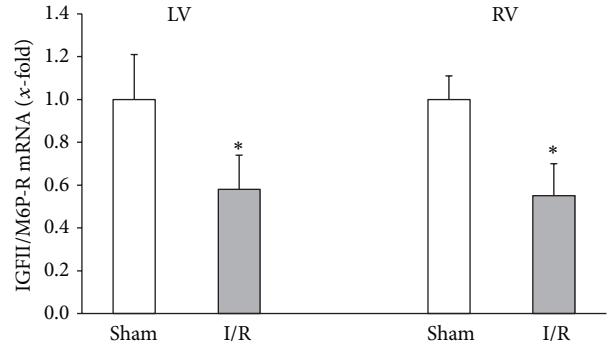

Figure 2: IGFII/M6P receptor mRNA expression in the left ventricle (LV) and right ventricle (RV) of rat hearts that underwent sham surgery or 30 min ischemia (ligation of the left arteria descendens) and one day of reperfusion (I/R). Data are means ± SD from $n = 8$ hearts. mRNA expression was quantified by real-time RT-PCR and expression is normalized to beta-2-macroglobulin (b2M). $^*P < 0.05$ versus sham (unpublished observation).

4. IGFII/M6P Receptors: Structure and Regulation of Their Expression

It was one of the main advantages in the field during the last decade that renin was identified as a molecule that directly acts on cells of target tissues such as the heart. Receptors known as the (pro)renin receptor activate inactive prorenin, enhance renin activity, and generate receptor signalling [33]. Another receptor, IGFII/M6P receptor, is less specific for (pro)renin because it recognizes proteins marked by mannose-6-phosphate. As outlined above renin fits these criteria. There is evidence for the existence of another pathway that is able to internalize nonglycosylated renin [30]. Yet the physiological relevance of this finding requires further work. Concerning binding to IGFII/M6P receptors it is noteworthy that renin has three different N-glycosylation sites by which the protein can be marked with M6P. Upon this M6P attachment, it is able to bind to and activate the IGFII/M6P receptor. This receptor may either internalize renin or trigger direct cell-specific effects (see below). Considering these aspects the IGFII/M6P receptor is central for cardiac nonenzymatic effects of renin. The structure and the biochemical aspects of this receptor have been worked out well. In principle, the IGFII/M6P receptor is a protein with 15 repeated segments of 124 to 192 amino acids in its extracellular part, a short 23 amino acid residue transmembrane domain, and a 167 amino acid residue cytoplasmic domain. Approximately 5–10% of the whole protein is located at the cell surface and is able to interact with ligands that cover M6P moiety such as renin, latent TGFβ_1, thyroglobulin, proliferin, leukemia inhibitory factor, and granzyme B. The receptor can also bind molecules that are not marked by M6P such as IGF-II, retinoic acid, urokinase-type plasminogen activator receptor, and plasminogen.

In contrast to its biochemical characterization less is known about its expression, specifically in the heart and the regulation of receptor expression under stress conditions. It is nevertheless confirmed that IGFII/M6P receptors are highly expressed in the heart specifically in the developing myocardium [44]. Mice deficient in IGFII/M6P receptors die around the time of birth and show severe cardiac defects [45]. The most likely explanation is the loss of cleavage function of the receptor in these mice because IGFII and IGFI null backgrounds are rescued from perinatal lethality [46]. Cardiac-specific knockout of the IGFII/M6P receptor, however, is not lethal and has no obvious phenotype [47]. IGFII/M6P receptor expression mimics the expression profile of our "so-called" foetal genes in the heart, such as ANP, creatine kinase B, and myosin heavy chain β. As found for these molecules, IGFII/M6P receptor expression is reactivated in chronic pressure overloaded hearts [48]. As mentioned above, RAAS does not only participate in adaptation to chronic pressure overload but also to postinfarct remodelling. Preliminary experiments from our lab investigated the cardiac mRNA expression of the IGFII/M6P receptor in response to ischemia and reperfusion. In these unpublished experiments we found a downregulation of the receptor 1 day postinfarction in rats exposed to 30 min occlusion of the left anterior descending (LAD) coronary artery and subsequent reperfusion (Figure 2). Surprisingly this was found in the left and right ventricles indicating a hormonal regulation of IGFII/M6P receptor mRNA expression rather than a direct consequence of ischemia and/or reperfusion. Little is known about the regulation of IGFII/M6P receptors in cardiomyocytes but preliminary data on myoblasts may give some indication that angiotensin II upregulates the receptor expression [48]. But it is unclear whether these findings correctly reflect the regulation of IGFII/M6P receptor expression in cardiomyocytes. Since angiotensin II downregulates renin expression and release (see above), it is unclear why the receptor expression should be increased. In conclusion the analysis of IGFII/M6P receptor expression and its regulation requires future attention that has to be properly addressed.

5. IGFII/M6P Receptors in Cardiac Tissue: Specific Role and Comparison to Their Role in Other Tissues

The various physiological functions of the IGFII/M6P receptor can be ascribed to the numerous ligands that bind to this receptor (see above). The receptor is organized in a way that it covers a large extracellular domain with 15 repeated segments allowing binding of different types of ligands (Figure 3). In addition, the structure of this receptor enables it to function in two ways: as a clearance receptor through endocytosis in order to process or degrade proteins and as a signalling receptor that is attributed to G-protein dependent signals [49]. Most of the data so far cover the former role of IGFII/M6P receptors. One well studied ligand is IGFII. Unlike renin, IGFII is not labelled with mannose-6-phosphate and it interacts with the receptor via M6P-independent mechanisms. It binds at repeated segment 11, whereas mannose-6-phosphate labelled ligands bind at repeated segments 3 and 9. After binding to the M6P/IGFII receptor, IGFII becomes internalized, transported to lysosomes, and degraded, whereas the receptor is recycled back to the membrane. In this way the IGFII/M6P receptor regulates the extracellular level of IGFII and thereby controls the availability of IGFII [50]. An important role of this receptor function for cardiomyocytes was already suggested by the work of Kiess et al. [51] who could show in L6 myoblasts that IGFII in the medium of cultured cells is degraded largely by an IGFII/M6P receptor-mediated process. Nevertheless, this finding was never confirmed with cell culture models that represent more directly a fully differentiated type of cardiomyocytes.

Interestingly, cardiomyocytes express high levels of IGFII/M6P receptors, and already during embryonic development, the heart has the highest expression of the receptor of any foetal tissue [45]. Since the high receptor levels in foetal tissues decline in most tissues in late gestation and/or in the early postnatal period [52], the IGFII/M6P receptor seems to have a role in controlling normal foetal growth and development. Investigations with IGFII/M6P receptor knockout mice proved these assumptions. Lack of IGFII/M6P receptor resulted in foetal overgrowth and perinatal lethality of the transgenic progeny [45]. Further examination of the IGFII/M6P receptor knockout embryos yielded a 4-fold higher heart weight in the mutants than in wild type embryos at day 18.5. Perinatal lethality seems to be a result of cardiac abnormalities, including cardiac enlargement (38% mural thickening of the left ventricle), dilatation (89% increase), and septal and valvular defects [46]. Overgrowth of the ventricular myocardium is thereby not associated with cardiomyocytes hypertrophy but with hyperplasia due to an increase in cell number.

Moreover, Lau et al. [45] measured elevated levels of circulating IGFII- and IGF-binding proteins in mice lacking the IGFII/M6P receptor. Downregulation of IGFII/M6P receptor led to a decrease in internalization of IGFII and endocytosis in neonatal cardiomyocytes [53]. These data suggest that increased IGFII stimulates cardiac growth by alternatively

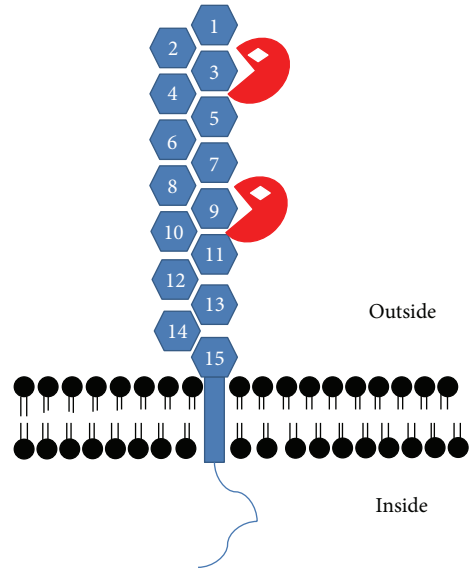

Figure 3: Structure of the IGFII/M6P receptor. The receptor has a cytoplasmic tail that triggers receptor internalization and signalling, a small transmembrane domain, and a large extracellular domain with 15 repeating segments. Mannose-6-phosphate labelled ligands (red symbol with white box for mannose-6-phosphate) bind to repeating segments 3 and 9. Unlike this schematic overview the most likely appearance of this receptor in living cells is that of a dimer.

binding IGFII to the IGFI receptor in such IGFII/M6P receptor knockout models. It remains to be elucidated whether cardiac downregulation of IGFII/M6P receptors as found in the early response to myocardial infarction is sufficient to reduce IGFII degradation and whether the same mechanism participates to the regulation of tissue-specific renin levels.

M6P/IGFII receptor-facilitated endocytosis is not restricted to IGFII. Work on cells distinct from cardiomyocytes suggests that IGFII/M6P receptors may also trigger cardiac growth responses modified by retinoic acid. In mouse macrophages overexpressing the IGFII/M6P receptor binding of retinoid acid induced growth inhibition and reduced spreading of these cells, which could not be seen in mouse macrophages lacking the IGFII/M6P receptor. So, IGFII/M6P receptor functions in mediating the growth-retarding effects of retinoids. Comparable effects of the retinoid acid have been seen in cultured neonatal rat cardiomyocytes [54].

Aside from IGFII and retinoid acid, neonatal cardiomyocytes as well as cardiac fibroblasts are able to bind and internalize recombinant renin and prorenin via M6P/IGFII receptors. Endocytosis of the prorenin/receptor complex results in intracellular activation of prorenin [29]. It was also shown that neonatal cardiomyocytes are capable of binding and activating native human prorenin of renal origin like plasma of probands with renal artery stenosis or plasma of hypertensive patients treated with captopril. However, native prorenin binds to a lesser extent than recombinant prorenin or renin possibly because the presence of growth factors in human body fluids leads to receptor dephosphorylation

resulting in decreased M6P/IGFII receptor internalization [55].

Besides its well documented role as a "clearance receptor," the IGFII/M6P receptor can also function as a signalling receptor. In neonatal cardiomyocytes interaction of the M6P/IGFII receptor with Gαq results in activation of PLCβ and calcineurin and leads to apoptosis [56]. Chen et al. [53] showed that IGFII/M6P receptor downregulation resulted in decreased sensitivity of cardiomyocytes to hypoxia- and TNFα-induced apoptosis. They explained these results with an improper trafficking and activation of cathepsins. It has been shown that these proteases can be bound, transported, and activated by the IGFII/M6P receptor [7]. Cathepsins are also known to induce apoptosis by TNFα in HeLa human epithelial carcinoma cells [57] or by oxidative stress in neonatal cardiomyocytes [58]. In neonatal rat ventricular cardiomyocytes IGFII induces apoptosis when IGFI receptor was downregulated. In this case the authors used IGFI receptor short hairpin RNA to downregulate the receptor [56]. Likewise, selective activation of IGFII/M6P receptor by ^{Leu27}IGFII results in apoptosis by activating the intrinsic apoptosis pathway. M6P/IGFII receptors are known to be involved in the activation of other precursor proteins carrying the M6P recognition site like procathepsin, other aspartyl proteases, or latent TGFβ [7, 59]. Some of them have been shown to trigger apoptosis in cardiomyocytes [60, 61]. In summary these data suggest the participation of IGFII/M6P receptors in proapoptotic events but the available data on cardiac cells are limited to neonatal cardiomyocytes. Any conclusion for the role in cardiac remodelling of the adult heart remains speculative unless a verification of such findings has been performed in adult cardiomyocytes and whole tissue preparations. As a controversial example, data of trophoblast cells with IGFII/M6P receptor stimulation may be taken. In these cells receptor activation resulted in decreased apoptosis possibly due to a different receptor G-protein coupling. In trophoblast cells IGFII-induced migration is mediated by IGFII/M6P receptor coupled to Gαi that leads to an inhibition of adenylate cyclase A [62].

