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Review Article

Arterial and Venous Thrombosis in Cancer Patients

Andrew D. Blann[1] and Simon Dunmore[2]

[1] *University of Birmingham Centre for Cardiovascular Sciences, Department of Medicine, City Hospital, Birmingham B18 7QH, UK*
[2] *Department of Biomedical Science & Physiology, School of Applied Sciences, Research Institute in Healthcare Sciences, University of Wolverhampton, Wulfruna Street, Wolverhampton WV1 1AD, UK*

Correspondence should be addressed to Andrew D. Blann, a.blann@bham.ac.uk

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The most frequent ultimate cause of death is myocardial arrest. In many cases this is due to myocardial hypoxia, generally arising from failure of the coronary macro- and microcirculation to deliver enough oxygenated red cells to the cardiomyocytes. The principle reason for this is occlusive thrombosis, either by isolated circulating thrombi, or by rupture of upstream plaque. However, an additionally serious pathology causing potentially fatal stress to the heart is extra-cardiac disease, such as pulmonary hypertension. A primary cause of the latter is pulmonary embolus, considered to be a venous thromboembolism. Whilst the thrombotic scenario has for decades been the dominating paradigm in cardiovascular disease, these issues have, until recently, been infrequently considered in cancer. However, there is now a developing view that cancer is also a thrombotic disease, and notably a disease predominantly of the venous circulation, manifesting as deep vein thrombosis and pulmonary embolism. Indeed, for many, a venous thromboembolism is one of the first symptoms of a developing cancer. Furthermore, many of the standard chemotherapies in cancer are prothrombotic. Accordingly, thromboprophylaxis in cancer with heparins or oral anticoagulation (such as Warfarin), especially in high risk groups (such as those who are immobile and on high dose chemotherapy), may be an important therapy. The objective of this communication is to summarise current views on the epidemiology and pathophysiology of arterial and venous thrombosis in cancer.

1. Introduction

The greater part of human mortality and morbidity (certainly in the developed world) focuses on cardiovascular disease and its risk factors, cancer, and connective tissue disease [1]. The pathophysiology of cardiovascular disease (endothelial damage leading to hypertension and thrombosis) is established [2], whilst those subjects with connective tissue disease (generally inflammatory) are also at risk of possible life-terminating atherothrombosis [3]. A relationship between cancer and thrombosis has been recognised for almost 150 years, and each year brings additional data that confirms this association [4, 5]. Furthermore, the large proportion of terminal events in neoplastic diseases are thrombotic, leading to the hypothesis that cancer is a prothrombotic disease [6–9]. However, such thromboses may occur in arteries and/or veins, and many authorities fail to differentiate between these two circulations, generally focusing on venous thromboembolism (VTE). Nevertheless, of PubMed citations of works on arterial and venous thrombosis, approximately 25% are to arterial thrombosis.

An additional aspect of thrombosis and cancer is the inevitably adverse effect of chemotherapy (often anti-neoplastic and cytotoxic) in promoting thrombosis [8, 9]. Although there are isolated reports where hypercoagulability and thrombosis closely follows chemotherapy [10, 11], guidelines advocating prophylactic anticoagulation therapy in the para-antineoplastic drug setting are becoming available. Indeed, one study named thromboembolism and infection as leading precise causes of death in cancer patients on chemotherapy [12].

The objective of this paper is to summarise potential pathophysiological mechanisms to explain this relationship, and to update facets of both arterial and venous thrombosis in various cancers. To achieve this aim, on-line search engines such as PubMed and Medline were probed using key

words cancer, arterial thrombosis, venous thrombosis, and anticoagulation. Whilst acknowledging advances brought by tissue culture and animal models, the paper will focus on human disease.

