Haemostatic frailty is an important factor affecting cardiac surgical patients’ outcome

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During the 20th century the average life expectancy almost doubled so the number of elderly people living on Earth is rapidly increasing. However, only one third of people are aging successfully, i.e. they remain healthy.1 Others gradually acquire diseases such as hypertension, coronary heart disease, diabetes, lung and kidney diseases or osteoarthritis. Two or more concomitant diseases are present in more than one third of individuals older than 65 years and in more than two thirds of those older than 80 years.2

The functional capacity of bodily organs is steadily decreasing due to aging as well as due to the impact of acquired diseases. It is known that approximately only one third of organ capacity is mostly sufficient for normal living.3 As the functional reserve diminishes, any imposed challenge going beyond usual demand can exceed the capacity for coping and recovery.

In addition, some aging people are also going to be frail. It is estimated that 7% of the US population older than 65 years and 30% of octogenarians are frail.4 Frailty is a consequence of decline in overall function and physiologic reserves and of dysregulation of bodily functions. It is associated with age and comorbidity, but not caused by them - frailty is not an inevitable part of old age nor of cumulative chronic disease.5 The exact cause of frailty is not fully elucidated yet, chronic inflammation may be involved among others.

Frailty is characterized by vulnerability to acute stressors.6 Frail patients have a reduced ability to maintain homeostasis in the face of acute stress. Patients with cardiovascular disease have a higher incidence of frailty than individuals of equal age without such a disease. Frailty, as defined by the Cardiovascular Health Study criteria,4 was observed in 20% of older patients (≥65 years) undergoing percutaneous coronary interventions7 and 27% of older patients (≥70 years) with serious coronary artery disease at cardiac catheterization.8

Generally, frailty predicts death, disability and adverse outcomes. For instance, Dasgupta et al.9 have shown in non-cardiac (mostly orthopedic) surgery that increasing frailty defined using Edmonton Frail Scale was associated with postoperative complications (p=0.02), increased length of hospitalization (p=0.004) and inability to be discharged home (p=0.01), independently of age. They conclude that a frailty screen can refine risk estimates of postoperative complications in older adults undergoing elective non-cardiac surgery.9 However, there are no studies examining the impact of frailty in cardiac surgery yet.

Frailty refers not only to factors defining this syndrome, such as weight loss, fatigue, weakness, low activity, slow motor performance, balance and gait abnormalities. Frailty is reflected in blood coagulation as well. Frailty is also characterized by increased inflammation and elevated markers of blood clotting and these changes persist regardless of diabetes and cardiovascular disease.10

There are many changes in blood coagulation, anticoagulation and fibrinolysis associated with aging. Their detailed description can be found elsewhere in the literature.11,12 Briefly, older patients tend to be hypercoagulable with impaired fibrinolysis. Thus, they are more threatened by thrombosis. In frail patients these changes are more expressed. For instance, in a study of 4735 community-dwelling adults 65 years and older, who were
participants of Cardiovascular Health Study, frail, intermediate, and nonfrail subjects were identified by a validated screening tool and exclusion criteria. Comparing frail vs. nonfrail subjects, frail individuals had increased mean +/- SD levels of C-reactive protein (5.5 +/- 9.8 vs. 2.7 +/- 4.0 mg/L), factor VIII (13 790 +/- 4480 vs. 11 860 +/- 3460 mg/dL), and, in a smaller subset, D dimer (647 +/- 1033 vs. 224 +/- 258 ng/mL) (P< or =.001 for all, chi² test for trend). These differences persisted when individuals with cardiovascular disease and diabetes were excluded and after adjustment for age, sex, and race.

We have studied the association between age and coagulation in cardiac surgical patients using thromboelastography (TEG). In a study population of 303 patients (227 men [74.9%] and 76 [25.1%] women, mean age 60 ± 11 (median 63, range 21-78) years) TEG was performed before and after cardiopulmonary bypass (CPB) after heparin neutralization with protamine.

