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Correlation between cardiac troponin I and dilated cardiomyopathy and mechanism analysis.

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Abstract

Objective: Compared with other myocardial enzymes like CK and CK-MB, this study investigates the theoretical basis of whether or not cardiac Troponin I can be used as a diagnostic index of dilated cardiomyopathy. Clinical significance of serum cTnI level of patients with dilated cardiomyopathy (DCM) and its mechanism are studied further.

Methods: Firstly, we detected serum cTnI, CK and CK-MB level of patients with DCM in hospital, then detected the change of serum cTnI, CK and CK-MB level of patients with DCM under different cardiac function levels and left ventricular ejections. Then, patients were divided into positive group when cTnI>0.05 μg/L and into negative when cTnI<0.05 μg/L. Each group consisted of 30 patients. We detected patients' left atrial diameter (LA), left ventricular end diastolic (LVED), left ventricular end systolic (LVES) and left ventricular ejection fraction (LVEF) by methods of echocardiography, and monitored cardiac arrhythmia with conventional ECG and 24 h dynamic electrocardiogram.

Results: Serum cTnI level of patients in DCM group was significantly higher than that of patients in control group (p<0.01).Serum cTnI level of class IV cardiac function patients was significantly higher than that of class III function (p<0.01). Serum cTnI level of LVEF ≤ 35% patients was higher than that of LVEF>35% patients. There was no significant difference in patients' level of CK or CK-MB, indicating that cTnI level is better indicator for molecular diagnosis of patients with DCM. We further divided patients with DCM into positive and negative group by level of serum cTnI. Results demonstrated that cardiac function, LVED and LVES of patients in positive group were significantly higher than those of patients in negative group while LVEF was lower (p<0.05). Patients in the negative group were prone to ventricular arrhythmia while those in positive group were prone to atrial arrhythmia and intraventricular block.

Conclusion: Level of serum cTnI can be used as indicator for molecular diagnosis of patients with DCM. Increase of serum cTnI in patients with DCM indicates severe myocardial damage and unfavorable prognosis.

Keywords: Dilated cardiomyopathy, Cardiac, Cardiac Troponin I (cTnI), Arrhythmia, Molecular diagnosis.

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Introduction

Primary dilated cardiomyopathy (DCM) is an agnogenic myocardial disease with left ventricular or biventricular dilated function impairment with systolic function impairment as major characteristics. Its clinical manifestations include progressive heart failure, cardiac arrhythmia, thromboembolism and sudden death. The disease turns progressively more severe and is of no specific therapy. It has poor prognosis, and its 5-year survival rate is less than 50% [1,2]. What's more, since there are no specific symptoms, physical signs and laboratory examinations for the diagnosis of DCM, plus its concealed or atypical clinical manifestations on early-stage patients, the early diagnosis of DCM is rather difficult. At present, the diagnostic standard proposed by Chinese Society of Cardiology in 1995 is most applied in the diagnosis of DCM. In recent years, with progress in research of molecular mechanism of dilated cardiomyopathy, damage and necrosis of cardiomyocytes, which is an important factor of cardiac function ingravescence, has been detected in development of DCM [3,4]. The rating of patients' cardiac

function has long been relying on indices including ventricular diameter, ventricular ejection fraction, NYHA (New York Heart Association) cardiac function grading and examinations of cardiac function, but there is still no sensible and specific biochemical indicator for the judgment of myocardial damage and prognosis of individual patient [5-7]. Therefore, we need a serum marker that detects myocardial damage, especially those with minute lesions precisely to detect the myocardial damage of patients with DCM.

Troponin has become the primary biological indicator for the diagnosis of myocardial damage in recent years. Cardiac troponin I (cTnI) is a type of cardiac specific troponin. It is highly-sensitive and highly-specific when used as indicator of myocardial damage [8] and has been widely applied in diagnosis and research of diseases including acute myocardial infarction and myocarditis. It is also acclaimed as major biological indicator in risk stratification for acute coronary syndrome and its prognosis. However, there are few reports of cTnI as used in diagnosis of myocardial damage in nonischemic myocardial diseases. In 1997, Missov et al. [9] made the first report about increase of serum cTnI in patients with chronic congestive heart failure, and researchers conducted several studies on cTnI in patients with nonischemic myocardial diseases thereafter. La Vecchia et al [10]. proved that level of cTnI increased in patients with nonischemic myocardial diseases, they also discovered that patients with higher cTnI level had notable hemodynamic abnormalities including increase in pulmonary capillary wedge pressure and decrease in cardiac index, thus were of higher incidence rate of ventricular dysfunction and death [11].

