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GERIATRIC ANESTHESIA (S AKHTAR, SECTION EDITOR)

Coagulation and Aging: Implications for the Anesthesiologist

Sarina L. Tschan[1] · **Daniel Bolliger**[2]

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Abstract

Purpose of Review This narrative review focuses on aging-related modifications in coagulation resulting in increased thromboembolic and hemorrhagic risk of the elderly. We further discuss the current evidence and emerging data relating the perioperative treatment of elderly patients with antithrombotic therapy.

Recent Findings Relevant changes in all elements of the Virchow's triad can be found with aging. Increased blood stasis due to immobility, progressive endothelial dysfunction with altered microcirculation, elevated concentrations of several coagulation factors, and increased platelet reactivity all lead to a procoagulant state. Elderly people are, therefore, commonly treated with oral anticoagulation and antiplatelet drugs. This antithrombotic therapy might be essentially causative for their increased bleeding risk.

Summary Elderly patients are at increased risk for thromboembolism due to changes in the hemostatic system in combination with frailty and multimorbidity. Both the thromboembolic due to aging and bleeding risk due to antithrombotic therapy need special attention in the elderly surgical patients.

Keywords Aging · Coagulation · Perioperative management · Thromboembolism

Introduction

According to the United Nations' *World Population Prospects 2019*, more than 700 million persons worldwide are older than 65 years of age [1]. This number is expected to double to about 1.5 billion elderly people in 2050 due to advances in science and medicine, meaning that one in six people will be aged > 65 years. Despite the more recent definition of "elderly" currently applied to those aged > 75 years, the increasing elderly population represents a major social, economic, and medical challenge. Of note, the number of elderly patients presenting for surgical interventions will further increase [2]. For the perioperative physician, physical deterioration associated with frailty, multiple comorbidities, and polypharmacy are distinctive features [3•] rendering these patients highly vulnerable in the perioperative period.

Under physiologic conditions, a hemostatic balance is achieved by complex interactions occurring between plasma coagulation proteins and enzymes, platelets, and other cellular elements including the vessel wall, eventually protecting the body from bleeding and inadvertent clot formation. Changes associated with aging might result in shifting this delicate balance towards thrombosis and bleeding disorders. In general, an increased risk of arterial and venous thrombosis has been associated with aging [4, 5 6, 7•]. Due to the increased thromboembolic risk and comorbidities, elderly patients are more commonly treated with anticoagulants and antiplatelet drugs than younger patients. Therefore, elderly patients frequently present with bleeding complications. Both the increased perioperative thromboembolic risk due to procoagulant changes associated with aging and the bleeding risk due to therapeutic interventions against thromboembolism need special attention in elderly patients scheduled for surgical procedures.

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✉ Daniel Bolliger
daniel.bolliger@usb.ch

Sarina L. Tschan
sarinalaura.tschan@usb.ch

[1] Clinic for Anaesthesiology, Intermediate Care, Prehospital Emergency Medicine, and Pain Therapy, University Basel Hospital, Spitalstrass 21, CH-4031 Basel, Switzerland

[2] Clinic for Anaesthesiology, Intermediate Care, Prehospital Emergency Medicine, and Pain Therapy, University Basel Hospital, University of Basel, Spitalstrasse 21, CH-4031 Basel, Switzerland

This review will focus on the aging-related hemostatic changes of coagulation and discuss the comorbidities contributing to an increased risk of thrombosis and bleeding events in the elderly patients. In addition, the current evidence and emerging data relating to the perioperative treatment of elderly patients with anticoagulants are discussed.

Search Strategy

An extensive literature search in PubMed was performed using the following terms: (coagulation) AND (aging); and (coagulation) AND (elderly) AND (perioperative). The search was restricted to clinical studies, clinical trials, meta-analysis, randomized controlled trials (RCT), reviews, and systematic reviews. Only publications in English between January 2000 and March 2021 were included, resulting in the identification of 526 and 611 references, respectively. Publications with potential importance were critically reviewed and eventually included in this publication.

