Cardiac Mortality-Risk Assessment Improved by Evaluation of Hemoglobin Level in Combination with Kidney Function in the Patients with Systolic Heart Failure: A Cohort Study

Takahiro Doi*, Tomoaki Nakata, Akiyoshi Hashimoto, Jyunichi Nishida, Atsushi Mochizuki, Satoshi Yuda, Kazufumi Tsuchihashi and Tetsuji Miura

Introduction

Anemia has recently been noted as a prognostic factor and as a therapeutic target in heart failure (HF) patients. However, anemia is a general comorbidity of HF and there are several causative clinical parameters that could influence the poor prognosis of HF patients [1-2]. On the other hand, a significant proportion of HF patients have concomitant chronic kidney disease (CKD), defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m². The prevalence of CKD has been reported to be in the range of 32% to 50% in the major chronic HF trials [3-9]. Population-based surveys in North America have found a similar prevalence of 38% to 56% [10-12]. The concomitance of CKD is a significant independent risk factor for poor prognosis in patients with HF [3-12]. Impairment of renal function and anemia are frequent comorbidity of chronic HF and may contribute to the progression of HF by enhancing the level of activation of multiple pathophysiological pathways leading to myocardial tissue damage [13]. Both impairment of renal function and anemia are indeed connected with increased activity of critical mechanisms of HF progression, e.g. sympathetic nervous system and renin-angiotensin-aldosterone axis activation, oxidation stress, and inflammation [14]. Silverberg et al. [13] advocated the association of HF, the disorder of renal function, and anemia the 'cardiorenal anemia syndrome', where HF may cause progressive the disorder of renal function further both may lead to anemia, which in turn can worsen HF and the disorder of renal function [15]. Therefore, regardless of the level of left ventricular systolic and diastolic dysfunction [16], cardiorenal anemia (CRA) syndrome might be shown as a state of HF in which the rate of progress of biochemical, cellular, and neurohormonal alterations leading to unfavorable clinical results is accelerated.

From these standpoints, we hypothesized that decreased hemoglobin (Hb) level and the disorder of kidney function augment cardiac mortality risk in chronic HF patients. In this study, we retrospectively analyzed prognostic parameter for 612 consecutive symptomatic chronic HF patients with reduced left ventricular ejection fraction (LVEF) combined with clinical evaluations, including evaluation of Hb level and kidney function.

Methods

Study patients

From April 1, 1997 to March 31, 2010, a total 644 of consecutive patients with symptomatic congestive heart failure were admitted to our hospital. The enrollment criteria for present study were LVEF less than 45% in echocardiography. Congestive HF was diagnosed by the following clinical symptoms and signs according to the Framingham criteria [17]: typical symptoms (palpitation, dyspnea or orthopnea), neck vein distension, peripheral edema, lung rale, S3 or S4 gallop and tachycardia together with findings of chest X-ray, such as heart enlargement, bilateral lung congestion and/or pleural effusion. HF patients were defined by several cardiologists in our hospital. The diagnosis and etiology of HF were established at admission or condition before discharge and were then followed up for an average interval of 54.6 months with a primary end point of cardiac events. For 107 (17.4%) fatal cardiac events documented, besides NYHA functional class and use of diuretics, nitrates and statins, multivariable Cox analysis revealed that estimated glomerular filtration rate (eGFR) and Hb were significant independent prognostic values with odds ratios of 0.741 (P<0.0001; 95% CI 0.657 to 0.834) and 0.987 (P=0.0256; 95% CI 0.974 to 0.998), respectively. ROC analysis showed 47.5 ml/min/1.73 m² of eGFR and 11.9 g/dL of Hb level to be thresholds for identifying patients at increased risk for cardiac events.

Conclusions: Decreased hemoglobin level and kidney dysfunction are independently and synergistically associated with increased cardiac events in chronic HF patients with reduced LVEF.

Keywords: Heart failure; Anemia; Kidney function; Mortality

Abstract

Background: Anemia and chronic kidney disease have been shown to be determinants of the prediction of poor prognosis in heart failure (HF) patients, but there is little information on their relationship with cardiac events. We examined prognostic interactions among kidney dysfunction, hemoglobin (Hb) level and other clinical variables in chronic HF patients.