In this study, we chose 104 patients of DCM in hospital to probe the abnormality in serum component of patients with DCM when compared with that of normal people. We focused mainly on the change of serum cTnI level in patients with DCM in order to probe the clinical significance of change of level of serum cTnI and seek after a molecule marker that diagnoses DCM at individual level.

Subjects and Methods

Subjects

We selected 104 patients diagnosed with DCM from 2012.8 to 2014.7 consisting of 67 males and 37 females with an average age of 51.7 ± 12.2. All cases accorded with diagnosis criteria proposed by Chinese Society of Cardiology in 1995. 19 cases were proved with normal coronary artery or stenosis degree <30% by coronary angiography. 12 cases were indicated as with DCM by radio-isotopic myocardial scintigraphy. The other 73 patients didn't take coronary angiography or radio-isotopic myocardial scintigraphy due to cognitional or economic reasons, but they were all younger than 50 years old, showed no clinical symptoms of myocardial ischemia, and no dynamic change indicating myocardial ischemia appeared in electrocardiogram. There were 41 cases of class III cardiac function and 63 cases of class IV cardiac function. We chose 42 male patients and 33 females with an average age of 42.4 ± 7.6 to make a control group totalling 75. None of the selected patients was with other diseases elevating their level of cTnI level including pulmonary embolism, acute or chronic dysfunction of liver or kidney, acute or chronic inflammation or refractory hypertension.

Patients with DCM were treated with conventional treatment protocol for heart failure, including digoxin, diuretic, and angiotensin converting enzyme inhibitor, β-blocker and long-acting oral nitrate preparation.

Serum cTnI, CK and CK-MB Determination by the ELISA Method

Two blood samples of patients with DCM were taken. The first sample was taken within the first 12 hours following their admission, the second in the 5-7th day of conventional treatment. Blood sample of control group was taken within the first 12 hours following their admission. We determined cTnI, CK and CK-MB of each serum sample respectively by the ELISA method.

We thawed ELISA kits and rat plasma samples at indoor temperature while diluted lotion, determined plasma, standard substance and streptavidin marked by horseradish peroxidase into required concentration. Then we added 50 μL of standard substance, reference substance and determined panel into each well respectively, sealed the panel and incubated it at indoor temperature for 2 hours, discarded liquid in the panel, added 300 μL of lotion to each well, discarded liquid again, patted test panel dry on absorbent paper, then repeated above steps for 6 times. Following that, we added to each well 100 μL of treptavidin marked by horseradish peroxidase, sealed the panel and incubated it at indoor temperature for 45 minutes, discarded liquid in the panel, added 300 μL of lotion to each well, discarded liquid again, patted test panel dry on absorbent paper, then repeated above steps for 6 times. Later on we added 100 μL of TMB to each well in dark room and incubated it at indoor temperature for 15 minutes. Then we added 100 μL of stop buffer to each well, tapped frame of testing panel to make the liquid homogeneous, turning wells kelly to visible extend. We then measured OD value of the ELISA panel by automatic enzyme-labeling measuring instrument under wavelength 450 nm. Abscissa of the curve represented concentration of standard substance while the ordinate represented OD value. We generated a standard curve using regression fitting process, and calculated the concentration of determined anti body in determined plasma with it.

Ultrasound cardiogram

We divided patients with cTnI level>0.05 μg/L into positive group and cTnIcTnI ≤ 0.05 μg/L into negative group and randomly chose 30 cases from both groups respectively. Doctors in our group operated a ViVi7 Doppler ultrasound diagnostic apparatus equipped with 2.5MHz probe to determine 2-dimensional and M-type ultrasonic parameters including left atrial diameter (LA), left ventricular end diastolic (LVED), left ventricular end systolic (LVES) and left

ventricular ejection fraction (LVEF) at parasternal long-axis section. All the parameters were average of those in 3 cardiac cycles. DCG data was obtained from a DSM 700 12-channel dynamic electrocardiogram recorder and artefact was rejected using a combination of computer analysis and manual analysis by high qualification attending physicians.

