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The relation of aminoterminal propeptide of type III procollagen and heart rate variability parameters in heart failure patients: A potential serum marker to evaluate cardiac autonomic control and sudden cardiac death

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Abstract

Background—Cardiac extra-cellular matrix (ECM) fibrosis plays an important role in the pathophysiology of heart failure (HF). It may provide electrical heterogeneity and substrate for arrhythmogenicity, which may cause sudden cardiac death (SCD).

Methods—Twenty-one Patients with HF manifestations, and left ventricular ejection fraction (LVEF) ≤ 50% were enrolled. The median age was 62 years and median LVEF was 33 %. Time- and frequency-domain analysis of heart rate variability (HRV) on 24-hour ambulatory electrocardiography recording was assessed. Serum markers of ECM turnover including type I and III aminoterminal propeptide of procollagen (PINP and PIIINP), matrix metalloproteinase-2 and 9 (MMP-2 and MMP-9), and tissue inhibitor of metalloproteinase 1 (TIMP-1) were analyzed.

Results—The serum PIIINP level was significantly correlated with standard deviation of all normal RR intervals (SDNN) (r=−0.722, p=<0.001), percentage of adjacent NN interval differences >50 ms (pNN50) (r=−0.528, p=0.014), percentage of adjacent NN interval differences

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>20 ms (pNN20) (r=−0.545, p=0.002), very low frequency (VLF) (r=−0.490, p=0.024), low frequency (LF) (r=−0.491, p=0.024), high frequency (HF) (r=−0.513, p=0.018). PINP, MMP-2, 9, TIMP-1 were not correlated with time- and frequency-domain analysis of HRV.

Conclusions—PIIINP was significantly correlated with time- and frequency-domain analysis of HRV in HF patients. PIIINP is a potential serological marker to evaluate cardiac autonomic control and risk of SCD in HF patients.

Keywords

extra-cellular matrix; heart failure; collagen; HRV

Introduction

Heart failure (HF) is a progressive disorder characterized by high morbidity and mortality despite state-of-art therapy (1). Even with the great improvements in medical therapy, the prognosis of patients with HF remains very poor, with nearly 20% of patients dying within 1 year and nearly 80 % 8-year mortality (2). Of the causes of deaths in these patients, sudden cardiac death (SCD) due to arrhythmic events is one the major cause of death (3). In people diagnosed with HF, SCD occurs at 6 to 9 times the rate of the general population (2). The majority of lethal cardiac arrhythmia in SCD is most often due to ventricular tachycardia or fibrillation (4). In the SCD prevention in HF patients, antiarrhythmic drugs have not as yet been shown to reduce mortality (3,5–6), and implantable cardioverter defibrillators is the only effective treatment for both primary and secondary prevention of SCD (3,7–8). However, due to the high cost and the potential risk of invasive procedure, the selection of the potential candidates is necessary. Heart rate variability (HRV) has been recognized as a useful non-invasive method to detect SCD in HF patients(9). Patients with HF had standard deviation (SD) of all normal-to-normal R-R intervals (SDNN) < 65.3 ms had higher SCD rate and worse survival during 50 months of follow-up period (10).

Recently, the serum markers of cardiac extra-cellular matrix (ECM) turnover provided the prognostic value and clinical implications in various cardiovascular disease, such as coronary artery disease (11), acute rejection of cardiac transplantation (12), or HF (13–17). Among them, serum type III amioterminal propeptide of procollagen (PIIINP) was one of the most important and well known markers (15–16,18). Cardiac ECM fibrosis may provide electrical heterogeneity and substrate for arrhythmogenicity, which may cause SCD. Therefore, the serum markers of ECM may be the potential markers to predict ventricular arrhythmia and SCD. However, in our knowledge, the relation between serological markers for cardiac ECM turnover and the risk of SCD in HF patients is still unclear.

Therefore, we designed this study was to evaluate the association between serological markers for cardiac ECM turnover and risk of SCD which access by HRV parameters.

Methods

Patients

We studied 21 patients with chronic HF secondary to left ventricular systolic dysfunction (left ventricular ejection fraction ((LVEF)) ≤50 % by echocardiography or Tc99m left ventriculography) and regularly visiting the heart failure clinics in National Taiwan University Hospital. In echocardiography, LVEF were measured via apical 4-chamber view (area-length method) according to the procedures of the American Society of Echocardiography (19). In all patients, a full clinical history was obtained and examination performed by cardiologists (Y-H L or Y-L H). Baseline demographic data, functional status,

cardiovascular risk factors and medication were also recorded. In the definition the etiology of HF, patients with a history of prior myocardial infarction or coronary intervention, either coronary artery bypass graft surgery or percutaneous coronary intervention were consider as ischemic heart disease. Patients with a history of chest pain who had pathologic Q waves on the electrocardiogram and/or dyskinetic areas on the echocardiogram were also included in this group (20). Dilated cardiomyopathy group comprised patients with dilatation of the left ventricle when another distinct etiology had not been found despite routine workup, which would always have included evaluation for the presence of ischemic heart disease (20). Patients with severe valvular disease were excluded in this study.

