Author's response to reviews

Title: PAI-1 and t-PA/PAI-1 complex potential markers of fibrinolytic bleeding after cardiac surgery employing cardiopulmonary bypass

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Author's response to reviews: see over
Response to the comments and critiques raised by Dr. Sniecinski (Reviewer 3)

Reviewer 3
The authors present a study of 88 patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) investigating the association between pre-operative PAI-1 levels and post-operative bleeding. This represents a revised manuscript that I have been asked to act as adjudicator between authors and Reviewer #2.

Authors:
Dear Dr. Sniecinski (Reviewer 3),
Thank you for spending your time on reviewing our manuscript and for your willingness to act as an adjudicator in our dispute with Reviewer #2. In our response to his review, it was important to stress that we respect his views on the protocol, but we hope that he will understand our reluctance about modifying the protocol after the study has been finished. Below we respond point by point to your comments and critiques. We have also shortened the manuscripts on a few places. When we made changes in the manuscript, these will be referred to by their page (P) and line numbers (L) in the last revised version. To avoid any misunderstanding, we also submit a version where we have accepted all the changes.

Reviewer 3
1) The association between low PAI-1 levels and increased clinical bleeding has been shown in other studies, although primarily related to the 5G polymorphism. There are not an abundant number of studies on this issue in cardiac surgery and the sample size is in-line with other published papers. One of the interesting aspects of PAI-1 is that patients with coronary disease may have higher levels to begin with. Therefore, this manuscript does add some data to this issue and, while it is not ground-breaking, I would say that it may be of more interest than indicated by Reviewer #2.

Authors
We agree with the reviewer and refer to the 5G polymorphism (please see P11, L11). We also admit that this is not a paper presenting any sensational news, but a study that could be carried out with limited resources besides the daily clinical work at the leading center for cardio-thoracic surgery in Latvia. If accepted by an international journal, an academic milestone would be reached for the clinic, that might encourage future grant applications making the hope to position for international grant applications come through. From our point of view, the fact that the group with the highest blood loss was still below 1000 ml/24 hours, makes the association with PAI-1 still more interesting than just confirmation of earlier findings (and to demonstrate this association, the sample size was more than large enough!), since the previous papers presenting the same associations had higher blood losses (to demonstrate this association, the sample size was more than large enough!).

Reviewer 3
2) I do agree with Reviewer #2’s issue on the authors’ definition of bleeding. While it is not uncommon for many papers on “bleeding in cardiac surgery” to use a metric of 24 hour chest tube drainage, 500 ml in 24 hours is on the low side. In fact, even the highest 24 hour output (~1600 according to Figure 3) would not really meet the recent BARC definition of excessive
bleeding which is >2L in 24 hours (Mehran et al. Circulation, 2011;123:2736-2747). I’m not really sure dichotomization at 500 ml/24 hr is appropriate. If you set the cut-off for “excessive” higher – to something more consistent with what is in the literature – you’d probably lose statistical significance between the 2 groups.

Authors
It is probably a goal for all clinics to keep bleedings at the lowest possible level. Although we admit that a 24 hour drainage of 500 ml might be looked upon as modest, and not to be characterized as excessive, most bleedings in our clinic gathered around this limit. Therefore, 500 ml was arbitrarily chosen, and we decided prospectively to assign the patients consecutively to one group below and one group above this limit. Since this decision was taken on the basis of the local experience with postoperative 24 h blood losses, we find it scientifically correct to dichotomize at this level. In our eyes, it would be a misconduct to change this criterion after the study was finished.

In a recent study of sepsis-induced lung injury lead by one of us (LJB), we noticed that the plasma concentration of endothelin-1 was significantly higher in patients with increased extravascular lung water index >7 mL/kg (Kuzkov V. et al. Crit Care Med 2006; 34:1647–1653). The latter was also an arbitrarily chosen value, like a drainage volume of ≥ 500 ml/24 hours in the present study.

Reviewer 3
3) I would also recommend removing most of the speculation in the discussion section about association of PAI-1 levels and diabetes, as well as things the study was underpowered to test (P 13).

Bottom line – this study showed a weak association between preoperative PAI-1 levels and 24 hour chest tube output (as shown in figure 3). If the authors could just focus on that, this paper may be of interest to some readers.

Authors
In the second revised version of the manuscript, we have taken advantage of these recommendations and removed the speculations about PAI-1 levels and diabetes and other items (like BMI) that the study was underpowered to test (please see P10, L 11, P 13. We have also deleted the diabetes II patients from Table 1. (P21).

Additional changes: We removed “The inhibitor”, which is a pleonasm (P4, L23).
On P5, L11-12, we added “the” before half-life and “the process” might lead to relative lack of…..
On P6, L16, we inserted a “the” before surgery
P7, L2 we inserted the words “intravenously” and “inhalation of”, respectively
In Discussion (P11,L2) we deleted the first sentence since these facts had been presented in Introduction.
P11, L4, we replaced “and” with a comma after fibrinogen
P11,L4, we replaced “larger bleedings” with “increased blood loss during”
On P11, L15, we inserted “on CPB” to avoid misunderstandings
P13, L5, we inserted (Figure 2)
P13, L7, we changed to “also supported”
P13, L17 we interposed (n = 67 in each group)

Acknowledgements and Funding, P15, L15, we added “American citizen”