Melatonin May Be Associated With Left Ventricular Diastolic Dysfunction in Pediatric Patients With Heart Failure

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Melatonin may be associated with left ventricular diastolic dysfunction in pediatric patients with heart failure

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Abstract

Background : Melatonin has a protective role in adults with cardiovascular diseases. Melatonin may affect nitric oxide (NO) availability in the cardiovascular system to maintain the constant hemodynamics. Diastolic dysfunction has been less well investigated in pediatric heart disease, and the effects of melatonin on cardiac diastolic dysfunction in children are not well understood. This study was designed to explore whether diastolic dysfunction is associated with the serum levels of melatonin or NO in children suffering from heart failure (HF) due to different etiology.

Methods: forty-seven pediatric patients with HF were enrolled in this study. Echocardiographic parameters were employed to evaluate the cardiac diastolic dysfunction. Diurnal serum levels of melatonin and NO were measured and analyzed in all pediatric patients.

Results: Diurnal serum melatonin levels were positively correlated with mitral valve E:A ratio (E/A) in children with HF (P=0.044), especially in children with HF due to cardiomyopathy (P=0.023). Moreover, serum melatonin levels showed significant

positive correlation with E/A ratio in children with deteriorate diastolic dysfunction when employing E/A < 1 or > 2 as an indicator (P=0.012), and especially in children with HF due to cardiomyopathy (P=0.0014). Serum melatonin levels demonstrated significant positive correlation with mitral regurgitation (MR) jet area (P =0.005) and showed significant negative correlation with pulmonary valve regurgitation (PVR) velocity (P =0.009). In addition, serum NO levels were positively correlated with isovolumetric relaxation time (IRT) in children with HF(P=0.0047). Furthermore, the optimal cutoff value of serum melatonin levels for diagnosis for predicting E/A > 2 in pediatric patients with HF was 84 pg/mL.

Conclusions: Diurnal serum melatonin and NO levels may be associated with left ventricular diastolic dysfunction in pediatric HF especially due to cardiomyopathy.

Key Words: melatonin, diastolic function, pediatric patients, heart failure, cardiomyopathy

Introduction

Heart failure (HF) is a common and serious clinical emergency. The etiologies may differ between children and adults with HF. The most causes of adult with HF in adults can be attributed to hypertension, coronary heart disease, cardiomyopathy and chronic obstructive pulmonary disease [1]. Relatively, the etiologies are mainly include cardiomyopathy, congenital heart disease (patent ductus arteriosus, ventricular septal defect, and aorto-pulmonary window et al) and arrhythmia in pediatrics [2]. The complex etiology of HF makes it challenging to study failing heart. Cardiomyopathy is an important cause of cardiac failure in children. It takes several years for adults to

develop heart failure, while cardiomyopathy progresses rapidly in children with atypical manifestations, and easy misdiagnosis[3]. Diastolic dysfunction is closely related to the prognosis of cardiomyopathy.

Cardiac dysfunction can measured by transthoracic echocardiography, a reliable noninvasive approach, and may reduce the need for invasive catheterization [4]. The echocardiography measures of systolic performance included: ejection fraction (EF) and shortening fraction (SF). On the other hand, the echocardiographic criteria for ventricular relaxation include the E wave, E/A wave ratio, and isovolumic relaxation time. Ventricular compliance can be assessed by the E/e' wave ratio, atrial volume, and Ap wave duration during pulmonary vein flow[5]. Unlike assessment of systolic function, diastolic function is more difficult to been measured and has limited study to determine its role in pediatric diseases [6, 7] .

Melatonin have been well known for its protection on the cardiovascular system as a secretory product of the human pineal gland. Melatonin has been shown to reduce hypertension through anti-inflammatory effect [8], protect the ischemic/reperfused heart as a result of anti-oxidative injury[9], and ameliorate the process of atherosclerosis[10]. The physiological peak of melatonin is approximately 150 pg/mL. Emerging studies suggest the levels of melatonin are reduced in patients with HF[11] and circulating melatonin levels as a useful marker for HF[11, 12].Treatment of melatonin is considered to be a potential therapy in HF[13]. Nevertheless, other reports show that biomolecules like melatonin can be increased in response to diseases in some HF pediatric patients[14], almost like an adaptive response to the disease.

There are many researches about the role of nitric oxide (NO) on cardiomyopathy in adults[15]. NO may be produced in congestive heart failure and control the mitochondrial respiration, but the role of NO on the pathological process of heart failure is still controversial. In another study, the researchers found that melatonin may also resist left ventricular fibrosis by affecting hemodynamic overload and nitric oxide (NO) availability[16].

To our knowledge, the association between melatonin, NO and diastolic dysfunction in pediatric cardiomyopathy has not been investigated. In our previous study, we found that diurnal serum melatonin levels were increased in children with severe HF, almost like an compensatory response to the disease [14]. Now, we further performed this study to investigate the role of serum melatonin in left ventricular diastolic function of pediatric children with HF.