The role of IGFII/M6P receptor activation in the context of cardiac hypertrophy is not fully understood. Specific activation of these receptors leads to cardiac hypertrophy in a G-protein-dependent pathway in H9c2 cardiomyoblast cells. Downstream effectors are PKCα and CaMKII resulting in upregulation of ANP and BNP [63]. Interestingly, our studies with cultured adult ventricular cardiomyocytes showed that renin stimulates the elongation of cardiomyocytes [64]. This effect of renin is clearly dependent on IGFII/M6P receptor activation because elongation of cardiomyocytes could be antagonized by M6P but not by glucose-6-phosphate. It requires an activation of ERK1/2 consistent with findings in HEK cells as well [65]. The renin effect on elongation was antagonized by activation of PPARγ, another hormone that has been introduced as a factor mediating the nonclassical renin effects (see above). These experiments in rats indicate that renin and PPARγ regulate the length of cardiomyocytes. As explained before, PPARγ may be of less relevance in rodents. Therefore mammals other than rodents have to be analyzed additionally to clarify this interaction in the light of clinical relevance of heart failure and remodelling. Nevertheless, renin is the first hormone identified so far to affect cell length rather than cell thickness as has been shown for all other pro-hypertrophic agonists. Of note, the effect of renin on cell shape of cardiomyocytes does not seem to be a cell culture phenomenon as it could be reproduced with cardiomyocytes isolated from transgenic rats (TGR (mRen2) 27). Future studies will have to analyze the interplay between renin and classical pro-hypertrophic agonists, such as angiotensin II, endothelin 1, and catecholamines on cardiac growth. A key question addressed so far is to define cellular mechanisms that may explain elongation of cardiomyocytes. Thereby the effect of increasing cell size by prolongation of contractile subunits (sarcomeres) in series compared to an increase in cell size by cell thickening that means positioning of sarcomeres in parallel on cardiac function needs to be analyzed. This is the cellular counterpart of concentric and eccentric hypertrophy and is not clarified on the cellular level.

In conclusion, all data so far show that IGFII/M6P receptors and their agonist renin are involved in cardiac remodelling. Increased cardiac IGFII/M6P receptor expression, found in patients with end-stage heart failure, underlines the relevance of this receptor system during the development of heart failure [66]. Yet, we still have to define the role of this system in this process in greater detail.

6. Interaction between TGFβ_1 and IGFII/M6P Receptor Stimulation

TGFβ_1 is a cytokine that regulates cardiomyocytes apoptosis [61]. It is upregulated in the transition from compensated hypertrophy to heart failure [67]. TGFβ_1 is embedded into RAAS because its cardiac expression is induced by angiotensin II [68]. TGFβ is synthesized as an inactive precursor molecule that consists of the TGFβ dimer, latency-associated proteins (LAPs), and latent TGFβ binding protein (LTBP) [69]. To obtain mature TGFβ this complex must be further processed. It is important in the light of this review that IGFII/M6P receptors play an important role in activating TGFβ. About two decades ago it has been shown that latent TGFβ (LTGFβ) can bind to IGFII/M6P receptor at M6P recognition sites with either recombinant LTGFβ [70] or LTGFβ isolated from platelets [71]. In face of this review it is essential that the IGFII/M6P receptor is required for the activation of latent TGFβ [59].

The physiological relevance of IGFII/M6P receptor in activation of latent TGFβ has been analyzed in several studies. Using a receptor inhibitor, PXS25, human proximal tubule (HK-2) cells exposed to high glucose released less amounts of active TGFβ. Also, hyperglycemia-induced increase in matrix proteins was inhibited by preincubation with PXS25. As the production of extracellular matrix proteins in this system depends on TGFβ activation these data demonstrate IGFII/M6P receptor's participation [72]. It is likely to assume that similar mechanism also participates in the induction of cardiac fibrosis. The activation of latent TGFβ by IGFII/M6P receptors may be more complicated and possibly requires

the involvement of plasmin. Cell culture experiments showed that migration of bovine aorta endothelial cells can be severely impaired by bovine smooth muscle cells and fibroblasts [55]. Cell-cell contacts induce the activation of latent TGFβ via plasmin since inhibitors of plasmin prevent this migration inhibition. Using antibodies against IGFII/M6P receptor migration of endothelial cells did not occur demonstrating that IGFII/M6P receptor is required for activation of TGFβ [59]. Another pathway for the activation of LTGFβ also involves the fibrinolytic system. IGFII/M6P receptor binds urokinase-type plasminogen activator receptor (uPA-R) and modulates its subcellular distribution [73]. In human monocytes the membrane contains a large complex consisting of IGFII/M6P receptor and uPA-R [74] that can additionally bind LTGFβ and plasminogen. A proposed mechanism is the binding of plasminogen to IGFII/M6P receptor that is converted to active plasmin by uPA-R leading to activation of LTGFβ. In HUVECs (human umbilical-vein endothelial cells) the association of IGFII/M6P receptor and uPA-R is essential for the activation of LTGFβ, release of TGFβ, and apoptosis induction [46]. Inflammation induced the generation of miniplasminogen (a proteolytic fragment of plasminogen) that then binds to IGFII/M6P receptor which associates with uPA-R. This binding results in formation of the active protease miniplasmin and activation of LTGFβ. Interestingly, human umbilical-vein smooth muscle cells cannot activate LTGFβ. This is due to the fact that IGFII/M6P receptor and uPA-R are not colocalized in these cells. Whether similar mechanisms occur in cardiomyocytes and contribute to the tissue-specific formation of active TGFβ remains to be evaluated. In summary, an activation of RAAS induces TGFβ_1 expression and release and the activation of the cytokine requires IGFII/M6P receptor interaction. Once activated, TGFβ induces apoptosis and fibrosis. On the other hand, inhibition of RAAS will decrease TGFβ release and increase plasma renin levels favouring renin-dependent effects of this receptor. Thus, IGFII/M6P receptors are required for renin-dependent and renin-independent effects in cardiac remodelling.

7. Conclusive Remarks

Renin is far more than an aspartyl protease. Via binding to IGFII/M6P receptors it directly participates in the process of cardiac adaptation to cardiac stress such as pressure overload or myocardial infarction. These effects of renin require specific attention as they are intensified under conditions of pharmacological blockade of RAAS. Cardiac renin-dependent effects seem to be part of beneficial effects evoked by RAAS inhibition independent of the reduction of afterload. However, IGFII/M6P receptors are not specific for renin and the interaction between the effects of different ligands of this receptor system remains to be clarified.

Acknowledgments

The authors thank Dr. Lorenz (Alcedis, Germany) for proofreading of this paper. This study was supported by the Deutsche Forschungsgemeinschaft (grant to K.-D.Schlüter).

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Hindawi Publishing Corporation
The Scientific World Journal
Volume 2013, Article ID 364236, 8 pages
http://dx.doi.org/10.1155/2013/364236

Research Article

Extracorporeal Rescue for Early and Late Graft Failure after Cardiac Transplantation: Short Result and Long-Term Followup

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Received 15 May 2013; Accepted 27 August 2013

Academic Editors: X. Ai and Y. Wang

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Objectives. Graft failure after heart transplantation led to poor outcomes. We tried to analyze the outcomes of extracorporeal membrane oxygenation (ECMO) rescue in graft survival after transplantation. *Methods*. A retrospective review of 385 consecutive heart transplants revealed 46 patients of graft failure requiring ECMO rescue (48 episodes). The pretransplant and ECMO-related variables were evaluated. *Results*. The median age was 37.7 ± 18.8 years, and the median support time was 155 ± 145 hours. Success rate was 47.9% (23/48). Pretransplant ECMO use was 25% (12/48) and they had 58.3% mortality. The success rate in "early" graft failures was 51.4% (18/35) and 50% for "late" graft failure. The ischemic time with graft failure (178 ± 70 min) was significantly longer than that without graft failure. Preoperative status and the longer ischemic time may be the major factors for failure. Long-term 5-year survival demonstrated significant survival difference between graft failure and nongraft failure. No survival difference was shown between "early" and "late" graft failure. *Conclusions*. Graft failure still carried high mortality if advanced circulatory support was required. Early graft failure and late graft failure had similar outcomes. Further investigation of the risk factors shows that ECMO does play a role of rescue in catastrophic conditions.

1. Introduction

Graft failure after cardiac transplantation remains a significant source of mortality, especially for the primary graft failure [1, 2]. It is defined as severe dysfunction of cardiac allograft without any anatomic cause. Also, it is characterized by hypotension, high filling pressure, and refractory low output [3]. The graft failure after heart transplantation may present a wide spectrum of clinically apparent allograft dysfunction, including right heart dysfunction without evidence of a high afterload, isolated left ventricular dysfunction, and even biventricular dysfunction [2]. The cause of graft failure may be related to immunological issues, insufficient myocardial protection, pulmonary hypertension, or possible underlying sepsis [1, 3]. Sometimes, it is difficult to clearly differentiate the real etiologies because there might be mixtures of the causes described above. Emergent retransplantation for this status had very poor results [4, 5]. They usually required mechanical circulatory support more than just a intraaortic balloon pump (IABP), but the mortality still remains quite high [1, 2, 5–7].

We have documented that extracorporeal membrane oxygenation (ECMO) could be applied in several situations, including myocarditis [8], postcardiotomy shock [9], and other conditions [10]. We applied ECMO in posttransplant status, either in the early or late stage for their critical condition since 1995; we tried to evaluate the role and result of ECMO in resuscitating this particular patient group.

2. Material and Methods

The present study was approved by the Institutional Review Board of Investigation.

2.1. Patients. Between 1987 (i.e., our institute began the first heart transplantation) and April of 2010, a total of 385 consecutive patients underwent cardiac transplantation. We

retrospectively reviewed our experience of applying ECMO after transplantation and followed these patients until 2012. The patients were either early or late phase and due to primary graft failure or late rejection were leading towards myocardial dysfunction. The present study described and analyzed the result of ECMO application to rescue graft failure after heart transplantation refractory to medical therapy and intraaortic balloon pump (IABP) in the posttransplant period. According to the definition of graft failure after heart transplantation given elsewhere [1, 5], the graft failure after heart transplantation was made by diagnosis with exclusion of possible anatomical factors, treatable pulmonary hypertension, and hypoxemia. We briefly categorized the graft failure after heart transplantation into "early" and "late" graft failure after heart transplantation. The "late" graft failure after heart transplantation was usually considered ECMO application > 60 days after cardiac transplantation. The "early" graft failure after heart transplantation was considered ECMO application within 7 days after transplantation. We also specified the subgroup with "immediate" graft failure after heart transplantation, ECMO support since operation room (OR), which might be usually considered to have poorer outcomes. An ECMO episode was only counted once for the first setup in the same admission. Different times of ECMO support in different admissions were considered to be different episodes.

2.2. Immunosuppressant Protocol. A "triple immunosuppression" regimen basically consisting of cyclosporine A (ciclosporin A), methylpredisolones, and azathioprine was utilized in the immediate post-transplant period. Rabbit antithymocyte globulin immunoinduction therapy was administered during the first 5 days of induction. Cyclosporine started 5 days after transplantation or after recovery of renal function depending on patient's clinical status. For clinical evaluation of cardiac graft rejection, transvenous endomyocardial biopsy was performed three to four times in the first month and then every 3 months in the first year. The dosage of immunosuppressants was adjusted by the results of endomyocardial biopsies. Tacrolimus (FK-506) and mycophenolate mofetil (Cellcept) were used for recurrent rejection or severe adverse reactions to cyclosporine and azathioprine. The immunosuppressant agent would be reduced when infection was highly suspected.

