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Original article

Predictive importance of left ventricular myocardial stiffness for the prognosis of patients with congestive heart failure

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Summary
Objectives: This study was designed to determine the prognostic importance of left ventricular (LV) myocardial stiffness, a hemodynamic index which is closely related to B-type natriuretic peptide (BNP) concentration in patients with congestive heart failure (CHF).
Background: While elevated BNP, an abnormality of cardiac neurohormones, is known to be an independent marker of death or re-admission, it remains to be clarified whether there is also a strong predictor directly related to cardiac dysfunction.
Methods: LV performance variables and stress–strain analyses including diastolic myocardial stiffness constant (K_m) were obtained from 37 patients with initial CHF by the combined simultaneous measurement of echocardiographic and hemodynamic data. Survivors were monitored for a mean of 23 months, with the main endpoint being combined death or first re-admission for CHF.
Results: Ten patients (27%) were primary endpoint cases. Both K_m and plasma BNP levels were higher in the event than in the event-free group. By Cox proportional hazards analysis, $K_m \geq 4.0$ was identified as the only variable with significant and independently incremental predictive power to affect the primary endpoint (adjusted hazard ratio = 7.354, 95% confidence interval 1.379–39.232, $p = 0.02$).

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Conclusions: In patients with CHF, increased myocardial stiffness may have greater prognostic significance compared to other conventional predictors. Increased myocardial stiffness may be considered to be an important prognostic factor independent of the loading conditions.

Introduction

Heart failure has become one of the major causes of death as the elderly population has been increasing. Hospitalization for congestive heart failure (CHF) carries a poor prognosis with frequent subsequent re-admissions [1—5]. Despite the substantial evidence of the lifesaving benefits of beta-blockers for patients with CHF [6—8], there are still many patients who suffer from recurrent decompensation. Conventional predictors for CHF prognosis include hemodynamic variables such as left ventricular (LV) ejection fraction (LVEF), LV end-diastolic pressure (LVEDP) (both are well-known predictors of mortality), end-diastolic volume index, or pulsed Doppler analysis of mitral inflow [9]. However, the predictive accuracy of these cardiac variables is not satisfactory [10,11]. Reported findings indicate that B-type natriuretic peptide (BNP), a well-known cardiac neurohormone specifically secreted from the cardiac ventricles in response to ventricular overload [12—14], is an independent marker of cardiac survival [10,15—17], although pre- and post-discharge BNP values vary widely in the same patient because of changes in cardiac loading conditions. Recently, we have shown that the baseline BNP concentration is strongly related to LV myocardial stiffness [18], which is considered to be an essential myocardial diastolic property independent of loading conditions [19]. Despite its potential importance, it is still unknown whether or how these novel indexes can predict post-discharge outcomes for patients admitted for CHF.

The aim of our study is to determine whether the novel index of passive diastolic myocardial stiffness can help predict major cardiac events such as death or re-admission for consecutive patients hospitalized for acute CHF.

Methods

Study design

Consecutive patients admitted between July 2003 and November 2005 for initial decompensated CHF were eligible, with the following exceptions: acute myocardial infarction, prior Q-wave myocardial infarction, renal dysfunction (defined as a creatinine value $\geq$2.0 mg/dl), significant valve diseases, atrial fibrillation, significant coronary artery stenosis (>50%), or poor adherence to therapy. The diagnosis of CHF was based on the Framingham criteria [20]. Steady-state plasma BNP levels were obtained following treatment with appropriate medications [21], clinical stabilization, and thorough diuresis. The patients were then examined by means of combined simultaneous measurements of echocardiographic and hemodynamic data, after which LV performance variables and stress—strain analyses were obtained. The study was approved by the local ethical committee.

Patients

Initially, 57 CHF patients who met the criteria were enrolled, but 12 were excluded from the study because they had not given informed consent, and a further eight patients because of the poor quality of echocardiographic images. Finally, 37 (65%) patients (63 $\pm$ 12 years, range 33—80 years) were enrolled in the study. The etiologies of heart failure for the study population were hypertensive heart disease for 19 (51%) and non-ischemic idiopathic dilated cardiomyopathy for 18 (49%) patients.

