

## EDITORIAL

### Fibrinogen Supplementation in Cardiac Surgery: Where Are We Now and Where Are We Going?

**T**HIS ISSUE OF THE *Journal of Cardiothoracic and Vascular Anesthesia* includes 2 interesting contributions focused on fibrinogen levels after coronary artery bypass grafting (CABG) with or without cardiopulmonary bypass (CPB)<sup>1</sup> and on fibrinogen supplementation after complex cardiac surgery (CABG plus valve surgeries or ascending aorta surgeries).<sup>2</sup> Momeni et al,<sup>1</sup> in an elegant study, including conventional coagulation tests and point-of-care (POC) tests (Multiplate, Verum Diagnostica GmbH, Munich, Germany and ROTEM, Tem International GmbH, Munich, Germany), found that patients undergoing CABG with CPB exhibited significantly lower values of fibrinogen during and after the surgeries compared with patients treated off-pump. In addition, they found that the values of fibrinogen obtained with the FIBTEM test using the ROTEM system correlated well with the conventional Clauss measurement.

Bilecen et al<sup>2</sup> investigated the effects of fibrinogen supplementation on a series of patients who underwent complex cardiac surgery, comparing them with a propensity-score selected patient population. They did not observe any effect of fibrinogen supplementation on decreased postoperative blood loss or allogeneic blood product transfusion containment. However, as the investigators admitted, the study was not randomized, the fibrinogen dose was lower (1-2 g in 60% of patients) than the dose reported by other investigators (often reaching 6-7 g), and the decision of giving fibrinogen and the dose used were not guided by the measurement of the fibrinogen level.

Fibrinogen supplementation in cardiac surgery is certainly one of the "hot topics" of the moment. Fibrinogen concentrate currently is not available in the United States for acquired bleeding, and in Europe its use greatly varies among the different countries. In Germany, Austria, Switzerland, the Netherlands, and other countries, fibrinogen concentrate is considered the standard of care for fibrinogen supplementation in acquired bleeding.<sup>3</sup> Conversely, in the United Kingdom and the United States, it is approved for use only in congenital fibrin-

ogen deficiency, and clinicians rely on fresh frozen plasma (FFP) and cryoprecipitates for the treatment of acquired bleeding.<sup>3</sup>

As a consequence of this discrepancy among licenses, guidelines, and clinical use, fibrinogen supplementation remains a matter of debate. There are open issues and gaps in knowledge to be addressed, including the behavior of fibrinogen levels during and after cardiac surgeries, the relation between low fibrinogen levels and postoperative bleeding, the most convenient way for measuring fibrinogen levels, the adequate dose for fibrinogen supplementation, and the efficacy and safety of fibrinogen concentrate supplementation.

#### FIBRINOGEN LEVELS IN CARDIAC SURGERY

Fibrinogen is the precursor of fibrin, and adequate levels of fibrinogen are fundamental for achieving correct clot firmness through the interaction between fibrin and platelets. During major acquired bleeding in the surgical or trauma setting, fibrinogen is the first coagulation factor to reach critical levels.<sup>4,5</sup> In the specific setting of cardiac surgery, the changes of fibrinogen and other coagulation factors during and after the surgery were investigated by Ternström et al.<sup>6</sup> In a series of 57 patients with CABG and after adjustment for hemodilution, the investigators observed a 14% decrease of fibrinogen levels after 2 hours from the completion of the surgery and a rebound to a value 45% higher than baseline after 24 hours. In their study, in which the fibrinogen values were not adjusted for hemodilution, Momeni and associates<sup>1</sup> found a greater decrease of 44% after 4 hours from the completion of surgery. When the length of CPB is prolonged, as for complex cardiac surgical cases, fibrinogen levels appear consistently lower immediately after

CPB, with a decrease from baseline values reported in the range of 40%.<sup>7,8</sup>

#### FIBRINOGEN LEVELS AND BLEEDING IN CARDIAC SURGERY

The decrease of fibrinogen levels after CPB should be seen within the context of postoperative bleeding. Actually, and with the only exception of factors VIII and IX,<sup>6</sup> this happens to all coagulation factors owing to hemodilution and consumption. However, Ternström et al<sup>6</sup> found that only the decreases in fibrinogen and factor XIII were associated with postoperative bleeding, suggesting that bleeding, in this setting, is more related to clot firmness than to thrombin generation.

