Preface

Hemostasis in Exercise and the Athlete

Murray J. Adams, BSc(Hons), PhD, MAIMS, FFSc(RCPA)[1] James W. Fell, BEd, MPhil, PhD[2]

[1] School of Veterinary and Life Sciences, Murdoch University, Murdoch, WA, Australia
[2] School of Health Sciences, College of Health and Medicine, University of Tasmania, Launceston, TAS, Australia

Semin Thromb Hemost 2018;44:707–709.

We are thrilled to bring you this cross-disciplinary special issue of *Seminars in Thrombosis and Hemostasis*. This issue focuses on two specific aspects of hemostasis and exercise: (1) how exercise affects the hemostatic system in healthy individuals, including professional and well-trained athletes, and (2) the effects of exercise on patient groups with hemostatic abnormalities, including thrombotic and bleeding disorders, in improving overall health and lifestyle. Paradoxically, the issue's focus on healthy and trained athletes explores the risks of hemostasis associated with exercise, while for patient groups, it is the benefits of exercise that unites the authors in this issue, with constructive recommendations for promoting exercise participation in these groups.

It is well known that physical activity is beneficial for health and can lower the risk of cardiovascular disease[1–3]; however, vigorous exercise is associated with thromboembolic and sudden cardiac events, particularly in untrained individuals. Exploring the concept of transitioning from risk to benefit, in the first review of this issue (by van der Vorm et al),[4] the authors provide an overview of existing literature on how training programs and training status influence hemostasis in healthy individuals. Furthermore, pilot study data are presented describing the effects of repetitive submaximal intensity cycling on procoagulant and anticoagulant processes in physically fit individuals.

This is followed by a series of chapters focusing on hemostatic issues in well-trained or professional athletes. Traditional "at-risk" groups such as those with malignancy, genetic, and acquired risk factors are often at risk due to one or more contributing factors identified from Virchow's triad.[5] Similarly, athletes are also exposed to various training, competition, and career-related challenges that might contribute to the risk factors identified by Virchow.[5] Zadow et al initially reviews the acquired thrombotic risk factors that are specific to the athlete.[6] Various repetitive forms of exercise, dehydration, and prolonged travel, especially in combination, represent significant athlete-dependent risk factors to athletes, particularly in the development of venous thromboembolism (VTE).

Anabolic androgenic steroid (AAS) use is suggested by Zadow et al[6] as one of the risk factors for athletes, so it is fitting that the next review by Chang et al[7] critiques the potential associations between AAS abuse and risk of thrombosis. The side effects of AAS are well described[8–10]; however, there are limited studies that describe the effects on the hemostatic system by these agents. From those studies that have been published, there is evidence to suggest that AAS abuse is associated with a significant risk of thrombosis, although improvements in study design to establish a clear causal relationship between AAS abuse and risk of thrombosis are required. How future prospective studies are designed, particularly in consideration of human ethics, to further explore these affects will be challenging.

The first full original study in this issue (by Lippi et al)[11] investigated the acute effects of middle-distance endurance running (half-marathon: 21.1 km) on blood coagulation parameters in 33 middle-aged male athletes. The study investigated changes to hemostasis before, immediately after the run, and 3 hours after run completion. Several prothrombotic changes in blood coagulation markers were observed after the run, including increases in prothrombin time, D-dimer, von Willebrand factor antigen, and factor VIII (FVIII), as well as a significant reduction in the activated partial thromboplastin time. These changes implicate an increased risk of thrombotic events in participants undertaking a half marathon.

Following on from the study of the effects of running on hemostasis, the next review by Kupchak[12] explores more deeply another factor that may impact on the risk of thrombosis in athletes, air travel. Exercise[13–15] and air travel[16,17] have independently been shown to increase the risk of thrombosis; however, few studies have investigated these in combination. The amount of air travel undertaken by

Address for correspondence Murray J. Adams, BSc(Hons), PhD MAIMS, FFSc(RCPA), School of Veterinary and Life Sciences, Murdoch University, 90 South Street, Murdoch, WA 6150, Australia (e-mail: M. Adams@murdoch.edu.au).

Issue Theme Hemostasis in Exercise and the Athlete; Guest Editors: Murray J. Adams, BSc(Hons), PhD, MAIMS, FFSc(RCPA) and James W. Fell, BEd, MPhil, PhD.