The management of these HF patients was according to the guideline of heart failure management (3). Specialist nurse-led telephone visiting was conducted as our previous report (21). Venous blood samples were collected in serum separation tubes after overnight fasting on the day of taking 24-h ambulatory ECG Holter recording. After clotting and centrifugation, the serum was stored at −60°C until analysis (~ 1 year). The study was approved by the ethical committee of the National Taiwan University Hospital and all subjects gave informed consent.

HRV analysis

All patients underwent 24-h ambulatory ECG Holter recording (MyECG E3–80, Mircostar Company, Taipei) 3 months after condition being stable. The ECG signals were sampled at 250 Hz and stored in SD card for offline analysis on a microcomputer. Abnormal complexes or noisy were visually inspected and rejected by comparison to the adjacent QRS morphologic features. The annotated signals which consisted of more than 80% of qualified normal sinus beats were then enrolled for the analysis of HRV including the time domain and frequency domain analysis. The following time domain parameters were computed. SDNN: standard deviation (SD) of all normal-to-normal R-R intervals for the 24-h recording. PNNx: the percentage of the number of paired adjacent NN intervals which absolute differences are greater than × ms during entire recording. We obtained the pNN statistics of not only 50 ms but also 20 ms which has been suggested to have better discriminative power between different physiological conditions (22).

Frequency domain parameters were calculated by using fast fourier transform and the density of the spectral in given bands were derived from the sum of area within specific frequency range suggested by the North American Society of Pacing and Electrophysiology (23)-the very low frequency (VLF) (0.0033–0.04 Hz), low frequency (LF) (0.04 to 0.15 Hz), and high frequency (HF) (0.15 to 0.4 Hz).

Laboratory analysis

Brain natriuretic peptide (BNP) was measured by an enzyme immunoassay kit (BNP-32, Phoenix pharmaceuticals, Belmont, USA). The intra-assay variation was <5% and inter-assay variation was <14%. The range of detection was 0–100000 ng/L (from manufacturer information). Serum type I amioterminal propeptide of procollagen (PINP) was determined by a rapid equilibrium radioimmunoassay kit (No. 67034, Orion Diagnostica, Espoo, Finland). The intra- and interassay variations were < 7%. The detection limit of this method was 2 μg/l (from manufacturer information). Serum PIIINP was determined by a coated-tube radioimmunoassay (No. 68570, Orion Diagnostica, Espoo, Finland). The detection limit of PIIINP was 0.3 μg/l. The intra-and interassay variations of serum PIIINP were < 5% (from manufacturer information). Serum tissue inhibitor of metalloproteinase 1 (TIMP-1) was measured by an enzyme immunoassay kit (DTM100, R & D systems, Minneapolis, USA). The intra- and interassay variations were < 5% (from manufacturer information). The detection limit of this method was 0.08 ng/ml. Serum matrix metalloproteinase-2 (MMP-2)

was measured by an enzyme immunoassay kit (DMP200, R & D systems, Minneapolis, USA). The intra- and interassay variations were < 6% and <8% (from manufacturer information). The detection limit of this method was 0.16 ng/ml. Serum matrix metalloproteinase-9 (MMP-9) was measured by an enzyme immunoassay kit (DMP900, R & D systems, Minneapolis, USA). The intra- and inter-assay variations were < 3% and μ8% and the detection limit was 0.156 ng/ml (from manufacturer information).

Statistical analysis

All continuous results are expressed as the median (25^{th}, 75^{th} percentile). Comparisons between groups for continuous data were made using the Mann-Whitney U-test. Differences between proportions were assessed by the Chi-square test or Fisher's exact test. Spearman non-parametric correlation test was used to analyze the association between serum markers of ECM turnover and HRV parameters. Using SDNN < 65.3 ms as a predictor, the receiver operating characteristic curve was performed and the optimal cut point was obtained from the Youden index (24). The sensitivity, specificity, positive prediction rate, negative prediction rate of cut point were expressed by value (95% confidence interval). Statistical analyses were performed with SPSS for Windows, version 10.0 (SPSS Inc., Chicago, IL, USA). A probability value of $p < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

A total of 21 (15 males and 6 females) patients were enrolled. The demographic and biochemical data and medication history are shown in table 1. The measurement of LVEF was performed by Tc99m left ventriculography in 6 patients, and by echocardiogram in the other 15 patients.