Other studies have found a correlation between low preoperative and postoperative fibrinogen levels and the chest tube output after cardiac surgery.<sup>9,10</sup> Therefore, it can be affirmed that there is a sound rationale for the hypothesis that fibrinogen supplementation may be effective in preventing and treating postoperative blood loss in cardiac surgery.

#### FIBRINOGEN LEVELS MEASUREMENT: CONVENTIONAL VERSUS POC TESTS

Traditionally, fibrinogen levels have been measured with the Clauss method,<sup>11</sup> using automated coagulation analyzers based on 2 different principles (photometric and mechanical detections of fibrin formation).<sup>12</sup> More recently, fibrinogen measurement has been proposed using POC tests based on the viscoelastic properties of the clot (thromboelastography and thromboelastometry). These tests provide a measurement of clot firmness, expressed as maximum amplitude in thromboelastography and maximum clot firmness (MCF) in thromboelastometry. These measurements represent the interaction of fibrin with platelets in generating clot firmness; therefore, they need to be modified by the elimination of the platelet contribution to estimate correctly the relative contribution of fibrinogen to clot firmness. This is obtained by blunting the platelet aggregation through the addition of abciximab in the thromboelastographic functional fibrinogen test or cytochalasin D in the thromboelastometric FIBTEM test.

These 2 POC tests have shown a good correlation with the standard Clauss determination of fibrinogen levels.<sup>13-17</sup> However, the functional fibrinogen test consistently seems to provide higher values of clot firmness than the FIBTEM test.<sup>13,17</sup>

The functional fibrinogen and FIBTEM tests can provide a rapid POC evaluation of fibrinogen levels, and their role in the setting of acquired bleeding diagnosis and treatment in cardiac surgery seems well established.<sup>18,19</sup>

#### FIBRINOGEN SUPPLEMENTATION: WHICH DOSE?

In surgical bleeding, fibrinogen supplementation is suggested when the values decrease to <1.0-2.0 g/L.<sup>20-22</sup> In cardiac surgery, higher target values (4.0 g/L) have been suggested.<sup>23</sup>

When using POC tests to assess fibrinogen levels, the maximum amplitude or MCF often is used to establish the correct dose of fibrinogen concentrate to administer, and an MCF target value of 22 mm has been suggested.<sup>22</sup> This value corresponds to a fibrinogen level of about 3.6 g/dL, higher than what

has been suggested for the correction of surgical bleeding but still within the normal range.

As a matter of fact, many patients, especially after complex cardiac surgical procedures with prolonged CPB, exhibit MCF values around 10-12 mm, as shown even in the study by Momeni et al.<sup>1</sup> Because increasing the MCF value of 1 mm in a 70-kg patient requires about 0.5 g of fibrinogen concentrate,<sup>24</sup> this approach usually leads to the administration of large doses (5-6 g) of fibrinogen concentrate. Actually, most studies dealing with fibrinogen supplementation in cardiac surgery have reported a fibrinogen concentrate dose of 6-7 g.<sup>8,24</sup> In their study, Bilecen et al<sup>2</sup> used lower doses of fibrinogen concentrate, and this could be a reason for their negative findings.

Overall, a convincing dose-finding study for fibrinogen concentrate supplementation remains to be published, and there is a great need for achieving this piece of information. Efficacy, safety, and costs are pending issues related to the correct dose of fibrinogen concentrate.