BNP assays

BNP assays were obtained before examination according to previously described methods [22]. In brief, the blood samples were withdrawn into plastic syringes, transferred to chilled siliconized disposable tubes containing aprotinin (1000 kallikrein inactivator units/ml) and EDTA (1 mg/ml), immediately placed on ice, and then centrifuged at 4 °C. An aliquot of the plasma was immediately frozen at −80 °C, and the plasma BNP concentration was measured with a specific immunoradiometric assay kit (Shionogi Co., Osaka, Japan).

Study protocol

After right heart catheterization to measure the pulmonary capillary wedge pressure (PCWP), left ventriculography was performed to measure the LVEF and LV end-diastolic and end-systolic volume indices (LVEDVI, LVESVI, respectively), which were derived from a single-plane angiogram by means of the area-length method. Next, LV dimensions and wall thickness were assessed by echocardiography, while the LV pressure was measured simultaneously. To alter the systolic blood pressure for more than 15 mmHg, phenylephrine hydrochloride (0.1—0.5 mg) was administered intravenously. All data were recorded on high-speed paper for off-line analysis.

Echocardiographic measurement

M-mode recordings were obtained with commercially available equipment (SONOS 5500™; Agilent Technologies Inc., Palo Alto, CA, USA) operating at 2.5 MHz. Two-dimensional imaging examinations were performed in the standard manner of parasternal long- and short-axis views and LV dimensions and wall thickness was measured on M-mode images according to standard criteria [23]. Pulsed Doppler analysis of mitral inflow included measurements of LV inflow early peak filling velocity (*E*), late peak filling velocity (*A*), *E*-to-*A* ratio, and deceleration time of the *E*-wave (DTE). Findings were categorized into three patterns: 1) an ''impaired relaxation'' pattern (*E*/*A* ratio < 1); 2) a ''restrictive'' pattern (*E*/*A* ratio > 2, or between 1 and 2 with

DTE $\leq$ 130 ms); and 3) a ''pseudonormal'' or ''normalized'' pattern (E/A ratio between 1 and 2 and DTE > 130 ms). LV mass was calculated with a formula derived from the method of Devereux et al. [24]. Measurements were performed by two experienced observers unaware of the clinical data.

LV pressure measurement

A 6F high-fidelity micromanometer catheter (CENTRON™; Centron International Inc., Mineral Wells, TX, USA) was inserted into the middle of the LV cavity to measure the LV end-systolic pressure (LVESP), LVEDP, and the time constant of the LV isovolumic-pressure decline (τ). τ was calculated with the method of Weiss et al. [25].

Data analyses

Chamber stiffness can be quantified by examining the relationship between diastolic pressure and volume. The operating stiffness at any point along a given pressure—volume curve is equal to the slope of a tangent drawn to the curve at that point (dP/dV). Since the diastolic pressure—volume relationship is curvilinear and generally exponential, the relationship between dP/dV and pressure is linear. This slope is called the modulus of chamber stiffness (diastolic chamber stiffness constant, K_c) and can be used as a single numerical value to quantify chamber stiffness.

Stress—strain relationships were calculated by using a cylindrical model of LV geometry. We used a simplified echocardiographic and hemodynamic method to assess stress—strain relationships in humans, which were then determined with the modified method of Esposito et al. [26,27]. Meridional stress (σ) of the LV mid-wall was calculated as $\sigma = P \times D_m/[h \times (1 + h/D_m)]$, where P is the LV pressure, D_m is the instantaneous mid-wall short-axis diameter of the LV, and h is the LV wall thickness [28]. Natural strain (ε) was defined as $\varepsilon = \ln(D_m/D_{om})$, where D_{om} is the zero-stress mid-wall short-axis diameter.

Myocardial stiffness can be quantified by determining the relationship between myocardial stress (σ) and strain (ε) during diastole. At any given strain, myocardial stiffness is equal to the slope ($d\sigma/d\varepsilon$) of a tangent drawn to the stress—strain relationship at that strain. Since the stress—strain relationship is curvilinear and exponential, the relationship between ($d\sigma/d\varepsilon$) and stress is linear, and the slope of this relationship is the modulus of myocardial stiffness (diastolic myocardial stiffness constant, K_m). Thus, K_m is a dimensionless constant that represents the myocardial passive diastolic properties [19].

Follow-up and endpoints

When patients had recovered from CHF and become stable, they were discharged and monitored at the outpatient clinic every month. The primary endpoint was the combined risk of cardiac mortality or re-hospitalization for CHF. Only one of these events was taken into consideration for any one patient.