Methods

Patient Enrollment

This single-center pediatric study was approved by the Ethics Committee. Based on the modified Ross criteria for cardiac function[17], pediatric patients with a score of >2 points were enrolled in the study. Blood samples from 47children diagnosed with HF were collected between December 2014 and December 2015 at the Clinical Examination Center. All serum samples were collected between 8:00-10:00 am around the time that the children also underwent clinical examination. All patient-derived blood samples were collected after written informed consent was obtained from parents or guardians. To analyze the association between relevant clinic data and the incidence

of HF in children, data on 47 children with HF were retrospectively collected. Data included each patient's age, gender, clinical measurement, echocardiographic examination and diagnosis when admitted in the hospital.

Melatonin and NO analysis

All serum samples were stored in a freezer at -80℃ before testing. Melatonin and NO levels were measured using the human melatonin ELISA kit (Arigo, Taiwan) and human NO ELISA kit (4A Biotech Products, China), respectively. All assays were performed following the manufacturers' instructions.

Statistical Analysis

All statistical analyses were performed with SPSS software (version 19.0). All data are shown as median (interquartile range). A Pearson correlation analysis was performed to determine the association between serum melatonin and NO levels with each of the echocardiographic measures in pediatric patients with HF. To determine the appropriate cutoff value of serum melatonin to diagnosis severe diastolic dysfunction in pediatric patients with HF, the area under the ROC curve (AUC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and Youden index (J) were analyzed. A P value of <0.05 was considered statistically significant for all tests.

Results

Patient Demographics and Study Data

The median age of children with heart failure was 0.5 year (interquartile range 0.31-11.33 years) with 31 patients aged less than 1 year (66%), 7 patients between 1 to 3

117 years (15%), 1 patients between 4 to 7 years (2%) and 8 patients aged > 8 years (17%).
118 Heart defects included: ventricular septal defects (n = 4), atrial septal defects (n = 1),
119 tetralogy of Fallot (n = 2), patent ductus arteriosus (n = 1), complex congenital heart
120 disease (n = 19), and aorta stenosis (n = 1). Other diseases included: cardiomyopathy
121 (n = 11), myocarditis (n = 1), arrhythmias (n = 4), pneumonia (n=2), and pulmonary
122 hypertension (n =1). The clinical characteristics of the 47 pediatric patients with HF are
123 summarized in Table 1 and Table 2.

124 **Correlation between Melatonin, NO and Echocardiographic Indices**

125 The correlation between serum melatonin or NO levels and echocardiographic
126 diastolic indices are display in Fig.1. Among the echocardiographic parameters, serum
127 melatonin levels demonstrated significant positive correlation with E/A ratio in
128 pediatric patients with HF (P=0.044) (Fig. 1A), especially in patients due to
129 cardiomyopathy (P=0.023) (Fig. 1B). In contrast, serum melatonin levels were not
130 correlated with E/A ratio in HF children due to congenital heart disease (P>0.05) (Fig.
131 1C) or other etiology (P>0.05) (Fig. 1D). Moreover, serum melatonin levels showed
132 significant positive correlation with E/A ratio <1 or >2 in which indicating deteriorate
133 diastolic dysfunction (P =0.012) (Fig. 1E), especially in HF patients due to
134 cardiomyopathy (P=0.0014) (Fig. 1F), due to congenital heart disease (P=0.045) (Fig.
135 1G), and due to other etiologies (P =0.028) (Fig. 1H). Among the other echocardiogram
136 parameters, mitral regurgitation (MR) jet area showed significant positive correlation
137 with serum melatonin levels (P =0.005) (Fig. 1I). Pulmonary valve regurgitation (PVR)
138 velocity showed significant negative correlation with serum melatonin levels (P =0.009)

(Fig. 1J). Due to technical limitations maybe including storing way of blood or detection method, the serum levels of NO were achieved in only 15 of the 47 patients in which it was attempted. There was a positive correlation between serum levels of NO and IRT (P =0.0047) (Fig. 1K). There was no significant correlation between serum levels of melatonin or NO and other echocardiogram measurements including systolic echocardiography indices (EF and FS) (data not shown).

The Concentrations of Melatonin that Best Predict Deteriorate Diastolic Dysfunction (E/A >2)

In our study, the diurnal serum melatonin concentrations ranging from 1.19-528.58 pg/ml were used to generate ROC curves and define the optimal value of serum melatonin to make a diagnosis for detection of E/A ratio > 2 in pediatric patients with HF. The AUC, sensitivity, specificity, PPV, NPV, and J value were assessed. Among all pediatric patients with HF, a cutoff value of 84 pg/ml yielded the highest J (0.773) with sensitivity of 1, specificity of 0.773, PPV of 0.188 and NPV of 1, indicating that this may be the optimal cutoff value for diagnosing severe diastolic dysfunction (Fig 2 and Table 3). But serum melatonin levels can not generate ROC curves for best predicting E/A ratio <1(data not shown).

Discussion

The role of melatonin in cardiovascular research that may lead to HF has become an important subject[18]. Melatonin interacts with the heart and blood vessels directly through its receptor-dependent and a free radical scavenger[19, 20].The protective effect of melatonin on failing heart through reducing collagen[21], extracellular matrix

deposition, and oxidative stress[21-23].

