VENOUS PULMONARY THROMBOEMBOLISM AND ATHEROTHROMBOSIS: NEED FOR A NEW APPROACH

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VENOUS PULMONARY THROMBOEMBOLISM AND ATHEROTHROMBOSIS: NEED FOR A NEW APPROACH (Abstract): Pulmonary venous thromboembolism and atherothrombosis are traditionally considered as distinct diseases. As the two entities share common risk factors and mechanisms current experimental and clinical studies support their mutual causal relationship. For the clinician, the current concept requires a different clinical, laboratory and therapeutic approach. The patient with a first arterial or venous thrombosis should be fully assessed for the risk of future clinical events, and, simultaneously addressed to aggressive preventive non-pharmacological and pharmacotherapy intervention. In this context, antiplatelet agents and statins have a potentially beneficial role. Keywords: VENOUS THROMBOEMBOLISM, ATHEROTHROMBOSIS, INTEGRATED APPROACH, RISK FACTORS, PREVENTION.

CONCEPTUAL EVOLUTION

The relation between the complications of atherosclerosis (ATS) and pulmonary venous thromboembolism (VTE) is a current topic as both entities are of major importance in the prevalence and potentially fatal consequences, and according to studies, are frequently associated in the same patient. The literature of recent years supports the "VTE-atherothrombosis concept", a dynamic point of view with three stages of development (1). The classical approach supports two distinct categories of diseases based on some different types of arguments. The hemodynamic arguments refer to vascular occlusion in areas with different shear stress regimens, and pathological arguments are based on the different structure of thrombi. Venous thrombi are mainly composed of erythrocytes and fibrin, while arterial systemic thrombi are platelet-rich. Epidemiological studies also make a clear distinction between the mechanisms involved and risk factors. The distinction is also therapeutic as anticoagulation is the cornerstone of treatment in VTE while antiplatelet agents play a key role in prevention of atherothrombotic events. The classic paradigm started to be questioned at the beginning of the 21st century when epidemiological studies suggested that the dichotomy is an artificial simplification (2-5). This new stage is based on data related to a significantly increased incidence of VTE compared to the general population in the elderly and patients with a history of
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Peripheral arterial disease, hypertension, and dyslipidemia. The observations referring to unprovoked VTE in over 30% of the cases also support the new point of view (6). Other studies suggest common risk factors for arterial and venous thrombotic events, such as hyperhomocysteinemia, thrombophilia, or first refer to the benefit of statins in VTE (7,8). These observations recall Macfarlane’s assertion in the 70s that "thrombosis is hemostasis in the wrong place" (9). In other words, the prothrombotic status secondary to platelet activation, coagulation, and increased fibrin turnover is a common event in atherothrombosis (ATT) and VTE. Based on this evidence, Prandoni examined whether asymptomatic carotid ATS is predictable for the risk of VTE (5). The study considered to be a reference for the evolution of the concept, included 299 patients with spontaneous and provoked deep vein thrombosis (DVT) and with no atherothrombotic events, and 150 control subjects, examined by ultrasound for carotid plaques detection. The authors concluded that asymptomatic carotid lesions had significantly higher prevalence in the subgroup with provoked DVT, suggesting the potential of ATS to induce VTE. The hypothesis of an association between arterial and venous thrombotic events develops simultaneously in many prospective studies in order to elucidate the relationship direction: ATT-VTE or VTE-ATT? Data published after ‘2000s are crucial for the evolution towards the modern conceptual stage. The current paradigm argues that VTE is part of "pan-cardiovascular syndrome" that includes all clinical manifestations of ATT as there are common risk factors and mechanisms. It is concluded that between VTE and ATT there is not a simple association but a mutual causal relationship (6).

