Critical Care

LETTER

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Anti-Xa activity and hemorrhagic event: isn't it time to consider time ?

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We read with great interest the publication by Descamps et al. which showed that in patients treated with extracorporeal membrane oxygenation (ECMO), mean anti-Xa activity was an independent risk factor for bleeding complications [1]. A non-negligible number of bleeding episodes (i.e., 29%) were observed for anti-Xa values at the lower limit of the official recommendations of 0.3 to 0.7 IU/ml [2]. We were surprised to see that the anti-Xa median value at the time the patients bled was equal to anti-Xa median value measured during the entire total treatment period of all patients who did not bleed. When comparing maximum anti-Xa median values in both groups, no statistical significance was observed; hence, another factor may need to be considered.

In the univariate analysis, the duration of treatment with ECMO was significantly longer in patients who bled. This time factor was not included in the multivariate analysis. We wonder whether a longer exposure to an effective anticoagulation treatment does not expose to a higher risk of bleeding (due to, e.g., manipulations, physiotherapy, sudden blood pressure variations, etc.)?

Karkouti et al. in its prospective study studying transfusion risk in cardiac surgery under cardiopulmonary bypass (CPB) compared 476 patients who received a massive transfusion with 6175 control patients who were not transfused. Massive blood transfusion (MBT) was defined by a transfusion greater than or equal to 5 units of concentrated red blood cells in the 24 h after surgery. A significant difference in the duration of cardiopulmonary bypass (CPB) (144 ± 68 min) was observed in MBT patients versus 98 ± 33 min in not transfused patients ($p < 0.0001$). CPB duration was an independent factor of MBT risk (OR 1.02, $p < 0.0001$with a linear correlation between CPB duration and MBT [3].

In addition, a comparison between group values of anti-thrombin III which play a role in the effectiveness of heparin may be useful to understand factors influencing the occurrence of bleeding [4].

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Response to: Anti-Xa activity and hemorrhagic event: isn't it time to consider time?

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To the Editor,

We greatly thank Redant et al. for their relevant comments on our article, addressing different issues. To explain the absence of difference between the anti-Xa median value of the non-bleeding group and the anti-Xa median value at the time of bleeding, the delay between the onset of the bleeding (including mostly internal hemorrhagic events such as intracerebral hemorrhage, hemothorax, pericardial or gastrointestinal bleeding (63% of bleedings in our cohort)) and its diagnosis must be pointed out, and may induce an underestimated anti-Xa

value at the time of diagnosis. Some patients of the bleeding group may have had their heparin stopped at the time of testing. Regarding the maximum value of anti-Xa, we believe there might a misinterpretation of the results since it was higher in the bleeding group in univariate analysis ($p = 0.05$). This variable was not tested in the multivariate model to avoid confusion bias related to its dependence with the mean anti-Xa values. Of note, the absence of association between max anti-Xa value and bleeding was already reported [5].

We agree that the association between the time of exposure to extracorporeal membrane oxygenation (ECMO) and bleeding must be assessed. A Cox proportional hazards regression analysis adjusted for SAPS II, duration of treatment with ECMO before bleeding, associated IABP/Impella was performed for risk of bleeding under ECMO and mean Anti-Xa. Survival time was duration of ECMO treatment, and the dependent variable was the occurrence of bleeding event. In this model, only SAPS II score (HR, 5.7; 95%CI, 1.01–1.05; $p = 0.02$) and mean Anti-Xa (HR, 14.9; 95%CI, 3.9–69.6; $p = 0.0001$) were associated with bleeding. Interestingly, duration of treatment with ECMO was not identified as independent risk factor of bleeding.

We think cardiac surgery patients are different for several reasons: higher doses of heparin, associated hypothermia, air / blood interface, greater degree of hemodilution, absence of pulsatility and reversal of anticoagulation at the end of surgery [6]. Cardiopulmonary bypass and ECMO populations are therefore not comparable.

Unfortunately, antithrombin data was not available due to the retrospective nature of the study. We agree that this variable may be useful. The benefit of antithrombin monitoring and supplementation in ECMO needs further studies since the use of antithrombin may not change the risk of bleeding events whereas its deficiency was recently associated with an increased risk of thrombosis [7].

Abbreviations
ECMO: Extracorporeal membrane oxygenation; MBT: Massive blood transfusion; CPB: Cardiopulmonary by pass.

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