Methods and Results: Following evaluations of Hb level, cardiac function and kidney functions, 612 consecutive HF patients with left ventricular ejection fraction (LVEF) less than 45% underwent echocardiography in a stable condition before discharge and were then followed up for an average interval of 54.6 months with a primary end point of cardiac events. For 107 (17.4%) fatal cardiac events documented, besides NYHA functional class and use of diuretics, nitrates and statins, multivariable Cox analysis revealed that estimated glomerular filtration rate (eGFR) and Hb were significant independent prognostic values with odds ratios of 0.741 (P<0.0001; 95% CI 0.657 to 0.834) and 0.987 (P=0.0256; 95% CI 0.974 to 0.998), respectively. ROC analysis showed 47.5 ml/min/1.73 m² of eGFR and 11.9 g/dL of Hb level to be thresholds for identifying patients at increased risk for cardiac events.

Conclusions: Decreased hemoglobin level and kidney dysfunction are independently and synergistically associated with increased cardiac events in chronic HF patients with reduced LVEF.
thereafter using a 12-lead electrocardiogram and two-dimensional/Doppler echocardiography and, when necessary, in combination with stress perfusion imaging of cardiac nuclear medicine study, coronary angiography or coronary computed-tomography angiography and computed tomography for exclusion of non-cardiac systemic diseases showing similar symptoms and/or signs. HF patients with reversible cause such as Takotsubo cardiomyopathy and tachycardia induced cardiomyopathy, post-cardiotomy were excluded before the enrollment in this study. Moreover, the following patients were excluded from this study: patients with end-stage of renal failure needing dialysis treatment (including hemodialysis and the peritoneal dialysis), patients with gastrointestinal bleeding or malignancy or chronic inflammation leading to severe anemia, and patients having undergone blood transfusion within one month before the registration to the present study. Following stabilization of the clinical conditions of heart failure after admission, patients underwent echocardiography and general blood tests.

Informed consent for enrollment in our database and usage for clinical study was obtained according to the guidelines of the ethics committee of our hospital.

Two-dimensional echocardiographic examination

General two-dimensional echocardiographic examinations were underwent by experienced cardiologists, who were blinded to clinical data, in our echocardiography laboratory using commercially available ultrasound machines equipped with a 2.5-MHz variable frequency transducer (SSH-160A, Toshiba, Tokyo; SSD760, Aloka, Tokyo; SONOS 2500, Hewlett-Packard, Andover, Massachusetts; Vivid 7, General Electric Medical Systems, Milwaukee, WI). Two-dimensional echocardiographic imaging modes were used from apical four-, three- and two-chamber views in a left lateral decubitus position. Left ventricular (LV) dimensions and wall thicknesses were measured and then LVEF was measured using the blipane modified Simpson’s method [18]. Echocardiographic examinations were performed when heart failure was stable one week before a discharge.

Blood tests and kidney function assessment

Blood sampling for measurements of hemoglobin (Hb) and serum concentrations of sodium and creatinine was done from an intravenous cannula in a supine position the day when echocardiographic examinations were performed. Kidney function was evaluated as estimated glomerular filtration rate (eGFR) using the following formulas: eGFR=${194×Cr}+1.094×\text{Age}^{0.203}$ for males and eGFR=${0.739×\text{male} eGFR}$ for females [15,16]. The samples for the assay of BNP concentration were transferred to chilled tubes containing aprotinin and immediately centrifuged and then the concentration was measured by a specific immunoradiometric assay using a commercial kit.

Follow-up protocol

After discharge from hospital, all patients were followed at least 3 months for a mean period of 54.6 months at the outpatient clinic of our hospital by cardiologists who determined the necessity of 12-lead electrocardiogram, chest X-ray, blood tests, echocardiography or other examinations. The primary endpoints were cardiac deaths consisting of pump failure death, sudden cardiac death. Sudden cardiac death was defined as witnessed cardiac arrest and death within 1 hour after onset of acute symptoms or unexpected death in patients known to have been well within the previous 24 hours.

