Faculty of Medicine, Cairo University Postgraduate Research Program Template

1. Proposed study title:

Detection of subtle myocardial dysfunction in symptomatic children with rheumatic heart disease using speckle tracking echocardiography.

Degree: M.D

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4. Background and Rationale

Acute rheumatic fever (ARF) is a postinfectious, nonsuppurative sequela of pharyngeal infection with Streptococcus pyogenes, or Group A β hemolytic Streptococcus. Of its consequences, only rheumatic heart disease (RHD) can become a chronic condition leading to congestive heart failure, strokes, endocarditis, and death **(Carapetis et al., 2005).**

While the incidence and prevalence of ARF and RHD have been decreasing in developed countries since the early 1900s, they continue to be major causes of morbidity and mortality among young people in developing countries. It is estimated that there are over 15 million cases of RHD worldwide, with 282,000 new cases and 233,000 deaths annually **(Carapetis et al., 2005).**

More recent data using echocardiography to screen for RHD in developing countries have led to a marked increase in the recognized prevalence in these regions **(Bhaya et al., 2010).**

Echocardiography is the preferred and most common method to evaluate for presence of myocardial dysfunction. It can be evaluated by use of conventional echocardiography, tissue Doppler imaging (TDI), and Speckle-tracking Echocardiography (STE) (**Friedberg et al., 2007).**

Follow up of many symptomatic patients with RHD may have normal systolic functions assessed by conventional echocardiography **(Sengupta and Narula, 2008).**

TDI and STE are new noninvasive ultrasound imaging techniques that may detect subtle myocardial dysfunction in asymptomatic patients with RHD **(Gorcsan and Tanaka, 2011).**

Data regarding the use of these novel techniques for evaluation of systolic functions in RHD patients in the literature are sparse or even nonexisting **(Gorcsan and Tanaka, 2011).**

5. Objective

The aim of this study is to assess whether symptomatic RHD patients with preserved systolic functions by conventional methods might have subtle changes that can be detected by nonconventional methods (TDI and STE).This can possibly guide to optimum timing of surgical intervention in these patients for optimum outcome of operation.

6. Study Design

Case - Control study.

7. List of Correlative Studies

- **Bhaya M, Panwar S, Beniwal R, Panwar RB.** High prevalence of rheumatic heart disease detected by echocardiography in school children. Echocardiography. 2010 ;27(4):448-53.
- **Carapetis JR, Steer AC, Mulholland EK, Weber M.** The global burden of group A streptococcal diseases. Lancet Infect Dis. 2005 ;5(11):685-94.
- **Friedberg MK, Silverman NH, Dubin AM, Rosenthal DN.** Mechanical dyssynchrony in children with systolic dysfunction secondary to cardiomyopathy: Doppler tissue and vector velocity imaging study. J Am Soc Echocardiogr. 2007 ;20(6):756-63.
- **Gorcsan J 3rd and Tanaka H.** Echocardiographic assessment of myocardial strain. J Am Coll Cardiol. 2011 ;58(14):1401-13.
- **Sengupta PP and Narula J.** Reclassifying heart failure: predominantly subendocardial, subepicardial, and transmural. Heart Fail Clin. 2008 ;4(3):379-82.
- **Tei C.** New non-invasive index for combined systolic and diastolic ventricular function. J Cardiol. 1995 ;26(2):135-6.

8. Study Methods

Population of study & disease condition

RHD children; who are following up regularly in the rheumatic fever outpatient clinic of the new Cairo University specialized pediatric hospital (CUSPH), Faculty of Medicine, Cairo University, who met the inclusion criteria included in the study.

Background and Demographic Characteristics

Inclusion criteria:

- Symptomatic RHD children with valvular affection
- Age group between 8 and 18 years.
- Both sexes.
- Normal ejection fraction and fractional shortening by conventional echocardiography.

For control group: age matched normal children coming to the outpatient clinics of the new children Hospital ,Faculty of Medicine, Cairo University for minor complains e.g. abdominal pain , sore throat ,headache.