In this study, we investigated the relationship between serum melatonin levels and the echocardiogram parameters in a cohort of children with HF. We identified 3 candidate echocardiogram measures that showed a significant correlation with serum melatonin. 1< E/A <2 represents normal diastolic function. E/A <1 implies impaired relaxation function of left ventricular with normal left ventricular filling pressure, and mild left ventricular diastolic dysfunction. E/A >2 means abnormal left ventricular restrictive filling and severe left ventricular diastolic disorder[24]. In our researcher, the serum melatonin levels had significant positive correlation with E/A ratio <1 or >2 in HF children especially with the etiology of cardiomyopathy, suggesting melatonin may have contribution in the diastolic dysfunction in pediatric patients with cardiomyopathy. In addition, the serum melatonin had significant positive correlation with MR jet area, and had negative significant with pulmonary valve regurgitation velocity, indicating melatonin may play a role in the abnormal hemodynamics in process of pediatric HF. In addition, we further investigate that the serum NO levels had positive correlation with IRT in HF children, suggesting NO with the vasodilatation function in the cardiovascular system may had contribution in the diastolic dysfunction in children. Using ROC analyses, cutoff values of serum melatonin concentrations were generated for potential use as deteriorate diastolic dysfunction of N/A >2. To our knowledge, this is the first study in pediatric patients to demonstrate potential utility of serum melatonin levels to evaluating the diastolic dysfunction.

Pediatric patients with cardiomyopathy present a treatment dilemma. Previous studies

have reported recovery of cardiac function in 21% - 37% of adults and children patients[25] with 5-year mortality or transplantation is 46%[26] depending on age, sex, therapies, clinical parameters of HF, and serum biomarkers[27, 28]. As such, defining the pathogenesis of cardiomyopathy means to might provide a therapy for reducing the rate of sudden death, atrial fibrillation following ventricular diastolic dysfunction and improving quality of children' life. In our study, melatonin may contribute the diastolic function and hemodynamics in children with cardiomyopathy, but further researches are need to confirm the hypothesis.

Ventricular diastolic dysfunction can be obtained by invasively cardiac catheterization, including left ventricular end diastolic pressure > 16mmHg or mean pulmonary capillary wedge pressure > 12mmHg, which is currently considered to be the most credible method[29, 30]. Prior studies found that no single noninvasive echocardiographic parameters is able to replace for cardiac catheterizatio[31, 32]. Despite multiple reports employing echocardiographic parameters of left ventricular diastolic function in adults, the directly validation of noninvasive measures in pediatric has been more challenging because of young age, low weight, cooperation difficulties et al. There is a need to develop specific guidelines for pediatric to evaluate diastolic function by echocardiography. In our study, we explore the role of serum melatonin in diagnosis diastolic dysfunction in children. We speculate that combining echocardiographic parameters and the serum melatonin levels may utilized in pediatric patients with HF to learn their diastolic function.

At last, there are several limitations were present in this investigation. First, the single-

center research, short follow-up time and low incidence rate of cardiomyopathy of this study led to insufficient sample size. Secondly, there are inherent technical challenges of pediatric that limit get more parameters of diastolic dysfunction by echocardiographic and no parameters of cardiac catheterization in our study. Finally, the lack of data of cardiovascular patients without HF in pediatric be as a control. It does not provide evidence to support this decision in other populations.

Conclusion

In our present study, we conclude that serum melatonin levels may contribute to left ventricular diastolic dysfunction in children with HF and could potentially serve as measures to identify HF children with severe diastolic dysfunction (E/A >2). These findings still need to prove in a multicenter prospective research.

References

[1] Ziaeian B, Fonarow GC. Epidemiology and aetiology of heart failure. Nat Rev Cardiol. 2016. 13(6): 368-78.

[2] Masarone D, Valente F, Rubino M, et al. Pediatric Heart Failure: A Practical Guide to Diagnosis and Management. Pediatr Neonatol. 2017. 58(4): 303-312.

[3] Weintraub RG, Semsarian C, Macdonald P. Dilated cardiomyopathy. Lancet. 2017. 390(10092): 400-414.

[4] Correale M, Tricarico L, Padovano G, et al. Echocardiographic score for prediction of pulmonary hypertension at catheterization: the Daunia Heart Failure Registry. J Cardiovasc Med (Hagerstown). 2019. 20(12): 809-815.

[5] Recher M, Botte A, Soquet J, Baudelet JB, Godart F, Leteurtre S. Assessment of left-ventricular diastolic function in pediatric intensive-care patients: a review of parameters and indications compared with those for adults. World J Pediatr. 2021. 17(1): 21-30.

[6] Sasaki N, Garcia M, Ko HH, Sharma S, Parness IA, Srivastava S. Applicability of published guidelines for assessment of left ventricular diastolic function in adults to children with restrictive cardiomyopathy: an observational study. Pediatr Cardiol. 2015. 36(2): 386-92.