2.3. Management of ECMO. The whole ECMO apparatus, including centrifugal pump and oxygenator (Medtronic Inc. Anaheim, CA) was primed with normal saline alone due to the emergent situation. The protocol and procedure had been described elsewhere [11]. Cannulation was performed with a modified open Seldinger method. The pressure in the superficial femoral artery was measured after cannulation. If the mean pressure was below 50 mmHg, a perfusion catheter (8.5 Fr, Super Arrow-Flex central venous catheter) was inserted distally [12].

The ECMO circuit consisted of a centrifugal pump, a hollow fiber microporous membrane oxygenator, and percutaneous thin-wall cannula (Medtronic Inc., Anaheim, CA), all of which were coated with a heparin-bound Carmeda Bioactive surface. VA ECMO was routinely instituted from the groin area. The 800 mL ECMO priming solution contained 1600 U heparin; the tubing sets in our ECMO circuit were heparin-bound, and expected that the duration of ECMO support. When a small femoral artery was found after exploration of the femoral vessels and the distal leg perfusion was not adequate after arterial cannulation, a small additional tube connected by a Y-adapter was inserted to the distal leg to prevent distal leg ischemia.

In the event of extension of the duration of ECMO support from temporary to prolonged use, low-dose heparin was administered to keep the activated clotting time at 160 to 180 seconds in order to prevent ECMO-related hemolysis or thrombotic complications.

When the ECMO-related hemolysis or plasma leaked from the oxygenator, then the entire circuit was changed.

Hemodilution after the hook-up of ECMO to the patients was corrected by packed red blood cells transfusion. Hematocrit was kept between 30% and 35%. Lower hematocrit compromised oxygen delivery, but higher hematocrit increased complications of clot formation and hemolysis by centrifugal pump.

Continuous monitoring of postoxygenator blood oxygenation saturation provided an indicator for the gas exchange function of the oxygenator. Systemic heparinization was not needed on the first day of ECMO support; there would be higher risk of bleeding immediately after the heart transplantation operation. Whatever happens, heparin infusion would not be used until the bleeding was controlled, which usually took 1 to 2 days. Once bleeding had decreased, we would begin heparin drip and keep the activated clotting time between 160 and 180 seconds. We changed the ECMO apparatus when oxygenator dysfunction, clot formation, or hemolysis were found. Symptoms and signs of low cardiac output were usually resolved after the ECMO support was initiated, and catecholamine infusion could be tapered accordingly. Arterial pulse pressure wave contour, serial echocardiography, and blood oxygenation saturation in the preoxygenator circuit were used to monitor the recovery of cardiac allograft.

From our experience, we were able to achieve initial cardiac recovery signs based on insufficient information about the patients on ECMO for the arterial pulse contour.

If hemodynamics could be well maintained by reduced ECMO blood flow at 0.5 L/min for 1 hour, perhaps ECMO should also be removed at bedside. Anyhow, the wound was primarily repaired.

2.4. Data Collection and Analysis. We treated each ECMO course for each episode. Each ECMO course was defined from setup to hospital discharge or death in hospital. We counted for the "failure" or "success" for each ECMO episode. "Failure" was defined as failed in surviving hospital discharge; even they might be weaned ECMO successfully and die in hospital because of complications. "Success" was defined as successful weaning ECMO and surviving to hospital discharge. Donor-, surgery-, and ECMO-related variables were evaluated for association among "failure" and "success."

Continuous variables were expressed as mean ± standard deviation, and means were compared by independent sample Student's t-test. Nominal variables were expressed as percentages and analyzed by the χ^2 test. Statistical significance was assumed at a P value of less than 0.05. The Kaplan-Meier survival curve was performed according to their long-term follow-up data.

3. Results

There were a total of 46 patients (37 males, 11 females) with 48 episodes of ECMO applications for graft failure after heart transplantation who were recruited in the present retrospective study. The mean age was in the range 37.7 ± 18.8 years. In the same period, there were 387 consecutive patients that underwent cardiac transplantation in our institution. There were 12 episodes requiring pretransplantation ECMO support (25%), and "early" graft failure after heart transplantation were 35 episodes (72.9%), in which 30 episodes were "immediate" graft failure after heart transplantation (62.5% in whole group, 85.7% in "early" graft failure after heart transplantation). Five episodes of ECMO setup occurred in intensive care unit within 7 days after transplantation. ECMO was set up in the rest of 13 episodes > 7 days after transplantation, and 10 of them were categorized as "late" graft failure after heart transplantation (>60 days after transplantation).

One male patient received 3 times of ECMO support after transplantation. He was a case of congenital corrected transposition of great arteries and received conventional repair when he was 2 years old. He developed systemic ventricular failure 9 years after repair. He also received emergent ECMO support under resuscitation due to the deteriorated congestive heart failure and sudden cardiac arrest. He received a heart transplantation after 68-hour support. graft failure after heart transplantation developed, and the ECMO was supported for additional 26 hours with successful decannulation and discharge from hospital. However, acute graft dysfunction happened 2 years after discharge. Therefore, he had to received another installation of ECMO for 132-hour support because of rejection leading to unstable hemodynamic conditions. He was discharged again uneventfully. Unfortunately, progressive graft dysfunction persisted due to vasculopathy leading to collapse at the fourth year after transplantation. He received ECMO for the third time and was listed for retransplantation due to a collapse. He underwent re-transplantation and early graft failure after heart transplantation occurred. ECMO was extended for an additional 173 hours with successful wean-off, but he still expired 63 days after the retransplantation due to multiple organ failure and sepsis.

The overall success rate of graft failure after heart transplantation was 47.9% (23 episodes surviving to discharge in 48 episodes). The success rate was 51.4% (18/35) in "early" graft failure after heart transplantation and 50% (5/10) in "late" graft failure after heart transplantation. The subgroup of "immediate" ECMO had 50% success rate as well (Table 1). Five episodes developed in intensive unit after transplantation within 7 days, and 4 episodes (80% success rate) were successfully survived to discharge. But the success rate was low (0/3, $n = 3$) in ECMO support between 7 and 60 days after transplantation. The data of the present study, "early," "immediate," and "late" graft failure after heart transplantation were demonstrated in Table 1.

The ECMO duration was 155 ± 145 hours, and IABP were applied in 31.3% of the study group. The ischemic time (Figure 1(a)) and donor age (Figure 1(b)) of graft failure after heart transplantation was 178.3 ± 70.4 min (median 169) and 31.8 ± 14.1 years (median age was 33). We compared the data with nongraft failure after heart transplantation group ($n = 339$), and it revealed significant difference in donor ischemic time (Figure 1(a)).

The 5-year survival curve was around 45% survival in 5-years (Figure 2(a)). The comparison with the survival curve of our center showed a significant difference during 5 year survival (Figure 2(b), black dash line, Log rank $P < 0.01$).

The 5-year survival curve between "immediate" graft failure after heart transplantation and "nonimmediate" graft failure after heart transplantation was demonstrated in Figure 3(a). The "early" graft failure after heart transplantation (ECMO < 7 days) also did not show a poorer survival than those with ECMO > 7 days after transplantation (Figure 3(b)).

The survival curve comparison between "late" graft failure after heart transplantation (ECMO at >60 days after transplantation) and those ECMO < 60 days also did not show any statistical difference (Figure 3(c)). The "late" graft failure after heart transplantation might be a different group of graft failure from the "early" graft failure after heart transplantation, which was mainly due to acute humeral rejection, vasculopathy, or sepsis.

We also examined the risk factors between the success and failure episodes. The only significant difference between the two episodes was the ECMO duration (91.9 ± 48.7 hr versus 202.8 ± 162.1 hr, $P < 0.01$, Figure 4(a)), which seemed reasonable since the failure episode tended to have longer support before expiration. The donor ischemic time did not show any difference between episodes (168 ± 72 min versus 185 ± 71 min, $P = 0.39$, Figure 4(b)).

4. Discussion

graft failure after heart transplantation requiring circulatory support is associated with significant mortality, not only in early graft failure after heart transplantation but also in late graft failure after heart transplantation. ECMO could work as a good rescue tool for these risky patients. The result was acceptable, Furthermore, it is improving than the previous literature [1, 5, 13]. It could be applied in the early stage after transplantation. It also acts as a rescue for those with acute rejection or acute developed sepsis. It offers enough safe evaluation periods for accurate diagnosis and proper treatment.

We previously, thought the "immediate" graft failure after heart transplantation might result in poor long-term outcome compared to that of "nonimmediate" graft failure after heart

Table 1: The basic data of the study and the "early" and the "late" graft failures after transplantation (graft failure after heart transplantation).

	Study group	Early	Immediate	Late
Episode, *n*	48	35	30	10
Age, yr (median)	37.7 ± 18.8 (43.3)	36.1 ± 18.6 (42.8)	34.7 ± 18 (35.4)	37.2 ± 20.3 (43.4)
Etiology				
DCMP, *n* (%)	21 (43.8)	15 (42.9)	13 (43.3)	5 (50)
ICMP, *n* (%)	17 (35.4)	14 (40)	11 (36.7)	2 (20)
Other, *n* (%)	10 (20.8)	6 (17.1)	6 (20)	3 (30)
Previous heart surgery	15 (31.3)	14 (40)	10 (33.3)	1 (10)
Pre-Tx ECMO	12 (25%)	12 (34.3)	11 (26.7)	0 (0)*
CPR before ECMO	20 (41.7)	15 (42.9)	12 (40)	4 (40)
ECMO during CPR	10 (20.8)	8 (22.9)	7 (23.3)	1 (10)
IABP use	15 (31.3)	13 (37.1)	12 (40)	2 (20)
Ischemic time, min (median)	178 ± 70 (169)	184 ± 7 (174)	181 ± 73 (171)	189 ± 71 (214)
>120 min, *n* (%)	35 (72.9)	25 (71.4)	21 (70)	7 (70)
>180 min, *n* (%)	23 (47.9)	17 (38.6)	14 (46.7)	6 (60)
>240 min, *n* (%)	11 (22.9)	8 (22.8)	7 (23.3)	3 (30)
ECMO duration, hr (median)	155 ± 145 (103)	148 ± 149 (103)	157 ± 159 (107)	186 ± 147 (143)
Success rate	23 (47.9)	18 (51.4)	15 (50)	5 (50)

*Significant difference for late group with other groups. CPR: cardiopulmonary resuscitation; DCMP: dilated cardiomyopathy; ECMO: extracorporeal membrane oxygenation; ICMP: ischemic cardiomyopathy; IABP: intraaortic balloon pump; Tx: transplantation; yr: year.

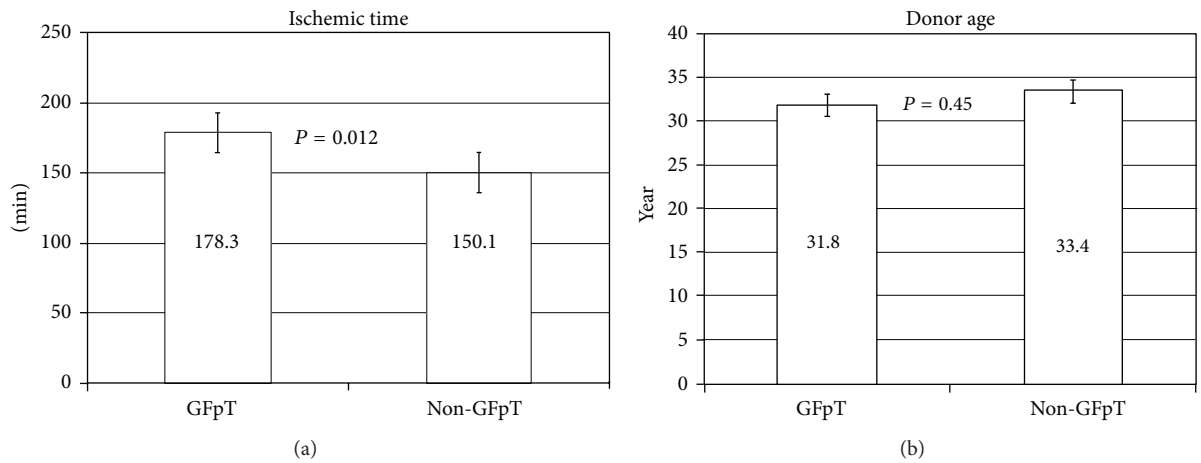

Figure 1: (a) Comparison of ischemic time between graft failure after heart transplantation (graft failure after transplantation) and nongraft failure after heart transplantation ($P = 0.0012$). Ischemic time in graft failure after heart transplantation was 178.3 ± 70.4 min (median 169 min); 47.9% of them were over 180 min. Ischemic time in nongraft failure after heart transplantation was 150.1 ± 64.9 min (median 132 min); (40 to 330 min), 32.9% of them were over 180 min. (b) Comparison of donor age and ischemic time between graft failure after heart transplantation versus nongraft failure after heart transplantation. Age: graft failure after heart transplantation 31.8 ± 14.1 yr (median 33), nongraft failure after heart transplantation 33.4 ± 12.8 yr (median 32), $P > 0.05$.

transplantation because the special subgroup was considered to have high mortality even when mechanical support was applied [2, 5, 13]. According to data of Table 1, "early" graft failure after heart transplantation might be considered to have longer ischemic time, poor myocardial preservation or poor recipient conditions since they had higher incidence of extracorporeal resuscitation (ECPR). But the result seemed to be unsupportive than what we had previously thought before. Our result may suggest that ECMO could work as a rescue tool for acute deterioration no matter what the cause is, and it offers a 50% survival rate.