Statistical analysis

Categorical data are presented as numbers (%), and continuous data as mean $\pm$ SD. Natural log transformation was used for BNP values because of skewed distribution. Fisher's exact test was used for dichotomous variables, and the unpaired t test for continuous variables. The receiver-operating characteristic (ROC) curve was calculated to assess the utility of K_m to distinguish between survivors and patients who were combined endpoint cases. Survival free for the primary endpoint for CHF was estimated with the Kaplan—Meier method, and the differences were assessed with the log-rank test. Cox proportional hazards regression analysis to determine the incremental prognostic power of outcome predictors was performed with the forced entry method. A p-value of less than 0.05 was considered to indicate statistical significance. All reported p-values are two-sided.

Results

Baseline patient characteristics

Of the 37 patients admitted to our institution with a clinical diagnosis of CHF, follow-up was completed for all patients (mean time interval from hospital discharge to follow-up was 23 $\pm$ 7 months). The pre-discharge heart failure status of 25 patients was New York Heart Association (NYHA) class II, that of the remaining 12 was class III. Ten patients (27%) were primary endpoint cases (event group: 2 cardiac deaths, 8 re-admissions for CHF). There were no differences between the event and the no-event group in age, gender, and medical treatments, and the only difference in the baseline clinical characteristics was the pre-discharge incidence of NYHA classification III [event group: 60% (6 patients); no-event group: 22% (6 patients); $p = 0.049$] (Table 1).

Baseline echocardiographic and hemodynamic variables and plasma BNP level

From the echocardiographic indices we found that end-diastolic posterior wall thickness, mitral E/A, and frequency of Doppler mitral ''restrictive'' pattern in the event group were higher than those in the no-event group ($p = 0.031$, 0.014, 0.009, respectively) (Table 2). The stress—strain analysis results showed that K_c and K_m were higher in the event group than in the no-event group ($p = 0.010$, 0.001, respectively) (Table 3), while plasma BNP in the event group was at a significantly higher level (363.0 $\pm$ 284.2 vs. 144.9 $\pm$ 116.2 pg/ml, respectively, $p = 0.002$) (Table 3). No significant correlation was observed between K_m and LVEDP ($R^2 = 0.014$) (Fig. 1).

Prognosis of patients with CHF

The ROC curve analysis identified $K_m \geq 4.0$ [area under curve (AUC) = 0.80, CI = 0.65—0.96], $p = 0.005$, sensitivity 60%, specificity 89%] as the optimal cut-off point for prediction of the primary endpoint (Fig. 2). The Kaplan—Meier curves for $K_m \geq 4.0$ are shown in Fig. 3. Finally, by Cox proportional hazards analysis of the clinical variables, including

Table 1 Baseline patient characteristics.

Variable, *n* (%)	Event *n* = 10	No-event *n* = 27	*p*-value
Age (years)	67 ± 9	61 ± 12	0.158
Gender (male)	9 (90)	18 (67)	0.229
Diabetes	5 (50)	7 (26)	0.240
Hypertension	6 (60)	21 (78)	0.407
NYHA classification on pre-discharge, II/III	4 (40)/6 (60)	21 (78)/6 (22)	0.049/0.049
ACEI/ARB	10 (100)	27 (100)	NS
Nitrates	4 (40)	6 (22)	0.407
Diuretics	10 (100)	27 (100)	NS
Beta-blockers, pre-discharge/post-discharge	0 (0)/10 (100)	0 (0)/27 (100)	NS/NS
Calcium channel blockers	2 (20)	6 (22)	NS

ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; NS = not significant; NYHA = New York Heart Association.
Data are presented as mean ± SD or number of patients (%).

Table 2 Baseline echocardiographic variables according to patient outcome.