[7] Kasner M, Westermann D, Steendijk P, et al. Utility of Doppler echocardiography and tissue Doppler imaging in the estimation of diastolic function in heart failure with normal ejection fraction: a comparative Doppler-

conductance catheterization study. Circulation. 2007. 116(6): 637-47.
[8] Prado NJ, Ferder L, Manucha W, Diez ER. Anti-Inflammatory Effects of Melatonin in Obesity and Hypertension. Curr Hypertens Rep. 2018. 20(5): 45.
[9] Reiter RJ, Tan DX. Melatonin: a novel protective agent against oxidative injury of the ischemic/reperfused heart. Cardiovasc Res. 2003. 58(1): 10-9.
[10] Ma S, Chen J, Feng J, et al. Melatonin Ameliorates the Progression of Atherosclerosis via Mitophagy Activation and NLRP3 Inflammasome Inhibition. Oxid Med Cell Longev. 2018. 2018: 9286458.
[11] Dzida G, Prystupa A, Lachowska-Kotowska P, et al. Alteration in diurnal and nocturnal melatonin serum level in patients with chronic heart failure. Ann Agric Environ Med. 2013. 20(4): 745-8.
[12] Dominguez-Rodriguez A, Abreu-Gonzalez P, Reiter RJ. The potential usefulness of serum melatonin level to predict heart failure in patients with hypertensive cardiomyopathy. Int J Cardiol. 2014. 174(2): 415-7.
[13] Dominguez-Rodriguez A, Abreu-Gonzalez P, Piccolo R, Galasso G, Reiter RJ. Melatonin is associated with reverse remodeling after cardiac resynchronization therapy in patients with heart failure and ventricular dyssynchrony. Int J Cardiol. 2016. 221: 359-63.
[14] Wu Y, Si F, Luo L, Yi Q. Serum levels of melatonin may contribute to the pathogenesis of heart failure in children with median age of 1 year. J Pediatr (Rio J). 2018. 94(4): 446-452.
[15] Matsumori A. Molecular and immune mechanisms in the pathogenesis of cardiomyopathy--role of viruses, cytokines, and nitric oxide. Jpn Circ J. 1997. 61(4): 275-91.
[16] Reiter RJ, Manchester LC, Fuentes-Broto L, Tan DX. Cardiac hypertrophy and remodelling: pathophysiological consequences and protective effects of melatonin. J Hypertens. 2010. 28 Suppl 1: S7-12.
[17] Ross RD. The Ross classification for heart failure in children after 25 years: a review and an age-stratified revision. Pediatr Cardiol. 2012. 33(8): 1295-300.
[18] Baker J, Kimpinski K. Role of melatonin in blood pressure regulation: An adjunct anti-hypertensive agent. Clin Exp Pharmacol Physiol. 2018. 45(8): 755-766.
[19] Paulis L, Simko F, Laudon M. Cardiovascular effects of melatonin receptor agonists. Expert Opin Investig Drugs. 2012. 21(11): 1661-78.
[20] Galano A, Reiter RJ. Melatonin and its metabolites vs oxidative stress: From individual actions to collective protection. J Pineal Res. 2018. 65(1): e12514.
[21] Simko F, Bednarova KR, Krajcirovicova K, et al. Melatonin reduces cardiac remodeling and improves survival in rats with isoproterenol-induced heart failure. J Pineal Res. 2014. 57(2): 177-84.
[22] Şehirli AÖ, Koyun D, Tetik Ş, et al. Melatonin protects against ischemic heart failure in rats. J Pineal Res. 2013. 55(2): 138-48.
[23] Chua S, Lee FY, Chiang HJ, et al. The cardioprotective effect of melatonin and exendin-4 treatment in a rat model of cardiorenal syndrome. J Pineal Res. 2016. 61(4): 438-456.
[24] Heiskanen JS, Ruohonen S, Rovio SP, et al. Determinants of left ventricular diastolic function-The Cardiovascular Risk in Young Finns Study. Echocardiography. 2019. 36(5): 854-861.
[25] Everitt MD, Sleeper LA, Lu M, et al. Recovery of echocardiographic function in children with idiopathic dilated cardiomyopathy: results from the pediatric cardiomyopathy registry. J Am Coll Cardiol. 2014. 63(14): 1405-13.
[26] Towbin JA, Lowe AM, Colan SD, et al. Incidence, causes, and outcomes of dilated cardiomyopathy in children. JAMA. 2006. 296(15): 1867-76.
[27] Molina KM, Shrader P, Colan SD, et al. Predictors of disease progression in pediatric dilated cardiomyopathy. Circ Heart Fail. 2013. 6(6): 1214-22.
[28] Levy WC, Mozaffarian D, Linker DT, et al. The Seattle Heart Failure Model: prediction of survival in heart

failure. Circulation. 2006. 113(11): 1424-33.
[29] Pourmoghaddas M, Sanei H, Tavassoli A, Shojaei M. Estimation of left ventricular end diastolic pressure (lvedp) in patients with ischemic heart disease by echocardiography and compare it with the results of cardiac catheterization. ARYA Atheroscler. 2011. 7(1): 1-6.
[30] Patel D, Robinson VJ, Arteaga RB, Thornton JW. Diastolic filling parameters derived from myocardial perfusion imaging can predict left ventricular end-diastolic pressure at subsequent cardiac catheterization. J Nucl Med. 2008. 49(5): 746-51.
[31] Ryan TD, Madueme PC, Jefferies JL, et al. Utility of Echocardiography in the Assessment of Left Ventricular Diastolic Function and Restrictive Physiology in Children and Young Adults with Restrictive Cardiomyopathy: A Comparative Echocardiography-Catheterization Study. Pediatr Cardiol. 2017. 38(2): 381-389.
[32] Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2016. 17(12): 1321-1360.

