Effects of childhood obesity on myocardial performance, autonomic and conduction properties of the heart

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Abstract

Background: Childhood obesity tends to persist into adulthood and associated with increase in developing ischemic and non-ischemic cardiovascular diseases. We aimed to evaluate the effect of obesity on cardiac functions, atrial electromechanical coupling, and heart rate response, which are considered to be predictors of atrial fibrillation and sudden cardiac arrest. *Methods:* Study population included 52 obese children and 52 healthy controls. We performed 12-lead electrocardiography, echocardiographic examination, and treadmill exercise testing. Mitral, septal, and tricuspid segments were analysed by tissue Doppler imaging. *Results:* Myocardial performance index (p = 0.011, p < 0.001, and p = 0.001, respectively) was higher and E'/A' ratio (p = 0.011, p < 0.001, and p < 0.001, respectively) was lower in obese group than controls. Atrial electromechanical coupling was longer in the obese group at all three segments (p < 0.001, p = 0.009, and p = 0.04, respectively). They had significantly longer interatrial (p < 0.001) and intra-atrial (p = 0.003) electromechanical conduction delay. While chronotropic index was similar between two groups, heart rate reserve was lower in obese children than controls (p = 0.043). The 1st- and 2nd-minute heart rate recovery indices of the obese group were lower compared to controls (p < 0.001 and p = 0.03, respectively). Body mass index was positively correlated with intra- and inter-atrial conduction times, whereas it was negatively correlated with heart rate recovery indices. *Conclusion:* We showed a deterioration in the diastolic function, atrial conduction, and heart rate response properties in children with obesity. Given the prognostic importance of these parameters, obese patients are might be at risk for atrial fibrillation and severe dysrhythmias from a young age.

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Obesity in children and adolescents is one of the most important and increasing public health problems in both developed and developing countries.[1] It is also strongly associated with adult obesity, which significantly increases the risk of type II diabetes, cardiovascular disease, cancer, and premature death.[2,3] Besides ischemic heart disease, recent studies have shown an increased incidence of non-ischemic cardiovascular diseases, including arterial hypertension, cardiac remodelling, arrhythmias, heart failure, and venous thromboembolism in these individuals.[4,5]