Variable	Event *n* = 10	No-event *n* = 27	*p*-value
LV end-diastolic diameter (mm)	52.0 ± 12.5	53.9 ± 10.3	0.647
LV end-systolic diameter (mm)	38.7 ± 13.9	41.3 ± 12.9	0.595
LV end-diastolic posterior wall thickness (mm)	11.7 ± 3.4	9.5 ± 2.3	0.031
LV end-systolic posterior wall thickness (mm)	15.2 ± 4.0	13.0 ± 3.9	0.135
LV fractional shortening (%)	30.9 ± 13.1	28.5 ± 14.1	0.639
Mitral *E*/*A*	1.56 ± 0.96	0.94 ± 0.50	0.014
Mitral deceleration time (cm/s)	174.1 ± 65.3	217.9 ± 61.1	0.659
Doppler mitral pattern[a]			
''Impaired relaxation'' pattern	4 (40)	19 (70)	0.132
''Restrictive'' pattern	5 (50)	2 (8)	0.009
''Pseudonormal'' or ''normalized'' pattern	1 (10)	6 (22)	0.647
LV mass index (g/m^2)	134 ± 27	124 ± 37	0.451

E/*A*, mitral valve early/late peak filling velocity; LV, left ventricular.
Data are presented as mean ± SD or number of patients (%).
[a] For an explanation of the patterns, see Methods (echocardiographic measurement).

Table 3 Baseline hemodynamic variables and plasma B-type natriuretic peptide according to patient outcome.

Variable	Event *n* = 10	No-event *n* = 27	*p*-value
LV end-diastolic volume index (ml/m^2)	110 ± 38	98 ± 27	0.284
LV end-systolic volume index (ml/m^2)	63 ± 41	54 ± 32	0.501
LV ejection fraction (%)	45 ± 15	46 ± 17	0.841
Pulmonary capillary wedge pressure (mmHg)	17 ± 7	13 ± 5	0.094
LV end-diastolic pressure (mmHg)	16 ± 6	14 ± 6	0.431
LV end-systolic pressure (mmHg)	138 ± 39	140 ± 33	0.862
Time constant of the LV isovolumic-pressure decline (τ) (ms)	55 ± 10	49 ± 20	0.376
LV end-diastolic stress (g/cm^2)	60.6 ± 28.1	56.2 ± 36.2	0.732
LV end-systolic stress (g/cm^2)	257.7 ± 130.6	290.1 ± 144.9	0.539
Diastolic chamber stiffness constant (K_c)	0.077 ± 0.056	0.038 ± 0.030	0.010
Diastolic myocardial stiffness constant (K_m)	4.340 ± 1.284	3.040 ± 0.842	0.001
B-type natriuretic peptide (pg/ml)	363.0 ± 284.2	144.9 ± 116.2	0.002

LV, left ventricular.
Data are presented as mean ± SD.

Table 4 Hazard ratios of predictors for clinical outcome with and without adjustment.

Predictors, numbers (%)	Event $n=10$	No-event $n=27$	Unadjusted HR (95% CI) / Adjusted HR (95% CI)	p-value
Elderly (age ≥65 years old)	7(70.0)	11(40.7)	2.124 (0.539—8.362)	0.281
			1.398 (0.212—9.219)	0.728
Diabetes (yes)	5(50.0)	7(25.9)	1.752 (0.504—6.087)	0.378
			1.878 (0.510—6.911)	0.343
Elevated PCWP (≥18 mmHg)	5(50.0)	3(11.1)	4.877 (1.397—17.026)	0.013
			2.173 (0.317—14.882)	0.429
Elevated K_m (≥4)	6(60.0)	3(11.1)	9.422 (2.329—38.276)	0.002
			7.354 (1.379—39.232)	0.020

HR, hazard ratio; PCWP, pulmonary capillary wedge pressure; K_m, diastolic myocardial stiffness constant.

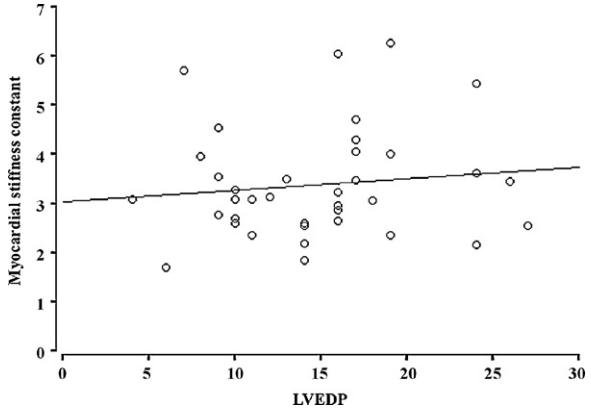

Figure 1 No significant correlation was observed between myocardial stiffness constant (K_m) and left ventricular end-diastolic pressure (LVEDP) ($R^2=0.014$).

