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Acoustic cardiography helps to identify heart failure and its phenotypes

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ABSTRACT

Background: The prevalence of heart failure (HF) is increasing as the population ages, but its rapid diagnosis and phenotype identification remain challenging. We sought to determine whether acoustic cardiography can accurately identify HF and its phenotypes.
Methods: Three cohorts of patients were studied [94 with hypertension, 109 with HF and normal ejection fraction (HFNEF, EF ≥ 50%) and 89 with HF and reduced ejection fraction (HFREF, EF < 50%)]. All participants received acoustic cardiography and echocardiography examinations. Acoustic cardiographic parameters included S3 score (probability that the third heart sound exists), electromechanical activation time (EMAT, interval from Q wave to the first heart sound; EMAT/RR is EMAT normalized by heart rate), and systolic dysfunction index (SDI, a combination of EMAT/RR, S3 score, QRS duration and QR interval). Receiver operative characteristic curves were used to determine diagnostic utility of acoustic cardiography.
Results: EMAT/RR significantly differentiated HFNEF from hypertension (area under curve [AUC], 0.83; 95% confidence interval [CI], 0.77–0.89) with an EMAT/RR > 11.54% yielded 55% sensitivity and 90% specificity. Similarly, an echo-measured E/e′ > 15 yielded 55% sensitivity, 90% specificity and 0.84 AUC in detecting HFNEF. Whereas SDI out-performed the other acoustic cardiographic parameters in differentiating HFREF from HFNEF (AUC, 0.81; 95% CI, 0.75–0.87), and an SDI > 5.43 yielded 53% sensitivity and 91% specificity. The E/e′ ratio had a similar diagnostic performance.
Conclusions: Our study demonstrates that this bedside technology may be helpful in identifying HF and its phenotypes, especially when echocardiography is not immediately available.

1. Introduction

Despite recent advances in its management, heart failure remains a major cause of disability and death and its prevalence is still increasing as the population ages [1]. With an array of diagnostic tests, rapid and accurate bedside diagnosis of heart failure still remains challenging. It was reported that as many as 10–20% of emergency department patients with acute decompensated heart failure were misdiagnosed [2–4].

Dyspnea is the most common presentation of heart failure, and it is also the common symptom of many other diseases, such as chronic obstructive pulmonary disease (COPD), pneumonia and anemia. Heart failure occurs most frequently in the elderly, a population often with similar comorbidities. Diagnosis of heart failure based on history and physical examination alone is often unreliable [5]. Consequently, accurate and rapid diagnosis of heart failure can be difficult when heart failure coexists with these diseases.

Over the past few years, there has been a growing recognition that a large number (more than 50%) of patients with heart failure have a relatively normal ejection fraction (EF), labeled as heart failure with normal (or preserved) ejection fraction (HFNEF) as opposed to heart failure with reduced ejection fraction (HFREF) [6]. Although the prognosis of patients suffering from HFNEF is equally bad as those suffering from HFREF, the epidemiology, clinical characteristics, and therapy of HFNEF are different from HFREF. Thus, it is necessary to differentiate these two phenotypes.

B-type natriuretic peptide (BNP) is often used to evaluate patients with possible heart failure, but its frequently encountered intermediate "gray zone" between 100 and 500 pg/ml limited its diagnostic utility [7]. Furthermore, BNP is sensitive to other biological factors, such as age, gender, weight, and renal function [8]. Likewise, elevated BNP levels can occur in other settings, such as pulmonary embolism and COPD [9]. All these limitations make it difficult to interpret BNP results during differential diagnoses.

Echocardiography is a well validated resource to detect and evaluate left ventricular (LV) dysfunction [10]. However, this technology requires specialized training for image acquisition and interpretation and is not always readily available.