Exclusion criteria:

- Patients of hypertrophic, restrictive or dilated cardiomyopathy.
- History of congenital heart diseases or acquired heart disease.
- Non sinus rhythm, or patients receiving any cardiac medications that can affect myocardial function (e.g.: beta blockers).
- Any acute or chronic systemic disease that can affect cardiac function e.g. hypertension, diabetes mellitus, uremia.

Methodology in details :

After obtaining a full informed consent from the participant,

1-**Full history taking** including: age, sex, duration of illness since diagnosis

2-**General examination:** weight, height, body surface area, heart rate and blood pressure.

3-**Cardiac examination**: heart sounds, added sounds and degree of heart failure.

4- **Imaging:**

Echo-Doppler examination will be performed for all cases in a supine, left lateral position using General Electric (GE, Vivid-5) system with probe 3 or 5MHz (multifrequency transducer) according to the age of patient, having tissue velocity imaging capabilities

The ECG cable will be connected to the ultrasound machine to define and to time the cardiac cycle events. The beginning of QRS complex will be used as a reference point and the following parameters will be measured:

A - Conventional Echo-Doppler measures:-

The examination will be performed by a pediatric cardiologist who is expert in echocardiography and TDI. The examination will consist of M-mode, 2D, pulsed, continuous wave and color Doppler blood flow velocity measurements of the heart valves.

M-mode measurements will be done at the level of the tips of the mitral valve leaflets in the parasternal long-axis view of the LV. Parameters that will be measured in systole and diastoles are: LV dimensions, interventricular septum (IVS) and LV posterior wall (LVPW) thickness. LV fractional shortening (FS) and ejection fraction (EF) will also be calculated.

Doppler blood flow velocities will be measured for each valve separately: for the mitral and tricuspid valves using apical four-chamber view; for the aortic valve using the apical 5 chamber view, and for the pulmonary valve using parasternal short-axis view. The following Doppler parameters will be measured: peak E wave velocity and peak A wave velocity of the mitral and tricuspid valves, deceleration time (DT) for the mitral valve E wave. For the aortic and pulmonary valves peak velocity acceleration and ejection time will be measured.

Tei index will be calculated and is defined as the sum of isovolumic contraction time (ICT) and isovolumic relaxation time (IRT) divided by ventricular ejection time (ET). To perform that, continuous wave cursor line will be placed midway between anterior mitral leaflet and LV outflow tract **(Tei, 1995).**

To reduce the effect of respiration on blood velocities and as breath holding is not applicable in young children, three cardiac cycles will be recorded and the cycle with the highest velocity will be selected.

To reduce intra observer variability 3 different measurements for each Doppler index will be done and the average will be taken.

B - 2D Longitudinal Strain Echocardiogram:-

Images will be obtained with a 3.0-MHz or 5.0-MHz phased-array transducer using the Vivid 5 echocardiographic scanner (GE Vingmed Ultrasound AS, Horten, Norway). The choice of an S3 or S5 transducer depended on the age of the child. 2D images will be obtained in the apical four chambers, apical long axis and apical 2 chamber views. Frame rates of 60 to 90 Hz will be used, because these rates are considered to be optimal for two dimensional speckle tracking. Data will be stored; Preferably images from three cardiac cycles triggered by the R wave of the QRS complex will be digitally saved in cine loop format.

Offline speckle-tracking analysis will be performed using software for echocardiographic quantification (EchoPAC version 110.1.2; GE Vingmed Ultrasound AS). The timing of aortic valve closure will be manually obtained. For these measurements, special care will be taken to keep the heart rate in the same range in the stored loops. Endomyocardial borders of the LV will be manually traced within the end-systolic frame. The second, epicardial tracing will be automatically generated by the computer algorithm and, when necessary, manually adjusted to cover the whole myocardial wall. The tracking algorithm then followed the myocardial speckles during the cardiac cycle. Tracking will be accepted only if both visual inspection as well as the EchoPAC software indicated adequate tracking. This means that tracking of any given segment will be accepted only when it was indicated with a green box. Automated Function Imaging (AFI) will be used that enables only the assessment of longitudinal strain.