Statistic process

The data was analyzed using SPSS18.0 commercial statistical software. All the measurement data were expressed as (x ± s). Independent-samples t test was applied for mean comparison between groups. A p-value less than 0.05 was considered statistically significant.

Results

Expression level of serum cTnI in DCM group is significantly higher than that of control group

In order to observe change of blood DCM in patients with DCM, we drew blood of patients diagnosed with DCM, determined change of cTnI level using ELISA method, and used change of CK and CK-MB level as comparison. Results demonstrated that serum cTnI level of patients with DCM was 0.371 ± 0.157 μg/L (0.01-0.75 μg/L), serum CK level was 76.22 ± 24.17 IU/L (36-187 IU/L) and serum CK-MB level was 16.29 ± 4.2 IU/L (6-53 IU/L). Level of serum cTnI, CK and CK-MB of control group were normal. Serum cTnI level in patients with DCM was significantly different than that of control group as indicated by statistic process (0.371 ± 0.157 μg/L:0.017 ± 0.005 μg/L, p<0.01), which meant that serum cTnI level in patients with DCM was significantly higher than that in control group, while level of serum CK and serum CK-MB showed no significant difference (Table. 1). Results proved that serum cTnI is better detection index than CK and CK-MB.

Table 1. *Determination of level of serum cTnI, CK and CK-MB (x ± s).*

Group	Number of cases	cTnI(μg/L)	CK(IU/L)	CK-MB(IU/L)
Control group	75	0.017 ± 0.005	70.34 ± 20.63	14.73 ± 3.9
DCM Group	104	0.371 ± 0.157*	76.22 ± 24.17	16.29 ± 4.2

Note: Compared with control group, *p<0.01.

Serum cTnI level in patients of class IV cardiac function is significantly higher than that in patients of class III cardiac function

In order to explore the correlation between serum cTnI level and cardiac function in patients with DCM, we further divided patients with DCM into groups by their cardiac function, and conducted statistical analysis of serum cTnI level in patients with DCM. Results demonstrated that patients of class III cardiac function (31 cases) had serum cTnI level of 0.158 ± 0.104 μg/L, and that of class IV cardiac function patients (42 cases) was 0.352 ± 0.141 μg/L, which was significantly different from the former (p<0.01), thus indicated that class patients of class IV cardiac function had significantly higher level of serum cTnI as compared with class III cardiac function patients while their serum CK and serum CK_MB level showed no significant difference (Table 2). Data implied that patients with higher cardiac function class were likely to possess higher serum cTnI level while level of serum CK or serum CK-MB seemed irrelevant with patients' cardiac function level, which further indicated usability of serum cTnI level in diagnosis of DCM.

Table 2. *Determination of serum cTnI, serum CK and serum CK-MB level in patients of varying cardiac function and ejection fraction (x ± s)*

Group	Number of cases	cTnI(μg/L)	CK(IU/L)	CK-MB(IU/L)
Class III cardiac function	46	0.173 ± 0.123	73.1 ± 29.6	15.3 ± 5.9
Class IV cardiac function	58	0.395 ± 0.162**	81.3 ± 30.5	17.2 ± 6.4
LVEF35%	39	0.168 ± 0.093	72.4 ± 30.2	14.8 ± 6.1
LVEF ≤ 35%	65	0.401 ± 0.136*	81.9 ± 32.5	17.9 ± 6.4

Note: compare class III cardiac function with class IV cardiac function**p0.01; compare LVEF ≤ 35% with LVEF35%*p0.05.

Serum cTnI level in LVEF≤35% patients were above that in LVEF>35% patients, demonstrating a negative correlation with LVEF

In order to further explore serum correlation between patients' cTnI level and LVEF, we divided patients into two groups by their LVEF and conducted statistical analysis of serum cTnI level in patients with DCM. Result demonstrated that serum cTnI level in LVEF>35% patients (29 cases) was 0.162 ± 0.082 μg/L, while LVEF ≤ 35% patients (44 cases) showed serum cTnI level of 0.368 ± 0.137 μg/L. There existed significant difference between two groups (p<0.05), which indicated that serum cTnI level in LVEF ≤ 35% patients were above that in LVEF>35% patients, while no significant difference of serum CK level and serum CK-MB level presented in the comparison between patients of different LVEF (Table 2). Therefore, analysis from perspective of LVEF also indicated that serum cTnI is of higher sensitivity than that of serum CK and serum CK-MB, and can be used as molecular indicator in diagnosis of DCM.