Impairment in atrial electromechanical coupling and the prolonged intra- and inter-atrial conduction times reflect inhomogeneous propagation of sinus impulses.[6] Therefore, it is considered the electrophysiological hallmark of fibrillation-prone atria. It is simply the interval from the onset of electrical activity to the actual myocardial contraction. Studies in children and adults have shown an increase in atrial electromechanical coupling and thus an increased risk of atrial fibrillation in different diseases.[7–10] The autonomic nervous system plays a central role in the regulation of cardiovascular function, and abnormalities in its function are associated with increased cardiovascular mortality.[11,12] Heart rate response during exercise is a complex combination of chronotropic reserve during exercise and heart rate recovery after exercise cessation.[13] Heart rate recovery is an important measure of autonomic nervous system dysfunction and is considered to be directly related to parasympathetic activity.[14] The heart rate recovery index is defined as the reduction from the heart rate at the peak of exercise to the heart rate at the 1st, 2nd, 3rd, and 5th minutes after the end of the exercise stress test. A delayed decline in heart rate may reflect decreased vagal activity and is a strong predictor of overall mortality.[12] To the best of our knowledge, it has not yet been assessed in childhood obesity. The aim of our study was to evaluate cardiac functions and impact of obesity on electrophysiological characteristics of the atria and heart rate response in children with obesity.
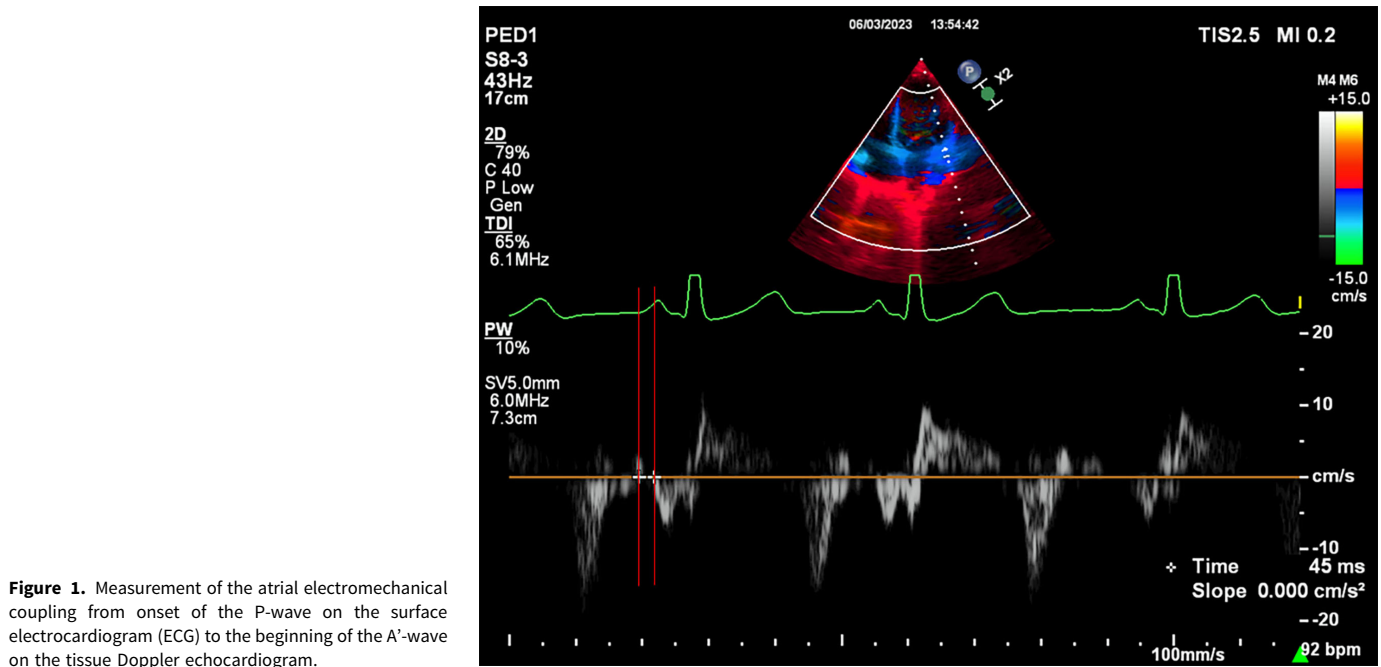
Figure 1. Measurement of the atrial electromechanical coupling from onset of the P-wave on the surface electrocardiogram (ECG) to the beginning of the A'-wave on the tissue Doppler echocardiogram.

Methods

The study population included 52 obese children (34 boys and 18 girls) and 52 healthy control subjects (32 boys and 20 girls). All of the obese children were recruited from cases between the ages of 6 and 18 years who were referred to our paediatric endocrinology outpatient clinic for obesity evaluation. Weight was measured using digital weighing scale (SECA 841, Hamburg, Germany) to the nearest 100 g, while subjects were wearing light clothes and were bare footed. Height was measured using stadiometer (Holtain Instruments Ltd, Crymych, UK) to the nearest 0.1 cm, while subjects were standing without shoes on a horizontal surface. The subjects underwent detailed physical examination including evaluation for syndromes and endocrine diseases. Children with syndromal obesity such as Prader–Willi and Bardet–Biedle syndromes and those with endocrinological pathologies (such as Cushing's syndrome and hypothyroidism, etc) were excluded. Obesity is defined as a body mass index ≥ +2 SDS. Age and sex-specific national cut-off points of body mass index were used to determine obesity.[15] The control group included age- and sex-matched non-obese healthy children with no cardiovascular disease. Exclusion criteria included patients with congenital heart disease, electrocardiography findings other than sinus rhythm or bundle branch block, patients taking anti-arrhythmic or sympatho-mimetic drugs for any reason, patients with valvular heart disease, systemic hypertension, and any concomitant systemic disease. All obese and control subjects underwent 12-lead electrocardiography, echocardiographic examination, and treadmill exercise testing. A written informed consent was obtained from all parents of the children, which was approved by the Hospital Ethics Committee.

