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Use of transesophageal echocardiography and contrast echocardiography in the evaluation of cardiac masses

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ABSTRACT

Objectives: To determine whether the combination of transesophageal echocardiography (TEE) and contrast echocardiography (CE) accurately diagnose suspected cardiac masses using large sample data.
Methods: Patients with cardiac masses undergoing surgical treatment were enrolled in this study. Routine transthoracic echocardiography (TTE) and TEE examinations were carried out, and CE examinations were carried out when needed. All patients' clinical data and imaging features were retrospectively reviewed. Surgery and histopathology served as the gold standard for diagnosing cardiac masses.
Results: A total of 252 consecutive patients were included in this study. Sixteen patients were lost to follow-up and were excluded from the study. The combinations of TEE and CE yielded the correct pathologic diagnosis in 225 of 230 patients (97.8%), while CT yielded the correct pathologic diagnosis in 122 of 141 patients (86.5%), $p < 0.01$. TEE yielded the correct pathologic diagnosis in 219 of 226 patients (96.9%), and CE yielded the correct pathologic diagnosis in 45 of 48 patients (93.8%). TTE alone yielded the correct pathologic diagnosis in 163 of 236 patients (69.1%), $p < 0.001$ for all. TEE imaging provided detailed and precise information regarding cardiovascular morphology, anatomy, hemodynamics and function, and CE provided information regarding tissue characteristics without subjecting patients to radiation exposure.
Conclusions: The combination of TEE and CE is feasible for the detection of suspected cardiac masses, especially in diagnosing and differentiating between benign and malignant lesions.

1. Introduction

Cardiac masses are rare, with an autopsy incidence ranging from 0.001 to 0.030% [1]. The greatest danger of cardiac masses is that they rarely cause symptoms early in their disease courses. However, these masses have the potential to cause serious harm to patients, often in the forms of heart failure, emboli, sudden death and other serious complications. Most symptomatic patients with malignant cardiac masses may not benefit from treatment. Therefore, timely and accurate diagnoses of cardiac masses are important with respect to providing early effective treatment and facilitating good outcomes. Echocardiography is the preferred imaging method for the initial assessment of cardiac masses. Most cardiac masses are first detected via transthoracic echocardiography (TTE), and some are detected via chest computed tomography (CT) performed for other indications. However, TTE or chest CT alone is not sufficient for obtaining more detailed information pertaining to cardiac masses, such as their exact locations, their relationships with adjacent tissue and their tissue characteristics. Thus, additional examinations are needed. Some studies regarding cardiac magnetic resonance imaging (MRI) have been reported [2,3]. In recent years, real-time (RT) two-dimensional (2D) and three-dimensional (3D) transesophageal echocardiography (TEE) have been found to be capable of producing high-quality images. Current matrix-array technology confers both 2D and 3D TEE functionality within a single transducer. This new imaging technology plays an important role in managing structural heart disease, as it offers real-time images and descriptions of the anatomic structures of the diseases and their effects on adjacent tissues [4–6]. In addition, contrast echocardiography (CE) may provide incremental information to help characterise cardiac masses, and allow improved definition of intra-cavity structures and

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assessment of vascularity. The difference in perfusion of cardiac masses may help distinguish between vascular tumor and non-vascular tumor or thrombus [7–9].

In this study, we performed a retrospective single-center analysis to examine the hypothesis that the combination of TEE and CE is feasible for providing comprehensive diagnostic information facilitating early diagnoses of cardiac masses, as well as anatomical information with which to optimize cardiac operative approaches, with surgery and histopathology serving as the gold standard for diagnosing cardiac masses. This study design is more relevant to the general population of physicians and hospitals all over the world, with limited access to expensive equipment such as Cardiac MRI and PET.