As stated by the International Society of Heart and Lung Transplantation (ISHLT) report, early graft failure is a major cause of death in the perioperative period after transplantation [14]. Its incidence varied from 4 to 24% depending on what the definition was [2, 5, 15, 16]. It might define

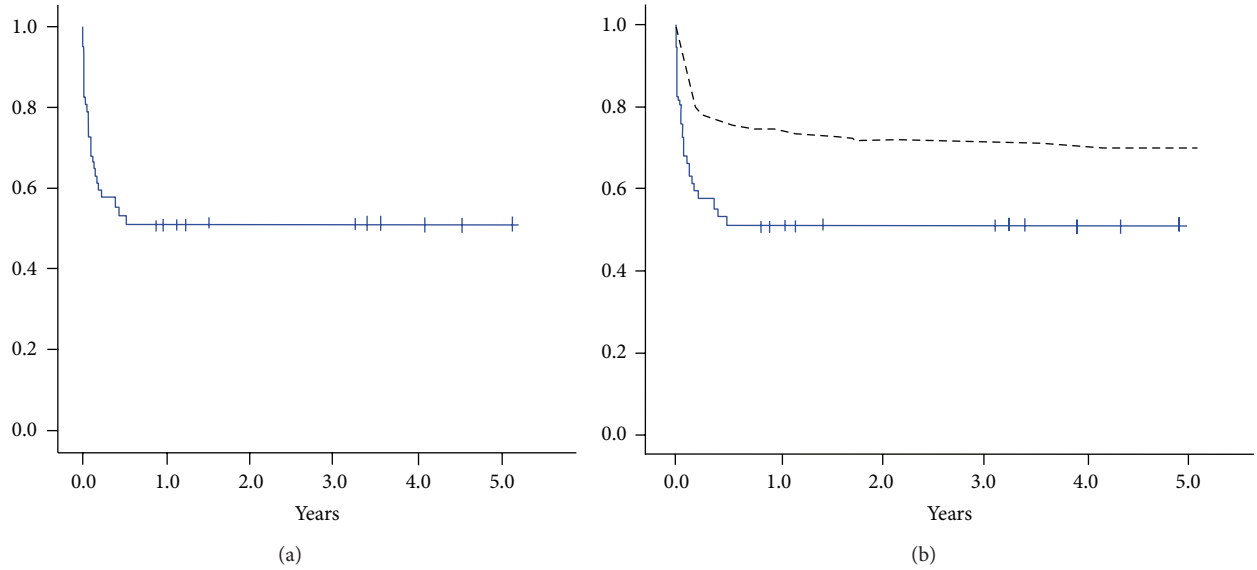

Figure 2: (a) The five-year survival curve of the study group (graft failure after heart transplantation). (b) Comparison of the nongraft failure after heart transplantation and Graft failure after heart transplantation survival curve. Blue: graft failure after heart transplantation, black dash line: nongraft failure after heart transplantation survival curve of our center.

the need for mechanical support or requiring high-dose inotropic support. We only recruited and defined the patients with the most severe status who were supported by ECMO, and it tended to have poorer results than ever. The incidence of "immediate" graft failure after heart transplantation was 7.8%, and the "early" graft failure after heart transplantation was 9.1%. In spite of the critical conditions, our result was comparable to the data from D'Alessandro et al., France [16]. We had almost a 50% success rate, in which the outcome was much better than that supported with ventricular assist device or re-transplantation [4, 5]. We agree with the concept that ECMO should be considered as the treatment of choice for graft failure after heart transplantation [17]. For our study, we extended the ECMO application in "early" graft failure after heart transplantation to also include "late" episodes.

We tried to figure out any risk factors for failure but failed to demonstrate any specific factor related to failure except the ECMO duration. The donor ischemic time and pretransplant ECMO application were not significantly different between successful and unsuccessful graft failure after heart transplantation. Even for CPR, we could not identify it as a risk factor. It might be due to the limited case number or the efficient resuscitation and ECMO initiation in our center [10].

We identified a specific subgroup within the study with extremely high mortality (100%), graft failure after heart transplantation patients receiving ECMO between 7 and 60 days. We thought it might be related to the heterogenic cause, mixture of rejection, and sepsis in the period or was a statistical issue only. The conclusion remains as further investigation and data collection in the future.

The causes of graft failures after heart transplantation sometimes were difficult to determine. The major cause for "late" graft failure after heart transplantation group was considered to be acute rejection, chronic vasculopathy with deterioration, and septic episodes for the "late" graft failure after heart transplantation group. However, it was difficult to differentiate these causes. The uncertain diagnosed causes in "early" graft failure after heart transplantation group were quite common [11, 16, 18]. It might be considered as primary graft failure, right heart failure, acute rejection, sepsis, pulmonary hypertension episodes, or unknown causes. Since it was difficult in differentiate the reasons clearly, we hesitated to list the suspicious causes in the study to confuse the result analysis because the causes of deterioration might come from consensus without strong evidence. We only focused on facts in patients' status without speculating on the causes.

The long-term result in graft failure after heart transplantation was inferior to those without graft failure after heart transplantation, which was reconfirmed when the data was published elsewhere [14]. graft failure after heart transplantation indicated some immunological or perseveration injury during the episodes, and it was reasonable to expect the result. We initially expected that the "early" graft failure after heart transplantation might have the poorer outcome than the "late" graft failure after heart transplantation, but the results showed these two groups were comparable. We also speculated that the "late" graft failure after heart transplantation which needed ECMO support was associated with rejection, which was also related to vasculopathy. Therefore, these groups of patients might be relisted for transplantation earlier before the collapse. Besides, from our previous experience [11], we set up ECMO more aggressively and earlier (72.3% of study group). All these reasons might lead to the similar outcomes between the two groups.

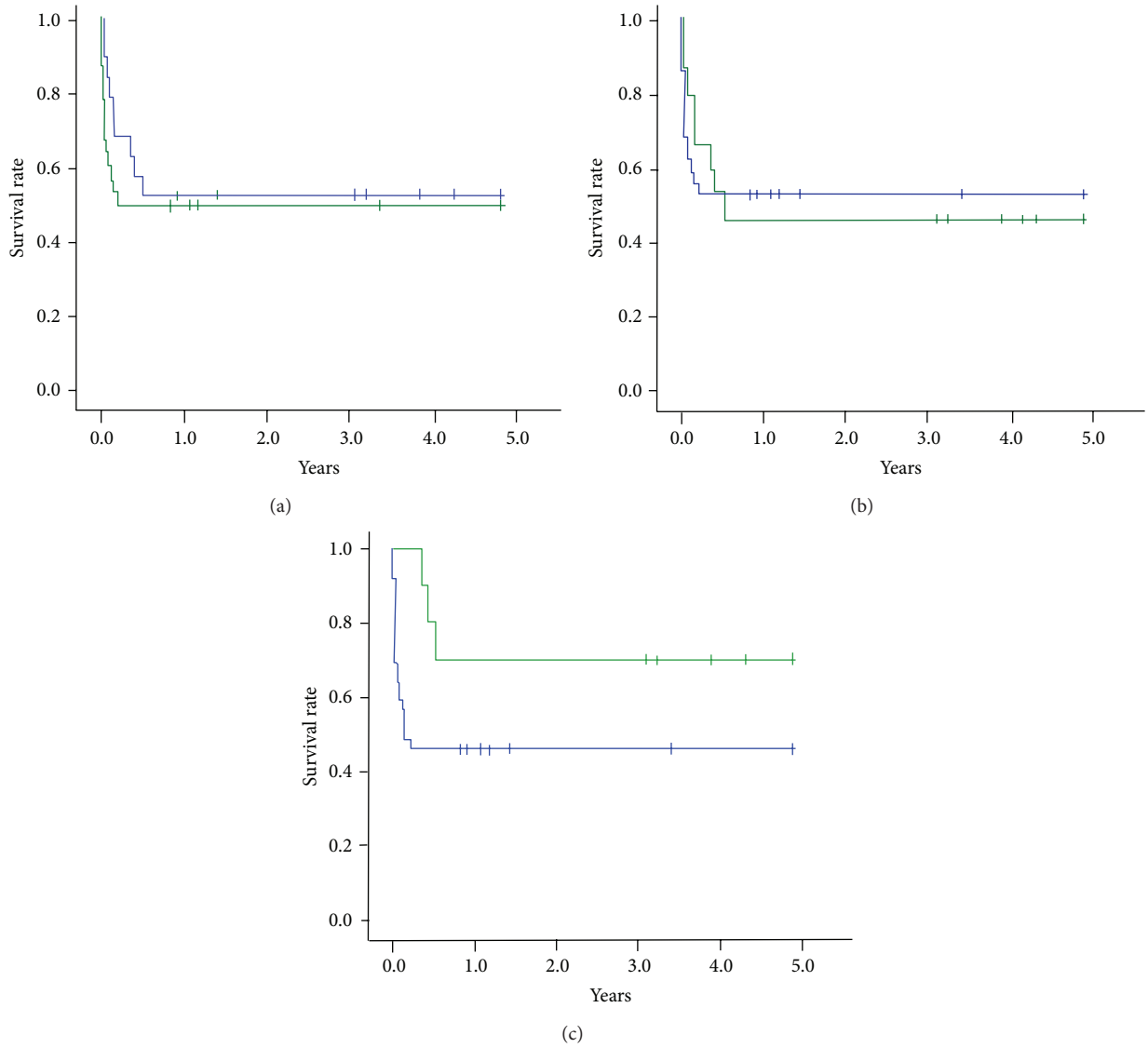

FIGURE 3: (a) The 5-year survival curve between immediate (green) versus nonimmediate (blue) graft failure after heart transplantation, log rank $P = 0.548$. (b) The 5-year survival curve between ECMO < 7 days (blue) versus ECMO > 7 days (green), Log rank $P = 0.971$. (c) 5-year survival curve between ECMO at <60 days (blue) versus ECMO at >60 days (green), log rank $P = 0.103$.

5. Limitations

There were some limitations for our present study. First, this is a retrospective study and it ranges for more than 20 years. The improvements in concept and technique might change greatly during this time period. It would definitely change the outcome, and the patients' condition might be more critical now than before. Second, the patient number is not enough for performing a statistic analysis. This is the reason that we only have a risk factor for "success" and "failure" analysis. Third, we hesitated to implant a ventricular assist device (VAD) for patients transplanted, because they had a priority in transplant wait list. It would cause a social and economic conflict. Therefore, we do not have the graft failure after heart transplantation supported with ECMO comparison.