Table 1. Patient characteristics

Age (years)	47	0.5(0.31-11.33)
Gender		
Male		24(51.1)
Female		23(48.9)
Clinical measurements		
Heart failure etiology		
Congenital heart disease		28(59.6)
Cardiomyopathy		11(23.4)
Others		8(17)
Heart rate(bpm)		137(129-157)
Respiratory rate (rpm)		48(32-57)
Body weight(kg)		6(5-10)
Height (cm)	26	61.5(56.25-65.25)
Body surface area(m^2)		0.31(0.28-0.45)
Size of liver under ribs(cm)	39	3(2-3.5)
Systolic blood pressure	23	100(85-113)
Diastolic blood pressure	23	60(53-68)
Hospital length of stay (days)		16(10-27)
Laboratory data		
Serum MB （mg/L)	40	23.67(15.36-36.26)
Serum Trop I (ng/L)	40	0.11(0.04-0.27)
Serum CK-MB (pmol/L)	38	3.58(2.31-7.03)
Serum BNP (ng/L)	34	54.47(26.52-201.69)
Melatonin (pg/ml)	47	36.48(16.91-101.46)
NO (umol/L)	15	89.86(31.88-156.52)

Continuous variables are expressed as median (interquartile range), and discrete variables are *n* (%).

Table 2. Echocardiogram measurements

Ejection fraction (%)	45	66(50-72)
Shortening fraction (%)	45	34(25-40)
Mitral valve E:A ratio	47	1.2(0.8-1.55)
Isovolumetric relaxation time （ms）	47	56(46-77)
Right ventricular diameter (mm)	47	13(12-15)
Left ventricular diastolic diameter (mm)	47	32(25-38)
Left ventricular systolic diameter (mm)	47	21(15-28)
Right ventricular outflow tract （mm）	47	16(13-19)
Aortic diameter (mm)	47	14(12-17)
Left atrial diameter (mm)	46	1.9(16-21)
Pulmonary artery diameter (mm)	45	16(14-18)
Pulmonary blood flow velocity （m/s）	44	1.2(0.87-1.56)
Aortic blood flow velocity （m/s）	46	1.03(0.94-1.28)
Tricuspid blood flow velocity （m/s）	47	0.78(0.68-0.9)
Mitral blood flow velocity （m/s）	47	0.94(0.8-1.12)
Descending aortic blood flow velocity （m/s）	45	1.26(1.04-1.55)
Tricuspid regurgitation velocity （m/s）	15	3.03(2.42-4.04)
Right ventricular systolic pressure （mmHg）	20	48(28-69)
Tricuspid regurgitation jet area (cm2)	39	1.27(0.59-2.31)
Mitral regurgitation jet area (cm2)	27	1.92(0.92-3.22)
Pulmonary regurgitation jet area (cm2)	16	0.65(0.55-1.04)
Pulmonary valve regurgitation velocity(m/s)	7	2.68(1.64-3.08)
Left ventricular end diastolic diameter / body surface area	47	8.7(6.4-10.1)

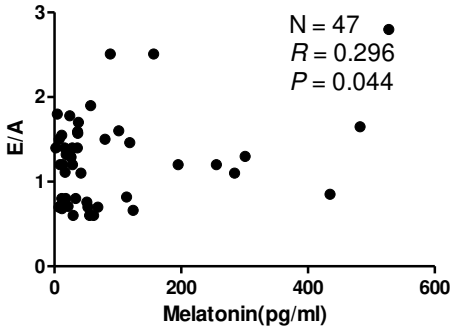
Continuous variables are expressed as median (interquartile range).

Table 3 Cutoff values of serum melatonin for predicting N/A＞2 in pediatric patients with heart failure

melatonin (pg/ml)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	J
84.0005	1	0.773	0.188	1	0.773
140.4404	0.667	0.864	0.302	0.864	0.531

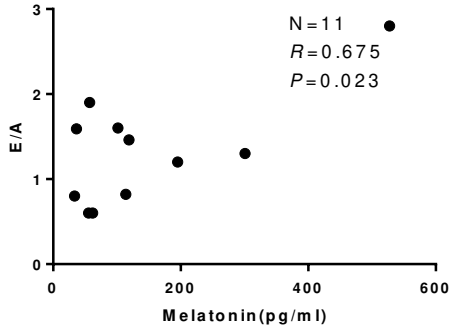
PPV: positive predictive value; NPV: negative predictive value; J: Youden index.