2. Patients and methods

2.1. Patient population

We performed a retrospective review of patients with cardiac masses who underwent surgery in Department of Cardiovascular Surgery of Xinqiao Hospital between February 2009 and June 2016. All patient clinical data and imaging features were retrospectively reviewed, including any available pathologic or follow-up imaging or clinical data. All patients signed an informed consent form. This study was approved by the Xinqiao Hospital Clinical Research Ethics Committee.

2.2. Methods

2.2.1. Echocardiographic diagnosis and follow-up

Comprehensive TTE and 2D and RT-3D TEE examinations were performed within 1 week before surgery using a Philips iE33 ultrasound system with a TTE probe (S5-1) and a matrix-array 3D TEE probe (×7-2 t; Philips Medical Systems, Andover, MA, USA). Each TEE evaluation entailed (1) confirming that a mass was present or absent, (2) measuring the cardiac chamber sizes, recording the locations, shapes, and sizes of the masses, and (3) observing the blood perfusion of the mass by reducing the color gain. Characterizing lesions as thrombi, benign, or malignant based on the spatial relationships between the cardiac masses and the surrounding tissues. There is a boundary between the thrombi and the surrounding tissue. Malignant tumors are usually displayed as invasive growth patterns. In addition, Color Doppler flow imaging (CDFI) was used to detect heart cavity blood flow information, atrioventricular valve orifice blood flow velocity and masses perfusion. Effective regurgitant orifice areas and mitral regurgitation (MR) or tricuspid regurgitation (TR) indices were used to grade MR or TR as absent, trivial or mild, moderate, or severe [10–12]. Left ventricular (LV) ejection fractions (EFs) were calculated using the Simpson method. All patients were regularly followed up with TTE and/or TEE during their hospitalizations and after discharge.

CE was performed when it was difficult to distinguish between different masses. The appropriate ultrasonic scanning plane was selected and fixed. By means of myocardial contrast imaging mode, real-time myocardial contrast imaging setting was used with a low mechanical index of 0.1 and a frequency of 2.5– 3.5 MHz. Two milliliters of blood pool contrast agent (SonoVue, Bracco Imaging B·V, Geneva, Switzerland) was injected into the left cubital vein at a rate of 1.25 ml/min followed by a slow 5 ml normal saline flush. After contrast medium injection, each cardiac lesion was scanned continuously for up to 4 min. Patient vital signs and responses to the contrast agent were carefully observed and recorded by a trained nurse. Using contrast echocardiography, qualitative and quantitative differences in the gray scale between the levels of perfusion in cardiac masses and sections of adjacent myocardium were evaluated. Mass perfusion was studied qualitatively as (1) no microbubbles perfusion suggesting either avascular tumor or thrombus, (2) when microbubbles perfusion is displayed in the mass at baseline, an ultrasound impulse of high mechanical index (1.0) would be generated (Flash). This causes destruction of microbubbles within the mass. Replenishment of microbubbles into the mass confirmed a vascular mass which is highly indicative of a malignant tumor [7,8]. The incremental value of contrast echo in diagnosing and differentiating between benign and malignant masses was analyzed using dedicated software (Qlab, Philips Medical Systems) [7]. The mean pixel intensity after a high mechanical impulse was calculated frame by frame for both the mass and a section of adjacent myocardium and fitted with the following exponential function of time [13]:

$$y = A\left(1-e^{-\beta t}\right)$$

where A reflects the post-impulse maximal steady-state intensity level (a surrogate measure for vascular volume) and β represents the initial rate of contrast replenishment after the high-mechanical index impulse (reflecting the velocity of blood flow) [14]. The A value and β value were calculated by Qlab Software automatically. The A values for each mass were divided by the A values for the section of adjacent myocardium to account for differences in contrast infusion rate and depth of mass.

Histological examinations of the masses were performed for all patients undergoing surgery or biopsy. Cardiac benign tumors and malignant masses were identified according to the World Health Organization 2015 Classification of Tumors of the Heart and Pericardium [15].