6. Conclusions

Graft failure after heart transplantation requiring mechanical support is still a challenging situation. ECMO can provide 50% survival in the devastating conditions. Early graft failure after heart transplantation and late graft failure after heart transplantation had similar outcomes. Further investigation on the risk factors analysis is required to prevent the graft failure after heart transplantation and improve the outcome.

Disclosure

The paper was presented and read during 24th EACTS Annual Meeting, 11th–15th September 2010, Geneva, Switzerland.

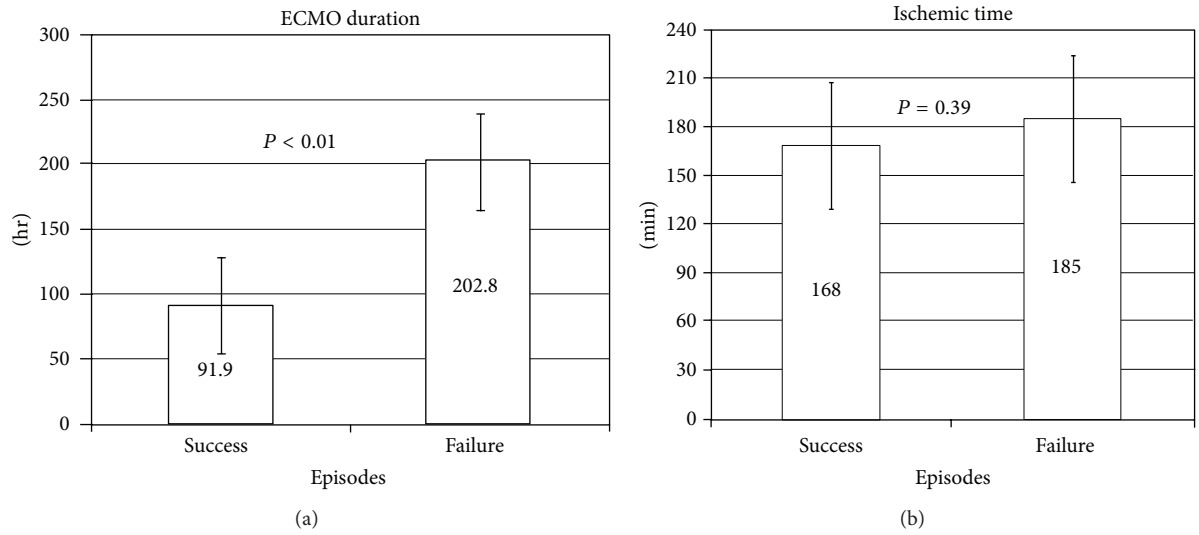

Figure 4: (a) Comparison of ECMO duration between success and failure episodes. ECMO duration is a significant risk factor for failure episodes. (b) Comparison of donor ischemic time between success and failure episodes. The donor ischemic time was not a risk factor for failure episodes.

Acknowledgments

The present study was partly supported by NTUH98P17, NTUH99P17, 98-2314-B-002-036-MY1-2, 97-2314-B-002-046-MY1-3, 100-2314-B-002-018-MY2, 102-2315-B-002-009-, NSC, Taiwan, and was supported in part by the Department of Medical Research of NTUH.

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Hindawi Publishing Corporation
The Scientific World Journal
Volume 2013, Article ID 784670, 10 pages
http://dx.doi.org/10.1155/2013/784670

Review Article

The Role of Natriuretic Peptides for the Diagnosis of Left Ventricular Dysfunction

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Received 17 June 2013; Accepted 20 August 2013

Academic Editors: X. Ai, Y. Wang, and Y. Yang

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Natriuretic peptides (NPs) are entered in current guidelines for heart failure (HF) diagnosis and management because of their high specificity and sensibility in screening patients with acute dyspnea. Due to their availability and relatively low cost, they became the first step examinations in HF patients evaluation at hospital admission together with clinical and chest radiography examination. NPs are released following any cardiac haemodynamic stress due to volume or pressure overload and should be considered as a mirror of cardiac condition helping in recognizing patients with poor outcome. Moreover, the exact role of NPs in early HF stages, in isolated diastolic dysfunction, and in general population is questioned. Several promising reports described their potential role; however, the wide cut-off definition, inclusion criteria, and intrinsic measurement biases do not actually consent to their clinical application in these settings. A multimodality strategy including both NPs and imaging studies appears to be the best strategy to define the cardiac dysfunction etiology and its severity as well as to identify patients with higher risk. In this review, we describe the current and potential role of NPs in patients with asymptomatic cardiac insufficiency, evaluating the requirement to obtain a better standardization for imaging as for laboratory criteria.

1. Introduction

Research regarding the role of serum biomarkers in patients with cardiovascular diseases has grown exponentially over the last ten years. In particular, multiple novel biomarkers have been developed for heart failure (HF), due in part to a well-established pathophysiology, including cardiac dysfunction, neurohormonal activation, and hydrosaline retention [1–3]. At the same time, the diversity of HF biomarker development reflects the heterogeneity of patients, with multiple etiologies, phenotypes, and comorbidities. In general, four categories of HF biomarkers have been developed, and these biomarkers should reflect the pathophysiology and heterogeneity of HF. The 4 categories are biomarkers (1) of cardiac injury, (2) adrenergic overdrive, (3) inflammation, (4) oxidative stress, and (5) systemic organ damage [4].

Although the classification of biomarkers helps differentiate each type, this also highlights a potential shortcoming of biomarker development: the fact that they are often studied in isolation, though this trend is recently changing. The ideal laboratory tool fulfills the three criteria outlined by Morrow and de Lemos. Traditionally, three different groups of biomarkers have been identified: (1) laboratory tests, such as natriuretic peptides (NPs) and troponins are defined as "laboratory or molecular biomarkers," (2) those related to signal, imaging, and functional tests are defined as "functional biomarkers," and (3) those related to genetic polymorphisms and other genomic tests are defined as "genetic biomarkers." In this sense, an integrate approach appears mandatory to establish early diagnosis and to optimize the outcome. Moreover, a cardiovascular biomarker can be classified in multiple categories according to its pathophysiological characteristics and/or clinical use. Although this classification is arbitrary, since each index can contain several of these characteristics, it is useful for interpreting the value of an individual clinical biomarker.

Regarding laboratory biomarkers, Morrow and de Lemos outlined the three major criteria of a clinically useful biomarker: (1) accurate, reproducible measurements must be rapidly available to the clinician at a reasonable cost; (2)

the biomarker must provide additional information beyond careful clinical assessment; (3) knowledge of the measured level should aid in medical decision making [5]. In clinical practice, it is hard to find a specific biomarker that contains all these characteristics. For example, significant troponin increase in patients with chest pain and any specific ST wave alterations address physician towards an ischemic etiology; similar model should be applied in patients with dyspnea in the absence of specific chest radiography or ECG signs whereby an increase in NPs levels leads to HF diagnosis [4, 6].

In the last decade, an "explosion" of data regarding the use of biomarkers in cardiovascular diseases is evident in the literature. This has happened for several reasons: to facilitate diagnosis, improve prognosis both early and late in the course of the disease, and guide management. However, each biomarker has various strengths and weaknesses: some requirements are linked to chemical detection (reproducibility and accuracy, in vivo and in vitro stability, low cost, sensitivity and availability, and international standardization reference tested for gender and age), while others need to respond to clinical requirements (good diagnostic and prognostic accuracy, useful in therapy monitoring, and reasonable cost-effectiveness ratio) [5, 7].

Laboratory tests are able to identify serial mechanisms potentially involved in the genesis of HF; however, it appears hard to find a single specific biomarker including diagnostic, prognostic, and clinical information all together at the same time. In this context, it appears difficult to identify through laboratory tests the early mechanisms that cause myocardial damage, in order to recognize those subjects at risk to develop the HF syndrome. Frequently, a single biomarker demonstrates exciting results in preliminary studies that cannot be confirmed later in prospective multicenter studies [6].

Early diagnosis of HF depends on the availability of specific, accurate, and effective markers of the disease. For this reason, a multimarker strategy including new and old biomarkers together with traditional diagnostic tools has been recently proposed.

Recently, Braunwald classified biomarkers on the basis of each pathophysiologic process that is involved in HF [7]. This classification is now universally accepted: inflammation, neurohormones, myocyte Injury, Oxidative Stress, and extracellular matrix remodelling biomarkers (Table 1).

In the HF setting, patients present with various clinical presentations and in distinct stages of progression; therefore, an ideal biomarker should be able to recognize not only disease severity but also the underlying causal mechanisms and the risk profile [8]. Moreover, application in clinical practice requires validation of each biomarker in multiple studies with a unique cutoff, given the categorical nature of the physician decision making. Ideally, this would include studies yielding diagnostic, prognostic, and therapeutic values further validated in the "real-world" setting for example, the evidence that triage guided by biomarkers improves the quality of treatment and shortens the diagnostic process. Probably an ideal biomarker that is able to include all this information is far from being conceived. Perhaps a multimarker strategy as applied in the acute coronary syndrome could be useful to better understand the etiology of HF and its severity and to assess early as well as long term risks. In this context, significant troponin increase associated with a high level of NPs is able to identify patients with myocardial infarction and the poor outcome for HF development [9, 10].

2. Haemodynamic and Nonhaemodynamic Determinants in Acute Heart Failure

Multiple pathophysiologic factors contribute to the development of HF and cardiac impairment. For simplicity, three principal disorders predominate: pump dysfunction, neurohormonal activation, and salt-water retention. However, the clinical presentation resulting from these underlying disorders varies greatly, in part determined by hemodynamic status, primary cardiac disorder, systemic pressure, and organ perfusion/damage [11, 12]. A recent report has divided the acute decompensated HF syndromes on the basis of primary cardiac dysfunction, coronary artery disease presence, and clinical presentation [1, 10]. Further subclassification by type of cardiac dysfunction has been proposed: most patients with HF have both systolic and diastolic left ventricular (LV) dysfunction, but in some cases the syndrome can occur with isolated systolic or diastolic dysfunction. HF with preserved left ventricular ejection fraction (HFpEF) is characterized by a nondilated, usually hypertrophied, left ventricle in which left ventricular ejection fraction (LVEF) is preserved at rest, and the parameters of LV relaxation and filling are markedly deranged. Patients with HFpEF are a heterogeneous and understudied group that includes subjects with both hypertensive heart disease and hypertrophic cardiomyopathy [11].

However, systolic HF is itself a heterogeneous condition with several mechanisms acting as potential contributors: preload, afterload, cardiac contractility and filling, peripheral vascular resistance, and heart rate variability are all important determinants of cardiac performance. The presence of viable myocardium, extension of necrosis, and severity of coronary disease are further determinants of LV function. One of the determinants is the diastolic function that is intimately related to cardiac afterload, and this load dependence is amplified in HF [12]. Acute increases in afterload lead to prolongation of isovolumic relaxation. Loading increases in systolic pressure have further impairing effects on the diastole. This increased passive stiffness, together with abnormal relaxation, will shift the diastolic pressure-volume relation curve upward and to the left, with retrograde elevation of LV end-diastolic, left atrial, and pulmonary pressures. Reduced myocardial release, augmented myocardial mass and stiffness, and delayed inactivation are all elements that contribute significantly to an increase in LV filling pressure and wall tension [13]. Beyond the hemodynamic factors, there are at least two principal actors playing an equally influential role in HF establishment and maintenance: neurohormonal activation and hydrosaline retention. Both mechanisms cause peripheral vasoconstriction that results in an increased LV afterload, the activation of inflammatory pathways, the increase of growth factors and endothelial dysfunction, and

Table 1: Classification of biomarkers for early cardiac damage identification.