2. The Pathophysiology of Thrombosis

Perhaps the oldest and most dominant theory of the pathophysiology of thrombosis is that of Virchow, which has three separate but overlapping parts: the contents of the blood, the blood vessel wall, and blood flow [13]. We currently interpret this triad in terms of, respectively, platelets and coagulation factors (with minor roles for red and white blood cells), the endothelium, and blood turbulence (as may be present at valves and at bifurcations) and venostasis [14]. Certainly, however, these principles are as equally applicable to arterial thromboses and to venous thromboses, and also to cancer (Table 1). Indeed, patients with various cancers frequently demonstrate abnormalities in each component of Virchow's triad, leading to a prothrombotic or hypercoagulable state. The mechanisms are likely to be multiple and, probably, synergistic. For example, tumour cells may be directly prothrombotic, inducing thrombin generation, whilst normal host tissues may stimulate (or be stimulated to) prothrombotic activity as a secondary response to the cancer. However, dissecting the exact mechanisms is frustrated by comorbidity and treatment effects, such as bed rest, infection, surgery, and drugs. Nevertheless, Virchow's triad also gives us the opportunity to dissect and identify different aspects of the causes of thrombosis.

Table 1: Virchow's triad in cancer.

Abnormal blood flow
(i) Increased plasma viscosity [114, 115]
(ii) Increased stasis due to immobility (e.g., being bed-bound, in a wheelchair)
Abnormal blood constituents
(i) Increased platelet activation and aggregability, for example, increased soluble P selectin, beta thromboglobulin [15–51]
(ii) Loss of haemostasis with increase in procoagulants for example, increased fibrinogen, cancer procoagulant, PAI-1 [66–89]
Abnormal blood vessel wall
(i) Damaged or dysfunctional endothelium (e.g., increased soluble E selectin, increased soluble thrombomodulin, possibly also related to chemotherapy) [95–97]
(ii) Loss of anticoagulant nature and therefore acquisition of a procoagulant nature (e.g., increased von Willebrand factor, tissue factor, reduced tPA, possibly also related to chemotherapy) [83, 93, 94]
(iii) Angiogenesis (altered release of, and response to, growth factors) [101–107]

2.1. The Contents of the Blood: Cells. Pathologists focus on cells and on plasma molecules. The former clearly centre on the platelet, although there are potential roles (if only minor) for white blood cells and red blood cells, the latter as ADP donors [15, 16]. Examples of platelet (hyper)activity in cancer include reduced life span in myeloma, reduced sensitivity to prostacyclin in endometrial, and cervical cancer [17, 18], with increased aggregability and higher levels of platelet specific products soluble P-selectin, platelet factor 4, thrombospondin and beta-thromboglobulin in lung, breast, prostate, ovarian, and other cancers [19–26]. These and other findings support the general hypothesis of altered platelet activity in cancer, especially in metastatic disease [27–29]. Furthermore, it has been suggested that inappropriate platelet activity promotes metastases [30, 31].

There are several plausible theories as to the causes of this excess platelet activity. Cancer cells may activate platelets *in vitro* by contact, by releasing platelet stimulators such as ADP and thromboxane A2, and by generating thrombin through the activity of the tumour-associated procoagulants. Increased von Willebrand factor, ristocetin cofactor, and enhanced ADP-induced platelet aggregation have all been demonstrated [32–36], and all these mechanism may promote thrombosis. However, in at least one clinical setting, the true value of this has been questioned, as Canobbio et al. [37] found that hypercoagulability was more likely to be related to coagulation than to the expected increase in platelet aggregability. Nevertheless, there are several calls for antiplatelet therapy in cancer [38–40], although concerns have been aired [41].

A rapidly expanding area is that of microparticles [42, 43]. Increased numbers of platelet microparticles have been described in gastric, colon, and breast cancer [44–46]. Interest in platelet microparticles follows a number of themes; in the promotion of angiogenesis and metastases [46–48], in the promotion of thrombosis (such as by bearing tissue factor and phospholipids, thus providing a platform for thrombosis) [45, 49, 50], and in the promotion of invasiveness [51]. The tumour itself may also shed microparticles, and these too may be prothrombotic [52–54].

