**Peer Review File**

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**Reviewer A**

The Author submitted a review on the role of echocardiography in the assessment of the right heart with an extensive introduction on pathophysiology. I congratulate with the Author for the clarity of the manuscript and for the accurate references.
I think the readers of the Journal would appreciate such lecture. However, I think that the manuscript could be improved if the Author is willing to deal with the following points:

**Reply:** Thank you very much for the overall very positive assessment.

**Comment 1:** • I believe that a paragraph on the role of right heart catheterization and comparison with echocardiography is needed, since RHC is the gold standard for the assessment of right heart and pulmonary circulation. I would explain RHC rationale, indications, procedure and interpretation of data. Also, the non-unusual situation with conflicting RHC and echocardiographic data should be discussed.

**Reply:** I totally agree with this important suggestion. In order not to exceed possible word count limits, I have indeed omitted some important aspects and I am thankful for the opportunity to do this in the revised manuscript. As suggested I have introduced these missing details on page 18 (lines 9-15) and on page 23 (lines 6-11).

**Comment 2:** • Since the overall manuscript is very technical, I would provide the readers with more figures and tables. For instance, I would add some echocardiographic images / videos / schematic representations of the various echocardiographic variables mentioned in the manuscript, both for geometrical and functional evaluation, also to help the reader deal with difficult concepts. Also, I think it is very important to provide the readers with a table with reference ranges of all echocardiographic variables (when available).

**Reply:** I totally agree also with these important suggestions. As suggested, I have introduced into the revised manuscript a new figure (Fig. 3) with 4 echocardiographic images and also an additional table (new Table 1) with the reference ranges of the echocardiographic variables.

**Comment 3:** • Briefly, I would comment in a dedicated paragraph on the pros and cons of the echo-cardiographic assessment of right heart with regards to other imaging techniques such as the CMR.

**Reply:** I totally agree with this proposal and, as suggested, I have introduced a brief comment related to this important aspect into the revised manuscript on page 17 (last 3 lines) and page 23 (lines 12-15).

**Comment 4:** • The assessment of tricuspid regurgitation must be addressed since it is very important for the overall evaluation of the right heart functioning. Therefore, complete description of TR assessment methods and grading, beside a pathophysiological overview should be reported. Also, estimation of pulmonary pressures from TR should be commented, along with the other available methods (PR, Act etc.), depicting for each advantages and limitations.

**Reply:** Like in the case of RHC, in order not to exceed possible word count limits, I have indeed omitted also this important aspect and I am thankful for the opportunity to do this in the revised manuscript. More details about the TR were introduced on page 17 (second paragraph, lines 5-26).

**Comment 5:** • Myocardial work should be further explained to the readers, from rationale, to calculation and the various indices obtained from the analysis besides RVGWE (RVGWI, RVGWW, RVGCW).

**Reply:** I have omitted to provide further details because of the fear to exceed a possible word count limit. As requested I have introduced the missing details into the revised manuscript on page 22 (second paragraph, lines 16-22).

**Comment 6:** • I cannot correctly visualize the provided figures; be sure they are properly formatted.

**Reply:** I had the same problem when I saw the PHF of my submission. I was assured that this problem will be removed before publication.

**Reviewer B**

This manuscript provides a thorough review on the current state of knowledge on the pathophysiology of right heart failure from different etiologies (with a converging point of pressure overload that leads to RV failure), the diagnostic and prognostic value of echocardiography in monitoring RV remodeling and function during the disease progression, and the particular considerations of the usefulness and limitations in the prediction of RV dysfunction in transplant patients (LVAD) and patients with acute ARDS and COVID-19-related ARDS. The review lists both strengths and limitations of each echo-cardiography methodology and measurement parameter. Such a summary will provide useful information and guidance to the clinical and research community for a better diagnosis of RV dysfunction in various types of RV failure.
Despite the significance and value of the review, there are a few minor suggestions:

**Reply:** Thank you very much for the overall very positive assessment.

**Comment 1:** There are different phases of adaptive and maladaptive RV remodeling. In the maladaptive RV remodeling, there are further stages of reversible RVF and irreversible RVF. Please discuss the current clinical criteria to distinguish these different types of RVF in the pathophysiology.

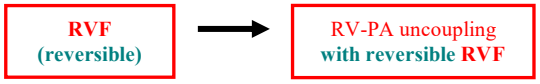
**Reply:** Thank you for this important remark. As suggested I have introduced these missing detail into the revised manuscript on page 6 (lines 9-26) and page 7 (lines 1-3).

