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Feasibility study on evaluating right ventricular diastolic function by new Tei'-Index

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ABSTRACT

Objective: Doppler-derived myocardial performance index (Tei) has been used in the evaluation of right ventricular (RV) function. However, the usage in isolated diastolic dysfunction is limited.We sought to find a new Tei'-index that is more appropriate for evaluating isolated diastolic dysfunction (IDD) based on the symmetry of cardiac structure and function.

Methods: 21 patients with impaired RV relaxation were compared to 44 control subjects. Tei and Tei' including their components, isovolumetric relaxation time (IRT), isovolumetric contraction time (ICT), the ejection time (ET), and RV rapid filling time (RFT) were measured from RV outflow and tricuspid inflow Doppler velocity profiles.

Results: Tei-index have no change between IDD group and control subjects (0.21 ± 0.08 vs 0.23 ± 0.07 P=NS). The Tei'-index was significantly shortened in IDD group(0.24 ± 0.09 vs 0.32 ± 0.12,p < 0.05).The decrease in Tei'-index was due to the prolongation of both IRT and RFT, and in the abbreviation of ICT. Tei'-index cutoff value of ≥0.31 identified impaired RV relaxation with a sensitivity of 50 % and specificity of 86 %.We also find that the Tei'-index correlated well with doppler measures of diastolic parameters like E/A, E/e', DT, which suggests its potential use as a noninvasive indicator of the right ventricular (RV) relaxation in patients with heart failure of different causes.

Conclusion: New Tei's index is highly effective and specific in the evaluation of early diastolic dysfunction of right ventricle, and can be used as an indicator for the detection of IDD in clinic.

1. Introduction

Tei index was proposed to describe combined systolic and diastolic left ventricular function in 1995, also called myocardial performance index [1]. It is calculated from Tei index=(ICT + IRT)/ET, where ICT is left ventricular isovolumic contraction time, IRT is

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left ventricular isovolumic relaxation time and ET is aortic ejection time. One year later, the idea [2] was copied similarly to describe the right ventricular function. The calculation method is similar, while the ICT is updated to right ventricular isovolumic contraction time, IRT is updated to right ventricular isovolumic relaxation time and ET is pulmonary ejection time. Since Tei-index is less affected by foreload, afterload, heart rate, and it is more sensitive than ICT or ET in terms of detecting the cardiac dysfunction, it is well accepted as a reliable index in echo labs and we can find the introduction of Tei-index in almost all the main stream Echocardiography textbooks [3–5].With more and more Tei-index application in daily clinic and basic research examinations, people found when describing diastolic function Tei index is not as good as it is used to describe systolic function [6–9].

The cardiovascular disease is still the first killer in industrialized countries. Heart failure tends to be present in almost all the end stage heart diseases. For historical reasons, evaluation of right ventricular function is not as thoroughly delivered as evaluation of left ventricular function [10]. The truth is nobody can claim right ventricular function is less important than the left ventricular function. Pretty much as its left neighbor, right ventricular diastolic dysfunction tends to present ahead of right ventricular systolic dysfunction, i.e., right ventricular diastolic dysfunction could stand alone. The independent right ventricular diastolic dysfunction might be as high as one-third of all right ventricular dysfunctions [11,12].and recently studies have pointed out that many diseases in the early right heart failure first appeared right heart diastolic dysfunction [13,14]. Again, the right ventricular diastolic function assessment has not been paid the same attention as to the right ventricular systolic function assessment. Better indexes to describe right ventricular diastolic function are, thereafter, desperately needed to both researchers and clinicians.

Recently, a new vision about cardiac function assessment was advocated [15]. It suggests two levels of symmetry exist, one is the symmetry between the left and right ventricular behaviors, and the other is the symmetry between the systolic and early diastolic processes. Calculation of new RV-Tei' is similar to calculation of RV-Tei except the ET is replaced by right ventricular rapid filling period (RFP), i.e. E wave duration: RV-Tei'=(ICT + IRT)/RFP. This research is designed to testify if the RV-Tei' is a specific alternative to the classical RV-Tei when evaluating right ventricular diastolic function.