Echocardiographic examinations

Echocardiographic examinations (Philips Affiniti 50 Cardiac Ultrasound, 5-1 MHz transducer; Bothell, WA, United States of America) of all patients and control subjects were performed by a paediatric cardiologist blinded to clinical details. A single-lead electrocardiogram was recorded continuously during echocardiographic studies. Two-dimensional, M-mode, pulsed-wave, continuous-wave Doppler, and tissue Doppler imaging echocardiographic images were obtained. Left ventricular ejection fraction, mitral annular plane systolic excursion, and the tricuspid annular plane systolic excursion were measured using M-mode as reliable markers of left and right ventricular systolic function. Peak early (E) and late (A) wave velocities of the mitral valve, and the E/A ratio were measured to evaluate the diastolic function of the left ventricle pulsed-wave Doppler. Also, pulmonary flow at the pulmonary valve level was recorded by pulsed-wave Doppler echocardiography to measure the acceleration time of the pulmonary flow trace/right ventricular ejection time ratio.

Tissue Doppler imaging studies were performed at the lateral mitral annulus, septal mitral annulus, and right ventricular tricuspid annulus (mitral, septal, and tricuspid segments, respectively). Longitudinal peak annular velocities during systole (S'), early diastole (E'), and late diastole (A') were measured, and the E'/A' ratio was calculated. Also, the myocardial performance index was calculated as follows[16]: ([isovolumic contraction time + isovolumic relaxation time] / ejection time).

Atrial electromechanical coupling was defined as the interval from the onset of the atrial electrical activity (P-wave on surface electrocardiography) to the beginning of the mechanical atrial contraction (A' wave) (Fig. 1). It was measured from the same three segments mentioned above. The difference between the lateral and tricuspid atrial electromechanical coupling intervals was defined as interatrial conduction delay, and the difference between the septal and tricuspid atrial electromechanical coupling intervals was defined as intra-atrial conduction delay.[17]

Treadmill exercise testing

All patients in the study underwent treadmill exercise testing using the Bruce protocol. The predicted peak heart rate was calculated as (220 − age), and the aim was to reach at least 85% of the age-predicted heart rates. The end of the exercise was marked, and the post-exercise heart rate was recorded for at least 5 minutes while the patient rested. Qualified exercise physiologists and/or a

cardiology fellow prospectively collected physiologic and haemo-dynamic data during testing, including symptoms, heart rhythm, blood pressure, estimated functional capacity in metabolic equivalents, heart rate reserve (increase in heart rate from resting level to peak exercise), chronotropic index (it was calculated by a formula as: [(peak heart rate–resting heart rate)/ (220–age–resting heart rate)],[18] and heart rate recovery indices (the reduction in heart rate from the rate at peak exercise to the rate at the 1st, 2nd, 3rd, and 5th minutes after the cessation of the exercise stress test).

Statistical analysis

Statistical analysis was performed using SPSS for Windows, version 26.0 software (SPSS, Chicago, IL, United States of America). All continuous variables were expressed as mean ± standard deviation or median and interquartile range. Categorical variables were defined as percentage and number of cases. Categorical data were compared using the χ^2 test. Continuous variables were compared between the groups using Student's t-test or the Mann–Whitney U-test depending on whether they were distributed normally or not, as tested by the Kolmogorov–Smirnov test. Pearson's correlation analysis was used to estimate the relationship between the test parameters. A p value < 0.05 was considered to be statistically significant.

Results

The mean age was 12.4 ± 2.7 years (range, 7.5–17.6 years) in the obese group and 12.5 ± 2.9 years (range, 6.7–17.5 years) in the control group (p = 0.87). While gender distribution was similar between groups (p = 0.69), body mass index and body mass index-SDS were significantly higher in obese group compared to controls (p < 0.001).

Electrocardiography findings revealed a significantly higher heart rates in obese group than controls (91 ± 13.2 beats/min versus 79.3 ± 13.2 beats/min, respectively; p < 0.001). However, PR interval (0.14 s versus 0.13 s, respectively; p = 0.22) and QTc duration (394.8 ± 12.8 ms versus 391.7 ± 15.6 ms, respectively; p = 0.27) were similar between two groups.

Echocardiographic examinations showed that the left ventricular diameter of obese group was significantly increased at both end-diastole and end-systole compared to the control group (p = 0.001 and p = 0.019, respectively). Left ventricular systolic function parameters obtained by M-mode echocardiography and diastolic parameters obtained by continuous-wave Doppler of mitral inflow velocities were similar between the groups. Mitral annular plane systolic excursion values were significantly higher in the patient group (p < 0.001). Although tricuspid annular plane systolic excursion values were similar between obese and control subjects (p = 0.5), tricuspid regurgitation velocity was significantly higher (p = 0.03) and acceleration time of the pulmonary flow trace/right ventricular ejection time ratio was lower (p = 0.029) in the patient group in accordance with increased pulmonary arterial pressure (Table 1).

