Author’s response to reviews

Title: General anesthesia and positive pressure ventilation suppress left and right ventricular myocardial shortening in patients without myocardial disease – a strain echocardiography study

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Version: 1 Date: 07 Jul 2019

Author’s response to reviews:

Dear dr Sicari,

We appreciate the constructive criticism from the reviewers. Below please find our responses to the reviewer comments. Finally, we believe that the manuscript has improved thanks to their comments. Changes in the manuscript are shown in red font.

Reviewer no. 1.

The article is interesting and provide physiological insights in loading conditions and strain.
-Thanks!

The sample size seems to be small (21 pts) considering the wide availability of this category of pts (see criteria of inclusion and exclusion); nevertheless the authors provide an estimation of sample size (17 pts needed to overcome strain SD and variability).
-We agree
Minor issues:

Pag 4 line 12-19: the influence on sepsis is not required in the introduction but in discussion

-The first sentence of the last paragraph of the introduction section has been rewritten as: “In the ICU, myocardial dysfunction occurs frequently and speckle tracking echocardiography has the ability to detect impaired LV systolic function not appreciated by conventional echocardiography”

Exclusion criteria: abnormal ECG not normal

- Abnormal has been changed to normal

Pag 12 line 22: echocardiography

- Echocardiohgraphy has been changed to echocardiography

Reviewer no. 2

Major comments:

1) The different impact of positive pressure ventilation and drugs on ventricular function is not explored and cannot be distinguished in this study. It's well known that both have impact on ventricular function, but it must be differentiated (for example by modifying PEEP or tidal volume or changing drug dosage).

-We fully agree with the reviewer. We also addressed that in the Limitation section (second last paragraph of the Discussion section: “One limitation of the present study is that we cannot distinguish the effects of the anaesthetics themselves to those of PPV on RV free wall strain and LV GLS, in the present study, as the patients need to be intubated and mechanically ventilated within minutes after induction of anaesthesia.”

2) Statistical approach as logistic regression could differentiate the impact of dosage of drugs and ventilation on ventricular function in a bigger sample

- We do not see how a logistic regression approach could differentiate between the effects of anaesthetics to those of positive pressure ventilation on ventricular function. To differentiate, one
would perform three measurements: 1) in the conscious state, 2) after induction anaesthesia without mechanical ventilation and 3) after intubation and mechanically ventilation. As the anaesthetics induce immediate apnea, there is no time to perform measurements after induction before the institution of positive pressure ventilation.

3) Fluid responsiveness parameters are not measured and can be one important point of ventricular adaptation to general anesthesia and positive pressure ventilation. Moreover, mean filling pressure should be integrated to corroborate the impact of loading condition on ventricular function.

-No, we did not measure fluid responsiveness parameters such as stroke volume variation (SVV) or pulse pressure variation (PPV) during the transition from wakefulness to anaesthesia and positive pressure ventilation. On the other hand, we measured changes in left ventricular end-diastolic volume (LVEDV) from the conscious state to the induction of general anaesthesia + positive pressure ventilation. LVEDV decreased by 18% (p=0.012), suggesting a decrease in LV preload. We did not measure filling pressures in this study on these healthy individuals undergoing elective low-risk surgery.

4) Authors studied arterial impact of general anesthesia and ventilation measuring EA, but not ventricular elastance, that can be assessed in a noninvasive manner. The information from noninvasive ventricular elastance can be of value in such analysis.

-As suggested by the reviewer, we have now measured LV end-systolic elastance (Ees) according to the method described by Chen et al. together with data on the ventriculo-arteriolar coupling (Ea/Ees). This information is now included in the revised version (Abstract, Key words, Results, Discussion, Table 2).

5) The impact of loading conditions on strain is debated in literature. The authors could corroborate their results adding strain rate parameters.

-Unfortunately, LV strain rate in systole or diastole were not measured in the present study. Our group has previously shown that LV strain and systolic strain rate are changing in parallel caused by changes in preload (Fredholm et al Acta Anaesthesiol Scand 2017), while neither LV strain or strain rate are affected by changes in afterload. Thus, in the present study, anaesthesia + PPV decreased not only LV strain but, would, most likely, have also decreased LV strain rate due to the fall in preload (LVEDV).
6) The intraobserver analysis shows big coefficients of variation (around 10%) with low modification of strain parameters (around 5%). In my opinion, considering these results, interobserver analysis and larger sample is needed.

-In our opinion a coefficient of variation (≈10%) is very good. Inter-observer analysis is less relevant for the present study as the same investigator performed all analyses.

7) It could be useful to analyze the same parameters after awakening from general anaesthesia. Restoration or amelioration of echocardiographic parameters could help to correlate drugs and ventilation to presumed reduction of ventricular function.

-We agree that data after the awakening from anaesthesia would be interesting. However, in the present study we only measured echovariables in the awake state and during anaesthesia + positive pressure ventilation.

8) Use of ephedrine to restore mean arterial pression could be an important source of bias.

-Yes, 3 out of 21 patients (14%) required vasopressor support. Two patients each needed one bolus dose of ephedrine and one patient received one bolus dose of phenylephrine to maintain mean arterial pressure > 60 mmHg, according to routine protocol. Ephedrine increases arterial blood pressure by an inotropic effect and by vasoconstriction, while phenylephrine only exerts vasoconstriction. For both drugs the effects are short-lasting (minutes), but we cannot exclude that these vasopressors attenuated the fall in blood pressure, cardiac filling and myocardial contractility in those three patients. The following sentence was inserted in the limitation paragraph of the Discussion section: “Furthermore, the use of single bolus doses of ephedrine and phenylephrine in three patients could have attenuated the fall in blood pressure, cardiac filling and myocardial contractility.”