Author’s response to reviews

Title: Real Time 3D echocardiography (RT3D) for assessment of ventricular and vascular function in hypertensive and heart failure patients.

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Version: 2 Date: 12 June 2012

Author’s response to reviews: see over
Dear Dr Sicari,

please find enclosed the revised manuscript: Real Time 3D echocardiography for assessment of ventricular and vascular function in hypertensives and heart failure patients. In plain text, Reviewers’ comments; in *italics*, reply to reviewers; in **bold**, parts added to the revised manuscript

**Response to Reviewer 1.**

General comments: Thank you for your thoughtful and constructive criticism

Scali et al studied with 2D and 3D echocardiography a total of 136 subjects (3 groups: normal; hypertensive heart disease with preserved ejection fraction; and systolic heart failure), aiming to assess the feasibility of 3D method for calculating several indexes of left ventricular (LV) and vascular function. In all 3 groups, the Authors tested these functional parameters (calculated using 3D volumes and stroke-volumes) and confirmed the expected significant differences among groups by this novel approach. The idea of taking advantage of the superiority of 3D over 2D echocardiography in assessing LV volumes to derive more accurate non invasive estimates of cardiac-vascular function is particularly attractive and in line with very recent research efforts (Gayat E et al. Am J Physiol Heart Circ Physiol 2011; Gayat E J Am Soc Echocardiogr 2012). However, there are several issues to be addressed:

The two suggested references have been added to the revised version of the manuscript: Gayat E et al. Am J Physiol Heart Circ Physiol 2011; Gayat E J Am Soc Echocardiogr 2012 (now refs 6 and 7 of the revised manuscript).

**Major Compulsory Revisions**

1. Since 3D does not seem to decrease the time required to obtain the same quantitative data and had lower feasibility (95%) in comparison with 2D echo (100%), more support from this study should be provided to the statements advocating for the use of 3D instead of conventional 2D method. It is unclear why the Authors performed the complete 2D echo study (apart to measure the time consumed) and then did not use also 2D ESV and stroke-volume to explore how 3D indexes relate to the 2D ones (since 2D ESVi in the noninvasive estimation of LV contractility was previously documented as clinically useful by the same group).

The data on volumes have been obtained both with 2D and 3D approach and the results on agreement are reported in the original version of the manuscript. However, the aim of the study was not to assess the agreement between 2D and 3D but to demonstrate that 3D is feasible in the everyday routine of a busy laboratory. Accurate 3D measurements can be obtained at a comparable time cost, in the vast majority of patients.
2. Although 3D was extensively validated, it also significantly underestimates LV volumes, albeit less than 2D method; its ability to provide reliable non invasive measures of stroke-volumes and ventricular/vascular functional parameters represents only an inference and was not actually verified yet. To my knowledge, there is a single study that validated 3D echocardiography for measuring LV stroke-volume against catheterization and only in patients with aortic stenosis, a study which is relevant to be cited in this manuscript (Gutierrez-Chico JL Eur Heart J 2008).

We do agree that 3D echo may underestimate LV volumes, depending on how accurate is the profile of LV cavity. A careful identification of LV cavity border, excluding trabeculae, does minimize the underestimation. We acknowledge it as a potential limitation of such methodology. The study by Gutierrez-Chico has been cited (reference 16).

Study population

1. Presumably, all subjects were in sinus rhythm; this should be included in the enrolment criteria.

   Yes, all subjects were in sinus rhythm, and this is now clearly stated in the inclusion criteria (methods section, inclusion criteria, page 4, line 12).

2. Definition of study groups could be further improved:
   - normal subjects: BP (why diastolic BP was not considered among the diagnostic criteria?); presence of risk factors that impact on arterial function (smoking, diabetes)
   - arterial hypertension: definition and citation
   - heart failure: clinical criteria and/or citation

   The text has been modified accordingly. (methods section, inclusion criteria, page 4, line 12).

   Definition of study groups:
   Normal subjects: we included in this group subjects with no structural heart disease, with normal BP, free from major coronary risk factors.

Heart failure subjects: we included in this group subjects with an history of heart failure, under active treatment with ACE-inhibitors, and/ or diuretics , and/ or ARB and, a reduced ejection fraction less than 40%.

3. In Table 1, indexed LV volumes are too large for the normal and hypertensive groups, unless they were not actually indexed. Please specify also whether these pertain to 2D or 3D echo, and include the indexed stroke-volumes and HR as well.

Volumes reported in table 1 are not indexed, and pertain to 3D echo. Thank you for noticing the error. Table 1 has been corrected, indexed stroke volumes and HR have been added (table 1, lines 5 and 6).

Methods

1. 3D echo, as applied in this study, is not actually a real-time method (i.e. single-beat) since several consecutive cycles are stitched together; additional technical details are needed: number of stitched cycles to obtain LV full-volume and mean temporal resolution in the study. This is particularly relevant, since low temporal resolution (as in single-beat full-volume acquisition) may adversely impact on the accuracy of ESV, EF and stroke volume measurement (Lang R et al. Eur Heart J Cardiovasc Imaging 2012).

We agree that 3D echo, as applied in this study is not a real time method, and address this issue in the revised version of the manuscript. "Four cardiac cycles are stitched together to obtain LV volumes." Mean temporal resolution can be easily estimated by this assumption. (Methods section, heading 3 D echo, page 6, 3 lines before the end)

2. Since small variations in both BP and HR (not rare in clinical settings) may significantly impact on calculations of hemodynamic parameters, the moment when these were collected should be specified.

We agree that variation in BP and HR may impact on hemodynamic parameters. Our measurements were all taken simultaneously during study examination. BP was derived from cuff sphygmomanometer and HR from EKG on echo monitor. (Methods section, heading 3 D echo, page 7, last line)
1. There are few typos to be corrected in the manuscript

   *The manuscript has been proofread and the typos corrected.*

2. In the Introduction section, LV should be spelled out the first time being used.

   *LV is spelled out the first time is used* (page 4, first line)

3. The term “technically good 2D echo study” as enrolment criteria may be confusing. I suggest to use “good 2D acoustic window” instead.

   *The term “technically good echo study” has been changed in “good 2D acoustic window” (study population, point 3, page 5, line 3).*

Response to Reviewer 2.

Minor compulsory revisions.

It is important to specify whether the patients were treated with medications affecting the vascular resistance. If this is not known, this must be specified as a limitation. Overall a well written report, deserving a publication,

*Medications taken by the patients have been specified in the text (section study population, page 5, points 5 and 6).*

5. Clinical-echocardiographic diagnosis of essential hypertension (HYP), with history of long standing high blood pressure under active treatment with ACE-inhibitors (68%), and/or diuretics (84%), and/or ARBs (36%), and/or Ca-channel blockers (25%), with EF>50%);

6. Clinical-echocardiographic diagnosis of heart failure (HF), with history of dyspnea on effort, under active treatment with ACE-inhibitors (86%), and/or diuretics (78%), and/or ARBs (28%), and/or β-blockers (68%), with EF<40%.