2. Patients and methods

2.1. Study population

This study was a retrospective case-control study. Those who were hospitalized in the Department of Cardiology of our hospital between June 1, 2019 and November 30, 2019 were selected. 65 subjects were included in the study, and 44 healthy participants were in the control group (CON group) and age-matched isolated diastolic dysfunction (IDD) group included 21 patients with RV isolated diastolic dysfunction.

The inclusion criteria for patients in the IDD group: (1) Cardiac diastolic dysfunction of stage I (TV E/A < 0.8, TV E/e' > 6, and DT > 120 ms) or stage II (TV E/A $= 0.8$–2.1, TV E/e' > 6, and DT > 120 ms) [16]; (2) Normal right ventricular systolic functions (TAPSE$\geq$16 mm, RV FAC $\geq$35 %, S'$\geq$9.5 cm/sec). The exclusion criteria for patients in the IDD group: (1) Patients with any cardiovascular symptoms; (2) LV systolic dysfunction on echocardiography; (3) History/evidence of congenital heart disease; (4) Any rhythm abnormalities in their medical records; (5) Diabetes or impaired glucose tolerance.

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Qingdao Municipal Hospital (ethics approval number: LSZ-031). All participants had signed the informed consent.

2.2. Echocardiographic examination

Images were recorded with patients in the left lateral decubitus position with a 3.75-MHz sector probe using a Philips CD30 echocardiography machine (both commercially available). For each patient, an electrocardiogram was simultaneously recorded. The echocardiographic examination was performed by two investigators who had no knowledge of the clinical or angiographic data of the patients. Standard views were recorded according to the guidelines of the American Society of Echocardiography [10,16].

Acquiring the heart of the four chamber heart map and the tricuspid valve were used to show the pulse Doppler sampling volume under the tricuspid valve at the tip of the tricuspid valve, so that the sound beam was first parallel to the ventricular septum and then based on the audio signal and the spectral form Carefully adjust the direction of the probe, so that the direction of the beam and blood flow as far as possible parallel, the two angle $<15^\circ$, access to the right heart system of conventional echocardiographic parameters: right atrium size (RA major dimension and RA minor dimension), right ventricular size(RVD1,RVD2,RVD3), Pulmonary artery systolic pressure (PASP)and right ventricular outflow tract(RVOT prox). RV systolic function was assessed using fractional area change (RV FAC), tricuspid annular plane systolic excursion(TAPSE), pulsed TDI S' (reflecting the velocity of the tricuspid annular systolic motion). Combining more than one measure of RV function was deemed to differentiate normal from abnormal function more reliably [17].

At the same time, a satisfactory tricuspid valve Doppler blood flow spectrum was recorded with pulsed Doppler tricuspid flow velocity (TVF), specific measurement method: The interval "a" from cessation to onset of tricuspid inflow is equal to the sum of ICT, ET, and IRT. ET "b" is derived from the duration of the right ventricular outflow Doppler velocity profile. The sum of ICT and IRT was obtained by subtracting "b" from "a". The index "ICT + IRT/ET" was calculated as shown in (a–b)/b. ICT was measured by subtracting the interval from the pulsed-wave DTI. IRT was calculated by subtracting ICT from a–b. This is the time interval between the closure of the pulmonary valve and the opening of the tricuspid valve. E peak time is the duration of the right ventricular rapid filling Doppler velocity time RFT (denoted as "e"), RV Tei'-index "(IRT + ICT)/RFT" was calculated as shown in (a-b)/e. Peak E-wave, A-wave velocities and DT were measured and the E/A ratio was calculated.

Peak systolic velocity of tricuspid annulus by pulsed-wave DTI (cm/sec), obtained from the apical approach, in the view that achieves parallel alignment of Doppler beam with RV free wall longitudinal excursion. At the apical four - chamber approach guided pulsed wave tissue Doppler sampling of tricuspid valve flap pedicel diastolic tissue velocity e ' peak and a' peak.