Serum BNP and ECM turnover markers, HRV parameter and its correlations

The data of serum BNP and ECM turnover markers are shown in table 2. The values of serum BNP and ECM turnover markers were not associated with LVEF, serum creatinine level and usage of medications. Besides, serum BNP levels were not correlated with serum PIIINP levels.

The HRV parameters are shown in table 3. The usage of spironolactone was significantly associated with pNN50 (r=0.575, p=0.006) and HF (r=0.470, p=0.032). The values of HRV parameters were not associated with LVEF, serum creatinine level and usage of other medications.

The correlations among serum markers of ECM turnover and values of HRV parameters are shown in table 4. The serum PIIINP level was significantly correlated with most HRV parameters, except LF/HF ratio. PINP, MMP-2, 9, TIMP-1 were not correlated with HRV parameters.

In table 5, patients with higher PIIINP levels (>mean level; group 2) had significantly lower SDNN, pNN50, pNN20, VLF, LF, HF value than patients with lower PIIINP level (<mean level; group 1).

Using SDNN < 65.3 ms as a predictor, the receiver operating characteristic curve was performed, and the area under curve was 0.894 for PIIINP. By using PIIINP 6.07μg/L as a cutoff point, the sensitivity, specificity, positive prediction rate, negative prediction rate, and accuracy were 100% (51%, 100%), 67% (39%, 87%), 55% (25%, 82%), 100% (66%, 100%), and 76%, respectively. (figure 1)

DISCUSSION

In the present study, we found the relationship between serum PIIINP level and HRV parameters, which are the indicators of cardiac autonomic control and SCD in HF patients. To our knowledge, this is the first study demonstrating such association and giving PIIINP a potential role to monitor cardiac autonomic tone in HF patients. In the present study, patients with elevated serum PIIINP level have depressed SDNN, pNN50, pNN20, VLF, LF, and HF which implied impaired cardiac autonomic control. The demographic and biochemical data and LVEF were comparable between two groups. Therefore, the difference of HRV parameters may not be due to the difference of cardiac systolic function or function status in HF patients.

In the development and progression of systolic HF, LV remodeling is a critical pathophysiologic process. Cardiac ECM turnover is an essential process of LV remodeling and interstitial fibrosis (14). Interstitial fibrosis may provide electrical heterogeneity and substrate for arrhythmogenicity. That may potentially contribute to the occurrence of ventricular tachycardia or fibrillation and subsequent SCD. In recent studies, altered expression of several markers of ECM turnover involving collagen synthesis or degradation in failing myocardium has previously been reported (13–14,25). In addition, the serum markers of ECM turnover provided the prognostic valve and clinical implications (13–17). Among them, serum PIIINP was one of the most important and well known markers. In patients with HF, serum PIIINP level was widely used not only to evaluate cardiac function (15) and exercise capacity (26), but to predict prognosis (16,18), and medication response (18). However, the relation between serological markers for cardiac ECM turnover and HRV parameter or the risk of SCD in HF patients is still unclear. Therefore we designed this study. In this study, we found PIIINP is highly associated with HRV parameters. Although the patient number is small, this study provides the evidence of the further large outcome study using PIIINP as a predict marker.

In our study, PIIINP, not PINP was associated with HRV parameter. Both collagen type I and III were present in cardiac tissue. Although type I collagen is predominant in myocardium, type III collagen is more specific to cardiac tissue (18,27). In the study of Alla et al., serum PIIINP rather than PINP changed in patients with congestive heart failure (27). Besides, the evidence of PIIINP in prediction of HF prognosis is much more abundant than PINP. Furthermore, serum PIIINP level decreases more significantly than PINP after spironolactone usage (18). Therefore, PIIINP seems to be a better marker than PINP in HF patients. However, one study involving post-myocardial infarction patients revealed paradoxical association between serum PIIINP and the occurrence of ventricular tachycardia (17). In that study, patients with higher PINP had higher incidence of ventricular arrhythmia, but with higher PIIINP had lower incidence of ventricular arrhythmia. Different patient setting, disease severity and disease causes may be the possible explanations. The patients included in that study are post myocardial infarction and with a median serum PIIINP level 4.3 μg/L and a median BNP level 64 ng/L. In our study, 52 % patients was non-ischemic origin in HF etiology, and with median serum PIIINP level 6.4 μg/L and a median BNP level 1840 ng/L. The mode of myocardial remodeling and type I/III ratio in remodeling may be different in patients in these two studies.