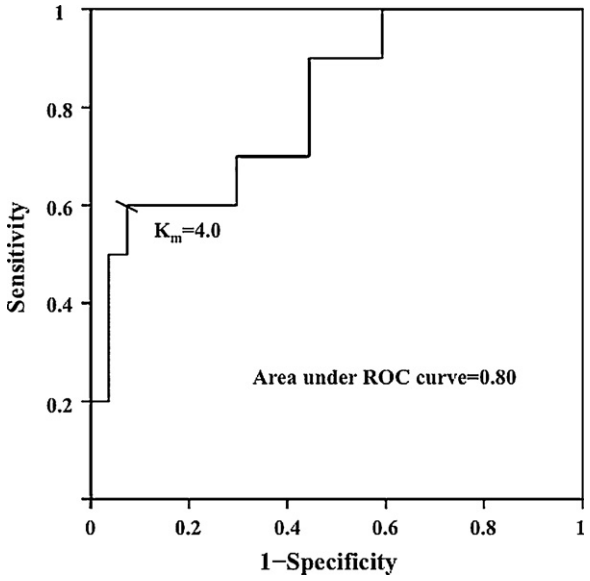

Figure 2 The receiver-operating characteristics (ROC) curve illustrates the sensitivity and specificity of diastolic myocardial stiffness constant (K_m) for differentiating patients who have reached the primary end-point from survivors. $K_m=4.0$ [area under curve = 0.80, $p=0.005$].

those that an epidemiological approach has shown to affect outcome, $K_m \geq 4.0$ was identified as the only significant and independent predictor for the primary endpoint (adjusted hazard ratio = 7.354, 95% confidence interval 1.379—39.232, $p=0.02$) (Table 4). Plasma BNP level was not included from the multivariate analysis because of the multicollinearity between K_m [18].

Discussion

Although many previous studies have demonstrated that elevated BNP is a useful neurohormonal prognostic marker for CHF, it is still not known whether this cardiac dysfunction is strongly associated with long-term prognosis. We have reported previously that in patients with CHF, plasma BNP concentration more closely correlates with passive myocardial stiffness, which is an independent factor of cardiac loading conditions than any other hemodynamic variables including end-diastolic stress [18]. To the best of our knowledge, this is the first study to assess the prognostic value of passive myocardial stiffness for determining patient outcome in CHF.

Prognostic importance of myocardial stiffness compared to conventional hemodynamic predictors

Our study found that conventional echocardiographic and hemodynamic parameters did not add a significant contribution to the predictive power of K_m and BNP. There were no differences between patients who reached the primary endpoint and patients who did not in terms of LV fractional shortening, LV mass index, LVEDVI, LVEF, PCWP, LVEDP, τ, and end-diastolic stress. On the other hand, pre-discharge

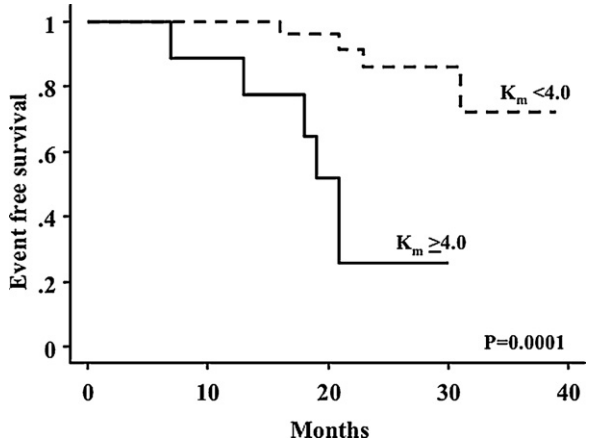

Figure 3 Kaplan—Meier analysis results showing cumulative rates of event-free survival for 37 patients with congestive heart failure stratified into two groups according to results of the receiver-operating characteristics curve analysis. Patients with diastolic myocardial stiffness constant (K_m) < 4.0 showed significantly better event-free survival than did patients with $K_m \geq 4.0$ ($p = 0.0001$).