Table 2 represents the comparison of the tissue Doppler imaging parameters and atrial electromechanical coupling char-acteristics between the groups. Unlikely conventional echocardi-ography, tissue Doppler imaging revealed statistically significant differences in terms of diastolic function of both ventricles. The obese group showed lower E'/A' and higher myocardial perfor-mance index levels in all three segments analysed compared to the control group. Also, obese children had significantly prolonged

Table 1. Comparison of demographic and conventional echocardiographic parameters related to ventricular systolic and diastolic function between groups.

	Obese group	Control group	p
Age (years)	12.4 ± 2.7	12.5 ± 2.9	0.87
Gender (M:F) (n)	34:18	32:20	0.69
BMI-SDS	2.6 ± 0.5	−0.62 ± 1	<0.001
SBP (mmHg)	130.7 ± 13.6	111.6 ± 12.9	<0.001
DBP (mmHg)	71.6 ± 12.9	63.6 ± 7.3	<0.001
EF (%)	71.1 ± 4	70.2 ± 3.3	0.2
LVEDd (mm)	45.1 ± 4.8	41.8 ± 4.9	0.001
LVESDd (mm)	26.8 ± 3.4	25.2 ± 3.4	0.019
Mitral-E	104.8 ± 15.5	103.4 ± 14.6	0.64
Mitral-A	62 ± 11.5	55.7 ± 10	0.004
Mitral-E/A	1.7 ± 0.4	1.6 ± 0.8	0.29
TRV (m/s)	2.5 ± 0.2	2.2 ± 0.1	<0.001
TAPSE (mm)	23.1 ± 3.4	22.7 ± 3.1	0.5
MAPSE (mm)	15.2 ± 2.2	14.3 ± 2.3	0.03
AT (ms)	122.9 ± 20.4	129 ± 22.5	0.15
RVET (ms)	323.6 ± 29.5	319.3 ± 30.3	0.46
AT/RVET	0.38 ± 0.1	0.40 ± 0.1	0.029

AT = acceleration time of the pulmonary flow trace; BMI = body mass index; DBP = diastolic blood pressure; EF = ejection fraction; LVEDd = left ventricular end-diastolic dimension; LVEDs = left ventricular end-systolic dimension; M:F = male:female ratio; Mitral-E = mitral early diastolic velocity; Mitral-A = mitral late diastolic velocity; MAPSE = mitral annular plane systolic excursion; RVET = right ventricular ejection time; SBP = systolic blood pressure; TRV = tricuspid regurgitation velocity; TAPSE = tricuspid annular plane systolic excursion.

Table 2. Comparison of the tissue Doppler imaging parameters and atrial electromechanical coupling characteristics between the obese and control groups.

	Obese group	Control group	p
Mitral E/E'	7 ± 1.7	6.6 ± 1.4	0.24
Mitral E'/A'	2.3 ± 0.6	2.6 ± 0.6	0.011
Mitral MPI	0.36 ± 0.07	0.33 ± 0.05	0.011
Septal E'/A'	1.8 ± 0.5	2.2 ± 0.4	<0.001
Septal MPI	0.40 ± 0.5	0.34 ± 0.5	<0.001
Tricuspid E'/A'	1.4 ± 0.4	1.7 ± 0.4	<0.001
Tricuspid MPI	0.37 ± 0.06	0.33 ± 0.04	0.001
Mitral AEC (ms)	48.8 ± 9.6	37.9 ± 7.5	<0.001
Septal AEC (ms)	28.8 ± 6.1	25.8 ± 5.4	0.009
Tricuspid AEC (msec)	11.8 ± 5.5	13.9 ± 4.4	0.04
Inter-atrial conduction delay (ms)	37 ± 12.6	24.1 ± 8.2	<0.001
Intra-atrial conduction delay (ms)	16.2 ± 8	12 ± 5.7	0.003

A' = peak late diastolic velocity; AEC = atrial electromechanical coupling; E = mitral early diastolic velocity by pulsed-wave Doppler; E' = peak early diastolic velocity; MPI = myocardial performance index.

atrial electromechanical coupling time than controls in mitral, septal, and tricuspid segments (p < 0.001, p = 0.009 and p = 0.04, respectively). Similarly, inter- and intra-atrial conduction delay

Table 3. Comparison of exercise stress test derived variables between the obese and control groups.