DOI https://doi.org/10.1055/s-0038-1675169.
ISSN 0094-6176.

competitive athletes, including long-haul flights (> 6 hours duration), have risen considerably in the last few decades, alongside increasing reports in the popular press of VTE occurring in athletes. The combination of exercise and air travel along with other risk factors such as dehydration, repetitive trauma, and injury, compounded by other factors such as use of oral contraceptives in females, or hereditary thrombophilia, may be a considerable contributing factor to VTE occurrence in a small number of susceptible athletes who regularly travel to train or compete.[12,16,17]

In contrast to the potential risk presented for higher trained competitive athletes, Evensen et al[18] review the effects of regular physical activity on overall risk of VTE and VTE-related complications. Despite a considerable amount of published research, the authors suggest that a clear association between physical activity and risk of incident VTE has yet to be thoroughly established, with evidence suggesting that physical activity has a beneficial effect on the risk of VTE, but not in a dose-dependent manner. The authors suggest that this may be due to methodological challenges related to research on physical activity, such as standardized assessment of physical activity, and sources of bias in previous studies, but also raises the question as to whether higher levels of training undertaken by elite and professional athletes may be an additional thrombotic risk factor not often considered.

Beyond a focus on the risk of VTE in athletic populations, the general consensus is that physical activity should be promoted for maintenance of health and disease; however, the risk of adverse events such as sudden death still exists. The review in this issue of the journal by Lippi et al[19] highlights that although the overall risk of sudden death in athletes is low, and comparable to the general population, up to 20% of sudden deaths occur during exercise. Frustratingly, recent research highlights the difficulty of identifying all at-risk individuals with underlying disorders such as hypertrophic cardiomyopathy and coronary artery disease, despite routine electrocardiographic and echocardiography screening.[20] However, the authors of this review recommend that individuals, particularly those at risk, who want to undertake moderate to high-intensity exercise undergo preparticipation screening and regular follow-up with their general practitioner or an accredited exercise physiologist to help reduce this risk wherever possible.

The next series of reviews focus on the use and role of exercise in patient groups with hemostatic disorders, including recommendations for safe and beneficial participations. The first is by Zetterberg et al,[21] who discuss the advantages and disadvantages of exercise in people with hemophilia. Traditionally, exercise has not been recommended for these individuals; however, randomized trials suggest that people with hemophilia do benefit from exercise through improved muscle function, endurance, and, very importantly, quality of life. Furthermore, there is evidence to suggest that exercise increases FVIII:C levels in healthy controls and patients with mild and moderate hemophilia, and that this increase was correlated with exercise intensity, further justifying potential benefits.

If exercise is likely to be beneficial for people with hemophilia, then what about other bleeding disorders? The next review by Franchini et al[22] explores the impact of exercise in people with other congenital bleeding disorders, with a focus on the rarer causes. Although there are limited studies investigating the impact of exercise in rare congenital bleeding disorders, it is likely that a similar approach be applied to these individuals as for those with hemophilia. This needs to be considered with caution as these disorders are less well studied, are heterogeneous in terms of clinical phenotype (compared with hemophilia), have a higher incidence of hemarthrosis in some and not others, and do not necessarily have prophylaxis that is practicable or available.

The next chapter from Hvas[23] reviews evidence of the influence of exercise on platelet function in patients at risk of arterial diseases. There are conflicting findings in various studies with some reporting patients having increased platelet aggregation and/or activation, some with no change, and others with decreased platelet aggregation following exercise, compared with healthy controls. These findings echo the argument presented previously in the issue by Evensen et al[18] in that there is a need for more structured measurement and prescription of physical activity (intensity and duration) in this area of research. It is clear that well-designed, controlled studies on the effect of regular long-term low-intensity exercise are needed to determine the long-term effects of exercise on platelet function.

The final chapter of this issue, by Nazha et al,[24] reviews the current VTE treatment guidelines from the perspective of treating elite athletes. An opinion on the individualized approach to the use of direct oral anticoagulants according to both the pharmacokinetic properties of these drugs as well as the athlete's competitive requirements is also provided. The authors suggest that their proposed risk management approach will allow mitigation against the recurrence of VTE while simultaneously reduce the chance of bleeding associated with injuries due to competition. This helps balance the need of the clinician to protect the athlete but at the same time enable the athlete's need to return to training and competition.

Finally, we thank all the authors of this issue who have shared their expertise across a range of professional and personal experiences. It has been a most interesting and rewarding cross-disciplinary exercise to bring the topics of this issue together. We hope that readers will similarly find something new, interesting, topical, and/or thought-provoking with regard to the effects of exercise on hemostasis, from patients to elite athletes.

Conflicts of Interest
None.