Hemostatic Changes in the Elderly

Hemostasis involves a complex series of procoagulant and fibrinolytic processes controlled by inhibitors and feedback mechanisms [8]. With aging, alterations in the hemostatic balance lead to a tendency towards thrombophilia and an increased risk for thromboembolic events and complications. For many years, the pathogenesis of thromboembolism has focused on the classical Virchow's triad including blood stasis, changes of the endothelium and the vessel walls, and hypercoagulability. Recently, vessel wall alteration, systemic inflammation, and infections with consecutive activation of the coagulation system have been suggested to be the main drivers of thromboembolism. In contrast, stasis might primarily act as a permissive condition rather than as a direct cause. However, relevant changes in all elements of Virchow's triad can be found with aging. First, elderly people are generally frail, have sedentary lifestyles, suffer from diseases that restrict mobility, and might require surgical interventions more often than younger people. All of these factors contribute to immobility and increased blood stasis. Second, aging of the vascular system leads to changes in vessel wall integrity and microcirculation [6]. The latter is aggravated by progressive endothelial dysfunction associated with aging. Such endothelial dysfunction leads to increased vascular permeability, reduced vascular tone, and loss of the endothelium's ability to regulate and control hemostatic processes [8]. Specifically, endothelial expression of von Willebrand factor (vWF), nitric oxide, prostanoids, endothelin-1, and thrombomodulin are altered with aging, generally leading to a procoagulatory state. Such endothelial changes are thought to be important in the development of venous thrombosis in the elderly [9]. Further, an overproduction of reactive oxygen species in red blood cells in the elderly could be involved in the etiology of arterial thrombosis [10]. Finally, it is well established that plasma concentrations of several coagulation factors (F) increase with age, especially evident for fibrinogen, FV, FVII, FVIII, FIX, and FXI (Table 1) [7•, 11]. Recently, the elevation of FVIII, FIX, and FXI have been specifically associated with the increased risk

Table 1 Hemostatic changes with aging

	Change	Estimated magnitude per decade
Procoagulants		
Fibrinogen (FI)	↑	0.8–1 g/l↑
FV	↑	5–10%
FVIII	↑	5–10%
FX	(↑)–↑	0–5%
FXIII	(↑)–↑	0–5%
vWF	↑	10–15%
Anticoagulants		
Protein C/S	↑	NA
Antithrombin	↑ (women)/↓ (men)	+ 10% (women)/ – 10% (men)
Markers of thrombin generation		
D-dimer	↑↑	10–20%
Platelets		
Platelet count	↔	–
Aggregation to ADP or collagen	↑	NA

ADP adenosine-di-phosphate, *NA* not available, ↑ increased, ↓ decreased, ↔ unchanged. Table adapted after [5, 12, 13, 80]

of venous thromboembolism in the elderly [7•]. Some of these coagulation factors (i.e., fibrinogen or FVIII) act as acute phase proteins, and their elevated levels can be attributed to a low-grade chronic inflammatory state in elderly patients [6]. Regarding age-associated changes of other coagulation factors and endogenous anticoagulants including protein C, protein S, and antithrombin, data from different studies are conflicting and inconclusive [12, 13]. Procoagulant tendency is further aggravated by reduced resolution of formed clots due to decreased fibrinolysis [6, 14]. Finally, increased platelet reactivity has been suspected in the elderly [15]. Despite no evident changes in platelet count, it seems that lower blood concentrations of platelet agonists including adenosine-di-phosphate (ADP) and collagen are necessary to reach similar levels of platelet aggregation in the elderly compared to younger people. This increased in vitro sensitivity to platelet aggregators suggests increased platelet reactivity [5, 13]. In addition, platelet activation might be stronger in the elderly due to elevated vWF level [16]. This can be attributed to increased endothelial expression as well as decreased degradation of vWF due to age-associated reduced activity of the ADAMTS-13, an enzyme that cleaves vWF multimers.

Laboratory Coagulation Testing

Aging has been associated with different responses to various laboratory coagulation tests. While it is obvious to use age-dependent coagulation parameters in pediatric patients [17], it is less clear whether adapted normal ranges should be used in elderly and very old patients compared to adults aged < 65 years. Increased levels of D-dimer are physiological in the elderly due to ongoing clot formation, and activated partial thromboplastin time (aPTT) is usually shortened [6] due to increased levels of various coagulation factors. These observations might complicate the correct interpretation of the results from most conventional coagulation tests in elderly patients [18, 19]. Recent literature suggests that it might be advisable to establish and use age-adapted normal ranges in elderly patients [6]. In agreement with findings in conventional coagulation testing, viscoelastic testing might appear "hypercoagulant" because of high levels of fibrinogen and lower hematocrit due to chronic inflammation [20, 21].