A B



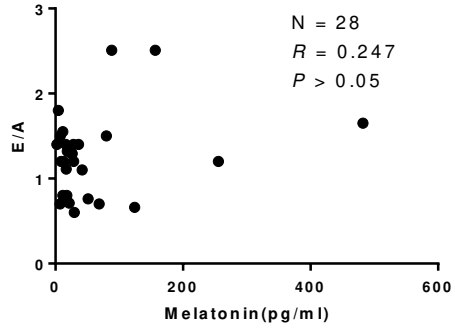
HF

C



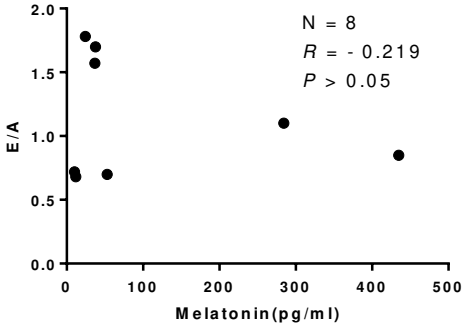
Cardiomyopathy

D



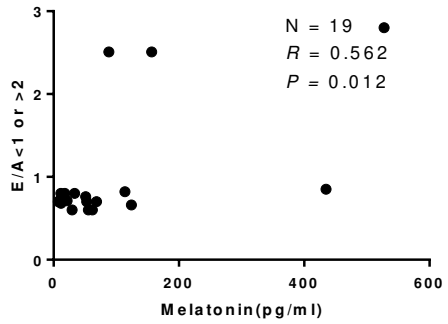
Congenital heart disease

E



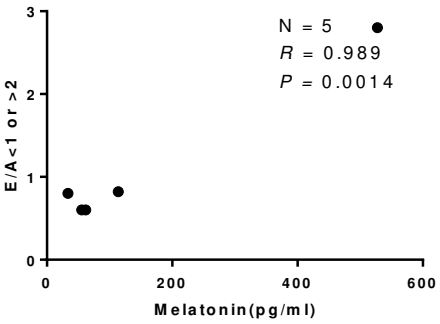
Other etiology

F



HF

G



Cardiomyopathy

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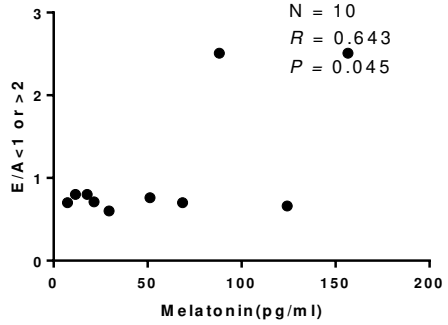
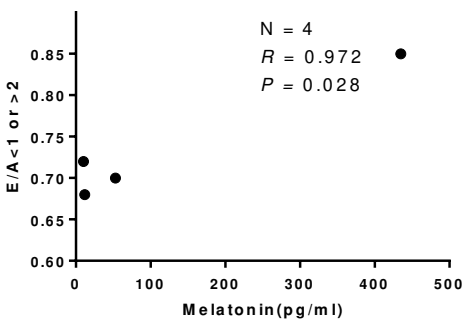


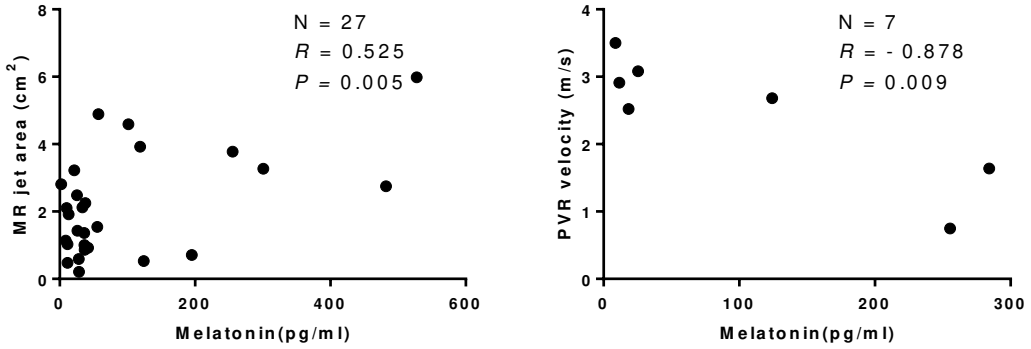
Congenital heart disease

I



Other etiology

J



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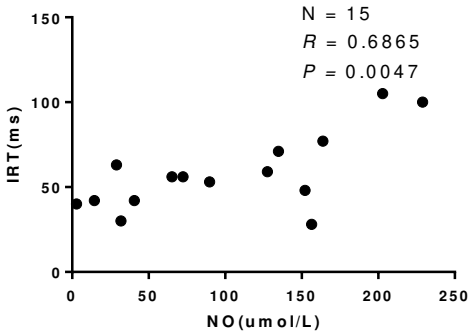

Fig. 1 Correlation of serum melatonin levels and E/A ratio in pediatric patients with HF (A), in pediatric patients with HF due to cardiomyopathy (B), in pediatric patients with HF due to congenital heart disease (C), in pediatric patients with HF due to other etiology (D). Correlation of serum levels of melatonin and E/A ratio in pediatric patients with deteriorate diastolic function employing E/A < 1 or > 2 as an indicator (E), in pediatric patients with deteriorate diastolic function due to cardiomyopathy (F), in pediatric patients with deteriorate diastolic function due to congenital heart disease (G), in pediatric patients with deteriorate diastolic function due to other disease (H). Correlation of mitral regurgitation jet area (I) and pulmonary valve regurgitation velocity (J) with serum melatonin levels in pediatric patients with HF. Relationship between serum NO levels and IRT in pediatric patients with HF (K).