Monocytes may also be involved in cancer [55]. Early work suggested a role in an immunological response to neoplasia [56, 57], and although this persists, a more recent view linking monocytes to coagulation has been introduced, based on their ability to express tissue factor [58–61]. However, other mechanisms may also be important, such as the delivery of cytokines and a role in angiogenesis [62, 63] and there are also reports of the procoagulant activity of monocyte microparticles [64], and also of cross-talk between the monocyte and the platelet [65], all of which have the potential to promote thrombosis.

2.2. The Contents of the Blood: Soluble Plasma Molecules. There is also considerable evidence which implicates soluble coagulation factors in cancer-related thrombosis [66]. The normal clotting-fibrinolytic system of haemostasis involves a fine balance between the activation and inhibition of platelets, procoagulant factors, anticoagulant factors, and fibrinolytic factors [67]. This can easily be disrupted as tumour cells can, for example, activate the coagulation

system directly through interactions with the clotting and fibrinolytic systems to generate thrombin [68]. The delicate balance between the coagulation and fibrinolytic systems can easily shift to induce a prothrombotic state, perhaps via an excess of procoagulant proteins such as tissue factor, fibrinogen and plasminogen activator inhibitor (PAI-1), and/or deficiencies in other molecules, such as anti-thrombin, Proteins C and S, and tissue plasminogen activator (tPA) [67, 69]. However, perhaps the greater part of the literature in this area considers tissue factor and cancer procoagulant.

Tissue factor is primary initiator of coagulation. Forming a complex with factor VII to activate factors X and IX, it is produced by monocytes and the endothelium [59] and is functional both at the surface of the cell and as a soluble component of plasma [70, 71]. Thus i*n vivo* expression of tissue factor, either by tumour and/or "normal" cells, and soluble tissue factor has been implicated in intratumoral and systemic activation of blood coagulation via the extrinsic pathway, as well as in tumour growth and dissemination [72–75].

Cancer procoagulant is a cysteine proteinase growth factor that is a calcium-dependent, Mn^{2+} stimulated enzyme [76]. Unlike tissue factor, cancer procoagulant is a direct activator of factor X without the need for factor VII and is found in malignant and fetal tissue, but not in normally differentiated tissue [77]. Concerns that at least some part of cancer procoagulant activity could be accounted for by contaminating tissue factors seem to have been dispelled [78]. In the presence of factor V, cancer procoagulant may further enhance thrombin generation by up to 3-fold. Increased cancer procoagulant levels have been reported in patients with acute promyelocytic leukemia, malignant melanoma, and cancers of the colon, breast, lung, and kidney, and there is *in vitro* evidence that it may also be involved in metastatic potential [79–82]

Numerous other proteins within the coagulation cascade have been shown to be abnormally elevated, often in association with a fall in the activity of "anticoagulant" factors. For example, reduced levels of t-PA activity have been described in patients with gastrointestinal cancer [83], whilst that of PAI-1 and other inhibitory factors of the fibrinolytic pathway can be elevated [84]. Both of these factors are likely to lead to a prothrombotic or hypercoagulable state. In addition, there are decreases in other anticoagulant factors, including anti-thrombin and resistance to activated protein C. The evidence of this on-going underlying state of heightened coagulation in cancer is clear from the numerous studies looking at levels of fibrinogen and other indices of fibrin turnover including D-dimers [71, 85–89]. Increased levels of the latter reflect increased clot turnover (thrombolysis) which in turn implies increased thrombotic load, as is present in actual venothromboembolic disease, and levels of D-dimers are part of the clinical assessment of subjects with suspected venothromboembolism [90]. However, there is evidence of very high D-dimer levels in patients with cancer who do not have VTE. This suggests that elevated D-dimer levels in patients with VTE and malignancy are not solely due to presence of thrombus. Knowlson et al. suggest that high D-dimer levels in malignancy are likely to reflect the biology of the underlying tumour, with higher levels observed in breast, prostate, and bowel cancers [91].

