Author's response to reviews

Title: Second-Opinion Stress Tele-Echocardiography for Aged Donor Heart Selection

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Author's response to reviews: see over
Dear Dr. Sicari, MD

Please, find attached the Revised Manuscript “Second-Opinion Stress Tele-Echocardiography for Aged Donor Heart Selection.”

We tried to address all criticisms raised by the reviewers. In plain text, Reviewers’ comments; in italic, our response; in red, parts added to the Revised Manuscript.

Reviewer #1:

1. As authors stated stress echocardiography relies on observer’s experience and a central core lab reading may reduce intra and inter-observer variability. The clinical implications of the study are beyond the study protocol and may be easily implanted on a larger scale. Authors may add the potential use of tele-medicine in stress echocardiography.

   Thank you for your interesting and constructive comment. We agree that the clinical implications of the study are beyond the study protocol and may be easily implanted on a larger scale. We added this comment in the Discussion section:

   Previous studies demonstrated that echocardiographic telemedicine (tele-echocardiography) for emergencies can provide rapid, 24-h consultation [24] and that dobutamine stress tele-echocardiography in the emergency department is feasible [25]. Normal results on stress echocardiography in the emergency department may obviate the need for hospital admission in patients presenting with noninfarction chest pain. Implementation of this program appears to be practical in the clinical setting but requires cooperation and commitment on the part of emergency physicians, cardiologists, nurses and sonographers. Use of modern communication technology in this context, is the sole decisive factor that makes such telemedicine system successful. Early results in brain dead marginal heart donors showed that the system is reliable, functions with a clinically acceptable performance, and transfers medical data with a reasonable quality, Thus, the system is applicable, and might be generalized in clinical practice in cardiology.

   We added the new # 24 and # 25 references in the References section:


2. In the methods section of the manuscript authors do not describe in detail the dipyridamole stress echo protocol (dosage etc.)

*Thank you for your thoughtful comments. We understand your point and we incorporated the following section in the Methods:*

**The dipyridamole stress echo protocol**

When resting echocardiography was normal a pharmacological stress echo test was performed following the European Association of Echocardiography (EAE) protocol [7], using dipyridamole (0.84 mg/kg in 6 min) (Fig.6). Where there were contraindications to dipyridamole (asthma, hypotension, bradyarrhythmias), the second-choice drug was dobutamine (up to 40 mcg/kg/min). The echo images were tape-recorded and periodically digitized. During the procedure, pressure and ECG were recorded every minute. Brachial blood pressure was measured with cuff sphygmomanometer. In each phase of the stress echo, the projections of the four chambers and of the apical two chambers were recorded to obtain the left ventricular end-systolic volume by biplane Simpson rule in order to calculate the left ventricular (LV) elastance (systolic pressure/left ventricle end-systolic volume ratio) [17, 18, 19, 20]. The diagnostic end points were: the development of obvious echocardiography positivity, obvious alterations of ECG (ST segment shift > 3 mm). The test was halted in the case of hypotension (relative or absolute) with decrease in blood pressure > 30 mmHg. A non-maximal diagnostic stress excluded donation since it provides inadequate diagnostic and prognostic information. Regional wall motion score index was assessed and graded on a scale from 1 (normal) to 4 (dyskinetic) at rest and after stress in each of the 17 segments [7].
ventricular wall motion core index was calculated by summing the scores and dividing the sum by 17. By definition, donors with abnormal stress echocardiography had rest wall motion abnormalities and/or stress-induced wall motion abnormalities. We also considered the changes in left ventricular volumes as an index of global dysfunction [19] and pressure/volume changes as an index of LV elastance [17,18].

We added a new Figure # 6 with a new caption:

**Fig. 6 The dipyridamole stress echo in the ADONHERS protocol**

When resting echocardiography was normal a pharmacological stress echo test was performed using dipyridamole (0.84 mg/kg in 6 min). We accepted a priori three criteria of stress echo positivity, excluding the heart from eligibility for donorship:

1) Regional wall motion abnormalities at rest or during stress

2) A LV elastance falling during stress

3) A submaximal stress halted due to non-diagnostic limiting effects before completion of the infusion, since a submaximal test dramatically lessens diagnostic and prognostic power.

Accepting a heart was done in conformity with clinical and emergency criteria in use.

3. In line with the previous comment please clarify the reason why vasodilator stress testing is more appropriate than inotropic stress testing in this setting.

*Thank you for your interesting and constructive comments*

*We added in the Discussion section:*

**Vasodilator vs. inotropic stress testing in the ADONHERS protocol.** Dobutamine, and vasodilators (at appropriately high doses) are equally potent ischemic stressors for inducing wall abnormalities in the presence of a critical epicardial coronary artery stenosis [5]. Dipyridamole acts through reduced subendocardial flow supply subsequent to inappropriate arteriolar vasodilation and steal phenomena and Dobutamine through catecholamine induced increased myocardial oxygen demand [7]. However a inotropic stress is potentially harmful in the particular setting of heart donation. The adrenergic storm,, in the phase preceding brain death, is associated with a prolonged release of norepinephrine from cardiac sympathetic nerve endings and leading to direct myocardial injury
and/or coronary vasospasm [2]. The secretion of large amounts of endogenous catecholamine, as may occur in subjects with subarachnoid hemorrhage, has been associated with the appearance of transient left ventricular apical diskinesis [3, 4]. Catecholamine may exert a direct toxic effect on the myocardium through changes in autonomic tone, enhanced lipid mobility, calcium overload, free radical production, or increased sarcolemmal permeability. Further more all donors are managed according to standardized organizational guidelines [1] that included: the use and inotropic agents (preferably noradrenalin or dopamine) to maintain a systolic blood pressure (SBP) > 90 mmHg, central venous pressure (CVP) 4 to 12 mmHg and urine output 1 to 2 ml/kg/h. A dobutamine instead of dipyridamole stress echocardiography may induce or enhance the typical myocardial catecholamine necrosis frequently observed at histological studies of brain dead heart donors [2].

Reviewer #2:

In the results, the second-opinion answer delay was reported only in the case of transplant protocol: if possible, it could be interesting to know the second-opinion answer delay for the simulation protocol (results of all 30 cases).

This study aimed to verify feasibility of a “second opinion” of digitally transferred images. The second-opinion answer delay for the simulation protocol was not measured.

About the writings, I have some comments: page 5, line 1: "were" should be "where"; line 4 transfer”s”; the last 3 lines are repeated twice.

Thank you for your thoughtful comments. We changed the manuscript according to your suggestions.

The legend of figure 2, 3, 4 and 6 could benefit from refined language revision.

We reviewed the English language according to your comments.

In the legend of figure 3, the authors need to correct “left ventricular hypertrophy > than mild” in “left ventricular hypertrophy < than mild”.

We changed accordingly the Fig. # 3 caption:
Fig. 3. Form for resting echo report

Potential donors are recruited for the stress echo protocol if in resting echocardiogram: wall motion score index is completely normal (WMSI = 1), left ventricular ejection fraction > 45%, no signs of diastolic ventricular dysfunction, no significant valve disease, and left ventricular hypertrophy ≤ than mild.

Quality of written English: Needs some language corrections before being published

*We corrected the English language throughout the manuscript*

*Looking forward to hearing from you.*

*Sincerely*

*Tonino Bombardini, MD*