References

1 Lavie CJ, Thomas RJ, Squires RW, Allison TG, Milani RV. Exercise training and cardiac rehabilitation in primary and secondary prevention of coronary heart disease. Mayo Clin Proc 2009;84 (04):373–383

2 Pollock ML, Franklin BA, Balady GJ, et al. AHA Science Advisory. Resistance exercise in individuals with and without cardiovascular disease: benefits, rationale, safety, and prescription: an advisory from the Committee on Exercise, Rehabilitation, and Prevention, Council on Clinical Cardiology, American Heart Association; Position paper endorsed by the American College of Sports Medicine. Circulation 2000;101(07):828–833
3 Shiroma EJ, Lee IM. Physical activity and cardiovascular health: lessons learned from epidemiological studies across age, gender, and race/ethnicity. Circulation 2010;122(07):743–752
4 van der Vorm L, Huskens D, Kicken C, Roest M, de Laat B, Miszta A. Effects of repeated bouts of exercise on the hemostatic system. Semin Thromb Hemost 2018;44(08):710–722
5 Virchow R. Gesammelte Abhandlungen zur Wissenschaftlichen Medicin. Frankfurt: Meidinger Sohn & Co.; 1856 [Reprint edition: Virchow RLK. Thrombosis and Emboli (1846–1856) (translated by AC Matzdorff and WR Bell). Canton, MA: Science History Publications; 1998]
6 Zadow E, Adams M, Kitic S, Wu S, Fell J. Acquired and genetic thrombotic risk factors in the athlete. Semin Thromb Hemost 2018;44(08):723–733
7 Chang S, Münster A-M, Gram J, Sidelmann J. Anabolic androgenic steroid abuse: the effects on thrombosis risk, coagulation, and fibrinolysis. Semin Thromb Hemost 2018;44(08):734–746
8 Bhasin S, Storer TW, Berman N, et al. The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. N Engl J Med 1996;335(01):1–7
9 Forbes GB, Porta CR, Herr BE, Griggs RC. Sequence of changes in body composition induced by testosterone and reversal of changes after drug is stopped. JAMA 1992;267(03):397–399
10 Giorgi A, Weatherby RP, Murphy PW. Muscular strength, body composition and health responses to the use of testosterone enanthate: a double blind study. J Sci Med Sport 1999;2(04):341–355
11 Lippi G, Salvagno G, Tarperi C, et al. Pro-thrombotic state induced by middle-distance endurance exercise in middle-aged athletes. Semin Thromb Hemost 2018;44(08):747–755
12 Kupchak BR. Exercise and air-travel induced alterations in blood hemostasis. Semin Thromb Hemost 2018;44(08):756–764
13 Kupchak BR, Creighton BC, Aristizabal JC, et al. Beneficial effects of habitual resistance exercise training on coagulation and fibrinolytic responses. Thromb Res 2013;131(06):e227–e234
14 Menzel K, Hilberg T. Blood coagulation and fibrinolysis in healthy, untrained subjects: effects of different exercise intensities controlled by individual anaerobic threshold. Eur J Appl Physiol 2011; 111(02):253–260
15 Möckel M, Ulrich NV, Heller G Jr, et al. Platelet activation through triathlon competition in ultra-endurance trained athletes: impact of thrombin and plasmin generation and catecholamine release. Int J Sports Med 2001;22(05):337–343
16 Kuipers S, Schreijer AJ, Cannegieter SC, Büller HR, Rosendaal FR, Middeldorp S. Travel and venous thrombosis: a systematic review. J Intern Med 2007;262(06):615–634
17 Schwarz T, Siegert G, Oettler W, et al. Venous thrombosis after long-haul flights. Arch Intern Med 2003;163(22): 2759–2764
18 Evensen L, Brækkan S, Hansen J-B. Regular physical activity and risk of venous thromboembolism. Semin Thromb Hemost 2018; 44(08):765–779
19 Lippi G, Favaloro EJ, Sanchis-Gomar F. Sudden cardiac and non-cardiac death in sports: epidemiology, causes, pathogenesis, and prevention. Semin Thromb Hemost 2018;44(08):780–786
20 Gerling S, Melter M, Michel H, Gündisch C, Loose O, Krutsch W. To prevent SCD in junior soccer players: screening for coronary abnormalities by echocardiography. Sport-Orthop-Traumatol 2018;34(02):172–173
21 Zetterberg E, Ljungkvist M, Salim M. Impact of exercise on hemostasis. Semin Thromb Hemost 2018;44(08):787–795
22 Franchini M, Fasoli S, Gandini G, Giuffrida A. Impact of exercise/sport on well-being in congenital bleeding disorders. Semin Thromb Hemost 2018;44(08):796–801
23 Hvas A. Influence of exercise on platelet function in patients with cardiovascular disease. Semin Thromb Hemost 2018;44(08): 802–812
24 Nazha B, Pandya B, Spyropoulos A, Kessler C. Treatment of venous thromboembolism in elite athletes: individualized anticoagulation approach. Semin Thromb Hemost 2018;44(08):813–822