Markers of neurohormonal activation	(i) Natriuretic peptides (ANP, BNP, CNP, and related peptides) (ii) Markers of renin angiotensin aldosterone system activity (iii) Arginine vasopressin
Markers of cardiac injury	(i) Cardiac troponins (cTnI, cTnT) (ii) Heart-type fatty-acid protein (iii) Myosin light-chain kinase I
Markers of inflammation and matrix remodelling	(i) Matrix metalloproteinases (MMPs) and MMPs tissue inhibitors (ii) C-reactive protein (iii) Cytokines and related receptors (interleukins IL-1, IL-2, IL-6, IL-8, and IL-18, TNF-α, osteoprotegerin, and Fas ligand)
Markers of systemic organ damage	(i) Renal injury: creatinine, BUN, NGAL, and cystatin C (ii) Hepatic injury: transaminases and gamma-glutamyl transferase
Aspecific laboratories indexes	(i) Anemic status and erythropoietin endogenous levels (ii) Low albumin levels (iii) Hyponatremia (iv) Carbohydrate antigen 125

B-type natriuretic peptide (BNP), atrial natriuretic peptide (ANP), C-type natriuretic peptide, tumor necrosis factor-α (TNF-α), blood urea nitrogen, neutrophil gelatinase-associated lipocalin (NGAL).

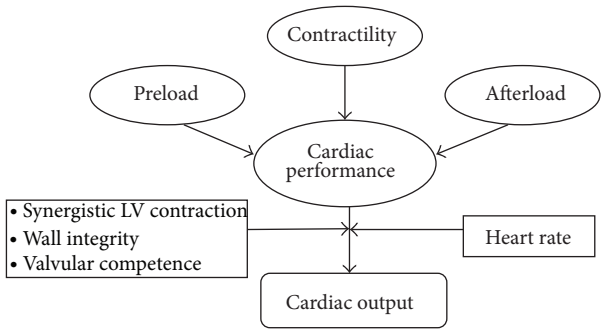

Figure 1: Haemodynamic and intrinsic cardiac factors influencing filling pressure and cardiac performance.

the induction of oxidative stress. The increased fluid overload results in elevated intracardiac pressure as well as pulmonary congestion [14]. It would be difficult to obtain all this information by a single biomarker; therefore, a multimarker strategy including clinical laboratory and imaging parameters is currently the most appropriate strategy. Among all the potential biomarkers, the ones that probably contain the most clinical hemodynamic and systemic information are NPs. Such dowries are due to its secretion mechanism: NPs are increased as a consequence of augmented cardiac pressure, volume overload and wall tension. NPs levels are also mediated by means of the renin-angiotensin system and neuroendocrine overdrive; therefore, for specific counter regulatory mechanisms, levels are augmented during idrosaline status retention. For all these reasons, NPs are able to provide some additive and complementary information with respect to the traditional tools in the HF setting [15] (Figure 1).

3. The Current and Potential Role of NP in Heart Failure

The discovery of NPs as diagnostic biomarkers has been one of the most important advances in the diagnosis of heart failure. Prior to NPs, several studies suggested the need to improve diagnosis, especially with the increasing prevalence of heart failure in the United States [26]. However, diagnosis may be delayed, due to the aspecificity of symptoms and the previous lack of a rapid, easily accessible, bedside gold standard protocol to facilitate diagnosis.

3.1. NP in Emergency Setting. The utility of NPs was initially demonstrated in emergency department (ED) patients presenting with acute dyspnea. B-type natriuretic peptide (BNP) levels were a more accurate predictor of HF diagnosis than history, physical exam and routine laboratory tests [16]. The Breathing Not Properly trial showed that a BNP level $\leq$ 100 pg/mL yielded 90% sensitivity and 76% specificity in separating cardiac from noncardiac etiologies of dyspnea [17]. N-terminal pro-B-type natriuretic peptide (NT-proBNP) has also been studied in the ED, during hospitalization and even in the outpatient setting, to facilitate diagnosis, ascertain severity of disease, confirming its utility as an excellent biomarker for risk stratification as well as subsequent resource utilization [27]. The NP literature is now extensive and confirms results from previous meta-analysis demonstrating NP's role in diagnosing cardiogenic dyspnea and reducing admission rates [28]. Elevated NPs levels also directly correlate to the respective functional NYHA class, intraventricular pressure, and pulmonary pressure and inversely to cardiac output [18].

3.2. NP in Risk Stratification. NPs measurements appear to be a useful tool for risk stratification; in fact, high levels are associated with recurrent hospitalization and risk of sudden death. Several studies that used natriuretic peptides in predischarge indicate that BNP levels appear to be the strongest predictor for identifying subsequent death or hospital admission within 6 months [25, 29]. In the Australia-New Zealand Heart Failure Group Trial in patients with

chronic HF and reduced systolic function, levels of NT-proBNP above the median were associated with an increased risk for new decompensate HF events and all-cause mortality during the 18-month followup [19]. The largest study is the Valsartan Heart Failure (Val-HeFT) trial in patients with chronic HF who received the recommended medical therapy: an increment of 500 ng/L above the baseline concentration of NT-proBNP carried an increased adjusted risk of 3.8% for mortality and 3.0% for hospitalization for HF. On a multivariate analysis, once again NT-proBNP was ranked as the first prognostic factor in these patients, proving to be independent of and more powerful than traditional risk factors, such as NYHA class, age, left ventricular dilation, or renal dysfunction [30].

3.3. NP and Cardiac Performance. NP measurements are also related to several indexes of systolic and diastolic functions. Traditionally, its samples are linearly increased in relation to the degree of systolic dysfunction and cardiac enlargement [20, 31]. Invasive measurements are the reference standard for establishing pulmonary pressure and filling pressure elevation in all subjects with dyspnea, but noninvasive methods of estimating LV filling pressure and pulmonary pressure are entering the current practice. Recently, it has been demonstrated that BNP in systolic HF is progressively increased in relation to the degree of diastolic dysfunction, the severity of mitral valve regurgitation, and right ventricular dysfunction [32]. NPs also reflect elevated LV filling pressure and pulmonary capillary wedge pressure measured invasively with good accuracy and specificity. On the contrary, sensitivity is often modest particularly in patients with preserved systolic function and normal LV volumes [21, 33]. The best correlation between BNP and invasive measurement has been demonstrated with end diastolic wall stress and end diastolic pressure. This suggests that diastolic stretch is one of the major determinants of NP induction [34]. Finally, in a more recent study that compared BNP levels with venous pressure, capillary wedge pressure, and diastolic filling pattern, evaluated by echo, authors showed that as BNP cutoff >400 pg/mL is able to identify patients with higher wedge pressure, it correlates well with all hemodynamic parameters [35].

Some reports have also demonstrated a positive correlation between NP and several markers of LV filling measured traditionally by transmitral Doppler and more recently by tissue Doppler as well as E/E^1 ratio. However, NP measurements are not able to differentiate between systolic and diastolic dysfunctions [22]. A combined approach with echo Doppler parameters and BNP data seems to be able to stratify patients with systolic dysfunction better. Therefore, tissue Doppler analysis demonstrated that BNP in the gray zone between 8 and 15 is able to differentiate patients with increased filling pressure providing a better stratification. The integrative approach could also improve the diagnostic accuracy in patients with systolic dysfunction and abashed echo diastolic parameters [36]. NP showed a significant elevation together with other parameters of the right ventricular function, increasing with greater dilatation and impairment, as with right and ventricular longitudinal dysfunction. Right ventricular systolic dysfunction is an independent prognostic factor in patients with moderate to severe HF, and it is strictly related to reduced effort tolerance and exercise capacity. In patients with right ventricular pressure overload, NP levels correlated with mean pulmonary artery pressure, right atrial pressure, RV end-diastolic pressure, and total pulmonary resistance [21]. The previously cited measurements have important prognostic power, and the combination of laboratory and imaging data provide a more precise risk prediction for rehospitalization and mortality in patients with HF.

3.4. NP for Therapy Monitoring. Many studies have demonstrated that there is a reduction in NP after the administration of loop diuretics and other drugs during the acute HF phases. This is due to reduced filling pressure and wall stiffness into LV as well as a decrease in idro-saline retention and in neurohormonal overdrive. In a chronic outpatients group STARS-BNP trial, it was clearly shown that a BNP-guided strategy reduces the incidence of death and rehospitalization for HF [23]. More definitive data were reported by Cohen-Solal in acute HF: patients with BNP reduction over 30% after therapy showed a significant reduction in mortality and rehospitalization compared with nonresponders [24]. These results suggest that the variations in BNP concentrations after therapy for acute HF are independent and objective predictors of therapy's adequacy.

For all the previously cited reasons, NP measurement entered in the last HF guidelines providing additive diagnostic and prognostic information with respect to the previous approach (Table 2).

Such dowries are due to its secretion mechanism: NP, are increased as a consequence of augmented cardiac pressure, volume overload, and wall tension. NP levels are also mediated by means of the renin-angiotensin system and neuroendocrine overdrive; therefore, for specific counterregulatory mechanisms, levels are augmented during idro-saline status retention. Even if NP cannot be considered as "araba fenice," they should be regarded as the best candidates to provide some additive and complementary information with respect to the traditional tools in the HF setting.

4. Natriuretic Peptides and Diastolic Dysfunction

HFpEF accounts for around 50% of patients with acute decompensated HF. The diagnosis, at times, may be difficult. Three major conditions need to be recognized: (1) signs and symptom of heart failure, (2) preserved systolic function (EF ≥50 %), and (3) left ventricular diastolic dysfunction (increased myocardial stiffness, elevated filling pressures, and abnormal diastolic relaxation) [37]. In clinical practice, differentiating HFpEF from heart failure with reduced ejection fraction (HFrEF) is often difficult on the basis of history, physical examination, chest X-ray, and ECG alone. Assessment of these patients demonstrates a left and upward shift in their end-diastolic pressure volume curve shifted with cardiac chambers dilatation without severe increase

Table 2: Clinical trials regarding NPs measurement for diagnosis, cardiac dysfunction, and therapy monitoring.

Author	Clinical setting	Patients	Study design	Main findings
Maisel et al. [16]	Patients with acute decompensated heart failure (ADHF).	464	Entrance criteria included a BNP level >100 pg/mL. Admitted patients were divided into two groups based on B-type natriuretic peptide (BNP) levels above and below 200 pg/mL to study differences in outcome rates.	The BNP levels can predict future outcomes and thus may aid physicians in making triage decisions about whether to admit or discharge patients. Emerging clinical data will help further refine biomarker-guided outpatient therapeutic and monitoring strategies involving BNP.
Luchner et al. [17]	Patients with ADHF	1086	Primary endpoint was hospital admission; secondary endpoints were intermediate/intensive care unit (IMC/ICU) admission, length of stay, rehospitalization and death, or rehospitalization.	Knowledge of N-terminal pro-B-type natriuretic peptides (NT-proBNP) had no significant effect on the primary endpoint hospital admission and the secondary endpoints. Patients with high open NT-proBNP (>1800 pg/mL) were more likely to be admitted to the hospital and IMC/ICU, whereas patients with low open NT-proBNP (<150 pg/mL) were less likely to be admitted compared with patients with blinded NT-proBNP.
Bettencourt et al. [18]	Patients with ADHF	182	The goal of the study was to evaluate the value NT-proBNP in predicting death or hospital readmission after discharge of HF patients.	Variations in NT-proBNP levels are related to hospital readmission and death within 6 months. NT-proBNP levels are potentially useful in the evaluation of treatment efficacy and might help clinicians in planning discharge of HF patients.
Masson et al. [19]	Patients with chronic and stable HFs.	3916	This work aimed to provide a direct comparison of the prognostic value of BNP and NT-proBNP in patients with chronic and stable HFs.	BNP and NT-proBNP showed subtle differences in their relation to clinical characteristics and prognostic performance in a large population of patients with chronic and stable HF. They were the most powerful independent markers of outcome in HFs.
Troughton et al. [20, 21]	Patients with systolic heart failure (SHF).	106	This study was designed to characterize the importance of echocardiographic indexes as determinants of BNP levels in patients with SHF.	Plasma BNP levels are significantly related to diastolic indexes measured from tissue Doppler imaging (TDI) and color M-Mode in SHF. BNP levels reflect the severity of diastolic abnormality, right ventricle (RV) dysfunction, and mitral regurgitation. These findings may explain the powerful relationship of BNP to symptoms and prognosis in SHF.
Bistola et al. [22]	Patients with advanced chronic HF (CHF).	102	Patients with CHF were studied by 2-dimensional conventional and TDI echocardiographies of the left and right ventricles. Patients were followed for 6 months for major cardiovascular events.	RV TDI systolic velocity, dilated cardiomyopathy, digoxin treatment, and female gender were associated with increased cardiovascular death. RV TDI indexes combined with increased plasma BNP additively predict adverse cardiac outcomes in advanced CHF.
Jourdain et al. [23]	New York Heart Association functional class II to III patients with CHF	220	Patients with CHF considered optimally treated were randomized to medical treatment according to either current guidelines or a goal of decreasing BNP plasma levels <100 pg/mL. The primary combined endpoint was CHF-related death or hospital stay for CHF.	In optimally treated CHF patients, a BNP-guided strategy reduced the risk of CHF-related death or hospital stay for CHF. The result was mainly obtained through an increase in ACEI and beta-blocker dosages.
Cohen-Solal et al. [24]	Patients with ADHF	1327	The purpose of this analysis was to examine whether decreases in BNP levels during the first few days of hospitalization were associated with greater survival in patients with ADHF.	Patients with lowered BNP on treatment for ADHF had reduced mortality risks (31- and 180-day) compared to those with little or no BNP decrease. These results suggest that early lowering of BNP predicts both short- and long-term mortality risks. BNP reduction may therefore serve as a suitable prognostic marker of all cause mortality.
Richards et al. [25]	Patients with ischemic LV dysfunction	297	They sought to assess plasma concentrations of NT-proBNP and adrenomedullin for the prediction of adverse outcomes and responses to treatment.	In patients with established ischemic LV dysfunction, plasma concentrations of NT-proBNP and adrenomedullin are independent predictors of mortality and HF. Carvedilol reduced mortality and HF in patients with higher pretreatment plasma NT-proBNP and adrenomedullin.