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>R (mm)</th>
<th>K (mm)</th>
<th>ALFA (deg)</th>
<th>MA (mm)</th>
<th>Ly30 %</th>
<th>Ly60 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before CPB</td>
<td>≤ 65</td>
<td>31.5</td>
<td>16.3</td>
<td>32.4</td>
<td>52.6</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>&gt; 75</td>
<td>24.7</td>
<td>14.6</td>
<td>37.9</td>
<td>54.0</td>
<td>2.1</td>
</tr>
<tr>
<td>After CPB</td>
<td>≤ 65</td>
<td>22.7</td>
<td>11.2</td>
<td>44.4</td>
<td>52.9</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>&gt; 75</td>
<td>21.3</td>
<td>7.9</td>
<td>46.4</td>
<td>55.4</td>
<td>2.3</td>
</tr>
</tbody>
</table>

R denotes reaction time, K coagulation time, both with the tracing speed 2mm/min. ALFA is the coagulation angle characterizing the speed of clot formation. MA, maximum amplitude, is the maximum width of the TEG trace representing the strength of the blood clot. Ly30 and Ly60 are decrements of the TEG amplitude 30, resp. 60 minutes after the MA, expressed as the ratio of MA in %. Fibrinolysis is defined as Ly30 ≥ 7.5% and/or Ly60 ≥ 15%.

Before CPB there was a tendency toward hypercoagulation evident from decreasing values R, K and increasing values ALFA and MA as well as to an impaired fibrinolysis defined by slightly lower values of Ly30 and Ly60 in older patients. After CPB the coagulation was activated with a more pronounced fibrinolysis in both age groups as reflected by shorter R and K values as well as by higher Ly30 and Ly60 than before CPB. In addition, when patients from this study population were divided according to the presence of fibrinolysis defined by the value of Ly30 ≥ 7.5%, fibrinolytic patients were older than nonfibrinolytic (63.4 ± 7.5 vs. 59.5 ± 11.1 years; P = 0.05). Fibrinolysis might not be associated with increased blood loss because it can easily and readily be treated by tranexamic acid.

In a study of 142 patients undergoing heart surgery using cardiopulmonary bypass we have investigated a postoperative course in fibrinolytic and nonfibrinolytic patients diagnosed by TEG. Using the same definition 20 patients (13.9%) were fibrinolytic. These patients tended to be older. Their blood loss in the first 12 hours after the surgery was comparable to non-fibrinolytic patients (499 ± 301 ml vs. 444 ± 201 ml) because fibrinolysis was immediately and efficiently corrected by tranexamic acid. However, their mortality was higher (3/20 vs. 0/123; P 0.002), the volume of colloids administered was higher (1784 ± 707 vs. 1338 ± 791; P 0.03) as well as the rate and duration of norepinephrine support needed due to the low systemic vascular resistance (8/20 [40%] vs. 22/122 [18%]; P 0.02, resp. 80.4 ± 62.9 hours vs. 29.7 ± 21.3 hours; P 0.02). We have concluded that fibrinolysis, although easily and readily corrected, is associated with a worse outcome.

Higher volume requirements together with lower systemic vascular resistance may also naturally lead to an increased transfusion rate. Furthermore, older patients tend to be anemic and red blood cell mass has lesser redundancy than most of other bodily functions (roughly one third, as noted above). It is generally acknowledged red blood cells transfusions are associated with mortality and significant morbidity, even up to 5 years. If fibrinolysis is
assumed to be a marker of more pronounced inflammatory reaction then it is conceivable transfusion can enhance it further and contribute to the development of complications. Indeed, Whitson et al.\textsuperscript{17} have demonstrated in a Society of Thoracic Surgeons’ database of 2691 patients undergoing coronary artery bypass and/or valve operations between 2000 and 2005 that patients requiring transfusion (64%) were older (mean 65.2 vs. 61.2 years, p < 0.001) and like others confirmed that perioperative blood transfusion was associated with increased postoperative complications (53.5% vs. 30.5%, p < 0.001) and increased operative mortality (3.4% vs. 1.7%, p = 0.005). In the following similar study the same authors have found infectious complications and organ dysfunction were independently associated with total blood product transfusion; the inflection point ascertained by ROC analysis was 5.5 units (sensitivity 73%, specificity 64%). For mortality, the inflection point was a transfusion of 7.5 units of total blood products (sensitivity 73%, specificity 71%).\textsuperscript{18} This was also corroborated by others.\textsuperscript{19,20}

In conclusion, hemostatic frailty in elderly cardiac surgical patients defined by an activated coagulation leading to higher susceptibility to thrombosis together with a more readily developing compensatory secondary fibrinolysis resulting in circulatory instability and prompting more aggressive circulatory support using volume and/or vasoconstrictive agents and perhaps transfusion may certainly negatively influence their outcome. Therefore, further research of these mechanisms is warranted. In addition, the indication of surgery in these frail patients should be set carefully.

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