Author's response to reviews

Title: Medium-term outcome of recipients of marginal donor hearts selected with new stress-echocardiographic techniques over standard criteria

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

Please, find attached the Revised Manuscript “Medium-term outcome of recipients of marginal donor hearts selected with new stress-echocardiographic techniques over standard criteria”.

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

Title: Medium-term outcome of recipients of marginal donor hearts selected with new stress-echocardiographic techniques over standard criteria

Version: 1 Date: 29 March 2014

Reviewer: Mario Previtali

Reviewer's report:

Minor compulsory revisions:

1) Results: The presentation of the data is not clear, at least to me: the authors say that 43 of the 57 marginal donor hearts deemed eligible for transplant were eventually transplanted. According to the data presented, the total number of pts deemed eligible but not transplanted should be 16 (9 pts in the stress protocol + 5 pts in the HT protocol + 2 additional pts in the HT protocol who had CAD at the pre-harvesting angiography), so the total number of marginal hearts transplanted should be 41 not 43. The alternative explanation of these data is that the pts in the Ht protocol were considered eligible only after coronary angiography ruled out the presence of coronary stenosis, so the 2 pts with CAD are not taken into account. This point should be clarified in the methods and in the results presentation.

We agree with you. The presentation of the data is not clear. We added in the Methods section:

The pts in the Ht protocol were considered eligible only after coronary angiography ruled out the presence of coronary stenosis.

We changed accordingly the results section:

Seven eligible donors enrolled in the HT protocol were not transplanted due to: opposition (N = 3), tuberculosis (N = 1), malignancy (N = 1), coronary artery stenosis at pre-harvesting.
angiography (N = 2);

We changed accordingly the Table 1

2) Results, Figure 2: The figure presents the survival curves of the 3 groups of pts using the Kapan-Meier method. Given the very small number of pts in the 3 groups, I doubt that an evaluation of the differences in the survival in the 3 groups is correct from a statistical point of view and, more important, has any clinical significance. The opinion of an expert statistician would be useful to assess this point.

Thank you for your interesting and constructive comments.
We agree with you that an evaluation of the differences in the survival in the 3 groups isn’t correct from a statistical point of view. However we did it to give some information to the reader of the different scenarios for use of new echocardiographic techniques to select marginal donor hearts. According to your suggestion we changed Fig. 2 and we added the survival curve of the whole group of patients.

We changed the Fig. 2 caption:

Figure 2. Survival curves in recipients of donor hearts selected with new echocardiographic techniques. Right panel. The survival curves of the 3 groups of pts. Left panel. The survival curve of the whole group of patients.

3) Discussion: Limitations of the study: The authors should give some references to support their statements that "the presence of donor-transmitted coronary atherosclerosis does not accelerate progression of intimal hyperplasia" and that "donor-transmitted coronary atherosclerosis increases the incidence of cardiac allograft vasculopathy"

You are right.
We added in the Limitations of the study section:

Recent studies indicate that deleterious transplant vasculopathy (TVP) as a result of chronic rejection is multifactorial and that atherosclerotic plaque in the donor heart may not necessarily progress to TVP [30, 31, 32]. Instead, using serial Intravascular Ultrasound (IVUS) measurements, Li et al. [33] demonstrated that pre-existing donor atherosclerotic
lesions do not accelerate the development of TVP either at the site of pre-existing donor atherosclerosis or elsewhere within the same artery.

However, donor-transmitted coronary atherosclerosis increases the incidence of cardiac allograft vasculopathy. Recently, Grauhan et al. [18] described an overall prevalence of donor-transmitted coronary atherosclerosis of 7.0%, and he stated that donor screening without coronary angiogram overlooks a significant proportion of coronary lesions. In that study, the prevalence of donor transmitted CAD in recipients who underwent coronary angiography within 6 months post-transplantation was 5.2%, whereas it was 15.1% on autopsy in those recipients who died within 6 months without coronary angiogram. Among all patients with early graft failure, prevalence was as high as 22.8% indicating that donor CAD represents a significant risk factor for early graft failure [34].

We added the new references:


Discretionary revisions:

1) Methods: the authors should specify the criteria used for selecting dipyridamole or dobutamine for the stress echo. It would also useful for the reader to know if in this population there are specific
contraindications to the use of the 2 drugs.

Thank you for your interesting and constructive comments.