Of note, most conventional coagulation tests including prothrombin time (PT) and aPTT as well as viscoelastic coagulation tests preferably detect hypocoagulability, but they might be less sensitive in detecting hypercoagulability [20]. Further, most coagulation tests have demonstrated limited ability in predicting perioperative bleeding in different surgical settings. These tests should be primarily used for decision making in bleeding patients and not for screening the bleeding risk in unselected patients before surgery [22].

Thromboembolic Risk in the Elderly

The interaction of multimorbidity, procoagulant changes, and chronic low-grade inflammatory processes, which are all evident in the elderly population, increases their thromboembolic risk [5, 12, 23]. The frequency of arterial thromboembolic events including myocardial infarction and stroke is significantly elevated with aging [5]. About 80% of all fatal myocardial infarctions occur in patients aged > 70 years [5]. Likewise, the risk of stroke increases with aging [24]. The higher prevalence of atrial fibrillation (AF) in the elderly population, in combination with age-associated hypercoagulability, significantly contributes to increased stroke risk. The importance of age as a major risk factor for stroke is well depicted in the CHA_2DS_2-VASc score, in which age > 75 years is counted as two points [25].

Potentially of even higher interest, the incidence of venous thromboembolism (VTE) greatly increases in the elderly population (> 75 years) by about factor 6 (for pulmonary embolism) to 10 (for deep venous thrombosis) compared to younger people (< 40 years) [5]. In fact, the majority of all VTEs occur in patients aged > 70 years [26–28]. Recurrent and fatal VTE are a major clinical concern in the elderly [3•, 15]. Table 2 provides a list of important comorbidities commonly associated with VTE in the elderly patients.

Aging and Acquired Bleeding Disorders

Given the increased thromboembolic risk and comorbidities associated with aging, the prescription of potent oral anticoagulants, including vitamin K antagonists (VKA) and direct-acting oral anticoagulants (DOAC), to the elderly is common. However, the administration of oral anticoagulants

Table 2 Comorbidities commonly associated with aging that increases thromboembolic risk

Congestive heart failure
Chronic obstructive pulmonary disease
Arteriosclerosis
Diabetes mellitus
Arterial hypertension
Atrial fibrillation
Malignancies (lymphoma, metastatic cancer)
Obesity
Sedentary lifestyle
Chronic venous insufficiency

might increase the risk of bleeding complications in the elderly, resulting in a negative clinical benefit. In fact, the increased bleeding tendency in elderly patients should not be neglected [29]. Higher age is a risk factor for major bleeding as represented in the HAS-BLED score [25].

Most common indications for antithrombotic therapy in the elderly are AF and arteriosclerosis, conditions that regularly lead to intensive antithrombotic therapy with increased bleeding risk [30, 31••]. Additional pathological mechanisms in age-related acquired bleeding tendencies include vascular wall alterations, impaired renal function potentially leading to functional platelet disorders, and, more rarely, acquired hemophilia A and von Willebrand disease. The combination of aortic valve stenosis and gastrointestinal bleeding (Heyde's syndrome) is typically associated with aging and is thought to be related to increased rate of cleavage of high molecular weight vWF multimers. Finally, malnutrition is common in elderly, and vitamin K deficiency might lead to reduced levels of vitamin K-dependent coagulation factors, particularly FVII [32].