2.3. Abnormalities of Vessel Wall. The role of endothelium in mediating the prothrombotic or hypercoagulable state is well-known, and disturbances in vascular function may be assessed by changes in plasma levels of certain molecules such as von Willebrand factor (vWf), soluble thrombomodulin, and soluble E-selectin [92]. Increased vWf has long been described in cancer [93, 94], and this may not only indicate endothelial damage but also seem likely to contribute to thrombosis by promoting platelet-platelet and platelet-subendothelium adhesion, as may increased fibrinogen [92–94]. Similarly, increased soluble (i.e., plasma) thrombomodulin (as in present in cancer [95]) may account for the loss of anticoagulant membrane thrombomodulin at the endothelial surface [96]. Thus changes in vWf and thrombomodulin are likely to promote coagulopathy and thus provide a paradigm for thrombosis in cancer. Increased soluble E selectin in cancer may simply be a marker of endothelial disturbance with no direct implications for hameostasis [97]

Endothelial cells may become prothrombotic under the influence of inflammatory cytokines such as tumour necrosis factor (TNF) and interleukin (IL)-1. Such cytokines suppress endothelial fibrinolytic activity, increase endothelial cell production of IL-1 and vWf, and downregulate thrombomodulin expression that diminishes the activation of the anticoagulant protein C [98]. Cytokines such as TNF and IL-1, often increased in cancer [99], also increase the endothelial expression of E selectin, platelet activating factors, and tissue factor [98, 100]. Thus hypoxia and/or cytokine-mediated endothelial cell damage or dysfunction has the potential to further contribute to hypercoagulable state. A damaged endothelium may also present less of a challenge to a metastatic tumour cell seeking to penetrate the vessel wall. Solid tumours growing outside of the blood vasculature may also increase the permeability of the microvasculature, allowing fibrinogen and other plasma-clotting proteins to leak into the extravascular space where procoagulants associated with tumour cells or with benign stromal cells can initiate clotting and subsequent fibrin deposition [100].

Several findings suggest a link between angiogenesis and thrombosis. One of the oldest provides a rationale for a role for platelet derived growth factor (PDGF), and platelet derived endothelial growth factor, possibly shed from para-neoplastic thrombus, in neovascularisation [101, 102]. Others have localised tissue factor expression in the vascular endothelium of breast cancer tissue, which strongly correlate with the initiation of angiogenesis, hence suggesting a further possible link between the prothrombotic states and angiogenesis in these patients [103, 104]. Tissue factor expression has also been shown to correlate positively with microvessel density and the expression of the angiogenic modulator, vascular endothelial growth factor (VEGF) [105]. Interestingly, VEGF induces hyperpermeability by a direct action on the endothelium [106] and (unlike basic fibroblast growth factor) promotes platelet activation and adhesion [107]

although both *in vitro*. An additional factor is the possibility that platelet-derived VEGF and other angiogenic molecules may be important in malignancy [108–110].

2.4. Abnormalities of Blood Flow. There seems to little firm *in vivo* data directly implicating this third aspect of Virchow's triad in the pathogenesis of human cancer, although imaging studies of blood flow may be a useful investigation [111]. What would seem to be a likely mechanism in cardiovascular disease [112] may not be the case in neoplasia, although there are *in vitro* data [113]. Nevertheless, blood viscosity at both high and low rates of shear [114], and a yield stress index measured preoperatively in cancer patients, has been correlated with the incidence of post-operative DVT [115]. The possibility arises that abnormal blood vessel formation (perhaps related to cancer angiogenesis and factors promoting this) may cause flow disturbance.

3. The Effects of Therapy and Staging on the Risk of Thrombosis

Apart from what may be described as the "natural" pathophysiology, as exemplified by Virchow's triad, many interventions to treat cancer are prothrombotic. There is ample evidence that numerous chemotherapeutic agents, including methotrexate, cisplatin and etoposide, as well as hormonal therapies used in cancer, such as medroxyprogesterone acetate and thalidomide, have all been implicated as risk factors for thromboembolism [116–121]. Other interventions such as central venous catheter placements, surgery, sepsis, and venous stasis from immobility also contribute to risk of thromboembolism [122], although some of this extra risk may be due to local inflammation and/or infection [123]. Furthermore, the general principle that chemotherapy induces thrombosis extends to nonmalignant diseases such as lupus [124]. An exact position for a role of radiotherapy in promoting thrombosis is marred in many studies by combination chemotherapy. Nevertheless, there are instances where radiotherapy does indeed increase the risk of thrombosis but may also damage the endothelium, and collectively, these issues prompt the need for pro-active anticoagulant therapy in high risk groups [121, 125–128].