DCM patients with higher cTnI level are also of higher-rated cardiac function

In order to probe the correlation between level of serum cTnI in patients with DCM and their cardiac function, we divided patients further into groups by their cardiac function

classification. And conducted statistical analysis of serum cTnI in patients with DCM. Results demonstrated that patients of class III cardiac function (31 cases) had level of serum cTnI 0.158 ± 0.104 μg/L while that of patients of class IV cardiac function was 0.352 ± 0.141 μg/L. There was significant differences between the two groups ($p<0.01$) as patients of class IV cardiac function possessed a significantly higher level of serum cTnI than that of patients of class III cardiac function while there was no significant difference in their level of serum CK or serum CK-MB (Table 3). Data implied that patients of higher cardiac function classification are also with higher level of serum cTnI, while there exists no correlation between cardiac function classification and level of serum CK or serum CK-BM. This fact further indicated that serum cTnI can be used in diagnosis of DCM.

Table 3. Cardiac function comparison of patients with DCM (cases).

Group	Cases	Class Ⅲ cardiac function	Class Ⅳ cardiac function
Positive	30	12	18
Negative	30	20*	10*

Note: Compare positive group with negative group, *$p < 0.05$.

LVED, LVDS and LVEF in patients of DCM rises with the elevation of serum cTnI level

In order to further probe how change of patients' serum cTnI level affects their physiological status, we divided patients with DCM into 2groups, those with cTnI>0.05 μg/L was divided into positive, cTnI ≤ 0.05 μg/L into negative group. We chose 30 cases randomly from each group and applied ultrasound cardiogram (UCG) monitoring. Results demonstrated that while LA in positive group was higher than that in negative group, the difference was insignificant ($p>0.05$). Table 4 further indicated that compared with negative group, there was significantly higher level of LVED, LVDE and LVEF ($p<0.01$, $p<0.01$, $p<0.01$). This result implied that with the increase of cTnI level, LVED, LVDS and LVEF also raised significantly, showing a positive correlation.

Table 4. Comparison of measured value of UCG in two groups of patients with DCM (x ± s).

UCG index	Positive	Negaive	t value	p value
Number of cases	30	30		
LA (mm)	46.1 ± 6.8	44.9 ± 7.1	1.37	0.05
LVED (mm)	76.7 ± 12.7	68.3 ± 11.9	6.31	0.01
LVDS (mm)	63.2 ± 11.2	55.3 ± 9.6	7.32	0.01
LVEF (%)	30.2 ± 8.1	36.9 ± 7.3	9.24	0.01

Patients with DCM experience arrhythmia more frequently as level of serum cTnI raises

We divided DCM patients with serum cTnI level>0.05 μg/L into positive group, those with serum cTnI level ≤ 0.05 μg/L into negative group. Then we chose 30 cases randomly from each group, calculated the frequency they experienced arrhythmia and analyzed correlation between change in level of serum cTnI and cardiac incidences experienced by patients with DCM. Table 5 suggested that arrhythmia appeared in negative group was mostly atrial arrhythmias including atrial fibrillation, frequent premature atrial contraction and atrial tachycardia while positive group suffered from ventricular arrhythmia like frequent premature ventricular contraction, conduction block including complete left bundle branch block (LBBB), ventricular fibrillation and complex arrhythmia (2 or more abnormalities above were detected).