The relation between PIIINP and HRV parameter may be also associated with renin-angiotensin-aldosterone (RAAS) signaling. RAAS activation is an important pathophysiological condition in HF involving autonomic imbalance and interstitial fibrosis (28). Aldosterone blockade acutely improves cardiac vagal control (29). In recent clinical studies, administration of an aldosterone antagonist, spironolactone, improves cardiac autonomic control measured by HRV (30–31), decease ventricular arrhythmia (32), reduced

serum PIIINP level (30) and improve survival (18,33). However, the impact of RAAS activation on the association of PIIINP and HRV parameter is not clear and needs further investigations.

This study had limitations. First, this study is cross-section design and the patient number is relative small. It cannot provide final evidence, but is suitable to stimulate further research into this area. Second, the values serum markers of ECM turnovers (for example, PIIINP) were not associated with LVEF, serum creatinine level and usage of medications. The discrepancy of the association between current study and previous study may due to small number of this study. However, unlike creatinine, spironolactone usage, or heart failure status (such us NYHA functional classification), the association between serum PIIINP and LVEF are not consistent. In previous studies, serum PIIINP is associated with serum creatinine and NYHA functional classification (34), rather than with LVEF (18,34–35). It seems that the relations between PIIINP and cardiac systolic function need to be further validated. Third, the method of LVEF measurement is not uniform in our study, it may add bias and decrease the power to detect the association among LVEF and other parameters. However, Tc99m left ventriculography is highly correlated with echocardiography, even in patients with regional wall motion abnormality. (36)

Fourth, this is not an outcome study, and we used HRV parameter as SCD outcome predictors. Further large scale outcome study is needed to demonstrate the prognostic value of PIIINP. Fifth, no histological evidence was available to demonstrate the relation between tissue formation of type III collagen and serum fibrosis markers. Besides, histological data provided more information about the mechanism among serum PIIINP, tissue fibrosis, inhomogenities of local nerve innervations and arrhythmogenicity. However, it is not ethical to perform endomyocardial biopsy in these patients routinely without other clinical indication.

Conclusions

PIIINP was significantly correlated with time- and frequency-domain analysis of HRV in HF patients. Elevated serum PIIINP is associated with more severe impairment of cardiac autonomic control. Serum PIIINP level is a potential serological marker to evaluate cardiac autonomic control and risk of SCD in HF patients.

List of abbreviations

HF	heart failure
SCD	sudden cardiac death
HRV	heart rate variability
SD	standard deviation
SDNN	standard deviation of all normal-to-normal R-R intervals
ECM	extra-cellular matrix
PIIINP	type III aminoterminal propeptide of procollagen
LVEF	left ventricular ejection fraction
PNNx	the percentage of the number of paired adjacent NN intervals
VLF	very low frequency
LF	low frequency

HF	high frequency
BNP	brain natriuretic peptide
PINP	type I amioterminal propeptide of procollagen
TIMP-1	tissue inhibitor of metalloproteinase 1
MMP-2	matrix metalloproteinase-2
MMP-9	matrix metalloproteinase-9

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REFERENCES

1. Yndestad A, Ueland T, Oie E, Florholmen G, Halvorsen B, Attramadal H, et al. Elevated levels of activin A in heart failure: potential role in myocardial remodeling. Circulation. 2004; 109:1379–1385. [PubMed: 14993131]
2. Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, et al. Heart disease and stroke statistics--2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2008; 117:e25–e146. [PubMed: 18086926]
3. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. Circulation. 2005; 112:e154–e235. [PubMed: 16160202]
4. Tomaselli GF, Zipes DP. What causes sudden death in heart failure? Circ Res. 2004; 95:754–763. [PubMed: 15486322]
5. Waldo AL, Camm AJ, deRuyter H, Friedman PL, MacNeil DJ, Pauls JF, et al. Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. The SWORD Investigators. Survival With Oral d-Sotalol. Lancet. 1996; 348:7–12. [PubMed: 8691967]
6. Singh SN, Fletcher RD, Fisher SG, Singh BN, Lewis HD, Deedwania PC, et al. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. N Engl J Med. 1995; 333:77–82. [PubMed: 7539890]
7. Kadish A, Dyer A, Daubert JP, Quigg R, Estes NA, Anderson KP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med. 2004; 350:2151–2158. [PubMed: 15152060]
8. Knight BP, Goyal R, Pelosi F, Flemming M, Horwood L, Morady F, et al. Outcome of patients with nonischemic dilated cardiomyopathy and unexplained syncope treated with an implantable defibrillator. J Am Coll Cardiol. 1999; 33:1964–1970. [PubMed: 10362200]
9. Chattipakorn N, Incharoen T, Kanlop N, Chattipakorn S. Heart rate variability in myocardial infarction and heart failure. Int J Cardiol. 2007; 120:289–296. [PubMed: 17349699]

