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EDITORIAL

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Vasovagal fainting as an evolutionary remnant of the fight against hemorrhage

Major bleeding is one of the most frequently occurring medical conditions that require the attention of physicians and surgeons. The most frequent causes of major bleeding in most hospitals are trauma, peri-operative bleeding (which can in fact be viewed as a variant of trauma), gastro-intestinal disease, and bleeding due to the use of anticoagulant agents [6].

Severe hemorrhage leads to an insufficient circulation and an inadequate supply of oxygen to tissue. Patients with serious bleeding often present with circulatory shock and collapse. Impaired brain perfusion and subsequent syncope seems an understandable sequence of events following a severe drop in systemic blood pressure as a consequence of acute blood loss.

However, it is intriguing to speculate whether syncope may not only be a logical consequence of major hemorrhage but can rather be viewed as a response with distinct protective effects for the organism and as such has been carefully preserved as a beneficial mechanism throughout the evolution. In this issue of *Clinical Autonomic Research*, Dr. Diehl proposes an interesting explanation for the occurrence of vasovagal syncope, as a mechanism that was originally developed as a protective strategy against exsanguination upon major bleeding in mammals [3]. Dr. Diehl hypothesizes that low blood pressure and bradycardia that is associated with vasovagal syncope is beneficial for the organism that is threatened by ongoing major blood loss, when the initial physiological and compensatory responses, such as vasoconstriction and tachycardia, have failed. Indeed, a low blood pressure is likely to result in reduced blood loss during major hemorrhage and clinical studies indeed suggest that to strive for normalization of blood pressure in patients with trauma and serious bleeding by large volume intravenous infusion may do more harm than good [7]. Based on this notion, strategies that employ permissive hypotension awaiting further medical intervention are currently being investigated [8].

Dr. Diehl's hypothesis is interesting and thought-provoking and is indeed supported by various physiological and clinical observations. As the author himself indicates, the hypothesis can be challenged by experimental studies in bleeding animals. In addition to this, we must also identify a mechanism by which fainting would not only be beneficial to slow the rate of bleeding but may be helpful in arresting the blood loss. The answer to this question may be found in the response of the coagulation system to circulatory collapse. Fainting leads to an immediate and marked increase in von Willebrand factor (and associated factor VIII), presumably due to release from Weibel Palade bodies in endothelial cells of the vessel wall [2]. Interestingly, post-fainting blood not only has a four-fold higher concentration of von Willebrand factor, but also the released von Willebrand factor occurs in unusually large multimers, which are known to be hemostatically much more potent than normal von Willebrand factor multimers. Under normal circumstances the constitutive release of large von Willebrand factor multimers is followed by enzymatic degradation by the von Willebrand factor cleaving protease (ADAMTS-13) [9]. It may be hypothesized that the immediate release of large amounts of von Willebrand factor as induced by fainting does not allow this cleaving protease to act properly, leaving the large multimers for

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a large part intact. Large multimers of von Willebrand factor can bind more efficiently to the glycoprotein Ib receptor at the platelet membrane, presumably because the binding site of von Willebrand factor for this adhesion receptor is more effectively exposed [4], and this will importantly stimulate platelet adhesion to the vessel wall at the site of bleeding and the initiation of the formation of a hemostatic plug. Hence, the quantitative and qualitative effect of fainting on von Willebrand factor will lead to a considerable pro-hemostatic response, which will lead to stimulation of hemostatic plug formation, which will further facilitate activation of the coagulation response. The mechanism by which fainting leads to release of von Willebrand factor from its endothelial storage sites is not completely clear, but it is likely that adrenergic responses are important [10]. Interestingly, beta-blockade has indeed been shown to lower plasma von Willebrand and factor VIII levels in a recent study [5].

Hence, the fight against life-threatening hemorrhage may indeed be the evolutionary background for vasovagal fainting and may have been a meaningful protective mechanism. In line with this hypothesis, Dr. Diehl also suggests that emotional or centrally induced syncope can be viewed as an evolutionary remainder of the original response towards bleeding. This may indeed be true, but as in that particular situation the benefit of fainting is much less clear and a collapse may in fact be to the disadvantage of the organism, this may be regarded as a situation where evolution has resulted in a mechanism that in our circumstances is less relevant or even harmful. A similar situation can be seen with the variety of physiological mechanisms that were very useful in the past to protect against peri-partum hemorrhage, but which in our modern times have lost their protective significance and rather contribute to thrombosis [1].

In conclusion, the hypothesis that fainting is not a mere consequence of bleeding but may be beneficial for the organism fighting severe hemorrhage is supported by a number of observations. Collapse may not only slow bleeding but also seems to evoke a potent response from the coagulation system, that may be helpful in arresting blood loss. It is tempting to speculate that this insight may be helpful in better managing patients with circulatory shock (for example by developing resuscitation strategies that permit a degree of hypotension) or in patients with emotional syncope.

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