of myocardial mass. Invasive measurement is the reference standard for establishing LV end diastolic pressure; however, this is not currently feasible in all subjects with preserved systolic function; therefore, echo-Doppler measuring is the most reliable method of estimating LV pressures [38]. NPs levels are known to be elevated in patients with increased ventricular filling pressures. Pressure overload and ventricular volume expansion are the causes of high levels of this cardiac neurohormone. Hence, NPs can predict diastolic dysfunction increasingly in patients with either symptomatic or asymptomatic diastolic abnormalities. Lubien et al. detected how this peptide can confirm the diagnosis of diastolic heart failure using two-dimensional Doppler echocardiography [39]. The mitral inflow velocity was recorded in most patients; when filling pressures are elevated, E velocity increases, and A velocity decreases producing a restrictive pattern. Tissue Doppler measurements of mitral annular side show a reduced early diastolic velocity (Ea); by this method, the E/Ea ratio can reliably estimate the ventricular filling pressures with reasonable accuracy. If the E/Ea ratio is <8, filling pressure is normal with normal myocardial relaxation, if it is >15 filling pressure is elevated, but if this ratio is between 8 and 15, the assessment of diastolic dysfunction is not clear. In this case, a rapid assay of BNP can detect diastolic dysfunction. Maeder proposed a BNP level > 200 pg/mL to confirm the diagnosis of heart failure with normal ejection fraction in patients with E/Ea in the gray zone [40].

In patients with HFpEF, BNP increases according to the degree of diastolic dysfunction: the noninvasive analysis of HF with preserved systolic function is often difficult to establish, LV filling estimation appears particularly complicated in those patients with pseudonormal pattern and E/Ea ratio between 8 and 15. In these patients, BNP can detect diastolic filling pressure helping in the screening and grading its severity [41]. These findings have been validated by a comparison between Doppler and invasive hemodynamic measurements, confirming the great reliability of NT-proBNP in diagnosing isolated diastolic dysfunction [42, 43]. In the same setting, NPs are as well related to atrial volume enlargement which is considered an indirect marker of filling pressure even in the absence of primitive mitral valve disease, Figure 2.

5. Natriuretic Peptides as a Screening Tool in the General Population

Although NPs have been emerged as a useful tool in the diagnosis of acute HF and are entered also in the American Guideline algorithms, their significance as a screening device for the general population, namely, to detect asymptomatic patients with LV dysfunction, is currently debated [44]. In the general population, NPs measurements are affected by several cardiac and noncardiac variables (see the following paragraph) that need to be taken into account during the patient's evaluation. Before the clinical syndromes of HF are displayed, several haemodynamic and LV pressure-volume modifications occur: the first step is an abnormal systolic or diastolic function that is succeeded by increased end diastolic pressure and wall tension. After this stage, the LV pressure-volume curve shifts downward to the right; in the remodelled heart, there is a further increase in LV filling, impaired relaxation with stiffness, and increased left atrial pressure. Clinical syndromes of HF with symptoms of fatigue, dyspnea, dizziness and so forth, begin to be evident at this stage, and it will be clearly evident when increased left chamber pressure reflects a raise in pulmonary pressures [45]. Importantly, these clinical syndromes represent the tip of the iceberg, as it would be ideal to recognize cardiac remodelling before the clinical syndrome is apparent during early stages (stages A and B) of the last HF classification. The importance to intercept patients during these stages is confirmed by epidemiological data showing that asymptomatic patients with mild to moderate LV dysfunction have worse outcomes. Whether NPs screening would recognize this process before clinical manifestations become evident is debated. Some reports seem to confirm a role in this context; in Olmstead county a study on 2042 subjects NTpro-BNP and BNP demonstrated high sensitivity and specificity in detecting moderate systolic and diastolic dysfunctions (86 and 81%, resp.) particularly in older patients [46]. In another report with a 3-year median followup, NT-proBNP was the strongest predictor of mortality and hospital admission in asymptomatic patients with evident cardiac dysfunction. Its values increased with the severity of cardiac dysfunction [47]. Opposite data were reported from Framingham in detecting elevated LV mass and systolic dysfunction. However, this study included both patients at a high risk and after myocardial infarction, including a wide range of values [48]. More recently, Costello-Boerrigter et al. found that NT-proBNP is an effective tool to make out patients with systolic dysfunction, while the identification of diastolic dysfunction was less effective [49]. However, the combination of BNP with Tissue Doppler seems to be able to recognize community patients with an increased risk and diastolic impairment [50]. The latter data supports the double echo and laboratory approaches in the detection of both systolic and diastolic dysfunctions, confirming NP's role as potential predictive marker of adverse outcome even in asymptomatic patients. Nevertheless, at this moment, a common cutoff does not exist, neither for BNP nor for NT pro-BNP that is universally accepted and clinically applicable as a screening tool in general population.

6. Limitations of Natriuretic Peptides

Looking all together at the previously cited data, NPs measurement could appear to be the best solution for few diagnostic and prognostic troubles in clinical practice: measuring NPs, we are able in theory to obtain a variety of information on HF diagnosis, severity, and identification of patients with poor outcome. Unfortunately, several conditions can potentially influence NPs measurements, as demonstrated by Framingham and the Dallas Heart Study data in which a BNP cutoff >80 was able to identify only subjects with severe systolic dysfunction in the general population [48, 51].

Physiologic status race, sex, age, and body mass index are all conditions that could alter NP's synthesis and clearance

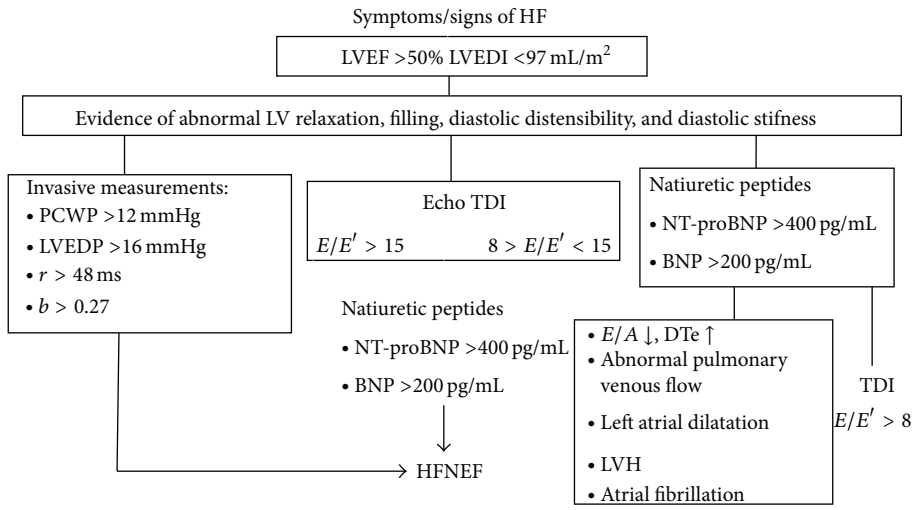

Figure 2: Algorithm including both echo and NP measurements to identify patients with HF and preserved systolic function (modified by Maeder and Kaye [40]).

[52]. Redfield et al. confirmed the impact of age and sex on BNP observed in subjects without cardiovascular disease; NPs measurements would be used taking into account discriminatory values adjusted for sex and age [53]. It has been demonstrated that age increases the levels of circulating BNP; this is related to a decline in myocardial function and myocardial fibrosis cardiovascular stiffness and the reduction in clearance of natriuretic peptides typical for senescence. However, an exact cut-off value for the difference among sample methods as for a wide variability is not well established in the literature. NPs are also inversely related to body mass, and patients with higher body mass index revealed lower circulating BNP concentrations [54]. This inverse relation may be due to increased expression of NP clearance receptors by adipose tissue, resulting in an increased clearance of NP in obese subjects. Race is another factor that could influence plasma NP levels: Hispanic and Black races have higher levels with respect to the Caucasian population for each corresponding NYHA class [55]. Besides physiologic conditions, several inflammatory and systemic diseases can affect NP values [56].

6.1. Comorbidities. The most important conditions are comorbidities like renal insufficiency (RI), diabetes, and anemia that are often associated with chronic HF particularly in older patients with more advanced stages [57]. Many studies demonstrated that the impact of RI on NPs is independent from the cardiac function. It depends not only on the RI severity but also on the duration of disease [58].

Influential authors calculated that, in the presence of these associated conditions, NPs values are at least 1/3 higher than those in patients with normal renal function [59]. Anemia is another condition frequently associated with more advanced HF stages, and its correction could reduce NPs levels [60, 61].

Cut-off limits of NPs have a grey zone in which it is not possible to ascertain their exact diagnostic role, their accuracy, and their predictive values [62]. This range is between 100 and 400 for BNP and 400 and 1400 for NT-proBNP; when values fall into these intermediate concentrations, it is not possible to have enough accuracy, and further clinical and investigational analyses need to be performed to make a diagnosis in patients with acute dyspnea. Furthermore, the outcome of patients who fall into this intermediate range is not clear [63, 64]. Another limitation in clinical practice is the moment of the measurement: NPs are released by increased volume load and wall stretch, which are influenced by systemic hydrosaline retention (wet versus dry). After treatment with drugs of proven efficacy, we observed a progressive reduction that is considered as a "measure" of congestion. Their prognostic role also depends on the time of measurement that reflects the volume status.

Finally, several cardiac factors can cause NPs alterations even in the absence of increased filling pressure and frank HF: increased LV mass, reduced right ventricular function, mitral valve disease, high pulmonary pressure for primitive or secondary respiratory disease, pulmonary embolism, and atrial fibrillation are all causes of potential NP increase. Overall, these reasons for NP measurement have high sensivity but low specificity, and laboratory test needs to be confirmed by clinical and traditional diagnostic screening processes.