2.2.2. Statistical analysis

Data are expressed as the mean ± SD or as n (%). Between-group differences in imaging diagnoses were assessed with the Tukey-Kramer test. Echocardiographic parameters were compared between the pre- and postoperation groups and heart rate was compared between pre- and post-CE using paired *t*-tests respectively. Correlations between echocardiographic findings and surgical results were calculated using Pearson's correlation coefficient. Individual morphologic features (location, size, mobility, myocardial infiltration, and presence of pericardial or pleural effusion) and imaging characteristics (homogenous/heterogeneous, signal intensity on contrast enhancement) were evaluated as potentially useful imaging measures for masses diagnosis using binary logistic regression analysis. The Wilcoxon rank-sum test was used to compare the number of times a correct histological diagnosis using pathology as the reference standard. All statistical analyses were performed using SAS version 9.3 software (SAS Institute Inc., Cary, NC, USA), and *p*-values <0.05 was considered statistically significant.

3. Results

3.1. Study population

There were 20,997 patients who underwent cardiac surgery because of various heart diseases in the Department of Cardiovascular Surgery of Xinqiao Hospital between February 2009 and June 2016. A total of 252 consecutive patients with cardiac masses were included in this study. Nineteen patients were managed conservatively because of poor surgical candidacy, masses unresectability, or patient preference. Of these 19 patients, 16 were lost to follow-up and could not be included in subsequent analyses. Histopathologic tissue specimens were obtained from 236 patients via either surgical ($n = 233$) or puncture biopsy ($n = 3$) after TEE and/or CE (Fig. 1). A total of 236 patients were included in the statistical analysis. The mean age of the patients was 49.5 ± 15.8 years (ranged from 0.5 to 83 years), and 150 patients (63.6%) were women. Two women had preexisting primary hepatic carcinomas, and 1 man had preexisting lung squamous carcinoma. Twenty-six patients had a history of emboli, and 15 patients had atrial fibrillation (Table 1). The histopathologic diagnoses of the 236 patients with cardiac masses—separated into no-tumor, benign tumor and malignant tumor groups—are shown in Fig. 1 and Table 1.

Table 2 demonstrates individual combined TEE and CE imaging parameters associated with tumor and malignancy. The combinations of TEE and CE yielded the correct pathologic diagnosis in 225 of 230 patients (97.8%), while CT yielded the correct pathologic diagnosis in 122 of 141 patients (86.5%), $p < 0.01$. TEE yielded the correct pathologic diagnosis in 219 of 226 patients (96.9%), and CE yielded the correct pathologic diagnosis in 45 of 48 patients (93.8%). TTE alone yielded the correct pathologic diagnosis in 163 of 236 patients (69.1%), $p < 0.001$ for all (Table 3). None of CE group had acute adverse reactions and there was no significant difference in heart rate between the pre- and post-CE groups (69.5 ± 8.3 b/m vs. 70.2 ± 6.7 b/m, $p > 0.05$). The TEE and CE features of the benign and malignant masses and thrombus are shown in Table 4. Invasion of cardiac structures and pericardial effusion were detected in most of malignant tumors. Malignant or highly vascular tumors demonstrated greater enhancement than the adjacent myocardium. Most benign tumors such as myxomas demonstrated partial perfusion on visual inspection and quantitatively less perfusion than the myocardium, while hemangiomas presented as high enhancement. The thrombi demonstrated no perfusion. The difference was significant between $A_{tumor}/A_{myocardium}$ in malignant group and that in benign group (1.34 ± 0.43 vs. 0.65 ± 0.17, $p < 0.01$). The difference was also significant between β value in malignant group and that in benign group (0.81 ± 0.20 vs. 0.45 ± 0.19, $p < 0.05$).

3.2. Benign tumors

In our cohort, 196/236 patients (83.1%) between 0.5 and 83 years of age (48.6 ± 11.7 years) had benign tumor. Approximately 65.3% of these patients were women ($n = 128$). The classification of benign tumors was shown in Table 1. All patients underwent surgery. A total of 191 patients were diagnosed via TEE, 27 of whom also underwent

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