EVIDENCE FROM TRIALS

1. Atherosclerosis and risk of VTE: is there a relationship?

A first group of observations refers to the impact of subclinical ATS on the risk of VTE. There are two reference prospective population trials with the same objective as the study by Prandoni, but with conflicting results. Atherosclerotic Risk in Communities, which included asymptomatic adults aged 45-64 years, does not support the relationship. The Cardiovascular Health Study, addressed to elderly over 65 years, states low risk of VTE irrespective of etiology only related to carotid ATS but without evidence of subclinical ATS in other arterial territories (10,11). Another group of studies addresses the issue of atherothrombotic cardiovascular events (CVE). There are consistent published data but differently supporting the positive relationship with increased risk of VTE. There are interesting observations published by Eliasson et al. in a retrospective study of 23,976 consecutive autopsies in patients with objectively verified arterial and venous thrombosis. The authors suggested a heterogeneous relationship since the risk of VTE was confirmed in patients with thrombosis of the aorta and its branches, except the coronary arteries. An inadequately motivated explanation of these results is related to the ‘90s when fewer therapeutic options for acute coronary syndromes were available, and thus many patients did not survive long enough to develop VTE (12). The results are contradictory to Tromsø and HUNT-2 studies supporting that family history of acute myocardial infarction (AMI) is significantly and independently associated with the
risk of VTE (13,14). More recent data confirm the high risk of VTE during the first 3 months after AMI or stroke, then it decreases but remains statistically significant (15).

2. VTE and the risk of atherothrombosis: is there a relationship?

One of the first relevant prospective studies belongs to Prandoni showing a doubling in the risk of atherothrombotic symptomatic events following an unprovoked VTE episode compared with a secondary VTE (15.1% versus 8.5%), irrespective of age and other cardiovascular risk factors (16). To the contrary, Spencer stated that the relation between unprovoked VTE and AMI is age-dependent. Thus, patients younger than 40 years without atherosclerotic risk factors had a 4-fold higher incidence of AMI over 10-years of follow-up as compared to the control group (17). In addition, the study highlighted the risk of VTE recurrence within 8 years of warfarin discontinuation (30% of cases) and an about 40% increase in the subsequent risk of all-cause death (17,18). Reference data are also available from a prospective Danish trial on a cohort of more than 200,000 patients followed-up for 20 years (19). The same temporal trend was noticed when VTE was related to AMI and stroke, with an excess of relative risk for major CVE during the first year of follow-up (1.6-fold increased risk for AMI, 2.6-fold increased risk for stroke in DVT cohort, and 2.6-2.93-fold increased risk in patients with pulmonary embolism). The risk was still increased by 20-40% over the 19 years of follow-up. In a meta-analysis summarizing the literature results published until 2010, Becattini stated that patients with unprovoked VTE have a 1.5-fold higher risk of arterial CVE over 10 years than patients with provoked VTE and the general population. The meta-analysis highlights common mechanisms such as thrombogenesis, endothelial dysfunction, and inflammation. These mechanisms are supported by the modern paradigm that is focused on the causal relationship between VTE and ATT (20,21). For a clinician, these studies imply a careful monitoring of cardiovascular risk factors in patients with a history of unprovoked VTE when considering an optimal primary prevention of atherothrombotic events concomitant with recurrent venous thrombotic event prophylaxis (22).

**VTE-ATHERO-THROMBOSIS CONCEPT: CLINICAL ASSOCIATION OR CAUSAL RELATION?**

Abandoning classical mechanistic thinking and the need of an integrated approach of these two entities were recognized by the North American Thrombosis Summit in 2011. At this point, the relationship is reviewed in terms of pathogenesis, clinical and therapeutic management. The new concept supports VTE and ATT clinical events as a continuous spectrum of the same disease in the same patient and the risk is increased in a mutual manner.