Drug-Induced Bleeding Disorders

The frequent treatment with oral anticoagulation, antiplatelet therapy, non-steroidal anti-inflammatory drugs (NSAID), and aspirin in the elderly might essentially be causative for most bleeding events. Anticoagulant therapy in elderly patients is challenging. Multiple comorbidities as well as physiological and pathological changes that occur with aging [28] render patients aged > 65 years more vulnerable to the inherent bleeding risk of anticoagulants. Specific age-associated changes in pharmacokinetics and pharmacodynamics have been described [33]. A relative increase in body fat due to a loss of lean body mass and reduced total body water modify distribution volume of lipid soluble drugs and drug kinetics [33]. Reduced renal and hepatic clearance leads to a prolonged elimination half-time of anticoagulant drugs [33]. Pharmacodynamic changes include an increased sensitivity to anticoagulants [34]. Together, these changes are responsible for more common side effects of anticoagulant drugs in the elderly and for an increased bleeding risk in anticoagulated patients aged > 65 years. However, withholding oral anticoagulation to avoid bleeding complications might not be justifiable in most elderly patients, as the absolute benefit of anticoagulation is highest in this population [35••, 36••]. It has been estimated that oral anticoagulation is underutilized in 25 to 50% of very elderly patients [35••, 36••]. To account for pharmacokinetic and pharmacodynamic changes, lower initiation and maintenance doses might be indicated in most administered anticoagulants [37]. Of note, the higher trough concentrations of DOACs have been described in the very elderly despite dose reduction [38•]. Regular laboratory monitoring to evaluate safe drug levels and adequate efficacy might be indicated in the elderly to allow safe administration of DOACs [28]. Further, repeated assessments of the risks vs. benefits of anticoagulation and the correction and minimization of adjustable factors for increased bleeding in elderly patients while on anticoagulant therapy is strongly recommended [25, 30, 39].

For many years, the mainstay of oral anticoagulation has been VKA therapy. Recently, anticoagulation with DOACs has been associated with an increased clinical benefit in elderly patients with AF as compared to VKAs [24, 40•]. In addition, the absolute risk reduction for both ischemic and bleeding events was more pronounced with DOACs [24, 40•]. Elderly patient might especially benefit from a reduction of bleeding events with DOACs. Subgroup analyses from the ENGAGE-AF TIMI 48 trial [41] and from the ARISTOTLE trial [42] in patients at risk of falling found DOACs to be associated with a larger absolute reduction in severe bleeding events and mortality compared to VKAs. Consistently, the risk of subdural bleeding and intracranial hemorrhage was lower in patients treated with DOACs as compared to VKAs [24]. In agreement, a recent systematic review of observational studies and RCTs found that DOACs are generally safer than VKAs in elderly AF patients, albeit that dabigatran users had a 48% increase in risk for gastrointestinal bleeding [43••].

In patients with parenteral anticoagulation, those aged > 72 years had a lower incidence of bleeding events when treated with low-molecular weight heparins (LMWH) compared to those initially treated with unfractionated heparin (UFH) for VTE [44]. Standard heparin doses commonly resulted in increased levels, prolonged aPTT, and higher anti-Xa levels in the elderly [44–46]. Therefore, lower, weight-adjusted doses of UFH might be recommended in order to avoid over-anticoagulation. In addition, tight control is necessary when therapeutic doses of heparin are administered. For initial therapy of VTE, an intravenous bolus of 80 units/kg followed by about 18 units/kg/h is suggested [44, 45]. On the other hand, the use of LMWH might raise concerns in the elderly, as LMWH effect is potentially prolonged in people with impaired renal function [29]. At therapeutic doses, even mild renal impairment might lead to LMWH accumulation. Nevertheless, there is lack of evidence for a clear cut-off value of creatinine clearance that would prohibit the administration of LMWH [44].

Polypharmacy

While prescribing oral anticoagulation, the physician must account for possible comorbidities and the impact of polypharmacy in the elderly that might result in considerable variability of drug effects [47, 48]. A post-hoc analysis of the ARISTOTLE trial showed a significant increase of mortality, thromboembolic events, and bleeding complications with the

number of concomitant drugs in patients under therapy with either apixaban or warfarin [49]. However, the relative risk reduction of stroke or thromboembolic events by apixaban was not influenced by the number of concomitant drugs. The study concluded that apixaban was more effective and safer than VKAs in patients with AF and polypharmacy [49].

Drug interactions might not only affect the potential drug efficacy but also side effects. In patients under anticoagulant therapy, the bleeding risk was massively increased by the concomitant therapy with platelet inhibitors or NSAIDs [31••]. The latter might be particularly important in patients with underlying gastrointestinal lesions and ulcers. Further, selective serotonin reuptake inhibitors, particularly escitalopram, are associated with increased risk of major bleeding when combined with oral anticoagulants [50].