2.3. Reproducibility

Intraobserver variability was assessed in 10 patients by repeating the measurements on two occasions (1–12 days apart) under the same basal conditions. To test the interobserver variability, the measurements were performed off-line from video recordings by a second observer who was unaware of the results of the first examination. Variability was calculated as the mean percent error, derived as the difference between the two sets of measurements, divided by the mean of the observations.

2.4. Statistics

All the statistical analyses were performed using statistical package for the social sciences (SPSS) for Windows Version 24 software. Continuous datum are expressed as the mean ± SD. Comparisons of all measurements between groups were made using unpaired Student's t-test. The relationships between the Tei'-index and the other echocardiographic variables were assessed using Pearson's correlation coefficient (r) and simple linear regression. Receiver operating characteristic (ROC) curves were constructed to determine optimal diagnostic cutoff values of Tei'-index for the diagnosis of impaired RV relaxation in patients with preserved ejection fraction. A P value ≤ 0.05 was considered statistically significant in all tests.

3. Results

A total of 65 subjects were included in the study, and 44 were in the control group (19 men and 25 women, aged 68 ± 13.3 years, CON group) and age-matched patient group included 21 patients with RV isolated diastolic dysfunction (9 men and 12 women, aged 65 ± 10.4 years, IDD group). There were no significant differences between the two groups in terms of age, sex, BNP, blood pressures, cholesterol, triglycerides, low-density lipoprotein, blood glucose and LV EF%. In addition, having no significant differences were observed in the majority of the right heart size parameters including RA dimension and RV dimension ($P > 0.05$) in the IDD group. But RV-EDV was significantly higher in IDD group ($P < 0.05$). Through the comparison between the two groups, no significant difference was found in the right heart structure. Tricuspid regurgitation was detected by color Doppler echocardiography in 10 patients (48 %) with RV isolated diastolic dysfunction. The systolic right ventricular pressure calculated by the peak velocity of tricuspid regurgitation was 16.4 ± 12.8 mm Hg in IDD Group, which was not different from that in the CON group ($P > 0.05$) (Table 1).

Table 1
The demographic and clinical features of the patients with isolated diastolic dysfunction.

Variable	CON group (n = 44)	IDD group (n = 21)	P
Age (years)	68 ± 13.3	65 ± 10.4	NS
Women (%)	58	57	NS
Diabetes mellitus (mmol/l)	7.2 ± 3.9	6.1 ± 1.7	NS
Heart rate (bpm)	81 ± 12.4	74 ± 10.4	P < 0.05
SBP(mmHg)	136 ± 22.9	132 ± 17.3	NS
DBP(mmHg)	82 ± 11.8	80 ± 9.6	NS
BNP	102 ± 228.5	162 ± 491.3	NS
cholesterol	5.3 ± 1.4	5.1 ± 1.0	NS
Triglycerides	1.3 ± 0.9	1.4 ± 0.9	NS
Low-density lipoprotein	3.1 ± 1.1	3.1 ± 0.7	NS
LV ejection fraction (%)	55.8 ± 15.5	48.7 ± 24.4	NS
RA major dimension(mm)	37.3 ± 5.6	36.9 ± 7.2	NS
RA minor dimension(mm)	25.5 ± 5.1	27.8 ± 5.9	NS
RVD1(mm)	29.1 ± 5.6	30.7 ± 6.7	NS
RVD2(mm)	24.4 ± 5.7	26.1 ± 6.7	NS
RVD3(mm)	46.1 ± 12.8	52.2 ± 8.7	NS
RV-EDV (cm2)	11.5 ± 4.3	15.7 ± 10.7	P < 0.05
RV-ESV (cm2)	5.4 ± 2.9	9.1 ± 11.8	NS
RVOT (mm)	2.7 ± 0.4	2.8 ± 0.6	NS
PASP(mmHg)	17.2 ± 10.5	16.4 ± 12.8	NS

Note: SBP = sistolic blood pressure; DBP = diastolic blood pressure; BNP: B-type natriuretic peptide, LV: Left ventricular, RVD1 = Basal RV linear dimension; RVD2 = Mid-cavity RV linear dimension; RVD3 = right ventricular longitudinal dimension; RV-EDV=Right ventricle end-diastolic volume; RV-ESV=Right ventricle end-systolic volume; RVOT-prox = Proximal RV outflow diameter; PASP = systolic pulmonary artery systolic pressure (4V2+10 m/s).