When the results of resting echocardiography were normal, pharmacologic stress echocardiography was performed following the European Association of Echocardiography and American Society of Echocardiography protocol, using either dipyridamole (0.84 mg/kg over 6 min) or dobutamine (up to 40 mg/kg/min). Per protocol, we suggested dipyridamole as a first-line choice, with dobutamine as a second-line option when dipyridamole was not available, when the operator did not have extensive experience with this stress agent, or when the patient had contraindications to the use of dipyridamole, such as asthma. Contraindications to the use of dobutamine were preharvest high inotrope dose (dopamine or dobutamine > 10 mcg/kg/min and/or adrenalin or noradrenalin > 6 mg/kg/min) and increased endogenous catecholamine release from sympathetic nerve endings in subarachnoid hemorrhage.

We added in the Discussion section:

The suggested first choice was dipyridamole, with dobutamine as the alternative, acceptable second choice. There were two reasons for the choice: dipyridamole is equally as accurate but technically simpler than dobutamine because of a lesser increase in heart rate, and the image quality is therefore less degraded during stress [3, 4] (this aspect is especially important in the technically challenging theater of testing potential donors who have high resting heart rates), and further catecholamine stress with dobutamine is in principle undesirable for these patients, because they already have high, and potentially toxic, levels of circulating catecholamines, which may damage the heart [19, 22, 25].

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests: I have no competing interests of any type to declare

Reviewer: Albert A Varga
Reviewer's report:

The Authors of the present manuscript assessed the medium-term outcome of recipients of “marginal” donor hearts selected with new echocardiographic methods over standard criteria. According to the established criteria by the Authors 43 hearts were selected for transplantation and after an average time of 30 months follow up 93% of the transplanted patients were still alive. The Authors concluded, that “strict use of new stress-echocardiographic techniques over standard criteria of marginal donor management, together with comprehensive monitoring of the donor, has the potential to substantially increase the number of donor hearts without adverse effects on recipient medium-term outcome.”

The topic is important, the paper is well written. I have only minor questions and comments, which are the following:

1. In the Introduction section the Authors stated that: “In Europe every year a pool of #4500 unused hearts (500 in Italy) with permission granted for heart donation is estimated, from which additional transplants could be generated, with more confidence in their post-transplantation performance (Council of Europe, Donation and Transplantation, 2011). Please, provide a reference. (Presumably: Dominguez-Gil et al, Transplant International 2011; 24:676–686?)

You are right. We understand your point

We added the new #1 and #2 references:


2. The description of the Statistical Analysis part on page 5 should be revisited and rewritten, since some of the methods mentioned were not used in the manuscript.

We agree with you. We rewrote the Statistical Analysis section
3. Due to the small sample size, the separate demonstration of the survival of the different donor groups in the Kaplan-Meier curve seems to be inappropriate.

*Thank you for your interesting and constructive comments.*

We agree with you that an evaluation of the differences in the survival in the 3 groups isn’t correct from a statistical point of view. However we did it to give some information to the reader of the different scenarios for use of new echocardiographic techniques to select marginal donor hearts. According to your suggestion we changed Fig. 2 and we added the survival curve of the whole group of patients.

*We changed the Fig. 2 caption:*

**Figure 2.** Survival curves in recipients of donor hearts selected with new echocardiographic techniques. Right panel. The survival curves of the 3 groups of pts. Left panel. The survival curve of the whole group of patients.

4. On page 6, line 5, “Two of the 42 eligible transplanted hearts showed significant…” Presumably 43.

*You are right. We changed accordingly 42 to 43*

5. In the limitation section the statement that: “It has been demonstrated that the presence of donor-transmitted coronary atherosclerosis does not accelerate the progression of intimal hyperplasia or affect the 3-year prognosis of transplant recipients.” should be bolstered by references.

*You are right. We understand your point. We added in the Limitations of the study section:*

**Recent studies indicate that deleterious transplant vasculopathy (TVP) as a result of chronic rejection is multifactorial and that atherosclerotic plaque in the donor heart may not necessarily progress to TVP [30, 31, 32]. Instead, using serial Intravascular Ultrasound (IVUS) measurements, Li et al. [33] demonstrated that pre-existing donor atherosclerotic lesions do not accelerate the development of TVP either at the site of pre-existing donor atherosclerosis or elsewhere within the same artery.**


6. The list of the references should be revisited and the older references should be cut.

Accordingly to your suggestion we deleted the references:


Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests: I declare that I have no competing interests