Table 5. Comparison of occurrence of arrhythmia in two groups of patients with DCM

Group	Number of cases	Sinus tachycardia	Frequent premature atrial contraction	Atrial tachycardia	Atrial fibrillation	Frequent premature ventricular contraction	Sinus tachycardia	LBBB	Complex arrhythmia
Positive	30	1	1	3	5	13	3	8	5
Negative	30	3	4	6	11	3	0	3	1

Serum cTnI level of patients with DCM decreases after conventional anti-heart-failure treatment

In order to probe the effect of anti-heart-failure treatment on level of serum cTnI in patients with DCM, we applied 5-7 days of conventional anti-heart-failure treatment to patients with DCM. After the treatment we took blood samples and detected its level of serum CK and serum CK-MB. Results demonstrated that serum cTnI level did decrease after treatment (from 0.315 ± 0.147 μg/L to 0.308 ± 0.111 μg/L), but the difference was not significant. The difference between treatment group and control group (0.308 ± 0.111 μg/L against 0.014 ± 0.006 μg/L) however, was significant ($p<0/01$). These facts suggested that serum cTnI level in patients with DCM is significantly higher than that of control group after treatment. Level of serum CK and CK-MB shows no significant change after anti-heart-failure treatment (Table 6).

Table 6. Determination of level of serum cTnI, CK and CK-MB in patients with DCM before and after treatment (x ± s).

Group	Number of cases	cTnI (μg/L)	CK(IU/L)	CK-MB(IU/L)

Before treatment	104	0.371 ± 0.157	76.22 ± 24.17	16.29 ± 4.2
After treatment	104	0.348 ± 0.163	74.68 ± 25.36	15.96 ± 4.5

Note: There were no significant differences after treatment.

Discussions

cTn, consisting of cTnI and cTnT, can make up complexus with tropomyosin to adjust contraction function of myocardium. When myocardial damage or death appears, integrity of cytomembrane gets damaged, making circulatory system accessible for cTnI and cTnT. In this condition cTnI and cTnT turn detectable in peripheral blood [12], and their specificity and sensitivity exceeding those of CK-MB make them the best marker in diagnosis of myocardial necrosis [13]. Results in this study accord with this theory. In this study we proved several perspectives including direct detection of serum cTnI level, cardiac function and LVEF that serum cTnI has higher sensitivity than that of serum CK level and serum CK-MB level thus serves well as molecular indicator in diagnosis of patients with DCM.

After taking samples of 1120 healthy Asian (with no diabetes, hypertension, heart disease, lung disease or kidney disease), Aw et al. [14] discovered that reference ranges of cTnI were 0-0.049 g/L. In this study we discovered that cTnI in patients with DCM was 0.02-1.92 μg/L, m was 0.05 μg/L. For convenience in statistical analysis, we divided chosen patients with cTnI>0.05 μg/L into positive group, those of cTnI<0.05 μg/L were divided into negative group and further probed the significance of rising of serum cTnI level in patients with DCM. We discovered that positive group had significantly higher incidence rate of class III or class IV cardiac function. Results of ultrasound cardiogram further indicated that level of LVED and LVES in positive group was significantly higher than that in negative group, while level of LVEF was significantly lower. These facts proved that patients on positive group had more severe left ventricular dilatation, significantly worsening cardiac function and other clinical symptoms suggesting unfavorable prognosis [15-17]. Recent literature references reported that LVEF<35% is the most effective indicator for total death and sudden death [18,19]. Our study demonstrated that most patients in positive group had LVEF<35% while it was only the case for few patients in control group, which was in accordance with previous studies.

Arrhythmia, especially ventricular arrhythmia and left bundle branch block was one of the major causes of sudden death of patient with DCM [20]. This study revealed that arrhythmia appeared in negative group was mostly atrial arrhythmias including atrial fibrillation, frequent premature atrial contraction and atrial tachycardia while positive group suffered from ventricular arrhythmia like frequent premature ventricular contraction, conduction block including complete left bundle branch block (LBBB), ventricular fibrillation and complex arrhythmia where 2 or more abnormalities above were detected. However, 2.5 years of follow-ups on patients with class II-III NYHA found no significant difference in sudden death rate and total death between patients with atrial fibrillation and those with sinus rhythm, which indicated that atrial fibrillation is not an independent predictor of death rate of patients with DCM [21]. Later on Beadle et al. [22] researched 9 cased of sudden death in patients with DCM and found that 8 cases of them were with ventricular arrhythmia, indicating that severe ventricular arrhythmia is an independent risk factor of DCM sudden death. What's more, scholars reported that all cases of ventricular conduction block were with QRs prolongation. Severe LBBB may affect systolic function of left ventricle. The wider the QRs wave is, the longer it takes to complete a systolic and diastolic process, the higher LVED and LVES are, the worse left ventricular systolic function is [23]. The appearance of conduction block in patients with DCM is highly related to the extent of patients' cardiac dilatation. There is a negative correlation between QRs prolongation and lowering of LVEF (r=-0.91) [24]. Therefore, ventricular arrhythmia and LBBB can serve as important indicator in prognosis of patients with DCM.