3.1. Comparison of Tei index and Tei' index related indicators in two groups

In Table 2, the group of isolated diastolic dysfunction was noted to have higher values for E(56.0 ± 13.0 vs. 45.5 ± 10.0, $P < 0.05$), and E/A (1.3 ± 0.5 vs. 1.0 ± 0.3, $P < 0.05$), and E/e' (7.3 ± 2.1 vs. 4.3 ± 1.0, $P < 0.001$),and DT(18 ± 48 vs. 14 ± 39, $P < 0.001$). The IRT was prolonged and ICT was reduced in the IDD group in comparison to controls. In those patients, RFT was prolonged in comparison to the control group. The ET was not significantly different between groups. In the IDD Group, the Tei'-index was also significantly shortened as compared with controls (0.24 ± 0.09 vs. 0.32 ± 0.12,$P < 0.05$) and the Tei-index have no difference between them (0.21 ± 0.08 vs. 0.23 ± 0.07,$P > 0.05$). Simultaneously, we tried to compare of the Tei-index and Tei' -index between CON group and patients with IDD group with Box Diagram. As a consequence, the Tei-index was no significant difference between IDD group and CON group (Fig. 1A). While the Tei'-index was significantly lower in the IDD group (Fig. 1B).

3.2. The correlation between Tei'-index and each Doppler parameter in patients with IDD

From Table 3, Tei'-index has been shown to correlate well with other parameters of global RV diastolic function($P < 0.05$). Tei'-index had a negative correlation with E/A (B = −0.109, p = 0.007), E/e' (B = −0.020, p = 0.005), DT(B = −0.972, p = 0.001). After stepwise multivariate regression analysis, E/e'and DT were still significantly independent predictors of Tei'-index.

Using ROC curve analysis to assess the predictive discrimination of the Tei'-index, a cut-off value < 0.314 for identification of IDD was derived. IDD was identified with a sensitivity of 50 % and a specificity of 84 %., and impaired RV relaxation was identified with sensitivity of 36 % and specificity of 81 %, with false negative rate of 64 % and false positive rate of 19 %. For the Tei-index, the area under the curve was 0.60 ± 0.07 and with a cutoff value of 0.262 (Fig. 2A). The area under ROC curve and the cutoff value of Tei'-index to detect impaired RV relaxation was 0.70 ± 0.07 (Fig. 2B).

4. Discussion

In our study an even more depth analysis of this new Tei'-index was performed investigating variation tendency in right heart diastolic function. The Tei'-Index was significantly decreased compared to control subjects, mainly due to prolongation of RFT and invariable ICT + IRT. Using ROC curve analysis to assess the predictive discrimination of the Tei'-index, a cut-off value > 0.314 for identification of IDD was derived. Using that cut-off value, IDD was identified with a sensitivity of 50 % and a specificity of 84 %. The area under the ROC curve was 0.70 ± 0.07 for the Tei'-index, which was significantly different from a random distribution. This result does not seem to be sufficient to account for the reliability of the Tei'-index in identifying isolated diastolic function. We further analyze the reason for that pathophysiology of RV diastolic dysfunction is much more complex than simply measuring the E/A, E/e' and DT to identify isolated diastolic dysfunction from normal subjects. The so-called "isolated" is only defined in the current measurement. However, Tei-index as a cutoff value to identify isolated diastolic dysfunction has not been universally accepted and the Tei'-index still proved to be the better discriminator of diastolic dysfunction compared to Tei-index.