**Comment 2:** It may be an oversimplification that the increased pulmonary vascular resistance (PVR) is the single factor to describe the increased afterload (overload). Resistance is only a measure of steady opposition of the pulmonary circulation to the RV output flow, and there may be other types of afterloads such as dynamic opposition of the pulmonary circulation due to pulsatile blood pressure/flow. Pulmonary vascular impedance (oi:10.1152/japplphysiol.00325.2016, doi:10.1152/japplphysiol.00325.2016) may be a more appropriate concept, although clinically PVR is more reported.

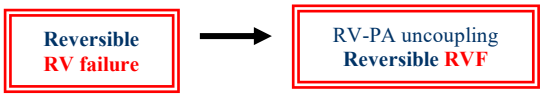
**Reply:** Thank you also for this important remark. As suggested, I have introduced those missing details into the revised manuscript on page 8 (lines 12-20).

**Comment 3:** In Fig. 3, RV-PA uncoupling is considered as the ultimate consequence of pressure overload leading to RV failure. But this component is missing in Fig. 1 & 2. What is the role of RV-PA uncoupling in the RVF patients with pressure overload or LV failure?

**Reply:** Thank you for very this important remark. Indeed, the mention of RV-PA uncoupling only in Fig. 3 could suggest that the uncoupling occurs only in SARS-CoV-2 pneumonia. I have made the necessary changes in figures 1 and 2.

In Fig. 1 I have 

modified

In Fig. 2 I have 

modified

**Comment 4:** Some texts in the figures are blocked (e.g., Fig. 3). Please revise the figure to include complete information of the diagram.

**Reply:** I had the same problem when I saw the PHF of my submission. I was assured that this problem will be removed, but only before publication.

**Reviewer C**

This review of right ventricular (RV) function and structure adaptation to afterload and its assessment and monitoring by echocardiography is difficult to read because of over-abundant recitation of studies without easily discernable line of thought. The updated list of echocardiographic measurements is of interest and indeed not yet to be found in other reviews, but there is an over-emphasis of poorly validated composite variables with uncommon abbreviations, and no physiologic or prognostic hierarchy.

**Reply:** I certainly understand the still existing concerns about the practical advantages of different composite variables derived from echocardiographic examinations with and without further combinations with heart catheterisation-derived hemodynamic measurements.

However, given the particularly high afterload dependency of RV function and the very high incidence of pressure overload-induced RV failure, as well as the high recovery rates of severe RV dysfunction with reduction of the afterload, there is hardly a chance for reliable clinical decision-making about the severity and potential reversibility of RV dysfunction without the use of composite variables which include RV size, geometry and function in relation to the RV loading conditions (particularly in relation to its afterload).

Given the lack of reliable validated composite variables, the "over-emphasis" of still poorly validated composite variables could attract more attention and interest towards initiatives to make further progresses in this field. To date, the highest predictive values for both RV failure and freedom from RV failure after LVAD implantation were found for the composite echocardiography-derived variables which reflect RV adaptability to load. These composite variables also appeared able to facilitate earlier decision-making for LVAD implantation before RV dysfunction and/or end-organ damage becomes irreversible. A comprehensible explanation for the shortage of relevant studies on this highly important issue is the worldwide relative reduced number of cardiac surgery clinics with sufficiently high numbers of VAD implantations and an own in-house echocardiography department which could enable the implementation of such studies. Having had the privilege to work in such a clinic where already more than 10 years ago the number long-term VAD implantations/year exceeded the 200 mark, and where echo-cardiography was a corner stone for final decision regarding the necessity of an additional mechanical temporary or long-term support also for the RV, I try to draw attention on the use of this important non-invasive technique which is underestimated and underused.

There is and there will be also in the future no single echocardiographic parameter which could reliably and also timely predict the exhaustion of all adaptive responses of the RV to persistent pressure over-loading and/or the RV capability for reverse remodeling and functional improvement after elimination of the cause of that pressure overloading (e.g. lung transplantation in therapy refractory PAH or LVAD implantation in end-stage congestive heart failure). However, given the vital importance of such predictions, as well as the wide heterogeneity of the study results on this topic, combined echocardio-graphy-derived parameters with a solid pathophysiological basis need a special attention before they can be considered as less irrelevant in comparison to parameters with less pathophysiological relevance.

**Comment 1:** There is allusion to it, but one does not see clearly the notion that the RV adaptation to afterload is initially homeometric with progression to heterometric adaptation when this basic mechanism gets exhausted (see ref # 4, 19 and 94, with also Vonk Noordegraaf et al J Am Coll Cardiol 2017). More recent reviews on the RV have been published recently following the same concept.

**Reply:** I totally agree with this remark and, accordingly, I have introduced a comment on page 6 (lines 9-26) and on page 7 (lines 1-3).