Statistics

Statistical values are shown as means ± 1 SD. Mean values were compared between the two groups using the unpaired t-test, and categorical variables were compared using the chi-square test. A p-value less than 0.05 were considered significant. Following univariable analysis, multivariable analysis with a Cox hazard proportional model was carried out using the statistically appropriate number of significant variables identified by univariable analysis, which depended on incidence of cardiac events. Receiver operating characteristic (ROC) analysis was performed to determine the optimal cutoff value of an independent significant parameter. The cut-off value of Hb and eGFR was selected with the point in the ROC curve that was the nearest to the top left corner of ROC graph in this study. Cox proportional hazards regression models were used to examine the association between the incidence of cardiac events and potential confounding factors. Variables that were significantly associated with the cardiac events at univariate analysis were included in the multivariable models if p value was < 0.05. Hazard ratios and 95% confidence intervals were estimated with the use of stratified Cox proportional-hazards models. Survival curves of patient subgroups were created by the Kaplan-Meier method to clarify the time-dependent, cumulative event-free rate and were compared using the log-rank test. For the assessment of incremental prognostic values of significant predictors, global chi-square values were calculated after adding in several independent predictors identified by multivariable analysis, based on increases in the overall likelihood ratio. These analyses were performed using a computer software program, SPSS statistical program package (SPSS version 11.0, SPSS Inc., Chicago, IL).

Results

Among 644 patients with symptomatic congestive HF, 612 met the inclusion criteria for the present study and included. Patients were 463 male and 149 females. The mean age 63.1 years. During observational period, primary cardiac events were documented in 107 patients (17.4%); pump failure death occurred in 93 patients and 14 patients died of sudden death. There were three non-cardiac deaths: one death from rupture of a thoracic aortic aneurysm, one death from hemorrhagic shock due to gastrointestinal bleeding and one death from lung carcinoma. Table 1 shows clinical backgrounds; 272 (44.4%) of the patients had HF with ischemic related etiologies and the remaining 340 (55.5%) had HF without ischemic related etiologies. The group with cardiac events had greater New York Heart Association functional (NYHA) class, less frequent history of dyslipidemia, higher BNP concentration, lower Hb value, and lower eGFR than those in the group without cardiac events. However, there was no significant difference in other clinical background or laboratory parameters between the two groups. Table 2 shows medication used. Patients of cardiac events group were more frequently prescribed with diuretics and nitrates but less frequently prescribed with nicorandil and statins than were patients of non-cardiac event group.

There was no significant difference in any functional parameters in echocardiographic examination between cardiac events group and non-cardiac event group (Table 3). Table 4 shows the nine significant variables with greatest chi-square values in the univariable analysis and shows the results of Cox-hazard proportional model analysis using these variables. Among the nine variables, NYHA functional class, prescription of diuretics, nitrates and statins, BNP concentration, Hb values and eGFR were identified to be significant predictors of cardiac event by multivariable analysis independently. The chi-square values
and hazard ratios were 21.2 and 1.696 (95% CI, 1.361-2.108, P<0.0001) for NYHA functional class, 5.34 and 1.815 (95% CI, 1.091-3.179, P=0.0209) for prescription of diuretics, 4.02 and 1.547 (95% CI, 1.010-2.349, P=0.0448) for prescription of nitrate, 6.02 and 0.481 (95% CI, 0.250-0.868, P=0.0141) for prescription of statins, 6.08 and 1.294 (1 Log [BNP concentration] increase, 95% CI, 1.033-1.630, P=0.0198) for Log [BNP concentration], 24.7 and 0.741 (1 g/dL increase, 95% CI, 0.657-0.834, P<0.0001) for HB value, and 4.92 and 0.987 (1 ml/min/1.73 m² increase, 95% CI, 0.974-0.998, P=0.0256) for eGFR, respectively (Table 4). ROC analysis revealed optimal thresholds of HB value and eGFR for identifying patients at greater risk of cardiac events, 11.9 g/dL for HB value and 47.5 ml/min/1.73 m² for eGFR (Figure 1). The sensitivity and specificity of the calculated cut-off values were as follows: 52.3% and 68.7% for HB value less than 11.9 g/dL and 59.8% and 75.9% for eGFR.
Cardio-renal anemia syndrome