In many clinical situations, a complete and accurate assessment of cardiac function is essential. Nowadays, the assessment of left ventricular systolic function has become a routine work in most clinical institutions [15]. More and more attention has been paid to the

Table 2
Comparison of Tei index and Tei' index related indicators in two groups.

	CON group (n = 45)	IDD group (n = 19)	P
E-wave(cm/s)	45.5 ± 10.0	56.0 ± 13.0	0.0012
A-wave(cm/s)	48.8 ± 10.8	48.5 ± 16.2	ns
E/A ratio	1.0 ± 0.3	1.3 ± 0.5	0.0161
e'-wave(cm/s)	10.3 ± 2.3	8.2 ± 1.9	0.0012
E/e'ratio	4.3 ± 1.0	7.3 ± 2.1	0.0002
DT(ms)	14 ± 39	18 ± 48	0.0002
TAPSE(mm/s-1)	25.6 ± 5.1	25.4 ± 4.4	ns
RVFAC%	55.3 ± 11.4	53.7 ± 10.3	ns
S'-wave(cm/s)	13.6 ± 2.8	13.0 ± 2.1	ns
ICT(ms)	39 ± 13	25 ± 10	0.0002
IRT (ms)	28 ± 12	35 ± 14	0.0271
ET(ms)	28 ± 30	30 ± 51	ns
RFT(ms)	22 ± 51	26 ± 42	0.0021
ICT + IRT(ms)	67 ± 21	61 ± 22	ns
TEI-index	0.23 ± 0.07	0.21 ± 0.08	ns
TEI'-index	0.32 ± 0.12	0.24 ± 0.09	0.0071

Note: E-wave = early diastolic tricuspid annulus flow; A-wave = late diastolic tricuspid annulus flow; E/A ratio = relation between the velocity of the early tricuspid filling E-wave and the E′- wave; DT = deceleration time of E-wave; TAPSE = tricuspid annular plane systolic excursion; RVFAC=Right ventricle fractional area change; S′-wave = Doppler derived systolic velocities of the annulus; ICT = isovolumic contraction time; IRT = isovolumic relaxation time; ET = ejection time; RFT = rapid filling period time; 1The difference is statistically significant at 0.05; 2 The difference is statistically significant at 0.001.