10. Bilchick KC, Fetics B, Djoukeng R, Fisher SG, Fletcher RD, Singh SN, et al. Prognostic value of heart rate variability in chronic congestive heart failure (Veterans Affairs' Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure). Am J Cardiol. 2002; 90:24–28. [PubMed: 12088774]
11. Lin YH, Ho YL, Wang TD, Liu CP, Kao HL, Chao CL, et al. The relation of amino-terminal propeptide of type III procollagen and severity of coronary artery disease in patients without myocardial infarction or hibernation. Clin Biochem. 2006; 39:861–866. [PubMed: 16919252]
12. Lin YH, Liu CP, Hsu RB, Lee CM, Wang SS, Kao HL, et al. Association of amino-terminal propeptide of type III procollagen and acute myocardial rejection in male patients receiving heart transplantation. Clin Chem Lab Med. 2007; 45:1004–1008. [PubMed: 17867989]
13. George J, Patal S, Wexler D, Roth A, Sheps D, Keren G. Circulating matrix metalloproteinase-2 but not matrix metalloproteinase-3, matrix metalloproteinase-9, or tissue inhibitor of metalloproteinase-1 predicts outcome in patients with congestive heart failure. Am Heart J. 2005; 150:484–487. [PubMed: 16169329]
14. Graham HK, Horn M, Trafford AW. Extracellular matrix profiles in the progression to heart failure. European Young Physiologists Symposium Keynote Lecture-Bratislava 2007. Acta Physiol (Oxf). 2008; 194:3–21. [PubMed: 18577182]
15. Rossi A, Cicoira M, Golia G, Zanolla L, Franceschini L, Marino P, et al. Amino-terminal propeptide of type III procollagen is associated with restrictive mitral filling pattern in patients with dilated cardiomyopathy: a possible link between diastolic dysfunction and prognosis. Heart. 2004; 90:650–654. [PubMed: 15145870]
16. Cicoira M, Rossi A, Bonapace S, Zanolla L, Golia G, Franceschini L, et al. Independent and additional prognostic value of aminoterminal propeptide of type III procollagen circulating levels in patients with chronic heart failure. J Card Fail. 2004; 10:403–411. [PubMed: 15470651]
17. Blangy H, Sadoul N, Dousset B, Radauceanu A, Fay R, Aliot E, et al. Serum BNP, hs-C-reactive protein, procollagen to assess the risk of ventricular tachycardia in ICD recipients after myocardial infarction. Europace. 2007; 9:724–729. [PubMed: 17526509]
18. Zannad F, Alla F, Dousset B, Perez A, Pitt B. Limitation of excessive extracellular matrix turnover may contribute to survival benefit of spironolactone therapy in patients with congestive heart failure: insights from the randomized aldactone evaluation study (RALES). Rales Investigators. Circulation. 2000; 102:2700–2706. [PubMed: 11094035]
19. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005; 18:1440–1463. [PubMed: 16376782]
20. Pecini R, Moller DV, Torp-Pedersen C, Hassager C, Kober L. Heart failure etiology impacts survival of patients with heart failure. Int J Cardiol. 2010
21. Ho YL, Hsu TP, Chen CP, Lee CY, Lin YH, Hsu RB, et al. Improved cost-effectiveness for management of chronic heart failure by combined home-based intervention with clinical nursing specialists. J Formos Med Assoc. 2007; 106:313–319. [PubMed: 17475609]
22. Mietus JE, Peng CK, Henry I, Goldsmith RL, Goldberger AL. The pNNx files: re-examining a widely used heart rate variability measure. Heart. 2002; 88:378–380. [PubMed: 12231596]
23. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation. 1996; 93:1043–1065. [PubMed: 8598068]
24. Perkins NJ, Schisterman EF. The inconsistency of "optimal" cutpoints obtained using two criteria based on the receiver operating characteristic curve. Am J Epidemiol. 2006; 163:670–675. [PubMed: 16410346]
25. Yamazaki T, Lee JD, Shimizu H, Uzui H, Ueda T. Circulating matrix metalloproteinase-2 is elevated in patients with congestive heart failure. Eur J Heart Fail. 2004; 6:41–45. [PubMed: 15012917]