Pathogenesis of DCM is still unclear. Some researchers proposed that it is the result of inflammatory factor-affected persistent damage and repair process of myocardium as immune reaction of innately susceptible individuals [25,26]. We suggest that abnormal change in level of cTnI is a manifestation of this result. Due to the damage, permeability of membrane increases; making it possible for free state cTnI to swell out of the cell, but this phenomenon is less noticeable than increase of combination state cTnI in the case of myocardial death [27]. The damage may include hypoxia, energy metabolic disturbance, ion channel dysfunction and Focal necrosis caused by ischemia. What's more, there might existed compensative repair function in intracellular, inter-tissue or systemic level [28]. When a balance of the two is reached, patients' cTnI may stay at certain level, with no severe clinical manifestation and a favorable prognosis. When the damage factor outdoes the repair factor, a raise of cTnI level takes place and myocardial degeneration or apoptosis accompanied by fibroustissue replacement. Dilation of heart, heart failure and severe arrhythmia gradually occur. The degree of serum cTnI increase is determined by how much damage factor outdoes repair function. The more serum cTnI increases, the more severe damage is and the worse repair function works, which may lead to massive myocardial apoptosis and expansion of fibroustissue replacement. The remaining myocardium may fail to give effective compensation, thus causes symptoms like severe decrease of contractive force and noticeable heart failure. Massive fibroustissue replacement of myocardium may further divide connected myocardium, constructing reentrant circuits, which may lead to ventricle arrhythmia [29-31]. Diffuse fibroustissue replacement may affect the conduction system, which may interact with interrupted impulse conduction caused by heart enlargement-elongated purkinje fibers to aggravate ventricular conduction block.

