

### **Reviewer Comments**

In this review paper applications of multiple computational methods and techniques and most importantly the model developed by the authors are discussed.

#### Comment 1:

On the first glance I believe there is little relevance between this topic and the pediatric journal. Most of the pathologies and techniques discussed in this paper are related to adult population.

#### Reply 1:

We thank the Reviewer for the insightful comment. We are fully aware that our models have been mostly validated in the adult population, but there is growing evidence, e.g., (as from our reference n. 89, and clinical studies such as n. 91, 92, and other) about the involvement of children positive for Covid-19 infections with cardiovascular issues, requiring hospitalizations, and not infrequently intensive care treatment, occasionally ending up with cardiocirculatory mechanical assistance and/or heart transplantation. This is an example of the impact of our computational methods on pediatric clinical care: the wide applicability of our methods, as discussed in the manuscript, shows the potential of their use to address several other clinical questions.

Even if we respectfully acknowledge your comment, the purpose of our contribution is to provide the readers with the instruments to better evaluate the different possibilities provided by computational methods and how they can impact on the clinical practice. Yet, to better clarify this perspective to the reader, we added comments in the motivation portion of the Introduction, in the statement of the Objective of this review (section 1.3), and in the Conclusions (section 4).

#### Changes in the text:

Introduction, lines 70-73. Added: “Specifically, we illustrate how innovative computational methodologies can have an impact on clinical practice, both in the present day and in the near future.”

1.3 Objective, lines 144-149. Added: “The computational models that we discuss were mainly developed on data coming from adult human heart observations and measurements, but their high flexibility allows them to be employed also in the pediatric context. Indeed, the same physical laws that we included in our models govern the blood flow, the electric signal propagation and the contraction of the heart in the general sense. An example of this wide applicability will be discussed in the case of an investigation of cardiovascular effect of COVID-19 on children (see Section 2.1.E and the following discussion).”

4. Conclusions, lines 394-397. Added: “Part of the results presented (see Section 2.1.E and the related discussion) regard the treatment of cardiovascular diseases in children, showing how the versatility of mathematical models allows for the translation of computational methods developed for adult patient care to the pediatric context.”

Comment 2:

Some specific issues in this paper:

1. In the title "cardiac medicine" is a vague description. More common terms are cardiovascular medicine or cardiothoracic surgery or cardiovascular surgery.

Reply 2:

We thank the Reviewer for the suggestion. The title has been modified accordingly.

Changes in the text:

In the title, "cardiac medicine" has been replaced by "cardiovascular medicine".

Comment 3:

2. As this paper deals with computational methods, one would expect more details on the process with figures, charts, tables etc. to make it more visually appealing for the reader.

Reply 3:

We thank the Reviewer for the suggestion. We have added 3 new figures illustrating results that need computational simulations to be obtained, in order to support the relevance of computational methods in the investigation of pathological conditions and planning of treatment.

The figures have been renumbered in order of appearance.

Changes in the text:

New Figure 1, referenced in Section 2.1.A, line 173: "(see, e.g., Figure 1)" and Section 3.2, line 330: "the transmembrane electric potential in the atria (18) and ventricles (108, 115), as shown in Figure 1,"

New Figure 4, referenced in Section 2.1.C, line 197: "(see Figure 4)" and Section 3.2, lines 302-304: "examples of detailed vortical structures of flow jets in pathological conditions (hypertrophic cardiomyopathy and mitral valve regurgitation), obtained by image-based computational fluid dynamics, are shown in Figure 4 and Figure 7."

New Figure 7, referenced in Section 3.2, lines 302-304: "examples of detailed vortical structures of flow jets in pathological conditions (hypertrophic cardiomyopathy and mitral valve regurgitation), obtained by image-based computational fluid dynamics, are shown in Figure 4 and Figure 7." and line 329: "or even on valve leaflets (110), as shown in Figure 7,"

Comment 4:

Above all the main issue here is that the authors deal with their own model more than the available methods and techniques in the literature. There are repeated statement talking about authors own constructed computational multi scale integrated model. If the authors plan to describe their own model, then this paper should not be a review paper but a description of their technique.

Reply 4:

Thank you for this comment: we have now better clarified that our perspective is based on the experience of our group in collaboration with different hospitals. We added clarifications of this in the Abstract (Background and Objectives) and in Section 1.3 Objective.

We point out that a more comprehensive literature review would be definitely suitable for a manuscript submitted as "Systematic Review", where an extensive literature review is required with mention and discussion of all the methodologies and techniques previously reported. However, our manuscript was submitted as "Narrative Review", where, as indicated on the "Instructions for the Authors"

*"A narrative review is less methodologically demanding than a systematic review, as it does not require a search of all literature in a field, nor does it necessarily require a rigorous appraisal on the included literature."*

Therefore we consider justifiable our limited list of alternative methodologies and techniques. First, based on the type of our submission as "Narrative Review". Second, because our message for the readers is to propose novel methodologies, never used before. In this sense, the present can be considered as a "review" of new methods that are used in a coordinated way to address different cardiovascular problems.

Changes in the text:

In the Abstract, lines 38-40, we added the following clarification: "This narrative review aims to systematically discuss the role that such integrated model had in addressing specific clinical questions, and how further impact of computational models on clinical practice are envisaged."

In the Introduction, lines 66 and 133, we specified that the manuscript is a "narrative" review. Moreover, we better clarified its perspective adding that "Specifically, we illustrate how innovative computational methodologies can have an impact on clinical practice, both in the present day and in the near future." (lines 68-69).

Throughout the text, we have pointed out that the methods and results reported and discussed in the manuscript are related to our computational models and heart simulator (lines 73, 137).

Comment 5:

3. Authors have used the term biomarkers of heart function which is confusing. The biomarkers related to heart function are a measure of cardiac dysfunction.

Reply 5:

We thank the Reviewer for pointing out this aspect. We now use "biomarkers" only when it refers to dysfunction and we replaced it with "(clinical) indicators/measurements/quantities" when they broadly refer to the heart function.

Changes in the text:

The word "biomarkers" has been replaced by "(clinical) indicators/measurements/quantities (of interest)" in lines 51, 140, 228, 233, 242, 279, 294, 311.

Comment 6:

4. On page 8 line 151, atrial fibrillation is not always with high heart rate and reduced contraction. Even though most cases of atrial fibrillation are consistent with these features, this is not a general rule, and this should be stated more clearly in the paper.

Reply 6:

We thank the Reviewer for their insightful comment. We have clarified that the abovementioned features characterize most atrial fibrillation occurrences, but not all of them.

Changes in the text:

The words “high and irregular rhythm and reduced contraction” have been replaced by “irregular rhythm and, in most cases, high heart rate and reduced contraction” (lines 163-164 in the revised version).