CRA syndrome was present in one-fifth of the patients, most of whom had normocytic normochromic anemia, e.g., anemia of chronic disease. The degree of agreement between the Cockcroft-Gault and MDRD equations for CRA syndrome was very good [24], most likely because the patients with CRA syndrome had substantially impaired renal function and both equations perform better at lower levels of renal function and both equations perform better at lower levels of eGFR. Impairment of kidney function, however, is likely to be responsible for decreased Hb value probably due to insufficient erythropoietin production in HF patients. When GFR decreases to less than 60 ml/min, erythropoietin production and Hb value linearly decrease [20]; 407 (66.5%) of the 612 HF patients in this study had eGFR of 60 ml/min/1.73 m2 or less. Chronic kidney disease is recognized not only as a comorbidity (with incidence ranging from 20% to 40%) but also as a prognostic risk in HF patients [20, 21]. The following cardiac factors, which are commonly seen in moderate to severe chronic HF patients, are at least partly responsible for reduced Hb or anemia: persistent systemic congestion causes hemodilution [9] and malnutrition or cardiac cachexia disrupts iron absorption and the subsequent erythropoietic process [22]. Independently of cardiac and kidney functions, however, Hb had a significant and additive prognostic value in this study, indicating that anemia plays a pivotal role in the occurrence of lethal cardiac events in chronic HF patients.

Kidney function and heart failure

Beyond our hypothesis of anemia-HF interactions in cardiac prognosis, impaired kidney function was also independently and incrementally associated with an increased risk for cardiac death in anemic patients with chronic HF. As is well recognized, chronic kidney disease or decreased GFR is related to increased cardiovascular events not only in patients without known cardiac diseases but also in HF patients. There are several possible explanations for cardiovascular risks of impaired kidney function in chronic HF patients. Simply, reduced GFR may be another aspect of severity of chronic HF such as blood flow reduction or ischemia in the kidney, which cannot be revealed by conventional clinical measures. Impairment of kidney function suggests the presence of endothelial dysfunction and microvascular damage, which are common underlying conditions and probably function as cumulative risks in cardio-renal correlations [23]. Decreased GFR could induce imbalances of water and electrolytes, leading to increases in volume-overloading and arrhythmogenicity in HF patients. These cardiorenal interactions possibly exacerbate patient prognosis via autonomic tone activation.

Discussion

This cohort study definitely showed that decreased hemoglobin value and impairment of kidney function are independently and synergistically associated with increased cardiac mortality in chronic HF patients with systolic dysfunction.

Anemia and heart failure

The Hb value of 11.9 g/dl was defined by ROC analysis as a cut-off value for indentifying a high-risk population of chronic HF patients rather than as the traditional definition of anemia. In previous studies, the prevalence of anemia in chronic HF patients ranged widely from 7% to almost 60% [1]. This reason is probably differences in patient backgrounds and etiology and the definition of anemia. Nevertheless, the Hb value was almost identical to the definition (12.0 g/dL) of anemia commonly adopted in several earlier heart failure studies [2] and to the cut-off value of the National Kidney Foundation [19]. Therefore, the cut-off value of Hb defined in present study may have several clinical implications for the detection of anemia, which is connected with a greater risk for cardiac events in systolic HF patients. As biopathological mechanisms behind cardiac damage of anemia, several possibilities can be offered. Anemia with an Hb value less than 11.0 g/dL is noted to reduce the volume of renal blood flow and occur kidney dysfunction [19] and to increase the volume of venous return and cardiac workload (including both preload and afterload) by stimulating the tone of cardiac sympathetic nerve in response to the shortage of oxygen supply, all of which result in the development and progression of left ventricular hypertrophy, remodeling and myocardial ischemia, leading to fatal clinical outcomes.

Because this study was retrospective, underlying causes of anemia were not determined and erythropoietin concentration was not measured. Impairment of kidney function, however, is likely to be responsible for decreased Hb value probably due to insufficient erythropoietin production in HF patients. When GFR decreases to less than 60 ml/min, erythropoietin production and Hb value linearly decrease [20]; 407 (66.5%) of the 612 HF patients in this study had eGFR of 60 ml/min/1.73 m2 or less. Chronic kidney disease is recognized not only as a comorbidity (with incidence ranging from 20% to 40%) but also as a prognostic risk in HF patients [20, 21]. The following cardiac factors, which are commonly seen in moderate to severe chronic HF patients, are at least partly responsible for reduced Hb or anemia: persistent systemic congestion causes hemodilution [9] and malnutrition or cardiac cachexia disrupts iron absorption and the subsequent erythropoietic process [22]. Independently of cardiac and kidney functions, however, Hb had a significant and additive prognostic value in this study, indicating that anemia plays a pivotal role in the occurrence of lethal cardiac events in chronic HF patients.