*Common risk factors and common mechanisms?*

The statement that the patients with atherothrombotic events are at increased risk of VTE and *vice versa* is based on several studies that support common risk factors. Age is also a powerful risk factor in VTE, as Worcester study show an exponential increase in incidence in both sexes (23). Ageno’s meta-analysis of over 65,000 patients included in 21 studies adds valuable information regarding the relation between
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the major risk factors and VTE (24). Obesity expressed by body mass index doubles the risk of VTE. This observation is consistent with other studies on cohorts of women, where obesity significantly increases the risk of DVT and triples the risk of unprovoked VTE (6). Hypertension is associated with a 50% increase in the risk of VTE, a relation admitted inconstantly by other studies because of the different ways of reporting high blood pressure. Diabetes mellitus is associated with a 42% increase of VTE incidence, regardless of the trials included in the meta-analysis and type of diabetes (24). As to dyslipidemia, only decreased HDL doubles the risk of VTE and triglycerides are on average 21 mg% higher. However, smoking has a controversial influence. Ageno does not support its role, while two recent studies confirm previous results on the effect dependent on the daily number of cigarettes. Therefore, more than 25 cigarettes doubles the risk of VTE, and more than 35 cigarettes triples it (25,26). Information is extended to other risk factors for ATT. Although there are data supporting that the metabolic syndrome increases the risk of VTE by up to 84%, it is not clear whether actually it is its components, mainly abdominal obesity and non-alcoholic fatty liver, that have a major role, (6, 22). There are also controversies about the influence of age, prevalence in males, and involved mechanism. The central role of prothrombotic status activated by athero-genic mediators released by adipocytes (leptin, IL-6, TNF-α) has been stated. The VLDL trigger effect on platelet activation and PAI-1 gene expression or hyperglycemia effect on the structure and function of fibrin, generating a clot more resistant to fibrinolysis (27), is discussed. Microalbuminuria is suggested as an independent risk marker for VTE and its recurrence by the Dutch trial PREVEND. The study states a direct relationship between the amount of urinary albumin and the annual incidence of VTE (28). Hormone replacement therapy is classically linked to both a triple risk of atherothrombotic events and a double risk of VTE, and Pomp’s study confirms the synergistic role of smoking (1.29). Nutritional factors are supported by numerous studies. In a cohort of 14,962 patients followed-up for 12 years, daily consumption of fruits and vegetables was associated with decreased risk, whereas dietary intake of red and processed meat doubled the incidence of VTE. Eating fish at least once a week is also demonstrated to reduce the risk by 30-45% (Stefen LM cited by 6). Other prospective studies independently associate stress with increased risk of VTE in men (30). An interesting idea is suggested by Sorensen demonstrating increased risk of VTE within the first 3 months in patients with cardiovascular diseases that are potential sources of thrombi (AMI, heart failure, atrial fibrillation, especially right heart valvulopathies) in the absence of DVT (31). Finally, risk factors and clinical conditions such as hyperhomocysteinemia, thrombophilia, anti-phospholipid syndrome, malignancy, chemotherapy, specific acute infections (AIDS, Chlamydia pneumoniae), intestinal inflammatory diseases, etc. have been linked with both arterial and venous thrombotic events (22). If the data on traditional risk factors are largely consistent, the underlying mechanisms responsible for this association are controversial. The classic triad of Virchow is still valid in VTE, but it is now believed that stasis and hypercoagulability are critical as experimentally the vascular endothelial surface is initially intact (27).
Activation and endothelial injury play a crucial role as a minor damage unprovoked by immobilization or surgery increases by 5-fold the risk of DVT (32). Based on experimental models of venous thrombosis and using electron microscopy studies, Mackman shows the role of inflammation in endothelial activation and injury, irrespective of hypoxia. It results in P-selectin, E-selectin and von Willebrand factor expression. Activated endothelial cell captures leukocytes, platelets and microparticles derived from activated monocytes. Both microparticles (membrane fragments) and neutrophils express tissue factor. It is considered that tissue factor activity is crucial for the activation of coagulation cascade and fibrin-rich, erythrocyte-rich thrombi formation (33,34). Venous wall inflammation is an early phenomenon, present in patients with uncomplicated varicose veins being induced by oxidative stress similarly to damage of the arterial wall (35). Clinical studies support the role of inflammation linking the intestinal inflammatory diseases, vasculitis or genetic polymorphisms of interleukins with the increased risk of VTE (6). For example, ARIC study demonstrates an increase by 76% of VTE risk related to C-reactive protein (36), and JUPITER trial states a 43% lower risk in patients with initially increased C-reactive protein level treated with rosuvastatin (37). Recent data also support the role of inflammation in promoting atherogenesis, destabilization of atheroma plaque, and atherothrombotic complications. The focus is on neutrophils, as there is a direct link between neutrophil count, neutrophil-related biomarkers (myeloperoxidase, elastase), and cardiovascular risk factors (38). Activated platelet-derived microparticles also seem to be involved in coronary events by inducing and stimulating massive platelet and fibrin deposition (39). All evidence supports the causal relationship between VTE and ATT, centered on the role of inflammation.