**Comment 2:** The rationale for each of the listed echocardiographic measurements is presented for some, less so for others. As most of them are only but loosely related to the gold standard of RV-pulmonary arterial coupling, i.e. the ratio of end-systolic to arterial elastances, it could perhaps be more enlightening to present a table showing only independent prognostic relevance for each as assessed by multivariate analysis. With ROC-derived cut-off values only for independent predictors as it should and brief criticism of these studies which will most often be too small sample sizes and over-fitting of models.

**Reply:** I totally agree with this remark. However, given the low number of studies which used multi-variate analysis I think it would be better to introduce these problems into the text. Thus, I have introduced short comments regarding this important aspect into the revised manuscript on page 24 (last 2 lines) and on page 25 (lines 1-9). In Table 3 I have also emphasized the studies which also used multivariate analysis for assessment of the prognostic relevance of the investigated echocardiographic parameters.

**Comment 3:** Some composite variables promoted in these review are really excessively contorted from a physiologic point of view and of little or no added value compared to simpler approaches. The worst are so-called "sRVCPI", "LAIRV", "PSSrL" and RVGWE. These composite variables add confusion.

**Reply:** Unfortunately I find that this comment goes a bit far. To consider the peak systolic longitudinal strain rate, irrespective of the used abbreviation (PSSr or PSSR) to be “one of the worst” parameters with little or no added value compared to simpler approaches is quite astonishing. The same also applies to RV load adaptation index based on the indisputable fact that a persistent supra-normal after-load (e.g. increase of the pulmonary vascular resistance) can induce different degrees on RV dilation, depending on the individual functional abilities to face that increased afterload. The first studies related to these echocardiography-derived parameters were published in Circulation (this article has reached already 102 citations) and in the J Heart Lung Transplantation. In their Editorial regarding the latter publication, Naeije R. and Guazzi M. (JHLT 2015;34(5):308-309) stated: “Dandel et al are to be commended for arguing persuasively, with physiologic concept and data, in favor of comprehensive imaging of RV function”… ”Their study is an important step in the right direction”.
Using the velocity-time integral of the tricuspid regurgitation jet as a surrogate of hemodynamic load (instead of the catheter derived PVR) in combination with 2 of the most easily measurable RV end-diastolic anatomical parameters allows a very easy calculation of that load adaptation index by an approach just as easy as other approaches like

TAPSE/systolic PAP. In the study by Amsallem et al. (J Thorac Cardiovasc Surg. 2019) the load adaptation index emerged as the strongest predictor of right heart failure not requiring RVAD implantation, with an AUC 45% higher than the TAPSE/systolic PAP ratio.
The "confusion" induced by the other two "worst composite variables" (i.e. sRVCPI and RVGWE) published in J Card Fail in 2012 (sRVCPI), Eur J Heart Fail in 2016 (sRVCPI) and Eur Heart J Cardiovasc Imaging in 2023 (RVGWE), which are all recognized journals, is for me also not clearly comprehensible. Given that no single echocardiography-derived parameter can reveal alone the whole real picture of RV dysfunction and, therefore, it is necessary to perform multi-parametric evaluations as well as to apply integrative approaches using parameter combinations which include also details about the RV loading conditions, we can not ignore newly proposed composite parameters as long as there is no evidence on their uselessness. In a prospective study on patients with acute decompensation of advanced CHF (Frea et al. Eur J of Heart Fail, 2016), the multivariate analysis revealed the presence of a low RVCPI as best predictor of outcome, whereas neither TAPSE or $FAC_{RV}$, nor TAPSE/systolic PAP or $FAC_{RV}$/systolic PAP revealed no significant predictive values. In 2020 another study confirmed the usefulness of the RVCPI as an independent predictor of short-term post-operative patient outcome (including RVF) after LVAD implantation (ref. nr. 102). In the revised manuscript on page 18 (last 6 rows) I have introduced a comment on the potential usefulness of RVCPI.
The last of the 4 "excessively contorted worst composite variables", the "RV global work efficiency" (RVGWE), which was presented this year in the Eur Heart J Cardiovasc Imaging in 2023, where it was found superior to that of both the TAPSE/sPAP and the RVFW longitudinal strain/sPAP ratio for the prediction of early right heart failure and long-term mortality after LVAD implant, is mentioned in the submitted manuscript only in two consecutive sentences. In the revised manuscript I have introduced on page 22 (lines 16-22) a short additional comment on this potentially important parameter.

**Comment 4**: RV failure in SARS-CoV2 induced ARDS is indeed a major problem, but is not clearly related to increased afterload, as in these patients pulmonary artery pressures are most often only mildly elevated or not at all (see D'Alto et al Crit Care 2020).