7. Conclusions

NPs are important biomarkers able to assess diagnosis and severity of heart failure as well as predict outcome and potentially guide therapy. Although echocardiography remains the

standard regarding detailed information on cardiac performance and structure, imaging data alone is not sufficient to better identify patients with adverse outcome. An integrated approach combining laboratory assays with imaging could lead to a better identification of patients at high risk. This behaviour seems particularly useful in some settings like in patients with isolated diastolic dysfunction as in asymptomatic patients. In patients with diastolic dysfunction, it is sometimes difficult to confirm diagnosis, and NP should help to identify and graduate diastolic dysfunction. In community patients, NPs diagnostic, and prognostic values need to be validated although it is an effective tool to recognize patients with moderate to severe systolic dysfunction. The major limitation consists in the lack of a universally accepted cutoff that could permit the application of NP assays to clinical practice in this setting. The hope is that in the future multimarker strategies together with specificity and cut-off improvements could accurately and early identify patients "under the iceberg" that will develop HF syndrome. In this ideal world biomarkers on one hand and imaging on the other hand could converge to identify patients with higher risk. To obtain this, we need to better standardize echo as well as laboratory parameters.

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Hindawi Publishing Corporation
The Scientific World Journal
Volume 2013, Article ID 925310, 4 pages
http://dx.doi.org/10.1155/2013/925310

Research Article

Transapical Approach for Mitral Valve Repair during Insertion of a Left Ventricular Assist Device

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Received 11 April 2013; Accepted 16 June 2013

Academic Editors: X. Ai and Y. Wang

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Background. Severe mitral regurgitation (MR) is common in patients who are undergoing insertion of a left ventricular assist device (LVAD). This study analyzes the outcomes of a transapical approach for edge-to-edge repair of the mitral valve during insertion of a left ventricular assist device in 19 patients with MR. *Methods*. This retrospective study includes 19 patients who were implanted between March 21, 2011, and August 31, 2011, at the University of Chicago. Clinical data include preoperative ejection fraction, post- and preoperative pulmonary arterial pressures, cardiopulmonary bypass time, post- and preoperative mitral regurgitation severity, endotracheal CO2, and LVAD pulse index. *Results*. All of the 19 patients had a reduction in mitral regurgitation. Fourteen of the 19 patients had at least a three-point reduction in MR severity. The average postoperative pulmonary arterial pressure (PAP) decreased after the surgical procedure from 44/22 ± 14/5 mmHg to 57/28 ± 9/5 mmHg. Average CPB time was 128 ± 27 minutes. Average length-of-stay (LOS) was 21 ± 10 days. *Conclusions*. Concomitant MV repair using a transapical approach is advantageous for this small cohort of patients. The surgical procedure is less complex and has a shorter CPB time and LOS, and all of the patients demonstrated significant improvement in postoperative MR and moderate improvement in PAP.

1. Introduction

As a consequence of left ventricular remodeling, severe mitral regurgitation (MR) is common in patients with end-stage heart failure who are undergoing insertion of a left ventricular assist device (LVAD). This valvular related pathology often develops in the absence of structural mitral valve abnormalities. Instead, regurgitation develops secondary to left ventricular cavity enlargement and/or increased ventricular sphericity with annular dilation [1].

Concomitant mitral valve repair during LVAD insertion increases the complexity of the operation due to the need for additional dissection and incisions in the heart, bicaval cannulation, and prolonged cardiopulmonary bypass times. Edge-to-edge repair, developed by Alfieri and associates, has been shown to be a fast and reliable method of mitral valve repair in appropriate patients [2, 3]. Here, we describe a transapical approach for edge-to-edge repair of the mitral valve during insertion of a left ventricular assist device in 19 patients with MR secondary to left ventricular (LV) dysfunction.

2. Material and Methods

2.1. Technique. The degree of MR is evaluated preoperatively by echocardiography and angiography. In the operating room, the mitral valve is again assessed preoperatively with transesophageal echocardiography (TEE). After a median sternotomy, preparation is made for initiation of cardiopulmonary bypass requiring only a single right atrial cannula for venous outflow and aortic cannula for arterial inflow. Cardiopulmonary bypass (CPB) is initiated and normothermic conditions are maintained. A left ventricular vent is placed

via the right superior pulmonary vein. The heart is lifted out of the chest, exposing the LV apex. The apical coring knife is then utilized approximately 1.5 cm lateral to the left anterior descending artery in the apical dimple. The left ventricle is inspected for thrombus. Apical sutures are then placed with large Teflon felt pledgets in a horizontal mattress fashion (Figure 1).

The mitral valve is then accessed through the apical incision. To better expose the mitral valve, a malleable retractor is used to retract the septum and a floppy sucker is passed between the anterior and posterior leaflet of the valve. The midpoint (equidistant from the two commissures) of the free edge of the anterior leaflet is identified, and the posterior leaflet is exposed. The midpoints of P2 and A2 are then sutured together using a 4-0 Prolene mattress suture buttressed with a felt pledget. The suture is placed approximately 5 mm from the free edge of the leaflets. The LVAD is then connected and secured in the standard fashion by passing sutures through the apical connector sewing ring and seating the apical connector in the LV apex. The LVAD is then attached to the apical connector and secured. The LVAD is positioned in the pericardium (HVAD, HeartWare, Framingham, MA) or preperitoneal pocket (Heartmate II, Thoratec Corp., Pleasanton, CA), and the driveline is tunneled and brought out in the right upper quadrant.

A partial occlusion clamp is then placed on the ascending aorta and an aortotomy is created. The distal anastomosis is then constructed between the outflow graft and the ascending aorta in an end to side fashion using running 4-0 Prolene suture. The outflow graft is then clamped and the partial occlusion clamp is released. Meticulous hemostasis is assured at the suture line. The outflow graft is then secured to the assist device. After deairing maneuvers, full VAD support is initiated and the patient is weaned from CPB. Transesophageal echo is then used to assess the degree of MR, mitral stenosis (MS), and ventricular function.

2.2. Data Collection. The study included 19 consecutive patients who underwent LVAD implantation with concomitant transapical edge-to-edge mitral valve repair between March 21, 2011, and August 31, 2011, at the University of Chicago. All data was collected retrospectively, and use of the data is consistent with the regulations of the University of Chicago's Institutional Review Board. Demographic and clinical characteristics are included in Table 1. Clinical data include preoperative ejection fraction, post- and preoperative pulmonary arterial pressures (PAP), cardiopulmonary bypass time, post- and preoperative mitral regurgitation severity, endotracheal CO2, and LVAD pulse index.

Table 1: Clinical and demographic characteristics of 19 patients who underwent concomitant LVAD insertion and transapical MV repair.

	N/average	%/std. dev.
Total	19	—
Age (years)	63.11	±8.92
Female	2	10%
White	11	58%
Black	5	26%
Asian	1	5%
Diabetes mellitus	6	32%
Hypertensive	8	42%
Previous LVAD	1	5%
Concomitant CABG	3	16%
BMI	30.02	±6.4
Current smoker	4	21%
Dialysis	1	5%
Chronic lung disease	10	53%

BMI: body mass index; CABG: coronary artery bypass graft.

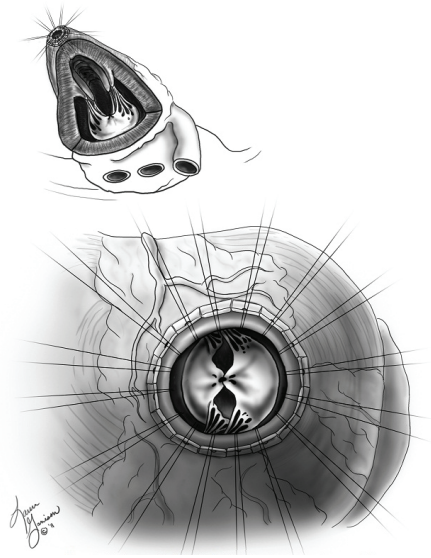

Figure 1: Apical sutures placed with Teflon pledgets in a horizontal mattress fashion.

3. Results

Relevant preoperative and postoperative clinical data are included in Table 2. Each of the 19 patients in this series experienced an improvement from moderate-to-severe MR to trace/trivial-to-mild MR. Sixteen (84.2%) of the 19 patients left the OR with 0 or level 1+ MR, and 14 (73.7%) of the 19 patients experienced at least a 3rd grade reduction in MR severity. None of the patients had measurable mitral valve stenosis. Further, there was a measureable decrease in postoperative PAPs. Before the LVAD insertion and MV repair, the mean PAP of 57/28 ± 9/5 mmHg and postoperatively the PAP average dropped to 44/22 ± 14/5 mmHg. Average LOS was 21 ± 10 days.

4. Comment

This report describes an early experience with edge-to-edge mitral valve repair in patients undergoing LVAD implantation. The described technique offers a simple method of

Table 2: Preoperative and postoperative clinical characteristics of 19 patients undergoing simultaneous MV repair and LVAD insertion.

Gender	Age	CPB time (min)	Preop EF	Preop PAP average (mmHg)	Postop PAP average (mmHg)	Preop MR (1–4)	Postop MR (1–4)	Preop ET CO2 (%)	Postop ET CO2 (%)	PI	LOS
M	71	167	15%	46/31	37/25	4	0	37	26	4.7 @ 8400	33
M	62	132	21%	55/30	27/15	4	1	31	33	4 @ 9200	35
M	69	138	29%	59/26	39/18	4	0	31	31	5.3 @ 8800	24
M	61	76	17%	53/26	45/19	4	1	34	30	5.7 @ 9600	26
M	66	108	13%	47/19	53/26	4	1	30	38	3.7 @ 9600	20
M	46	92	20%	57/23	28/19	3	1	34	27	6.0 @ 9200	11
M	68	132	15%	49/20	34/16	4	1	34	32	3.0 @ 8600	35
M	42	125	21%	63/36	46/23	4	1	37	35	3.0 @ 9200	16
M	70	130	10%	55/24	33/21	4	2	36	34	5.5 @ 9600	26
F	51	121	6%	48/25	52/28	4	1	32	34	5.0 @ 8600	22
M	63	126	22%	78/39	68/31	4	1	32	32	N/A	8
M	63	248	19%	68/26	32/22	4	1	35	31	5.0 @ 8800	14
M	67	113	20%	66/31	34/19	4	2	36	40	5.0 @ 8800	Deceased in hospital: 20
M	63	102	25%	53/32	66/24	4	1	40	34	5.0 @ 9200	Deceased in hospital: 18
M	70	127	15%	N/A	N/A	4	1	N/A	N/A	6.0 @ 9200	20
M	74	141	20%	70/22	45/27	4	1	31	35	4.0 @ 9600	13
F	54	95	15%	63/31	37/20	4	1	30	28	5 @ 9200	20
M	75	148	24%	47/29	35/17	3	1	32	35	N/A	10
M	68	130	17%	55/30	75/28	4	2	36	38	6.0 @ 9200	32

CPB: cardiopulmonary bypass; EF: ejection fraction; ET CO2: end tidal CO2; LOS: length of stay; MR: mitral regurgitation; PI: pulse index; postop: postoperative; preop: preoperative.

correcting MR. Other authors have described using an edge-to-edge repair via a transaortic approach [4, 5] and via an LV aneurysm [6].

The transapical approach described here requires only a single atrial cannulation without the need for additional dissection, cardiotomy, or application of a cross-clamp. Given its simplicity, the approach may promote a more aggressive correction of concomitant MR. This method is unlikely to be suitable for all patients. In particular, it is not suitable for patients with complex mitral valve disease. Rather it should be reserved for cases where LV dysfunction is the predominant mechanism of lacking coaptation of the mitral leaflets. Further, in our brief experience, we have repaired the valve both before and after the placement of pledgeted apical sutures, and we have found that placing the pledgets first serves to tent open the ventriculotomy and improves the exposure to the mitral valve.

Previous studies have demonstrated that MR improves with LVAD support [7]. Early findings here, however, suggest that this MVR approach may provide an even more significant reduction in MR. Thus, in early experience, edge-to-edge repair offers an efficient method of mitral valve repair in appropriate patients undergoing LVAD implantation without adding significant time or complexity to the procedure. Additional followup, however, is needed to more fully assess the long-term hemodynamic and clinical implications of the approach and to compare these findings with a control group.

Conflict of Interests

Dr. Jeevanandam is a Consultant for Thoratec Corporation and HeartWare. All other authors have no conflict of interests to disclose.

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