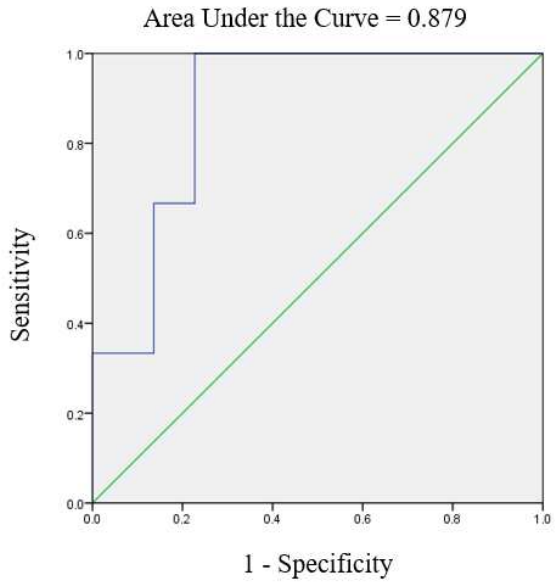

Figure 2. Comparison of ROC curves for the diagnostic performance of melatonin in identifying E/A> 2 in pediatric patients with HF. AUC=0.879 for melatonin (*P* = 0.03). The maximal cut-off value was 84 pg/mL for melatonin (sensitivity=1, specificity=0.773, PPV = 0.188, NPV= 1 and J = 0.773). PPV: positive predictive value; NPV: negative predictive value; J: Youden index.

Figures

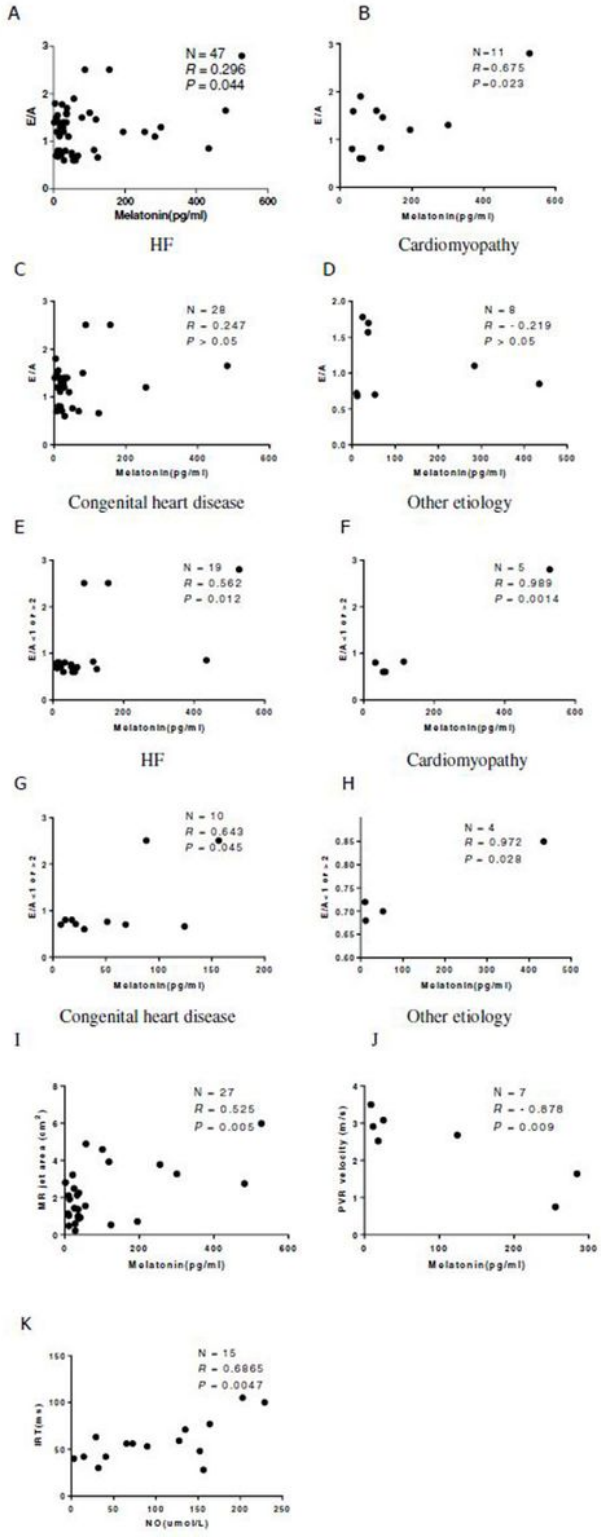

Figure 1

Correlation of serum melatonin levels and E/A ratio in pediatric patients with HF (A), in pediatric patients with HF due to cardiomyopathy (B), in pediatric patients with HF due to congenital heart disease (C), in pediatric patients with HF due to other etiology (D). Correlation of serum levels of melatonin and E/A ratio