Renal Impairment

Aging is associated with reduced renal function and drug elimination. In addition, renal impairment affects drug binding to plasma proteins, volume of distribution, and thereby also the non-renal clearance of many drugs. Such interactions might lead to either toxicity or insufficient treatment with too high or too low drug levels, respectively [51]. Patients with chronic kidney disease (CKD) or impaired renal function who are treated with DOACs or VKAs are known to have an increased bleeding risk. The effect of impaired renal function is also reflected in different bleeding scores (e.g., HAS-BLED score) [25]. CKD might not only impair platelet function, but it is also a strong risk factor for patients to be over-anticoagulated with VKA, again increasing their bleeding risk [52]. In addition, all DOACs undergo renal elimination, at least in part. For dabigatran, renal elimination might account for up to 80% of drug clearance [53]. Regular monitoring of renal function is, therefore, of great importance in patients receiving DOACs. However, a 2017 meta-analysis evaluating RCTs comparing VKA and DOAC therapy found the latter to be associated with a lower risk of stroke and major bleeding. In patients with renal insufficiency DOACs might offer a larger net clinical benefit than VKAs [54]. Further, patients treated with DOACs showed a lower deterioration of the glomerular filtration rate over time compared to those treated with VKAs [54]. Whether these data can be directly transferred to elderly patients with limited renal impairment is not clear.

The Anticoagulated Elderly Patient in the Perioperative Setting

Older age increases the risk of multiple postoperative complications including thromboembolic events. Surgical procedures are accompanied by an intrinsic thromboembolic risk related to direct vascular damage, tissue trauma, and inflammation leading to activation of the coagulation pathways. Intraoperative positioning and postoperative immobilization increase the risk of blood stasis. For adequate estimation of perioperative thromboembolic risk, the type and extensiveness of surgery, the perioperative management, and the patient's basal conditions and comorbidities must be respected [55, 56••].

Patient age is associated with increased risk for perioperative stroke and myocardial infarction. A previous study reported an odds ratio (OR) of 1.43 (95% confidence interval 1.35–1.51) in the risk for perioperative stroke for each 10-year increase in age [57]. This resulted in a two- to ten-times increased risk for perioperative stroke in octogenarians when compared to younger populations [58]. Similarly, the risk of perioperative myocardial injury/infarctions was found to increase slightly with age [59]. Further, the postoperative risk of VTE increases with age. In the recent European Society of Anaesthesiology (ESA) guidelines on perioperative thromboembolism prophylaxis in elderly patients undergoing surgery [56••], age > 70 years was identified as clear risk factor for perioperative VTE based on several systematic reviews and large cohort studies [60–62].

However, it is important to acknowledge that individual risk for developing perioperative thromboembolism is a combination of age plus additional VTE risk factors such as obesity, a history of thromboembolic events, AF, artificial heart valves, coronary stents, cancer, lymphoma, and renal impairment [63–65]. For example, a large cohort study in more than 75,000 postoperative patients found a twofold increased for VTE in patients with renal insufficiency, leading to a significantly increased 30-day mortality [66]. It has been questioned whether age itself is an independent risk factor for postoperative thromboembolic events [56••, 67]. Rather, age might be a proxy for conditions such as frailty, multimorbidity, immobility, and low-grade coagulation activation leading to increased incidence of postoperative thromboembolic events.

Prevention

Older patients require a thoughtful preoperative geriatric assessment that should also include the use of cardiovascular risk assessment, estimation of functional capacity, and surgical risk calculators [68]. Ideally, preoperative evaluation leads to pre-habilitation, adapted anesthesia plans, minimally invasive surgical procedures, and programs for early recovery after surgery [2, 68]. Risk factors for arterial and venous thromboembolic complications should be identified. Some common risk factors in the elderly, such as anemia or malnutrition, could potentially be corrected before elective surgery, thereby reducing adverse outcomes. Perioperative hypothermia might contribute to bleeding complications. Early application of warming systems is recommended in

the elderly patient [69]. Although it is commonly assumed that the geriatric patient should not become hypotensive during the perioperative period to prevent stroke and myocardial ischemia [70•], there is no consensus on the most appropriate targets of perioperative blood pressure or how to achieve them. To date, there have been no RCTs showing a superiority of keeping blood pressure above a defined threshold in the perioperative period. A common practice is to maintain mean or systolic blood pressure within 20% of baseline [58]. Similarly, the use of regional or combined anesthesia rather than general anesthesia alone might reduce thromboembolic events, but the evidence is limited [71].

