Reviewer’s report

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

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Reviewer: Nicola Riccardo Pugliese

Reviewer's report:

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.). I agree regarding the need of more studies above all in HFpEF, HFrEF 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 Hear Fail 2016;4(8):607-16; Guazzi M. Circ Hear Fail 2014;7(2):367-77).

- 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 Hear Fail 2014;7(5):782-90)

- 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):e694-711).

- 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).

- 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 Hear Fail 2016;4(8):625-35; Pugliese NR et al. Eur Heart J Cardiovasc Imaging 2019;20(6):700-8)
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 AVO2diff (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).

Ref 2 should be updated: Corrà U et al. Eur J Heart Fail 2018:1501.

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