Levels of plasma markers of thrombin and plasmin generation have been related to staging, prognosis and intervention in patients with various cancers, including those of the cervix, lung, ovary, prostate, and breast. For example, in the study by Gadducci et al. [128], levels of prothrombotic indices were significantly raised in patients with cervical cancer, and related to surgical-pathological stage and tumour size, but not to histologic type. Similarly, several studies have shown an association between activation of blood coagulation and fibrinolysis with distant metastasis, histologic type of tumour and response to chemotherapy; indeed, gross abnormalities of prothrombotic indices might even be a sign of unfavourable prognosis in certain patients [129–131]. However, others failed to note any changes in preoperative or sequential measurements up to 9 months postoperatively of fibrinopeptide A, fibrin fragment B beta 15–42, fibrinogen and serum fibrin degradation products that correlated with early recurrent breast cancer, although some markers were higher in patients with oestrogen receptor positive tumours, or increased postoperatively, largely because of an increase in patients with oestrogen receptor negative tumours [132].

4. Arterial Thrombosis in Cancer

As discussed, there is considerably more data on venous thrombosis than for arterial thrombosis in cancer. Nevertheless, thrombosis in arteries has long been recognised, although the exact mechanisms, in many cases, remain obscure [133–135]. However, increased levels of coagulation molecules, concurrent disease (such as endocarditis), use of growth factors, and cytotoxic chemotherapy may all precipitate thrombosis [136–140]. A potential mechanism for the latter may be endothelial damage with the loss of its natural anticoagulant nature and acquisition of a procoagulant profile [141]. However, the fact that a large proportion of these studies are case reports underlines the rarity of arterial thrombosis in cancer [138–141]. Ross et al. provided additional possible pathogenic mechanisms related to atherosclerosis whilst Lowe summarised common risk factors for arterial and venous thrombosis [142, 143].

5. Prophylaxis and Treatment

A detailed discussion of the prevention and treatment of thromboembolism in cancer is beyond the scope of this paper, although at least one commentator refers to treatment of arterial cancer with anticoagulants [134]. Nevertheless, primary prevention of VTE, possibly by vitamin K antagonists (VKAs) should be considered for "high-risk" cancer patients during and immediately after chemotherapy, when long-term indwelling central venous catheters are placed, during prolonged immobilization from any cause, and following surgical interventions [118, 127]. For example, in cancer patients going for general surgery without prophylaxis, the incidence of deep vein thrombosis is approximately 29% as compared to 19% of patients without cancer [144]. Thus a possible route for the prevention of VTE in high-risk cancer patients undergoing surgery or adjuvant chemotherapy may be the use of long-term low-intensity anticoagulation [145]. However, there are concerns of the safety of VKA anticoagulants in cancer as these may cause an increase in all bleeding, major bleeding, and minor bleeding compared to patients free of cancer [146]. A meta-analysis found no evidence that warrants treatment with VKAs with the aim of improving survival [147].

These and other data suggest that, for many, low molecular weight heparins (LMWHs) will be the therapy of choice [155], not merely because of a reduced rate of complications such as haemorrhage [127], but also because it improves overall survival [156]. Lee et al. reported a rate of recurrent VTE of 17% in patients on VKA anticoagulants compared to 9% in those on an LMWH [157], and later noted that the use of a LMWH relative to coumarin derivatives was associated with improved survival in patients with solid tumours who

Table 2: Potential treatments of patients with cancer.