Perioperative thromboembolism prophylaxis must be considered in most elderly patients due to an increased inherent risk of thromboembolic complications. With respect to arterial thrombosis, timely stopping of anticoagulants and antiplatelet drugs seems important. Aspirin might be continued during the perioperative period in most patients. Aggressive bridging with LMWH or UFH should be avoided in patients with low CHA_2DS_2-VASc scores treated with VKA or DOACs. The latter has been associated with increased intraoperative and postoperative bleeding events without reducing thromboembolic complications [72•, 73]. Given the common renal and hepatic impairment with aging, polypharmacy, and the generally higher DOAC levels in the elderly, prolonged preoperative stopping intervals and laboratory drug monitoring should be considered [28, 74]. Postoperative VTE prophylaxis might be more difficult to implement in the older vs. younger patients. The recent ESA guidelines, therefore, recommended early mobilization in addition to careful prescription of postoperative VTE prophylaxis (grade 1C) [56••]. Additional multi-faceted interventions including pneumatic compression devices should be considered (grade 1C) [56••]. However, these guidelines did not recommend specific timing and dosing of pharmacological VTE prophylaxis in the elderly as compared to the younger population [56••].

Despite intensive VTE prophylaxis, a recent retrospective study in nearly 570 patients with traumatic femoral and pelvic fractures found a consistently high incidence of postoperative thromboembolic events [75]. The authors concluded that there might be a window of opportunity by optimizing perioperative blood transfusion management, preoperative lung disease, hypoproteinemia, anemia, and potentially the inflammatory state associated with aging [75].

Treatment of Thromboembolic Complications

Early diagnosis including specific screening for perioperative thromboembolic events is thought to be the key to improving outcome after arterial and venous thromboembolic events. Systematic perioperative troponin screening for perioperative myocardial infarction has been shown to potentially reduce long-term mortality [76]. Further, the early and prompt cardiac workup including cardiac imaging and therapy of perioperative myocardial infarction might potentially improve survival, but the best strategy remains unclear. Similarly, therapy for perioperative stroke is poorly defined but increased awareness and early detection should result in improved outcomes [58].

Anticoagulation should start as soon as possible when deep venous thrombosis is diagnosed or suspected. Treatment options include subcutaneous LMWH, subcutaneous fondaparinux, or intravenous UFH. LMWH should be preferred in the elderly, as it is associated with a lower bleeding risk and less heparin-induced thrombocytopenia [77]. When administering LMWH (or fondaparinux), special attention should be paid to regularly impaired renal function to avoid excessive anticoagulation and increased bleeding risk.

In patients with postoperative pulmonary embolism, hemodynamic and respiratory support is of vital importance. Anticoagulation reduces mortality and should be administered in all elderly patients without contraindications [78]. In case of hemodynamic instability due to acute right ventricular failure, thrombolysis with streptokinase might be considered in younger as well as in elderly patients. A recent study showed a reduced mortality with acceptable bleeding complications in patients > 65 years with pulmonary embolism [79•].

Conclusions

Age-related changes in the hemostatic system in combination with frailty, reduced mobility, and age-associated comorbidities place the elderly patient at increased risk for thromboembolic events. Thereby, elderly people are especially increased risk for deep venous thrombosis and thromboembolism associated with AF. Anticoagulation should not be withheld despite an increased risk of adverse side effects and hemorrhagic complications due to changes in pharmacokinetics and pharmacodynamics associated with aging. Adapted dosing regimens and intensified drug monitoring might be considered.

In the perioperative setting, specific geriatric workup and preoperative optimization of risk factors potentially improve the outcome of the elderly surgical patients. Several strategies to prevent postoperative thromboembolic events have been suggested but evidence is limited. Early postoperative anticoagulation and monitoring of potential thromboembolic complications is recommended.

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Declarations

Conflict of interest There is no conflict of interest to declare.

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