References

1. Richardson P, McKenna W, Bristow W. Report of the 1995 World Organization/International Society and Federation of Cardiology Task Force on the definition and classification of cardiomyopathies. Circulation 1996; 93: 841-842.
2. Dandel M, Englert A, Wallukat G. Immunoadsorption can improve cardiac function in transplant candidates with non-ischemic dilated cardiomyopathy associated with diabetes mellitus. Atheroscler Suppl, 2015; 18: 124-133.
3. La Vecchia L, Mezzena G, Zanolla L. Cardiac troponin I as diagnostic and prognostic marker in severe heart failure. J Heart Lung Transplant, 2000; 19: 644-652.
4. Olivetti G, Abbi R, Quaini F. Apoptosis in the failing human heart. N Engl J Med 1997; 336: 1131-1141.
5. Roshanali F, Vedadian A, Shoar S. Efficacy of papillary muscle approximation in preventing functional mitral regurgitation recurrence in high-risk patients with ischaemic cardiomyopathy and mitral regurgitation. Acta Cardiol 2013; 68: 271-278.
6. Li X, Luo R, Jiang R. The prognostic use of serum concentrations of cardiac troponin-I, CK-MB and myoglobin in patients with idiopathic dilated cardiomyopathy. Heart Lung 2014; 43: 219-224.
7. Vaĭkhanskaia TG, Kurushko TV, Sidorenko IV. Electrocardiographic predictors of response to cardiac resynchronization therapy of heart failure in patients with dilated cardiomyopathy. Kardiologiia 2013; 53: 48-54.
8. Adams JE 3rd, Bodor GS, Davila-Roman VG. Cardiac troponin I. A marker with high specificity for cardiac injury. Circulation 1993; 88: 101-106.
9. Missov E, Calzolari C, Pau B. Circulating cardiac troponin I in severe congestive heart failure. Circulation 1997; 96: 2953-2958.
10. La Vecchia L, Mezzena G, Ometto R. Detectable serum troponin I in patients with heart failure of nonmyocardial ischemic origin. Am Cardiol 1997; 80: 88-90.
11. Horwich TB, Patel J, MacLellan WR. Cardiac troponin I is associated with impaired hemodynamics, progressive left ventricular dysfunction, and increased mortality rates in advanced heart failure. Circulation 2003; 108: 833-838.
12. Aldrin VG, Tunor AB, Keita H. Role of troponin Tin disease. Molec Cellular Biochem 2004; 263: 115-129.
13. Keller T, Zeller T, Peetz D. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. N Ensl J Med 2009; 361: 868-877.
14. Aw TC, Phua SK, Tan SP. Measurement of cardiac troponin I in serum with a new high-sensitivity assay in a large multiethnic Asian cohort and the impact of gender. Clin Chim Acta 2013; 422: 26-28.
15. Agewall S, Giannitsis E, Jemberg T. Troponin elevation in coronary vs non-coronary disease. European Heart Journal 2011; 32: 404-411.
16. Setsuta K, Kitahara Y, Arae M. Elevated cardiac troponin T predicts adverse outcomes in hypertensive patients. Int Heart J 2011; 52: 164-169.
17. Wong S, French R, Bolson E. Morphologic features of the rheumatic mitral regurgitant valve by three-dimensional echocardiography. Am Heart J 2001; 142: 897-907.
18. Schalla S, Jaarsma C, Bekkers SC. Right ventricular function in dilated cardiomyopathy and ischemic heart disease: assessment with non-invasive imaging. Neth Heart J 2015; 23: 232-240.
19. Gatzoulis KA, Vouliotis AI, Tsiachris D. Primary prevention of sudden cardiac death in a nonischemic dilated cardiomyopathy population: reappraisal of the role of programmed ventrieular stimulation. Circ Arrhythm Electrophysiol 2013 66: 504-512.
20. Adabag AS. Sudden cardiac death:epidemiology and risk factor. Nat Rev Cardio 2010; 7: 216-225.
21. Carson PE, Johnson GR, Dunkman WB. The influence of atrial fibrillation on prognosis in mild to moderate heart failure. The V-HeFT Studies The V-HeFT VA Cooperative Studies Group. Circulation 1993; 87: VI102-110.
22. Beadle RM, Williams LK, Kuehl M. Improvement in cardiac energetics by perhexiline in heart failure due to dilated cardiomyopathy. JACC Heart Fail 2015; 3: 202-211.
23. Lin X, Xu H, Zhao X. Sites of latest mechanical activation as assessed by SPECT myocardial perfusion imaging in ischemic and dilated cardiomyopathy patients with LBBB. Eur J Nucl Med Mol Imaging 2014; 41: 1232-1239.
24. Zencir C, Ozdemiroglu FA, Cetin M. Evaluation of left ventricular systolic and diastolic functions in bipolar patients during lithium therapy. Int J Clin Exp Med 2015; 8: 2917-2922.
25. Massilamany C, Gangaplara A, Reddy J. Intricacies of cardiac damage in coxsackievirus B3 infection: implications for therapy. Int J Cardiol 2014; 177: 330-339.
26. Martín R, Cordova C, San Román JA. Oleanolic acid modulates the immune-inflammatory response in mice with experimental autoimmune myocarditis and protects from cardiac injury. Therapeutic implications for the human disease. J Mol Cell Cardiol 2014; 72: 250-262.
27. Zhang L, Chen X, Su T. Circulating miR-499 are novel and sensitive biomarker of acute myocardial infarction. J Thorac Dis 2015; 7: 303-308.
28. Frustaci A, Russo MA, Morgante E. Oxidative myocardial damage in human cocaine-related cardiomyopathy. Eur J Heart Fail 2015; 17: 283-290.
29. Jefferies HJ, Tertti R, Wittfooth S. Elevated serum free pregnancy-associated plasma protein-a independently predicts mortality in haemodialysis patients but is not associated with recurrent haemodialysis-induced ischaemic myocardial injury. Nephron, 2015; 129: 171-178.
30. Horjen AW, Ulimoen SR, Enger S. Impact of atrial fibrillation on levels of high-sensitivity troponin I in a 75-year-old population. Scand J Clin Lab Invest, 2015; 75: 308-313.
31. Diao YQ, Jiang L, Zhang HF. Changes of plasma cardiotrophin-1 levels in neonates with myocardial ischemic injury. Zhongguo Dang Dai Er Ke Za Zhi, 2015; 17: 118-121.

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