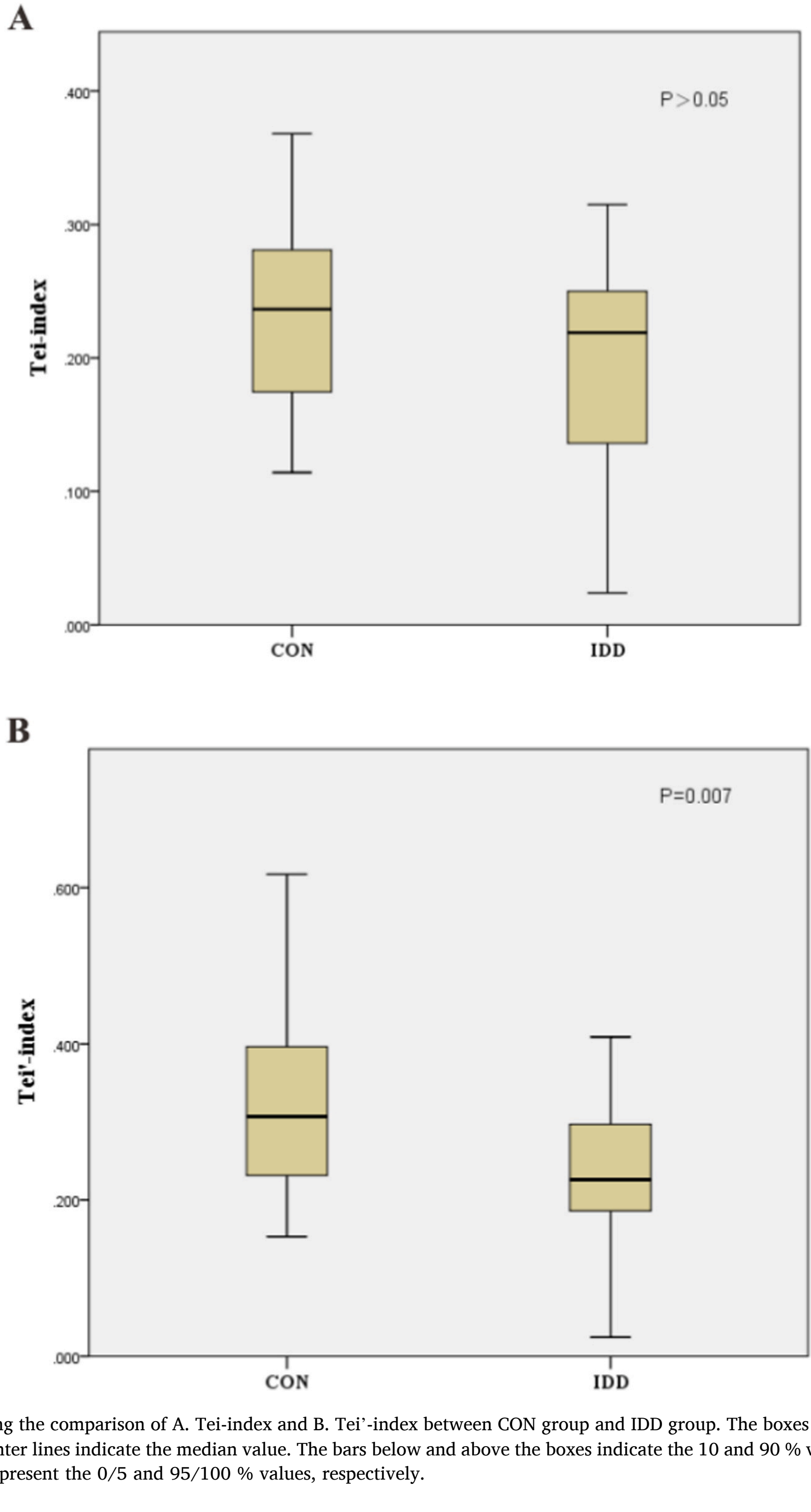

Fig. 1. Box plot showing the comparison of A. Tei-index and B. Tei'-index between CON group and IDD group. The boxes represent the lower and upper quartiles. The center lines indicate the median value. The bars below and above the boxes indicate the 10 and 90 % values. The circles below and above the boxes represent the 0/5 and 95/100 % values, respectively.

measurement of left ventricular diastolic function, but unfortunately, due to the lack of reliable indicators, the ideal evaluation indicators of right ventricular function are still being explored. The symmetry of cardiac function assessment was presented to us as a new approach to look over the cardiac function. The first level of symmetry, between the left ventricular and right ventricular behaviors, is rather easy to be accepted for the fact that some applications have already been there. For example, dp/dt was used to assess

Table 3
The correlation between Tei'-index and each Doppler parameter in patients with RV diastolic dysfunction.

Linear Regression of Tei'-index				
	Simple Linear Regression		multivariable linear regression	
	Beta	P	Beta	P
E-wave	−0.002	ns	0.003	ns
A-wave	0.003	0.009	0.001	ns
e'-wave	−0.001	ns	−0.016	ns
E/A ratio	−0.109	0.007	0.001	ns
E/e'ratio	−0.020	0.005	−0.033	0.013
DT	−0.972	0.001	−0.907	0.007