Patient group	Role of VTE prophylaxis
Hospitalised	Consider UFH, LMWH, or fondaparinux (strongly consider if bedridden and active cancer)
Ambulatory patients free of VTE but receiving systemic chemotherapy	Routine prophylaxis not recommended (conflicting data, risk of haemorrhage, low risk of VTE)
Patients with myeloma free of VTE on thalidomide or lenalidomide plus chemotherapy or dexamethasone	LMWH or low dose warfarin (target INR 1.5)
About to undergo surgery	Consider UFH, LMWH, or fondaparinux for 7–10 days. Consider extended (4 week) prophylaxis with LMWH after major surgery, obesity, and a history of VTE.
Those with established VTE to prevent recurrence	LMWH 5–10 days in the initial phase, then long-term treatment (6 months) with LMWH preferred to oral anticoagulation.
Active cancer (metastatic disease, continuing chemotherapy).	Indefinite anticoagulation should be considered

Table amended from [148]. See also [149, 150]. UFH: unfractionated heparin. LMWH: low molecular weight heparin. VTE: venous thromboembolism.

Table 3: Evidence that not all cancers are associated with the same risk of VTE.

Rank	Reference [151]	Reference [152]	Reference [153]	Reference [154]
1	Ovary	Pancreas	Kidney	Bone
2	Pancreas	Head/neck	Pancreas	Ovary
3	Liver	CNS	Gastric	Brain
4	Blood	Upper GI	Brain	Pancreas
5	Brain	Endocrine		Lymph nodes
6	Kidney	Lung		Cervix
7	Lung	Colorectal		Stomach

See particular references for fine details. CNS: central nervous system; GI: gastrointestinal. A model for predicting chemotherapy-associated VTE places more emphasis on cancers of the stomach and pancreas than on cancers of the lung, bladder, testes, lymph nodes, and female reproductive system [12].

did not have metastatic disease at the time of an acute VTE [158]. Indeed, a recent international guideline on the use of anticoagulants in cancer for prophylaxis and treatment is dominated by LMWHs [148] (Table 2). Although use of LMWH compared to unfractionated heparin confers a survival advantage, the precise role of LMWHs in survival in those free of VTE is unclear but demands careful prospective analysis [159]. But whatever treatment mode is adopted, its use is likely to be long-term in high risk groups [148, 149, 160].

6. Conclusion

It has been long been recognised that cancer confers a prothrombotic or hypercoagulable state, most likely through an altered balance between the coagulation and fibrinolytic systems [161]. More recently it is clear that this risk can be related to long-term prognosis and treatment [162–164], and hospitalisation for a VTE is a risk factor for a second cancer [165]. Whilst most thromboses in cancer are venous, arterial thrombosis is common, possible because the two share many risk factors [140]. Indeed, patients with an unprovoked VTE are at increased risk of an arterial thrombosis [166]. Procoagulants such as tissue factor are expressed by many tumours [73, 75, 104], and although platelet turnover and activity are also increased, it is unclear whether or not platelets themselves and/or their products actively promote thrombosis [167, 168], although a high platelet count is a risk factor for chemotherapy-associated thrombosis [169]. Risk factors for VTE whilst on chemotherapy include presence of metastases, high leukocyte count and platin-based chemotherapy [170]. There is also a growing view that some cancers are more prothrombotic than others (Table 3). Although a flawed analysis, a crude summation of this table suggests that pancreatic cancer and ovarian cancer are most likely to provoke a VTE.

Although guidelines and a consensus statement for anticoagulant treatment are available [148–150, 171], further work is needed to elucidate the mechanism (s) leading to the prothrombotic state in cancer, the potential prognostic and treatment implications, and the possible value of quantifying indices of hypercoagulability in routine clinical practice. Carefully designed studies with the appropriate methodology to establish the predictive value of various abnormalities of the prothrombotic or hypercoagulable state are needed. In this respect the development of a risk factor score, which includes leukocyte count, platelet count, and levels of tissue factor, soluble P-selectin and D-dimer, points a possible way

forward in identifying those at greatest risk of thrombosis, possibly due to chemotherapy, and who therefore warrant treatment [172–174]. In support of this hypothesis is data showed the value of adding soluble P-selectin and D-dimer to a risk calculator [175].

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