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Letter to the Editor

„Clinical Relevance and Practical Value of Platelet Function Assessment Using Multiple Electrode Aggregometry During Extracorporeal Circulation “

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We read with great interest the recently published study by Mutlak et al [1]. The authors conducted prospective observational study with aim to assess capability of the multiple electrode aggregomatry (MEA) to reflect the extent of cardiopulmonary bypass (CPB) associated platelet dysfunction [1]. Study cohort consisted of patients that underwent either hypothermic or normothermic CPB. Adenosine di-phosphate test induced platelet aggregation (ADP test) was considered as a primary endpoint. Put briefly, platelet function as assessed using MEA ADP test reflected the time-dependent extent of CPB-induced platelet dysfunction [1]. Study by Mutlak et al [1] certainly adds to the current knowledge; however some methodological considerations should inevitably be addressed.

In cardiac surgery patients, disturbances in platelet function predominantly root from either preoperative antiplatelet drugs administration or are acquired during CPB pump run. In our opinion, clear distinction between these two predominant causes of platelet dysfunction should be made, as holds great practical value.

This study [1] is of great value, however confirms findings that are well known so far[1]. Such studies should be focused towards the gaps in our knowledge pertaining to this specific issue. First of all, the relationship between platelet dysfunction and bleeding outcomes/transfusion requirements should be validated in prospective multicentric trials [2]. Our working group has recently published studies evaluating predictability of bleeding complications by using MEA both preoperatively [3] and intraoperatively [4]. Even though we reported positive results with calculated receiver operating curve cut-off values, the fact is that the literature reveals controversial data on predictability of bleeding complications using platelet function testing [5-7]. Therefore, further efforts to elucidate this field are warranted.

Despite emerging evidence on a) widespread variability in platelet inhibitory response to antiplatelet therapy and b) the effects of CPB and hypothermia on platelet function, the fact is that use of numerous platelet function testing devices in heterogeneously designed studies hamper pooling of the evidence which in turn results in the lack of consensus on platelet reactivity level that would be associated with bleeding events in different time points pertaining to the cardiac surgery procedures. In their study [1], authors considered patients as eligible if their *ex vivo* arachidonic acid and ADP-induced platelet aggregation were within normal reference values after the induction of anesthesia [1]. Preoperative administration of antiplatelet drugs was considered as exclusion criterion [1]. We understand that authors wanted to exclude the possible underlying effects of preoperatively administered antiplatelet drugs in order to elucidate more precisely the role of CPB itself on platelet function. However, in the real-life, there is growing number of patients that are scheduled for complex procedures with antiplatelet drugs being administered for some reason in close proximity to surgery. We need answers how to manage these patients at particular risk for excessive bleeding. In our opinion, the influence of preexisting antiplatelet therapy on platelet function should be weighed against the influence of CPB on platelet function. Also, it should be elucidated whether the underlying platelet dysfunction caused by preoperatively administered antiplatelet drugs influences dynamics of platelet function changes during CPB? Authors should consider possibility to conduct a new "historically controlled" study where the findings obtained on patients exposed preoperatively to antiplatelet drugs would be compared to findings obtained in the present study [1]. The study by Mutlak et al [1] certainly adds to the current knowledge, however, further research on this field is warranted in order to provide further refinements in hemostatic management of cardiac surgery patients. So far, valuable algorithm provided by Weber et al [8], has shown that hemostatic therapy based on point-of-care testing may reduce patient exposure to allogeneic blood products and provide

significant benefits with respect to clinical outcomes[8]. Nowadays, evolution of hemostatic management warrants further refinements in hemostatic management. There are several areas of gaps in our knowledge related to hemostatic management that should be addressed in upcoming studies:

1) The role of antiplatelet drugs is not clearly understood. Current guidelines on preoperative antiplatelet administration/discontinuation management rely on "one-size-fits-all" strategy despite emerging evidence on huge individual variability in platelet inhibitory response to antiplatelet drugs. Using drug specific platelet function tests, the exact cut-off values that increase odds for bleeding complications should be defined and antiplatelet drug administration/discontinuation management should be adjusted accordingly. The impact of preoperatively administered antiplatelet drugs on bleeding complications should not be underestimated [9,10]. Huge variability in individual platelet inhibitory response to antiplatelet drugs deserves attention and clear distinction between patients who have pronounced platelet inhibition from those who have high degree of residual platelet reactivity should be made and preoperative administration/discontinuation management should be adjusted accordingly. That would be a significant shift towards personalized management in patient care for which we may assume that would probably result in more favorable clinical outcomes.

2) Next generation of hemostatic algorithms should be developed. These should encompass preoperative, intraoperative and postoperative time points with respective measures. Preoperative part should pertain to risk stratification and measures to prevent bleeding risk (i.e. personalized preoperative antiplatelet therapy management). Intraoperative part should, as concept, remain very similar to present one published by Weber et al[8], albeit some refinements are required, particularly in defining triggers for transfusion administration. Cut-off values that delineate

bleeding tendency and that are validated in studies recruiting the population of particular interest (ie. Cardiac surgery patients) should be used in transfusion management rather than “normal range” values. Apart from the fact that “normal range” values are usually derived from healthy volunteers, the fact is that cut-of values defined by ROC analysis [11] are by statistical chances more precisely related to some endpoints with the best sensitivity/specificity ratio comparing to values expressed as range. If defined in prospective studies and applied to similar patients, cut-of values may the most reliably direct transfusion practice and are easy to follow in clinical practice since decision making is based on binary decisions (Simplified decision making: i.e. below/above cut-of value – do/do not transfuse).

Finally, we congratulate authors on timely and elegant study. Moreover, we call for prospective multicentric study that would be conducted by centers with expertise in this particular field. The aim of such a study would be to re-visit the hemostatic management algorithms and provide new concepts consisted of bundle of hemostatic strategies encompassing measures in pre- , intra- and postoperative period.

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