Author’s response to reviews

Title: Cardiopulmonary exercise testing and echocardiographic exam: an useful interaction

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Reply to Reviewers:

Reviewer #1:

I read with interest the Review of Santoro et al. about the clinical role of the integrated cardiopulmonary exercise test and exercise stress echocardiography (CPET-ESE).

I have some remarks:

The Authors stated that one of the significant limitations to the routine use of CPET are mainly represented by the lack of measurement standardisation and limited data from randomised multicentric studies. This statement should be scaled-down because there is evidence derived from multicentre studies about the use of CPET in HFrEF (Myers J et al. Circ Hear Fail 2013;6(2):211-8; Agostoni P et al. Int J Cardiol 2013;167(6):2710-8). In particular, CPET has class I recommendation and level A in patients with HFrEF being considered for heart transplantation or mechanical device implantation. (Guazzi M et al JACC 2017;70(13):1618 - 36.).
We acknowledge the appropriate observation of this reviewer. Accordingly, the sentence stated in the “conclusion” on the “lack of measurement standardisation and limited data from randomised multicentric studies” has been eliminated in the new draft of the manuscript (see page 14). Moreover, all the references suggested have been added in the Reference list.

I agree regarding the need of more studies above all in HFpEF, HFmrEF and heart valve disease, albeit some parameters (e.g. VE/VCO2 slope and peak VO2) are showing a prognostic value in patients with HFpEF (Malhotra R et al. JACC Heart Fail 2016;4(8):607-16; Guazzi M. Circ Hear Fail 2014;7(2):367-77). The results of these studies are now reported at page 8, lines 4-9 (and references listed accordingly).

Please, include a more detailed description of the "hockey stick" pattern, using the more common expression of "ΔVO2/ΔWork Rate Flattening" (Bandera F et al. Circ Heart Fail 2014;7(5):782-90). Thank you for the kind note. Accordingly, when dealing with the combined use of CPERT and echo in pulmonary arterial hypertension, we state “It is also worthy of note that in patients symptomatic for dyspnea, the occurrence of ΔVO2/Δwork rate (WR) flattening, i.e. the "hockey stick" pattern demonstrated to reflect a significantly impaired functional phenotype whose major cardiac determinants are the excessive PAPs increase and the reduced peak RV longitudinal systolic function (reduced TAPSE)” (see page 13, first 4 lines).

Please, include a more detailed description of OUES, mainly underlining its prognostic role in submaximal exercise test (Guazzi M et al. Circulation 2016;133(24):e694-e711). More detailed description of OUES is now provided at the end of page 6, where we state "The oxygen uptake efficiency slope (OUES) is derived from the relationship between VO2 and the log transformation of VE and expresses the ventilatory requirement for a given O2". The prognostic value of OUES is underlined at the end of page 8, lines 19-20.

Not only peak VO2, but also the percent-predicted peak VO2 appears not be able to predict adverse events in HFpEF. Probably, this is related to the fact that the Wasserman and other current algorithms work poorly in HFpEF (JACC Heart Fail 2018 Aug;6(8):665-675).

See again page 8, lines 4-9, where these considerations have been reported and reference listed.

The authors should mention that the integrated CPET-ESE technique proved to increase patient risk stratification also in HFrEF, thanks to possibility of directly studying both right and left contractility (Guazzi M et al. JACC Heart Fail 2016;4(8):625-35; Pugliese NR et al. Eur Heart J Cardiovasc Imaging 2019;20(6):700-8).

We deal with this issue at page 10, lines 15-17, of the new draft of the manuscript.

The authors should emphasise that CPET-ESE can non-invasively evaluate multiple aspects of the cardiovascular system, offering a more personalised O2 pathway analysis, which in the recent past was obtained only with invasive monitoring to measure hemodynamics (Houstis NE et al. Circulation 2018;137:148-161). In particular, the authors should stress more the role of CPET-ESE in identifying non-cardiopulmonary causes of dyspnoea, which are mainly related to an impaired oxygen extraction (AVO2diff) (Guazzi M. JACC 2017;70(13):1618-36). This is of
utmost importance above all in HFpEF and HFmrEF: different groups have demonstrated that the effort intolerance observed in these HF subtypes could be related to an impaired A VO2diff (peripheral component of Fick equation) and near-normal cardiac output (Dhakal BP et al. Circ Hear Fail 2015;8:286-294; Shimiaie J et al. JACC Hear Fail 2015;3(10):803-14; Pugliese NR et al. Eur Heart J Cardiovasc Imaging 2019;20(7):828-36).

We acknowledge with this important suggestion. We deal with these important issues at page 9 (Chapter "Heart Failure") of the new draft.

Ref 2 should be updated: Corrà U et al. Eur J Heart Fail 2014:1501.

We checked the reference on Pubmed and again we found 2014 as the year of publication.


Cardiopulmonary exercise testing in systolic heart failure in 2014: the evolving prognostic role: a position paper from the committee on exercise physiology and training of the heart failure association of the ESC

Reviewer #2:

The Authors wrote an interesting review about the integration of CPET with exercise stress echocardiography. The manuscript is well written and comprehensive. Please find below some comments:

I would suggest to insert a schematic table with the typical CPET abnormalities (e.g. using arrows) for each different pathological condition (cardiac, pulmonary, metabolic, deconditioning, obesity, etc). According to the suggestion of this reviewer, we have added a new Table (Table 3) including the CPET abnormalities and the conditions in which CPT parameters are increased or reduced.

In table 1, I would insert also the breathing reserve (VE/MVV), which represents the ratio between maximal ventilation during exercise (VE) and maximum voluntary ventilation (MVV) (estimated as forced expiratory volume in the first second [FEV1] x 40). Table 1 has been modified according to the suggestion of this reviewer.

Similarly to table 1, I would suggest to insert a table about the most important systolic and diastolic parameters that should be reported in a standard stress echo exam, with their normal values. A new Table (Table 4) - including the most important echo systolic and diastolic parameters - has been added.

I would suggest to cite in the text the importance of CPET for congenital heart disease, particularly for GUCH; this is an emerging field of application for both CPET and stress echo.
We deal now with this important issue at the beginning of page 9 (CPET in congenital heart disease), where we state "CPET provides an integrated evaluation of cardiac, pulmonary, and metabolic function and may be used to identify the source of exercise limitation in many patients. Because CPET measurements have also been associated with outcome in adults with congenital heart disease, CPET is now considered as an important prognostic indicator and also be useful for surgical stratification in this population".

I would insert subheadings in the paragraph "Integration of CPET and Echocardiography", similarly to what the Authors did in the preceding paragraph. Subheadings have been added in the “Integration of CPET and Echocardiography” chapter.

Please revise some typing errors throughout the text Typing errors have been corrected.

Page 8: "a VE/VCO2 slope < 33.3 showed a sensitivity of 97% and a specificity of 40 % in predicting mortality and cardiac-related hospitalization in patients left ventricular ejection fraction (LVEF) > 50%" should be probably read as "a VE/VCO2 slope <33.3". Thank you for noting the typing error which has been corrected in the new draft of the manuscript.