in pediatric patients with deteriorate diastolic function employing E/A < 1 or > 2 as an indicator (E), in pediatric patients with deteriorate diastolic function due to cardiomyopathy (F), in pediatric patients with deteriorate diastolic function due to congenital heart disease (G), in pediatric patients with deteriorate diastolic function due to other disease (H). Correlation of mitral regurgitation jet area (I) and pulmonary valve regurgitation velocity (J) with serum melatonin levels in pediatric patients with HF. Relationship between serum NO levels and IRT in pediatric patients with HF (K).

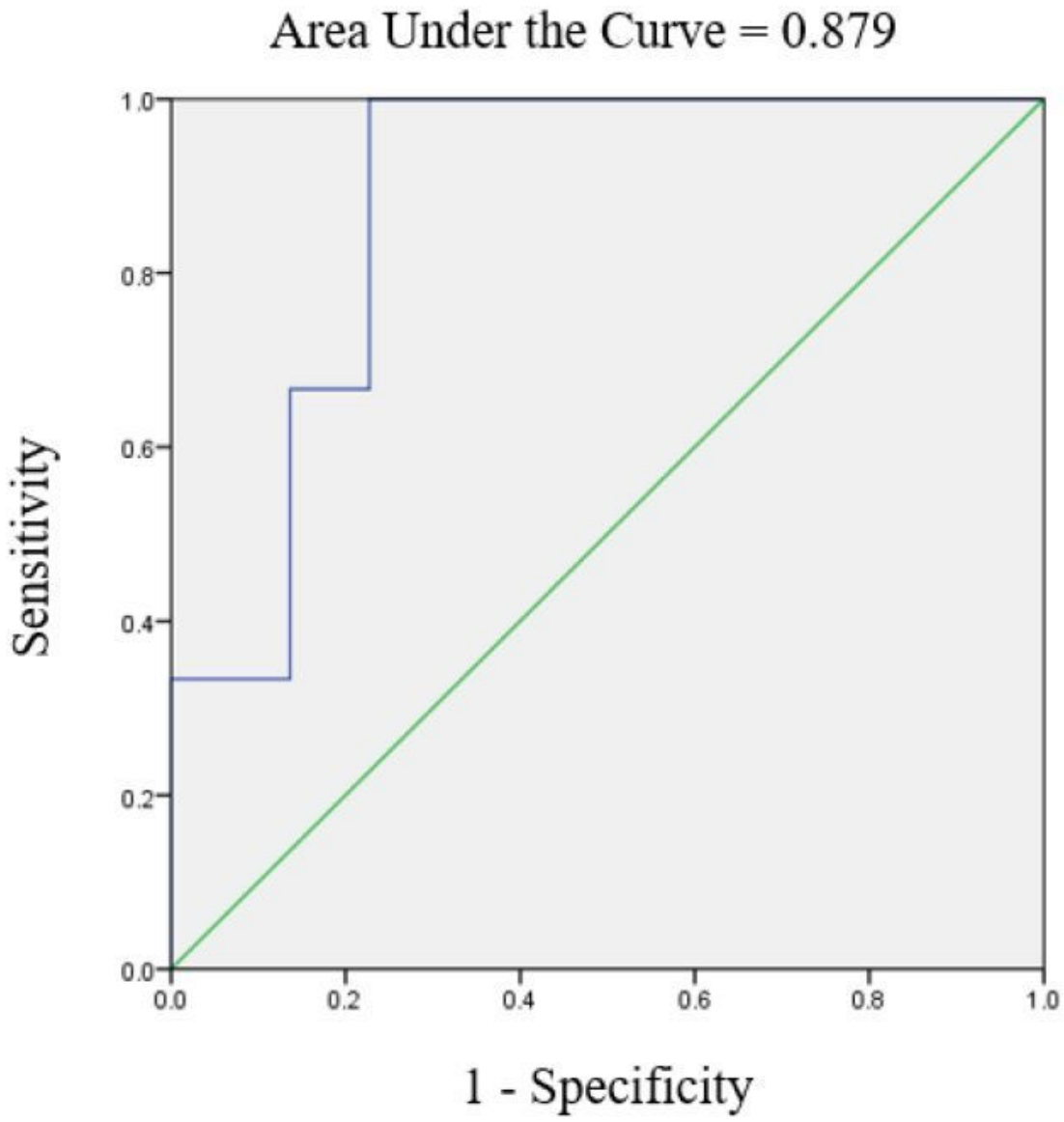

Figure 2

Comparison of ROC curves for the diagnostic performance of melatonin in identifying E/A> 2 in pediatric patients with HF. AUC=0.879 for melatonin (P = 0.03). The maximal cut-off value was 84 pg/mL for melatonin (sensitivity=1, specificity=0.773, PPV = 0.188, NPV= 1 and J = 0.773). PPV: positive predictive value; NPV: negative predictive value; J: Youden index.