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The abnormal diastolic heart sounds, especially the third heart sound (S3), have long been recognized to be a specific clinical sign for LV dysfunction and a predictor for adverse outcome of patients with heart failure [11]. Systolic time intervals (STIs) are also well validated indicators of heart failure reported by previous studies [12,13]. Acoustic cardiography (AUDICOR, Inovise Medical, Inc., Portland, OR, USA) is an inexpensive and easy to use equipment which can be used in a wide variety of clinical conditions [14]. With proprietary dual-functional sensors, this technology permits simultaneous acquisition of detailed information regarding STIs and diastolic heart sounds and provides a computerized interpretation of the findings. In this study, we sought to determine whether this new technology could accurately identify heart failure and its phenotypes.

2. Methods

2.1. Participants and study design

Our study population consisted of 3 separate cohorts including 94 patients with hypertension, 109 patients with HFNEF and 89 patients with HFREF. Patients' medical records had been reviewed to determine the diagnoses of heart failure or hypertension based on the established criteria [9,15,16]. Heart failure patients with EF<50% and EF≥50% were categorized into HFREF and HFNEF groups, respectively. All the heart failure patients were enrolled from in-patients. Exclusion criteria for hypertension cohort included age<18 years old, pregnancy, secondary hypertension with underlying causes, diabetes mellitus, known structural heart diseases, coronary heart disease, EF<50% and pacemaker implantation. Exclusion criteria for heart failure cohort included age<18 years old, systolic blood pressure<90 mm Hg, mitral stenosis, constrictive pericarditis, use of mechanical ventilation and pacemaker implantation. Informed consent was obtained from each patient and the study was approved by local ethics committee of the institution.

2.2. Echocardiography

Echocardiography was performed (Vivid 7, Vingmed-General Electric, Horten, Norway, and IE33, Phillips, Andover, MA) in all patients of three groups. Investigators who interpreted echocardiographic findings were blinded to the clinical and acoustic cardiographic data. End-diastolic and end-systolic volumes were calculated using the biplane Simpson's method. And then these volumes were used to calculate left ventricular ejection fraction (LVEF). Early diastolic mitral annular velocity obtained by pulsed wave Doppler was used to determine e′ and ratio of E/e′.

2.3. Acoustic cardiography

Each subject underwent the acoustic cardiographic examination in supine position. Acoustic cardiographic raw data were transferred to Inovise Medical and were analyzed by the computerized algorithm for the measurement of heart sounds and related STIs. This algorithm has been validated by blinded interpretation of heart sound tracings by experts. And the relationship of these variables to hemodynamic measurements obtained by invasive and non-invasive methods were previously reported [3,17,18]. At least 3 examinations had been performed to each patient and the average values of each variable were used for analysis.

The following acoustic cardiographic variables were evaluated in the present study:

1. QR interval: the time from the Q wave onset to the peak of R wave (or S wave for QS morphologies).
2. QT interval: the time from the Q wave onset to the end of the T wave.
3. QTc interval: QT interval divided by the square root of the R to R interval (Bazett's formula).
4. QRS duration: the time from the QRS onset to QRS offset.
5. EMAT (electromechanical activation time): the time from the Q wave onset to the mitral component of the first heart sound (S1) (Fig. 1). EMAT reflects the time required for LV to generate sufficient force to close the mitral valve.
6. LVST (LV systolic time): the time from S1 to the second heart sound (S2) (Fig. 1).
7. LDPT (LV diastolic perfusion time): the time from S2 to the next Q wave onset.
8. S3 intensity: the measurement of the intensity of S3.
9. S3 score: the probability that S3 exists. On the basis of timing, persistency, intensity, frequency of the sound, one value between 0 and 10 is reported. Values >5 indicate S3 is present.
10. SDI (systolic dysfunction index): SDI = exp (S3 score/10) × QRS duration × QR interval × EMAT/RR. The SDI value undergoes a nonlinear transformation and is mapped into a scale of 0–10, where SDI>5 indicates EF<50% and SDI>7.5 indicates EF<35% and elevated LV filling pressure [19].