Kidney function and heart failure

Beyond our hypothesis of anemia-HF interactions in cardiac prognosis, impaired kidney function was also independently and incrementally associated with an increased risk for cardiac death in anemic patients with chronic HF. As is well recognized, chronic kidney disease or decreased GFR is related to increased cardiovascular events not only in patients without known cardiac diseases but also in HF patients. There are several possible explanations for cardiovascular risks of impaired kidney function in chronic HF patients. Simply, reduced GFR may be another aspect of severity of chronic HF such as blood flow reduction or ischemia in the kidney, which cannot be revealed by conventional clinical measures. Impairment of kidney function suggests the presence of endothelial dysfunction and microvascular damage, which are common underlying conditions and probably function as cumulative risks in cardio-renal correlations [23]. Decreased GFR could induce imbalances of water and electrolytes, leading to increases in volume-overloading and arrhythmogenicity in HF patients. These cardiorenal interactions possibly exacerbate patient prognosis via autonomic tone activation.

Table 4: Results of univariate and multivariate analyses.

<table>
<thead>
<tr>
<th>Univariable Analysis</th>
<th>Multivariable Cox-hazard Model Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>95% CI</td>
</tr>
<tr>
<td></td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>49.1</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>13.2</td>
</tr>
<tr>
<td>Diuretics</td>
<td>24.1</td>
</tr>
<tr>
<td>Nitrate</td>
<td>13.4</td>
</tr>
<tr>
<td>Nicorandil</td>
<td>2.05</td>
</tr>
<tr>
<td>Statins</td>
<td>13.9</td>
</tr>
<tr>
<td>BNP concentration</td>
<td>11.3</td>
</tr>
<tr>
<td>Hemoglobin level</td>
<td>53.7</td>
</tr>
<tr>
<td>Estimated GFR</td>
<td>31.3</td>
</tr>
</tbody>
</table>

CI: Confidence Interval; NYHA: New York Heart Association; GFR: Glomerular Filtration Rate

This cohort study definitely showed that decreased hemoglobin value and impairment of kidney function are independently and synergistically associated with increased cardiac mortality in chronic HF patients with systolic dysfunction.

Discussion

This cohort study definitely showed that decreased hemoglobin value and impairment of kidney function are independently and synergistically associated with increased cardiac mortality in chronic HF patients with systolic dysfunction.

Kidney function and heart failure

Beyond our hypothesis of anemia-HF interactions in cardiac prognosis, impaired kidney function was also independently and incrementally associated with an increased risk for cardiac death in anemic patients with chronic HF. As is well recognized, chronic kidney disease or decreased GFR is related to increased cardiovascular events not only in patients without known cardiac diseases but also in HF patients. There are several possible explanations for cardiovascular risks of impaired kidney function in chronic HF patients. Simply, reduced GFR may be another aspect of severity of chronic HF such as blood flow reduction or ischemia in the kidney, which cannot be revealed by conventional clinical measures. Impairment of kidney function suggests the presence of endothelial dysfunction and microvascular damage, which are common underlying conditions and probably function as cumulative risks in cardio-renal correlations [23]. Decreased GFR could induce imbalances of water and electrolytes, leading to increases in volume-overloading and arrhythmogenicity in HF patients. These cardiorenal interactions possibly exacerbate patient prognosis via autonomic tone activation.

Cardio-renal anemia syndrome

CRA syndrome was present in one-fifth of the patients, most of whom had normocytic normochromic anemia, e.g., anemia of chronic disease. The degree of agreement between the Cockcroft-Gault and MDRD equations for CRA syndrome was very good [24], most likely because the patients with CRA syndrome had substantially impaired renal function and both equations perform better at lower levels of kidney function [23].
Figure 1: Receiver operating characteristic (ROC) analysis of estimated GFR (right panel) and hemoglobin (Hb) level (left panel), indicating that optimal cutoff values for identifying cardiac events are 47.5 ml/min/1.75 m² (P < 0.0001) for eGFR and 11.9 g/dL (P < 0.0001) for Hb level.