**Reply 4:** Thank you very much for this important remark. Indeed, although in the study by D'Alto, et al. the systolic PAP was significantly higher, and the D-dimer levels were 3 times higher in non-survivor patients, which suggest the possible involvement of pulmonary microangiopathy with widespread small vessel thrombosis in the occurrence of RV-arterial uncoupling, the only moderately increased PAP values are rather unusual when compared to the higher values reported the majority of other studies on this subject. In a study by

Norderfeldt et al. (Acta Anaesthesiol Scand. 2021), 39% had acute pulmonary hypertension with median value of 50 mmHg (37-76 mmHg), and RV dilation was present in 86% of those patients. The 21-day mortality in the acute PH group reached 46% and was nearly sevenfold higher than in the group with systolic PAP median value 32 mmHg (22-35). It is proven that the increase in the pulmonary arterial resistance and pressure may be a factor 4 to 5 compared with only about 50% in the systemic circulation (Vonk-Noordegraaf et al. JACC, 2017). However, this adaptive response can be attained only during chronic pressure overloading and not without the development of a pronounced RV hypertrophy. When faced with an acute increase in afterload, the normal RV is able to increase peak systolic pressure to ~60 mmHg, associated with RV dilation, before RV contractile failure and systemic hypotension ensue (Greyson et al. Am J Physiol Heart Circ Physiol 2000). Thus, systolic PAP values which are considered moderately increased in patients with RV chronic overload (i.e. 42±12 mmHg in the D'Alto study) can be considered as more than moderate in those with acute RV pressure overload. Unfortunately D'Alto et al. provided no data about the RV size and geometry. The simultaneous detection of RV dilation and dysfunction by TTE performed on median day 6 after admission to intensive care units was fond independently associated with in-hospital mortality (Chotalia et al. Crit Care Med. 2021). In a study on hospitalised patients with severe COVID-19, a multivariate analysis revealed high afterload-induced RV dilation as the only variable associated with mortality (Argulian E. et al. JACC Cardiovasc Imaging, 2020).

An important detail regarding the SARS-CoV-2 pneumonia is also the observation that the cardio-respiratory decompensation occurs typically only one week after initial symptom onset (McFadyen et al. Circulation Research. 2020). This could also explain the observation that even in patients with SARS-CoV-2 pneumonia characterized by greater radiological abnormalities than influenza pneumonia, their baseline radiography did not correlate with the clinical outcome (Lyons et al. EBioMedicine 2022;85:104295). Thus, the early appearance of RV dilation in hospitalized patients with SARS-CoV-2 pneumonia should be considered as a potentially important indication for an acute increase of the RV afterload even in the presence of a rather moderate increase of the systolic PAP, when compared to the much higher PAP values in relative stable patients with chronic pulmonary arterial hypertension. Given that the life-threatening SARS-CoV-2 related widespread small vessel thrombosis occurs typically only several days after the onset of clinical symptoms, the monitoring of RV size and geometry appears necessary in all patients with moderate RV dilation especially in those with systolic PAP $\geq$ 40mmHg.

As suggested by the reviewer I have introduced a comment on this important aspect into the revised manuscript on page 28 (lines 12-26) and 29 (lines 1-3).

**Comment 5**: The author repeatedly thinks of validation of measurements by correlations to others (that are not always gold standards by the way..., but as Bland and Altman used to emphasize, this is poor agreed statistics.

**Reply 5:** Thank you very much for this important remark. Indeed, in many cases it is not appropriate toconsider the results of statistical evaluations as validation. As suggested, have introduced additional comments into the revised manuscript on page 25 (lines 3-9) in which I have emphasized that the available study results are insufficiently reliable for the establishment of an effective hierarchy of echocardiography-derived parameters based one their ability to predict post-implant RV function in LVAD candidates.

**Comment 6**: Please omit uncommon abbreviations such as C-ARDS, ECHO (acronym for what?), A4C, PSSL, LAIRV... Echocardiography relies on many abbreviations that are inevitable, do not make matters worse.

**Reply 6:** I totally agree with this suggestion. I have introduced these acronyms in order to save space and to facilitate the reading of the article. Especially words like echocardiography or parameters designations of excessive length like peak systolic longitudinal strain rate, which were often mentioned in the manuscript were replaced by acronyms. For echocardiography, the journals use the acronyms Echo, echo, or ECHO. For example: “ECHO, ECHO AGAIN: PROSTHETIC MITRAL REGURGITATION PRESENTING AS B-TYPE SYMPTOMS. JACC, 2022, 79 (9)”, or **“**ECHO OVERESTIMATES TRANS-AORTIC GRADIENTS IMMEDIATELY POST TAVR: A PRESSURE RECOVERY PHENOMENON IN A SIMULTANEOUS CATH AND ECHO STUDY. J Am Coll Cardiol 2019,73 (9)”. However, I removed all those uncommon abbreviations.