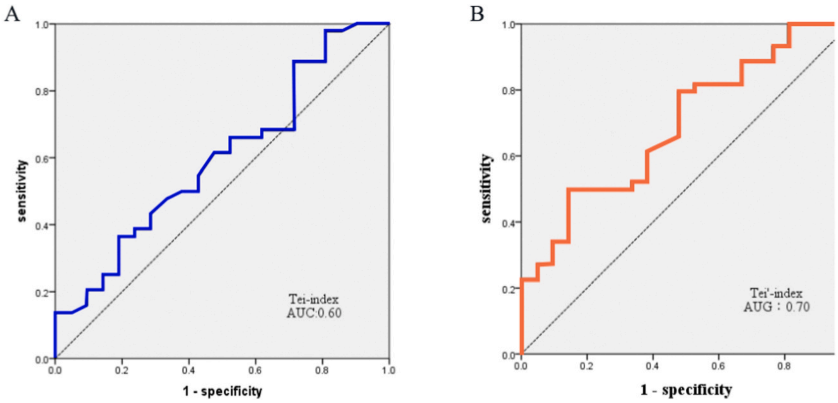

Fig. 2. Receiver operating characteristic curves for A. Tei-index and B. Tei'-index to detect patients with impaired RV relaxation. AUC = area under the curve.

the left ventricular systolic function and then was used to assess the right ventricular systolic function. So were the two classical Tei indexes (LV-Tei and RV-Tei). The second level of symmetry is between the ventricular systole and the early ventricular diastole. The idea comes from years of study of Tau (left ventricular diastolic time constant) calculation. Tau was found after people realized that the left ventricular pressure could be fitted into an index equation during isovolumic diastolic period. With the symmetry theory in mind, the authors realized the classical two Tei indexes (LV-Tei and RV-Tei) might be only good at assessment of ventricular systolic function [18]. For the ventricular diastolic function assessment, the ejection time (ET) should be updated to ventricular rapid filling period, i.e. E wave duration. Specifically, the RV-Tei' should be calculated from RV Tei'-index=(ICT + IRT)/RFP [19]. Again, we all know the systolic function and diastolic function are relatively independent issues, though they are connected and can affect each other. We prefer to description of two issues with two indexes instead of one. Other researchers also found the classical RV Tei-index is more likely to evaluate the RV systolic function [13,20] and a detailed analysis of systolic and diastolic performance should not be replaced by a single measurement of the Tei-index [21].

With respect to the assessment of right ventricular diastolic function, there is no widely accepted gold standard. Tricuspid valve E/A ratio, E/e' ratio and DT (E wave decelerate time) are the parameters most commonly used for the assessment of RV diastolic function and the tricuspid E/A ratio, E/e' ratio has been shown to correlate well with cardiovascular outcome and thus have immense clinical relevance [9,10,22,23]. In the multivariate regression analysis, it was found that the Tei'- index showed a significant correlation with the E/e 'and DT, which representing the early diastolic function, indicating that the new index was more effective in evaluating RV early diastolic dysfunction. Active myocardial processes are suppressed in patients with early diastolic dysfunction and result in prolongation of RV rapid filling time (RFT). While prolonged relaxation (decreased negative dp/dt) is initially associated with an increase in IRT, progressively worsening degrees of ventricular dysfunction will abbreviate this interval because of the dependence of IRT on factors other than active relaxation [3]. Early studies have found that patients with impaired relaxation on the borderline hypertension(BLH) and hyperkinetic essential hypertension (HEH) can responsible for augmentation of cardiac output by increasing myocardial contractility, which leading to ICT and PEP shortened. Bruch C et al. [24] found that the effect shortened of ICT on the value of the Tei-index was counterbalanced by prolonged of IRT in patients with isolated diastolic dysfunction. The rationale for the utility of the new Tei'-index in right ventricular diastolic dysfunction lies in the fact that (ICT + IRT)/RFT reflect important period of RV relaxation. As RV diastolic dysfunction results in the prolongation of both IRT and RFT, and in the abbreviation of ICT, this new Tei'-index is decreased in patients with isolated diastolic dysfunction.

The present study of a newly Tei'-index was designed to prove a better correlation with tricuspid valve E/e' ratio and E/A ratio. However, early diastolic tricuspid valve flow velocities will depend on factors that govern instantaneous atrial and right ventricle pressure before and after tricuspid valve opening and the resultant atrial-ventricular pressure gradient (filling load). Because Tei'-index is similar to Tei-index both measures relatively large time intervals (tricuspid closure-to- opening interval and rapid filling time), there is a good reason for feeling that RV Tei'-index is relatively unaffected by significant changes in preload or afterload in the pediatric clinical setting.