	Obese group	Control group	p
Resting heart rate, beats/min	104.3 ± 13.8	98.7 ± 13.8	0.044
Peak heart rate, beats/min	186.4 ± 8.9	186.4 ± 9.4	0.999
Maximal METs	14.2 ± 2	16 ± 2.9	<0.001
Exercise time, min	10.4 ± 1.5	12.8 ± 2.6	<0.001
Heart rate reserve, beats/min	82.17 ± 12.5	87.8 ± 14.9	0.043
Chronotropic index	0.79 ± 0.08	0.82 ± 0.07	0.16
HRR_1	23.6 ± 9.9	34.5 ± 16	<0.001
HRR_2	45 ± 10.6	51 ± 16.4	0.03
HRR_3	52.4 ± 10.7	56.9 ± 16.3	0.1
HRR_5	58.2 ± 9.4	62.8 ± 16.7	0.08

HRR = heart rate recovery index; METs = metabolic equivalents (1 MET = 3.5 ml/kg per min of oxygen consumption).

Table 4. Correlation of BMI-SDS with atrial conduction time and exercise testing variables.

	r	p
Mitral AEC	0.485	<0.001
Septal AEC	0.198	0.044
Tricuspid AEC	−0.212	0.03
Intra-atrial conduction delay	0.262	0.007
Inter-atrial conduction delay	0.482	<0.001
Maximal heart rate	0.018	0.861
METs	−0.388	<0.001
Exercise time	−0.488	<0.001
HRR_1	−0.390	<0.001
HRR_2	−0.220	0.025
HRR_3	−0.185	0.061
HRR_5	−0.167	0.089

AEC = atrial electromechanical coupling; HRR = heart rate recovery index; METs = metabolic equivalents; R = correlation coefficient.

was significantly prolonged in the patient group (p < 0.001 and p = 0.003, respectively).

Comparisons of the exercise stress test data among obese and healthy subjects are summarised in Table 3. While chronotropic index did not differ between two groups, heart rate reserve, maximal metabolic equivalents attained during the exercise stress test, and exercise time of obese children were significantly lower in obese children compared to healthy control group (p < 0.001). Heart rate recovery indices at 1st and 2nd minutes of recovery phase in the obese group were significantly lower than those of the healthy control group (23.6 ± 9.9 versus 34.5 ± 16, p < 0.001 and 45 ± 10.6 versus 51 ± 16.4, p = 0.03, respectively). Heart rate recovery indices at 3rd and 5th minutes were also lower in obese subjects compared to the control group, without statistical significance (p > 0.05).

Correlation analyses of body mass index-SDS with atrial conduction time and exercise testing variables are shown in Table 4. In the study group, there was a positive correlation between body mass index-SDS and intra- and inter-atrial conduction times. We also showed a negative correlation between body mass index-SDS and heart rate recovery indices at the 1st and 2nd minutes of the recovery phase of treadmill exercise testing.

Discussion

This study demonstrated that childhood obesity has a significant impact on ventricular function and remodelling, atrial conduction, heart rate response, and autonomic properties of the heart. In addition to significant differences in systolic and diastolic function parameters and atrial electromechanical coupling obtained by tissue Doppler imaging examinations, we demonstrated lower heart rate recovery indices by exercise testing in obese children compared to healthy controls. Also, obese children had significantly higher systolic and diastolic blood pressure values compared to controls in the present study.