Figure 2: Kaplan-Meier event-free curves of two groups classified by cutoff values of Hb level of 11.9 g/dL (left panel) and eGFR of 47.5 ml/min/1.75 m² (right panel) after adjustment using New York Heart Association functional class, dyspnea, diuretic use, and BNP concentration. Patients with Hb level less than 11.9 g/dL or eGFR less than 47.5 ml/min/1.75 m² (red line) had significantly lower event-free rates than did patients with Hb level or eGFR not less than those values (blue line).

Figure 3: Kaplan-Meier event-free curves of three subgroups classified by both cutoff values of Hb level and eGFR after adjustment using New York Heart Association functional class, dyspnea, diuretic use, and BNP concentration. There were significant differences in survival rates among the four subgroups: the subgroup that had both Hb level less than 11.9 g/dL and eGFR less than 47.5 ml/min/1.75 m² (in red) had a lower survival rate than those in the other subgroups (in green and blue and orange).

Figure 4: Global χ² values for predicting lethal cardiac events incrementally increase in combination with the four independent predictors, i.e., BNP concentration, New York Heart Association (NYHA) functional class, hemoglobin (Hb), and eGFR. The predictive value is maximal when all of the four predictors are combined.

Although the mediating role of anemia for increased mortality in HF remains uncertain, it has been hypothesized that the correction of anemia in patients with a combination of HF and impaired renal function may prevent the progression of both conditions [25], thus improving symptoms and survival. Iron supplementation and treatment with erythropoiesis-stimulating agents (ESAs), or a combination of both, are potentially valuable therapeutic options [26,27].

However, three recent meta-analyses of studies testing ESA therapy in anemia and HF patients failed to show evidence for mortality benefit [15,28,29]. The pilot study of low-dose epoetin-β in symptomatic ischemic heart failure, which aims to determine the feasibility and efficacy of low-dose epoetin-β [30] might elucidate the uncertainties about whether and how to use ESAs in HF and the interaction between renal function, on-treatment Hb levels, and effects on morbidity and mortality. Additionally Oda et al mentioned that erythropoietin might take a new part of therapeutic strategies against multiple neurohumoral dysregulation underlying chronic heart failure [31]. In the recently published Ferinject®. Assessment in patients with iron deficiency and chronic Heart Failure (FAIR-HF) trial, treatment with intravenous ferric carboxymaltose improved symptoms, functional capacity, and quality of life [32]. The possible variability of Hb concentrations, due to the interplay of clinical status, cardiac function and renal function [33], may complicate the management of anemia in HF patients. Volume overload is a frequent feature of HF, and haemoconcentration leading to increased Hb concentration may occur during aggressive diuretic treatment. Conversely, haemodilution with decreased Hb concentration may result from worsening congestive HF or a reduction in diuretic dose.

Limitations

This was a retrospective and observational study using a clinical database in our laboratory of the university hospital. Despite consecutive enrollment based on inclusion criteria, the possibility of selection bias cannot be completely ruled out because of the limited number (612) of patients. Although limited by inherent design flaws, however, patients in observational studies better represented those seen in a real-world setting of clinical practice. Women accounted for only 24.3% of the study population.
There might have been other prognostic variables that were not analyzed in this study. In addition to evaluation of the causes of anemia and kidney dysfunction, further studies are required to reveal the mechanisms of accumulated risks for cardiac death. From more clinical points of view, there is a need to establish prophylactic management and effective therapeutic strategies against anemia and kidney dysfunction in chronic HF patients at increased risk for cardiac death. Finally, we did not measure haematinic parameters.

Conclusions

Decreased Hb value and kidney dysfunction are independently and synergistically associated with increased cardiac mortality in chronic HF patients with reduced LVEF. This study demonstrated that combined assessment of these variables can improve risk stratification of systolic HF patients for long-term cardiac death.

Acknowledgements

The authors are particularly grateful to the Cardiology staff, Sapporo Medical University School of Medicine, for cooperation with clinical services. The authors also sincerely thank the staff of the Division of Nuclear Medicine and Radiology, Sapporo Medical University Hospital, Hokkaido Cardiovascular Hospital and Sapporo Cardiovascular Hospital for their assistance in techniques.

Disclosure

There was no financial support for this study.

References

18. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, et al. (2005) Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 18: 1440-1463.