plasma BNP levels were significantly higher in the event than in the no-event group. Furthermore, the Doppler mitral ''restrictive'' pattern, K_c and K_m were significantly higher in the former. The Doppler mitral ''restrictive'' pattern is widely used as a prognostic index for adverse outcome [29], while LV chamber stiffness (K_c) is known to reflect the degree of LV remodeling and/or enlargement [30]. Furthermore, alterations in chamber stiffness may reflect changes in passive myocardial stiffness as well as in other factors such as loading conditions, wall thickness, and LV geometry. The results of our study indicate that the parameters of LV size, such as LV mass index or LVEDVI, were not significant but tended to be larger in the event than in the no-event group. K_c is therefore considered to be a more sensitive index of LV remodeling and enlargement, although in this study the Doppler mitral ''restrictive'' pattern and chamber stiffness did not add to its predictive power, since these variables are influenced by the underlying hemodynamic abnormalities including myocardial systolic or diastolic properties. Myocardial stiffness, on the other hand, is considered to be an essential myocardial diastolic property independent of the loading conditions [19].

Mechanism of increased myocardial stiffness as a prognostic marker for CHF patients

Cox proportional hazards analysis performed in our study disclosed that K_m was the only significant and independent predictor of the primary endpoint. We consider that one possible reason for this is that, when we performed our examination, our study subjects had become clinically stabilized in terms of their general and physical condition and had been thoroughly diuresed by the optimal treatment. As a result, the volume and/or pressure overload to the LV had been attenuated to the minimum level in every patient, so that the value of BNP under these conditions is probably underestimated compared to its post-discharge value, since BNP has proven to be an excellent marker of cardiac disease compared to LV filling pressure. On the other hand, myocardial stiffness is considered to be an essential diastolic property, since it is comparatively less influenced by cardiac morphologic variables and supposed to reflect the degree of progressive interstitial LV fibrosis regardless of the type of heart failure.

We consider that increased myocardial stiffness in CHF patients represents a transition from compensated to decompensated heart failure in conjunction with progressive interstitial LV fibrosis [31,32]. In the failing heart, changes in the myocardial fibrillar collagen matrix influence myocardial stiffness characteristics. Although analysis of the precise mechanism of the increase in myocardial stiffness in our patients is beyond the goal of this study, this increase has been attributed to various factors. Experimental studies of augmented myocardial diastolic stiffness in spontaneous hypertensive rat hearts showed that myocardial hydroxyproline concentrations increased and myocardial collagen phenotype ratios (type I/type III) were altered [33]. Similarly, such an augmentation in diabetic cardiomyopathy was found to be associated with an increment in myocardial collagen cross-linking but not with changes in myocardial total collagen content [34]. In addition, the giant molecule titin spans half of the sarcomeres of striated muscle and accounts for most of the passive force of cardiomyocytes. Makarenko et al. [35] reported that the relationship between titin-based and collagen-based passive stiffness is altered in the human dilated cardiomyopathy heart. We therefore speculate that both collagen-based and titin-based passive stiffness may play important roles in an increase in myocardial stiffness.

Study limitations

By limiting our study to the use of a simple cylindrical model of LV geometry for calculating the stress—strain relationships, we could not deal with hypertrophic cardiomyopathy or ischemic cardiomyopathy because of the presence of LV asymmetric hypertrophy or asynergy. The number of patients was not sufficient to permit a true multivariate analysis of the many predictors, so that univariate analyses were used. Another limitation is that the number of patients who reached the primary endpoint was small compared that reported in previous studies. Since all patients were discharged with adequate circulatory stabilization and carefully followed up at our outpatient clinic every month, we think that the re-admission rate of our study (27%) is reasonable.

Clinical implications

The evaluation of myocardial stiffness in patients with initial hospitalization for CHF has clinical implications. Our study results suggest that the primary factor responsible for recurrent decompensation depends on passive myocardial stiffness regardless of hemodynamic and neurohormonal conditions. Since heterogeneity in the symptoms of heart failure and in the prognosis for patients with impaired diastolic and/or systolic function is well recognized, our method to assess passive myocardial stiffness in the clinical setting

may facilitate exploration of the mechanism of the transition from any form of LV maladaptive progressive fibrosis to recurrent decompensation.

Conclusions

Although plasma BNP monitoring is well known as a less invasive method to evaluate CHF prognosis, its prognostic value is affected by changes in the loading conditions. It therefore remains to be clarified whether plasma BNP monitoring is an essential predictor for CHF patients. On the other hand, increased myocardial stiffness is likely to play a crucial role in triggering deleterious cardiac disorders and may be considered to be an essential and important predictor of cardiac death or re-admission for CHF. Further studies are needed, however, to develop an easier method to calculate myocardial stiffness in vivo.

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