#### EFFICACY AND SAFETY OF FIBRINOGEN CONCENTRATE

Recent studies,<sup>8,22-25</sup> including some randomized controlled trials, have shown a beneficial effect of fibrinogen supplementation after CPB in cardiac surgical patients regarding decreased bleeding and a lesser need for transfusions. However, different findings have been reported.<sup>2</sup> The main point of discussion probably is the source of fibrinogen supplementation, rather than its role in controlling postoperative bleeding.

In cardiac surgery, the replacement of coagulation factors with FFP or cryoprecipitates is a well-established strategy and supported by the existing guidelines.<sup>26</sup> FFP is easily available and relatively inexpensive; however, to guarantee a fibrinogen dose of 1 g, up to 4 U of FFP is required; therefore, to reach the large dose of fibrinogen used in the existing positive trials on fibrinogen supplementation, large volumes of FFP are required, leading to the risk of volume overload. Cryoprecipitates are no longer available in many European countries because of safety concerns.<sup>27</sup> Given the present scenario, and considering the need for further randomized controlled trials in cardiac surgery, the role of fibrinogen concentrate to correct acquired hypofibrinogenemia and bleeding appears attractive.

Most existing studies, including the study published in this issue of the *Journal of Cardiothoracic and Vascular Anesthesia*, have not raised concerns about the safety of fibrinogen concentrate supplementation. There is only one retrospective study<sup>28</sup> published in an open-access journal not indexed in PubMed reporting an increased rate of thromboembolic events in cardiac surgical patients treated with fibrinogen.

Differently from other drugs and blood components, which act by increasing thrombin generation (prothrombin complex concentrates, recombinant activated factor VII), fibrinogen concentrate acts downstream of thrombin generation by increasing clot firmness. This peculiar effect may be less deleterious for thromboembolic complications. However, high fibrinogen concentrations have been associated with an increased prevalence of coronary artery disease.<sup>29</sup> and more data on the safety of the use of (large) doses of fibrinogen concentrate should be collected.

### CLINICAL PERSPECTIVE AND FUTURE DIRECTIONS

Clot firmness is the result of an interaction between platelets and fibrin. Conditions characterized by a low platelet count or function result in decreased clot firmness. It has been hypothesized that, under these circumstances, increasing the level of fibrinogen may help compensate for the poor platelet contribution to clot firmness. Velik-Salchner et al,<sup>30</sup> in a swine model, found that fibrinogen administration in thrombocytopenic animals was more effective than platelet transfusion in restoring clot firmness according to the FIBTEM test, and a similar effect was observed by Lang et al<sup>31</sup> in platelet-depleted plasma from healthy volunteers. Platelet dysfunction after CPB, as detected by multielectrode aggregometry, resulted in a decreased clot firmness that was corrected successfully with fibrinogen concentrate in a recent study.<sup>32</sup>

The current era is dominated by the use of antiplatelet agents in patients with ischemic cardiac disease, and the standard of care has moved from the use of aspirin toward the application of double antiplatelet therapy. The first generation of thienopyridines included ticlopidine and clopidogrel, which partly

have been replaced by the new generation of P2Y<sub>12</sub> platelet receptor inhibitors, prasugrel and ticagrelor. The discontinuation of these agents is suggested before cardiac surgeries,<sup>26</sup> because whenever patients undergo surgery under the effects of these drugs, an increase in postoperative bleeding is anticipated. Data on the use of fibrinogen in postoperative bleeding related to drug-induced platelet dysfunction are lacking, but this area may represent an interesting field for future studies.

As a confirmation of the interest in fibrinogen therapy in the prevention and treatment of postoperative bleeding in cardiac surgery, currently there are 5 ongoing randomized controlled trials investigating this drug in adult cardiac surgical patients (<http://ClinicalTrials.gov> identifiers: NCT01283321, NCT01471730, NCT00968045, NCT01623531, NCT01124981). Once completed, these trials probably will answer many of the questions discussed in this editorial.

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