In summary, Tei-index is a great discovery when assessing cardiac function. It has a better sensitivity in terms of detecting cardiac dysfunction, and it is less affected by foreload, afterload and heart rate. Later, people realized it is not that satisfactory when dealing with diastolic function. Recently, the symmetrical theory of cardiac function assessment seems to be able to settle the problem. The theory predicts two more Tei-indexes with the focuses on diastolic function, one is left ventricular Tei' -index(LV-Tei'), the other is right ventricular Tei'-index (RV-Tei'). This study testified that RV-Tei' is better when dealing with right ventricular diastolic function compared with the classical RV Tei-index. The verification of LV-Tei' is on the way. Once the work done, we can proudly announce the Tei-index measurement is still a great idea but some modification is needed. There should be four Tei-indexes to address the RV/LV systolic/diastolic function separately. At last, we'd like to rename the four Tei-indexs to make things clear and better represented: the first is to evaluate left ventricular systolic function, LS-Tei (classical); the second is to evaluate the left ventricular diastolic function, LD-Tei (LV Tei', verification is on the way); the third is to evaluate the right ventricular systolic function, RS-Tei (classical); the fourth is to evaluate the right ventricular diastolic function, RD-Tei. (This is what we verified in this study, the RV-Tei'). We hope that the combination of the four indexes can provide a more comprehensive and detailed on evaluating the relaxation and contraction of the cardiac function.

5. Limitations

This study has several limitations. First of all, the sample size is relatively small, which limits the extension of this study. Statistical differences in subgroups divided by other factors such as gender may not be obtained. Assessment of right heart function remains relatively difficult despite technological advancement in echocardiography because of the unusual crescent shape, the irregular endocardial surface, complex contraction mechanism and location of the RV. This test group is based entirely on the latest guidelines of the American Society of Echocardiography and does not use the invasive check method to verify the correctness of the group, which may lead to certain cases into the group error. Tricuspid inflow can be affected by atrioventricular block or atrial flutter, and using the pulse Doppler method to measure the Tei'-index can not be obtained in the same cardiac cycle, which greatly narrow the scope of its application. In addition, we did not track the progress of the cases or the results after treatment, and did not use the new index to assess the patients again, therefore, its clinical application value to be further investigated. More further studies with larger sample sizes will be conducted to verify the universality and generalizability of the conclusions obtained in this study.

6. Conclusion

New Tei's index is significantly correlated with E/E 'and DT, which represent early diastolic function, suggesting that the new Tei's index is highly effective and specific in the evaluation of early diastolic dysfunction of right ventricle, and can be used as an indicator for the detection of IDD in clinic.

Declarations

6.1. Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Qingdao Municipal Hospital (LSZ-031). Informed consent was signed by all participants in this study.

6.2. Consent for publication

Not applicable.

6.3. Data availability statement

Data related to this study were not deposited into a publicly available repository. Data will be made available on request.

6.4. Competing interests

All of the authors had no any personal, financial, commercial, or academic conflicts of interest separately.

Authors' contributions

Yicen Zhang, Guotong Sun: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Wenyuan Zhu, Peixin Wang: Performed the experiments; Analyzed and interpreted the data.

Lei Wang, Hongyan Dai: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

CRediT authorship contribution statement

Yicen Zhang: Conceptualization, Formal analysis, Methodology, Software, Writing – original draft, Writing – review & editing. **Guotong Sun:** Conceptualization, Methodology, Software, Writing – original draft, Writing – review & editing, Formal analysis. **Wenyuan Zhu:** Data curation, Formal analysis, Writing – review & editing, Investigation. **Peixin Wang:** Data curation, Formal analysis, Investigation, Writing – review & editing. **Lei Wang:** Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. **Hongyan Dai:** Data curation, Formal analysis, Investigation, Writing – review & editing, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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