Due to the fact that EMAT, LVST and LDPT are influenced by heart rate, indices normalized by heart rate were used, and those were EMAT/RR, LVST/RR and LDPT/RR, respectively. To reduce the detrimental effect of unstable heart rate in patients with atrial fibrillation (AF), at least 5 examinations were performed in each AF patient and the average values were used.

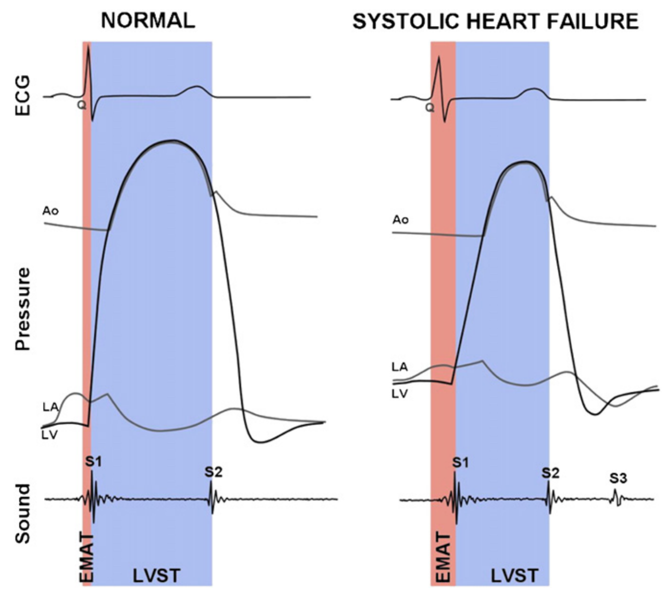

Fig. 1. Schematic of normal and abnormal S3 and STIs. Those with heart failure may have S3, longer EMAT and shorter LVST. ECG, electrocardiogram; Ao, aortic; LA, left atrial; LV, left ventricular; S1, the first heart sound; S2, the second heart sound; S3, the third heart sound; STIs: systolic time intervals; EMAT: electromechanical activation time; LVST: left ventricular systolic time.

2.4. Assessment of reproducibility

Inter-operator reproducibility was assessed in 20 randomly selected patients involving 2 operators. Intra-class correlation coefficient (ICC) was used to determine consistency between operators. The reproducibility was considered excellent if ICC≥0.75 [20,21].

2.5. Statistical analysis

Data were described with mean and standard deviations for continuous variables and frequency and proportions for categorical variables. Comparisons among hypertension, HFNEF and HFREF groups were performed using one way analysis of variance for normal distributed data and Kruskal–Wallis H test for skewed data. Post-hoc Bonferroni test and Mann–Whitney *U* test were used for two-group comparison according to data type. Because of imbalanced age in these three groups, analysis of covariance was performed to determine cardiac function effect on EMAT/RR and SDI separately with age as covariate. Receiver operative characteristic (ROC) curves were generated to determine area under curve (AUC), sensitivity, specificity, positive likelihood ratio (LR+), and negative likelihood ratio (LR−) for predicting heart failure and its phenotypes. LR+ = sensitivity/(1-specificity), and LR− = specificity/(1-sensitivity). Unlike positive and negative predictive values, diagnostic inferences based on LR+ and LR− were independent of the prevalence of disease in the tested population. A two-sided p value less than 0.05 was considered to indicate statistical difference in all analyses. Statistical analyses were performed using SPSS, version 13.0 (SPSS, Inc., Chicago, Illinois).

3. Results

3.1. Characteristics of study subjects

Table 1 summarizes the demographic data, clinical history and medications of our patients who were subdivided into 3 groups according to cardiac function.

3.2. Acoustic cardiographic and echocardiographic characteristics

Table 2 shows the acoustic cardiographic and echocardiographic data in the 3 groups. Compared with patients in hypertension group, patients in HFNEF group had a shorter QR and QT interval, lower LDPT/RR, greater EMAT/RR, S3 intensity and SDI. However, there was no statistical difference in S3 score between these 2 groups,