secondary thromboprophylaxis via indefinite anticoagulation.

Additionally, PTS, as defined by a Modified Villalta Scale (MVS) score >1, was very common; nearly half of patients in the cohort met this criterion. PTS onset and progression were confirmed to be indolent, over the course of years, with earliest onset occurring in the non-LR group, for which median time to detection was 2.0 years after diagnosis compared with 10.5 years for the neonatal LR group. Notably, >95% of cases were classified as mild by the MVS classification, with no cases of severe PTS or skin ulceration. How clinically significant were these cases of so-called “mild” PTS? On the one hand, some evidence suggests that mild PTS may not measurably detract from quality of life. Conversely, the possibility that the MVS may not adequately discriminate PTS that is clinically important or that does impact meaningfully on quality of life, should be considered. For example, the MVS does not uniformly assess for severity of individual signs and symptoms of PTS but merely their presence or absence for most of the scoring components. To illustrate, a child with severe chronic pain or swelling from PTS could still exhibit an MVS score that tallies as only “mild” despite the significant symptom severity.

The study results highlight additional areas deserving further attention. In the final analysis, the apparent lack of association between more intensive treatment (ie, thrombolysis) and PTS outcome in this cohort is notable in light of limited pediatric data and the more extensive adult experience supporting the efficacy of catheter-directed thrombolysis in reducing PTS risk. Results from completed adult (#NCT00790335) and planned pediatric (#NCT02767232) trials are expected to provide more definitive guidance on this point. Furthermore, the high rate of inadequate thrombus resolution (>25% of patients with clot extension or no resolution) underscores the need for identifying more effective DVT treatment approaches. Finally, a standardized, well-validated PTS assessment tool that can easily incorporate into clinical practice is another need. The ideal tool will identify clinically important PTS and track severity of distinct signs and symptoms over time. Such future development requires concurrent quality of life assessment using appropriate instruments and studies of the economic impact of PTS, so that the effects of this potentially burdensome disorder can be more completely understood in children.

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### THROMBOSIS AND HEMOSTASIS

**Comment on Deguchi et al, page 1870**

**Adding some muscle to blood coagulation**

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In this issue of *Blood*, Deguchi et al have established a mechanism by which skeletal muscle promotes thrombin generation through binding of factor Xa and factor Va to myosin.1

A procoagulant effect of muscle has been reported in the surgical literature going back to the start of the 20th century. Surgeons reported using muscle grafts to control troublesome bleeding. For example, in 1935, Howard Clute wrote that “It has been repeatedly demonstrated to me that troublesome bleeding may be readily stopped by the use of free muscle grafts.” Muscle was found to be more effective at stopping oozing than fat or fascia.

Had I been asked about the mechanism by which muscle grafts promote hemostasis, I would have speculated, incorrectly, that the damaged muscle might present an appropriate lipid surface for coagulation. Lipids surfaces have been thought to be the dominant surface on which coagulation occurs since Chargaff et al showed that the procoagulantly active component of platelets could be found in the lipid extract and not in the defatted protein. This idea was further strengthened when the group from Maastricht showed in the 1980s that one specific lipid, phosphatidylserine, is essential for lipid surface activity of the IXa/VIIa and Xa/Va complexes.4
Deguchi et al came at the problem from a different direction. They previously reported in an abstract at the American Society of Hematology meetings that polymorphisms in the myosin gene could be found in patients with recurrent venous thromboembolism.\(^5\) Deguchi et al follow up on that observation with the studies reported in the current issue of *Blood*. Through direct binding studies, Deguchi et al establish that factor Xa and Va can bind to myosin. Through thrombin generation assays, they establish that this binding can result in prothrombin activation. Thus, as shown in the figure (taken from Deguchi et al), a functional prothrombinase complex can be formed on isolated myosin without a lipid surface. This finding establishes that it is biochemically possible for myosin to promote thrombin generation.

However, there are many reactions that are biochemically possible without being physiologically relevant. Deguchi et al go on to use whole blood flow assays that monitor platelet and fibrin deposition to show that myosin actively promotes thrombus formation. They also show that antibodies against myosin can block thrombin generation. They used these antibodies to study thrombin generation in plasma from trauma patients. Anti-myosin antibodies decreased thrombin generation in patients from these trauma patients more than thrombin generation in plasma from nontrauma patients. This result suggests that circulating myosin from damaged muscle might contribute to the thrombotic risk seen in some trauma patients. This result also suggests the possibility that antibodies or small molecules that target the myosin binding site have potential as antithrombotic therapies.

In addition to the insight that this paper gives us regarding a possible antithrombotic target to help trauma patients, the work of Deguchi et al adds to our understanding of how surfaces other than phospholipids can contribute to hemostasis at sites of injury. Factor IX binds tightly and specifically to the structural protein collagen IV; this binding has been implicated in promoting hemostasis. The inorganic polymer polyphosphate has been shown to bind factor XI and thrombin, leading to factor XI activation.\(^7\) Deguchi et al showed that, in a purified system with added factor Xa and factor Va, myosin, a structural protein, has as much activity as an equimolar amount of lipid. Future studies in complex systems like whole blood and in animal models will establish the relative contribution of myosin to in vivo hemostasis and thrombosis. At the very least, these studies may increase the surgical awareness of an old technique that still holds relevance in our current era.\(^8\)

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