26. Radauceanu A, Ducki C, Virion JM, Rossignol P, Mallat Z, McMurray J, et al. Extracellular matrix turnover and inflammatory markers independently predict functional status and outcome in chronic heart failure. J Card Fail. 2008; 14:467–474. [PubMed: 18672194]
27. Alla F, Kearney-Schwartz A, Radauceanu A, Das Dores S, Dousset B, Zannad F. Early changes in serum markers of cardiac extra-cellular matrix turnover in patients with uncomplicated hypertension and type II diabetes. Eur J Heart Fail. 2006; 8:147–153. [PubMed: 16198628]
28. Brilla CG, Matsubara LS, Weber KT. Anti-aldosterone treatment and the prevention of myocardial fibrosis in primary and secondary hyperaldosteronism. J Mol Cell Cardiol. 1993; 25:563–575. [PubMed: 8377216]
29. Fletcher J, Buch AN, Routledge HC, Chowdhary S, Coote JH, Townend JN. Acute aldosterone antagonism improves cardiac vagal control in humans. J Am Coll Cardiol. 2004; 43:1270–1275. [PubMed: 15063441]
30. MacFadyen RJ, Barr CS, Struthers AD. Aldosterone blockade reduces vascular collagen turnover, improves heart rate variability and reduces early morning rise in heart rate in heart failure patients. Cardiovasc Res. 1997; 35:30–34. [PubMed: 9302344]
31. Yee KM, Pringle SD, Struthers AD. Circadian variation in the effects of aldosterone blockade on heart rate variability and QT dispersion in congestive heart failure. J Am Coll Cardiol. 2001; 37:1800–1807. [PubMed: 11401114]
32. Ramires FJ, Mansur A, Coelho O, Maranhao M, Gruppi CJ, Mady C, et al. Effect of spironolactone on ventricular arrhythmias in congestive heart failure secondary to idiopathic dilated or to ischemic cardiomyopathy. Am J Cardiol. 2000; 85:1207–1211. [PubMed: 10802002]
33. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999; 341:709–717. [PubMed: 10471456]
34. Ho YL, Lin YH, Lee CM, Hsu RB, Ting HT, Chou NK, et al. Prognostic significance of adipocytokines and extracellular matrix activity in heart failure patients with high B-type natriuretic peptide. Clin Biochem. 2009; 42:1407–1412. [PubMed: 19560452]
35. Lin YH, Lin LY, Wu YW, Chien KL, Lee CM, Hsu RB, et al. The relationship between serum galectin-3 and serum markers of cardiac extracellular matrix turnover in heart failure patients. Clin Chim Acta. 2009; 409:96–99. [PubMed: 19747906]
36. Chua T, Yin LC, Thiang TH, Choo TB, Ping DZ, Leng LY. Accuracy of the automated assessment of left ventricular function with gated perfusion SPECT in the presence of perfusion defects and left ventricular dysfunction: correlation with equilibrium radionuclide ventriculography and echocardiography. J Nucl Cardiol. 2000; 7:301–311. [PubMed: 10958271]