C - Assessment of ventricular and atrial function using real-time 3D echocardiography (RT3DE):-

RT3DE will be performed from an apical four-chamber view using a 3D matrix array transducer (GE Vingmed Ultrasound AS, Horten, Norway). A wide-angle acquisition "full volume" mode will be used, in which 6 wedge-shaped sub-volumes were acquired for 6 consecutive cardiac cycles during a single breath-hold as possible as we can , resulting in a study in temporal resolution of 6 frames per cardiac cycle with a minimum frame rate of 42/s. Special care will be taken to include the entire ventricular and atrial cavity in the 3D pyramidal volume. Acquisitions will be stored in a DICOM format and transferred to a separate workstation for offline data analysis. 3D wall motion tracking software 4D Auto LVQ and Tom Tec Imaging Systems were used to analyze the LV and left atrium (LA) respectively. The LV ejection fraction (LVEF) will be calculated according to the formula LVEF = (LVEDV— LVESV)/ LVEDV.

Global longitudinal, circumferential and radial strain will be automatically calculated by the software. In addition to these standard parameters the area strain, which integrates longitudinal and circumferential deformations, will be calculated automatically. For evaluation of the LA function, the LA endocardial border in the three planes will be manually traced (pulmonary veins and coronary sinus and the appendages were excluded), starting the measurements in the frame with the largest atrial dimension, corresponding to ventricular end-systole, just before the opening of the atrio-ventricular valves. Then the frame with the smallest atrial dimension (at ventricular end-diastole, just before the closure of atrio-ventricular valves) is selected and the same manual tracing is applied.
The software generates a time volume curve. From the plotted LA time-volume the kick volume of the atria just before the P-wave will be obtained. The reservoir function of the LA will be calculated according to the formula ((LA volume max)–(LA volume kick)) / (LA volume max) and the pump function of the LA according to the formula ((LA volume kick)–(LA volume min)) / (LA volume kick), while the LA EF will be calculated according to the formula LA EF = ((LA volume max)–(LA volume min)) / (LA volume max). The recordings from 10 patients and 10 normal subjects were randomly selected and analyzed by two independent examiners to assess the inter-observer variability of the speckle tracking parameters related to ventricular deformation.

For control group: The same echocardiographic study will be done.

Primary outcome Parameter (maximum two)
Subtle myocardial changes in children of rheumatic heart disease which are apparent using nonconventional echocardiography (TDI and STE).
Secondary outcome parameters
1. Correlation between the severity of valvular affection and degree of myocardial impairment. 2. Impact of changes in ejection fraction and fractional shortening on strain pattern.
Sample size (number of participants included)
One year study with minimum of thirty patients.

Statistical analysis

Data management and analysis will be performed. Statistical analysis will be performed with Statistical Package for Social Science (SPSS). Numerical data will be summarized using means and standard deviations or medians and ranges. Categorical data will be summarized as percentages. Comparisons between groups will be calculated using: Student's t test& paired t tests. Correlation between variables will be evaluated using Pearson's correlation coefficient. P-values < 0.05 will be considered significant.

Possible Risk

Risk approach zero as the study does not involve the use of x-rays, but uses ultrasound waves; there are no known side effects.

Source of funding

Self funding

9- Time plan (when to start / when expected to finish / when to publish)

18 months

- Collection of data: from September 2015 – September 2016

- Reviewing of literatures: from September 2015 to March 2016.

- Data analysis and writing thesis: from September 2016 to December 2016.

10. Ethical committee approval

11. Cooperation with other departments

None

12.عنوان الرسالة

الكشف عن التأثر الخفي في الوظيفة الإنقباضية القلبية لمرضي الحمي الروماتيزمية باستخدام خاصية التتبع النسيجي المشتقة من الموجات الصوتية علي القلب.