Recent studies have shown that obese people have an enhanced risk of developing atrial fibrillation. El-Assaad et al.[19] analysed 1500 paediatric cases and showed that the risk of isolated atrial fibrillation was higher with obesity and increasing age. They

conclude that obesity alone was also a risk factor compared with normal body mass index. Similarly, Frost et al.[20] reported that obesity is associated with an increased risk of atrial fibrillation or atrial flutter diagnosis in adults. Another study showed that overweight and obese young men had more than twice the risk of atrial fibrillation compared with young men of normal weight.[21] The possible association between obesity and enhanced risk of atrial fibrillation is attributed to impaired atrial conduction. It is primarily caused by structural and electrical remodelling of the heart in these people. Briefly, increased heart work and systemic hypertension in obese people lead to thickened left ventricular myocardium, diastolic dysfunction, and left atrial enlargement. Activation of the sympathetic nervous system and renin angiotensin system leads to increased inflammatory process. Changes in atrial size and fibrosis may cause dispersion of refractoriness and alterations in atrial conduction.[5,9,22,23] This can result in arrhythmias, particularly atrial fibrillation.[22,23]

Atrial conduction characteristics can be evaluated by both invasive (recordings of atrial conduction during electrophysiologic study) and non-invasive indices of atrial conduction (P-wave dispersion on electrocardiogram and atrial electromechanical coupling measurement by echocardiography).[24,25] These are considered to reflect atrial remodelling and are predictive of atrial fibrillation.[26] In this study, we compared the duration of atrial electromechanical coupling in obese children and non-obese healthy control subjects. It was significantly prolonged in obese children in all three cardiac segments we evaluated indicating impaired intra- and inter-atrial conduction. Similar findings consistent with diastolic dysfunction and atrial conduction disturbances have been reported in adult patients with obesity, non-alcoholic fatty liver disease, and systemic hypertension.[7,22,23,27] In the single study conducted in obese children, Temiz et al.[9] showed significant prolongation in mitral and septal atrial electromechanical coupling. In agreement with our study, they showed that intra-atrial and inter-atrial conduction delay was significantly prolonged in the obese group. Also, inter- and intra-atrial electromechanical coupling was positively correlated with body mass index values.

The autonomic nervous system plays a central role in the regulation of cardiovascular function. The increase in heart rate during exercise is thought to be due to activation of the sympathetic nervous system and simultaneous suppression of the parasympathetic nervous system. On the other hand, the decrease in heart rate immediately after exercise is thought to be due to parasympathetic reactivation with sympathetic withdrawal.[28,29] Abnormal cardiac chronotropic response during exercise test is associated with an increased risk of adverse cardiovascular events, and it has been reported in obese adult patients.[30] In our study, obese children showed significantly higher resting heart rate and lower heart rate reserve during exercise testing compared to the control group. Although the chronotropic index was lower in the obese group than in healthy controls, it did not reach statistical significance. However, there are concerns regarding the applicability in the paediatric age group and cut-off level (accepted as ≥ 0.8 in adults) of the formula defined in the adult population for the calculation of the chronotropic index.[13]

Imai et al.[28] showed that heart rate recovery was rapid in athletes but was blunted in patients with heart failure and was completely abolished by the administration of atropine. Cole et al.[12] stated that a low value for heart rate recovery after exercise testing was a powerful and independent predictor of cardiovascular and all-cause mortality. This marker is simple to calculate from data that are already contained in the results of standard exercise tests and may be valuable for the assessment of risk in routine clinical practice. Özveren et al.[31] reported that heart rate recovery index was deteriorated in adult patients with non-alcoholic fatty liver disease, and this may help explain the increased prevalence of cardiac death. Similarly, we found significantly lower values of heart rate recovery indices at 1st and 2nd minutes of recovery phase in obese children compared to controls (p < 0.00 and $p = 0.003$, respectively). Metabolic equivalents and exercise duration were also significantly lower in obese children. Although these findings are consistent with adult patients, heart rate recovery indices have not previously been evaluated in obese children.

The current study has some limitations. First, we conducted our study with a relatively small numbers of patients, which may have affected the power of the study. Second, since the design of the study was cross-sectional, patients could not be followed up for long-term atrial fibrillation development. Finally, although all echocardiographic measurements were performed by a single experienced physician, inter-observer variability was not assessed.

In conclusion, obesity is associated with significant ischemic and non-ischemic cardiovascular mortality. Childhood obesity tends to persist into adulthood. The current study showed that obese children have impaired diastolic function of both ventricles. They also have longer atrial conduction time, lower heart rate reserve, and heart rate recovery indices that are thought to be predictors of atrial fibrillation and sudden death. They can be evaluated by non-invasive tests, which are simple to use and may be clinically useful in identifying high-risk patients.

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