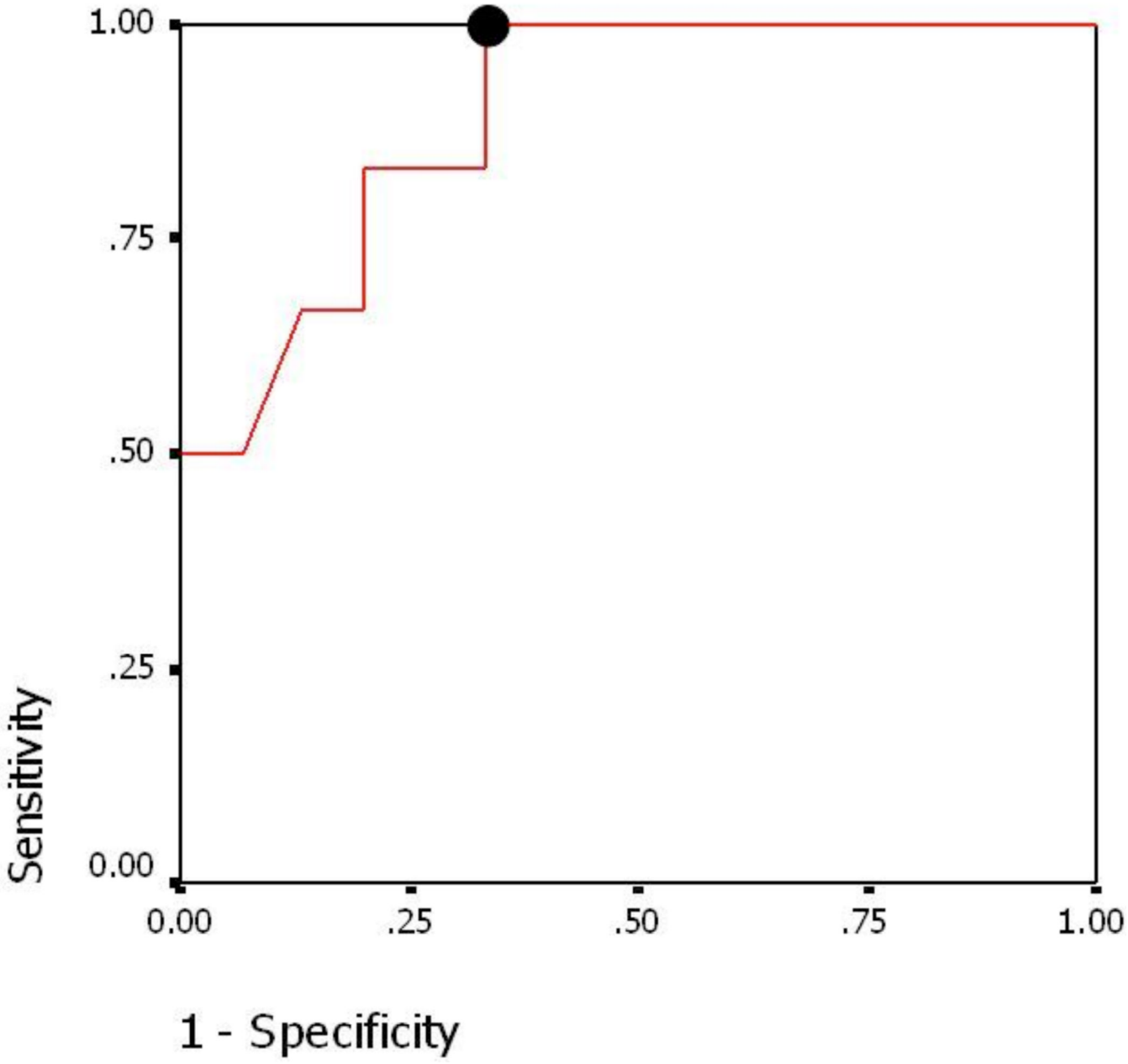

Figure 1.
Receiver operating characteristic curves for the ability of PIIINP to detect SDNN < 65.3 ms. Area under the curve is 0.894. By using PIIINP 6.07μg/L as a cutoff point (black dot), the sensitivity and specificity were 100% and 67%, respectively. The optimal cut point is calculated by the Youden index

Table 1

Clinical data of patients (n=21)

Patient characteristics	Data
Age, years	62 (52, 78)
Male/Female	15 (71) /6 (29)
LVEF(%)	33 (23,41)
NYHA	
I	2 (10)
II	11 (52)
III	8 (38)
IV	0 (0)
Creatinine, μmol/L	92 (65, 103)
Body weight, kg	63 (52, 72)
Body height, cm	165 (154, 170)
Body mass index, Kg/m^2	23 (22, 28)
Fasting glucose, mmol/L	6.4 (5.4, 7.8)
Triglyceride, mmol/L	1.6 (1.0, 2.6)
Cholesterol, mmol/L	5.3 (4.5, 5.7)
High-density lipoprotein, mmol/L	1.0 (0.9, 1.2)
Low-density lipoprotein, mmol/L	3.3 (2.4, 3.8)
Hemoglobin, g/L	129 (116, 144)
Uric acid, μmol/L	440 (357, 467)
Etiology of heart failure	
Ischemic heart disease	10 (48)
Dilated cardiomyopathy	11 (52)
Hypertension	6 (29)
Diabetes mellitus	8 (38)
Medication	
ACE-I/ARB	16 (76)
β-blocker	10 (48)
Loop diuretics	12 (57)
Digoxin	12 (57)
Spironolactone	6 (29)

Data are expressed as the median (25^{th}, 75^{th} percentile) or number (percentage).

Abbreviations: NYHA= New York Heart Association; LVEF= left ventricular ejection fraction; ACE-I= angiotensin converting enzyme inhibitor; ARB= angiotensin receptor blocker.

Table 2

Serum markers of cardiac extra-cellular matrix turnover

BNP, ng/L	1840 (1345, 2090)
PINP, μg/L	32 (22, 46)
PIIINP, μg/L	6.4 (4.6, 7.2)
TIMP ng/ml	143 (108, 173)
MMP-2 ng/ml	241 (203, 271)
MMP-9 ng/ml	58 (32, 117)

Data are expressed as the median (25^{th}, 75^{th} percentile).

Abbreviations: BNP= brain natriuretic peptide; PINP = type I amioterminal propeptide of procollagen; PIIINP = type III amioterminal propeptide of procollagen; TIMP = tissue inhibitor of metalloproteinase; MMP = matrix metalloproteinase.

Table 3

heart rate variability parameter

Time domain	
SDNN, ms	75 (60, 98)
pNN50, ms	1.2 (0.3, 4.0)
pNN20, ms	13.8 (2.6, 21.5)
Frequency domain	
VLF, ms^2	600 (254, 868)
LF, ms^2	124 (27, 209)
HF, ms^2	54 (17, 112)
L/H ratio	1.7 (0.9, 2.7)

Data are expressed as the median (25^{th}, 75^{th} percentile).

Abbreviations: SDNN=standard deviation of all normal RR intervals; pNN50= percentage of adjacent NN interval differences >50 ms; pNN20=percentage of adjacent NN interval differences >20 ms, VLF=very low frequency, LF=low frequency; HF=high frequency; L/H ratio: low frequency /high frequency ratio.

Table 4

Correlation between serum markers of cardiac extra-cellular matrix turnover and heart rate variability parameter

		PINP	PIIINP	TIMP	MMP2	MMP9
SDNN	R	−0.214	−0.722	−0.204	−0.396	0.066
	p	0.351	<0.001	0.375	0.075	0.775
pNN50	R	−0.190	−0.528	−0.249	−0.389	0.093
	p	0.410	0.014	0.277	0.082	0.689
pNN20	R	−0.112	−0.545	−0.208	−0.412	0.099
	p	0.630	0.002	0.366	0.064	0.670
VLF	R	−0.178	−0.490	−0.338	−0.294	0.087
	p	0.440	0.024	0.134	0.197	0.708
LF	R	−0.227	−0.491	−0.229	−0.357	0.134
	p	0.225	0.024	0.319	0.112	0.563
HF	R	−0.192	−0.513	−0.235	−0.344	0.047
	p	0.404	0.018	0.305	0.127	0.841
L/H ratio	R	−0.106	0.103	−0.109	−0.149	0.205
	p	0.646	0.658	0.638	0.51	0.372

Abbreviations: BNP= brain natriuretic peptide; PINP = type I amioterminal propeptide of procollagen; PIIINP = type III amioterminal propeptide of procollagen; TIMP = tissue inhibitor of metalloproteinase; MMP = matrix metalloproteinase; SDNN=standard deviation of all normal RR intervals; pNN50= percentage of adjacent NN interval differences >50 ms; pNN20=percentage of adjacent NN interval differences >20 ms, VLF=very low frequency, LF=low frequency; HF=high frequency; L/H ratio: low frequency /high frequency ratio.

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Table 5

Character between two groups

	Group 1 (n=10)	Group 2 (n=11)	P
PIIINP, μg/L	3.6 (4.6, 5.4)	7.2 (6.5, 8.7)	<0.001
BNP, ng/L	1570 (1240, 2113)	1900 (1780, 2130)	0.275
Age, years	70 (49, 80)	59 (52, 68)	0.314
Sex	7 (70)	8 (73)	1.000
LVEF	36 (23, 44)	32 (21, 40)	0.341
NYHA, functional classification	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	0.605
Creatinine, μmol/L	72 (59, 101)	92 (69, 107)	0.349
Body mass index	23 (20, 29)	23 (22, 27)	0.756
Etiology of heart failure			
Ischemic heart disease	4 (40)	7 (64)	0.395
Dilated cardiomyopathy	6 (60)	4 (36)	
Hypertension	1 (10)	5 (45)	0.149
Diabetes mellitus	3 (30)	5 (45)	0.659
Medication			
ACE-I/ARB	8 (80)	8 (73)	1.000
β-blocker	3 (30)	7 (64)	0.198
Loop diuretics	3 (30)	9 (82)	0.030
Digoxin	5 (50)	7 (64)	0.670
Spironolactone	4 (40)	2 (18)	0.361
HRV parameter			
SDNN	93 (76, 105)	62 (36, 73)	0.003
PNN50	4.0 (0.7, 6.2)	0.6 (0.1, 1.4)	0.006
PNN20	22 (12, 32)	5.6 (0.9, 13.8)	0.004
VLF	768 (547, 1174)	383 (74, 658)	0.020
LF	209 (102, 247)	33 (15, 162)	0.005
HF	98 (29, 200)	30 (10, 61)	0.016
L/H ratio	1.8 (0.8, 2.6)	1.7 (1.0, 2.8)	0.973

Data are expressed as the median (25^{th}, 75^{th} percentile) or number (percentage).

Abbreviations: PIIINP = type III amioterminal propeptide of procollagen; NYHA= New York Heart Association; LVEF= left ventricular ejection fraction; ACE-I= angiotensin converting enzyme inhibitor; ARB= angiotensin receptor blocker; SDNN=standard deviation of all normal RR intervals; pNN50= percentage of adjacent NN interval differences >50 ms; pNN20=percentage of adjacent NN interval differences >20 ms, VLF=very low frequency, LF=low frequency; HF=high frequency; L/H ratio: low frequency /high frequency ratio