HOW THE CURRENT CONCEPT SHOULD BE APPROACHED IN PRACTICE?

In clinical practice, is fundamental to use an integrated clinical, laboratory and therapeutic approach for assessing each patient with a first arterial or venous thrombotic event. According to this concept, VTE is an early event that expresses a generalized vascular disease, present from the beginning in both types of circulation. As a result, therapeutic interventions should be similar as for a patient with severe ATS, with emphasis on active detection and optimization of risk factors. A routine screening for asymptomatic ATS following a VTE episode remains a goal of future studies (1). To the opposite, patients with atherothrombotic CVE are an underrecognized population at risk for VTE. The analysis of the Healthcare Cost and Utilization Project Nationwide Inpatient Sample database found that more than 1 million patients with AMI and stroke develop VTE (6). Identification of VTE high risk subgroup in this large category of patients may be an additional target in its primary prevention. According to evidence from trials, major cardiovascular risk factors optimization could also be an additional way of prevention (1,6). When referring to laboratory assessment, an ambitious goal is to determine individual vulnerability inherent in venous thrombosis. Although in practice there are multiple parameters for coagulation and fibrinolysis assessment, most patients with VTE have normal tests (40). The development of sensitive tests specific to
other pathogenic pathways is a currently studied direction. Platelet membrane phospholipid, inhibition of leukocyte-released tissue factor or monocyte recruitment are some of the studied targets. Also, platelet clot volume or the particular fibrin clot phenotype characterized by a highly branched network structure with lower clot permeability and prolonged lysis time are suggested as common mechanisms linking arterial and venous thrombosis (40,41). For therapy, the major objective remains prophylaxis optimization. The multicenter, multinational trial ENDORSE points out that 51.8% of hospitalized patients have increased risk of VTE, and yet, the rate of suitable prophylaxis is reduced – 58.5% in surgical patients and 39.5% in high risk medical patients (42). Therefore, for vulnerable patients the U.S. medical system recommends implementation of computerized algorithm-based strategies, and the introduction of this issue to health policies (43). The anticoagulation benefit is extended to prophylaxis of recurrences, so as in patients with unprovoked VTE an indefinite period is recommended (6). The potential for primary prevention of AMI (reducing the incidence by 39%) is an additional reason according to a randomized trial in healthy men at high cardiovascular risk (5). A largely debated direction is the role of aspirin in primary and secondary prevention of VTE. The potentially beneficial effect is based on inhibition of platelet activation and aggregation together with interfering with acetylation of protein molecules such as fibrinogen (39). Early studies and the related APTc meta-analysis indicate a 25-30% decrease of VTE incidence in hospitalized patients at high risk treated with aspirin. The same data suggest the prevention of VTE recurrence when aspirin is given to patients at risk higher than 2% for coronary heart disease or stroke who had discontinued the oral anticoagulant therapy (44). Two recent trials with similar design support the benefit of aspirin in secondary prevention of unprovoked VTE. The WARFASA prospective study demonstrates that aspirin 100 mg/day reduces the recurrence rate by about 40% without increasing bleeding risk in patients who had completed 6 to 18 months of oral anticoagulation treatment (45). Similarly, the ASPIRE study states a 32% reduction in the rate of recurrent VTE and by 34% of major CVE without clinically relevant bleeding risk during 37.2 months of follow-up (46). However, current guidelines do not recommend antiplatelet prevention given the higher net benefit of anticoagulant therapy, including new anticoagulants. The role of antiplatelet agents for long-term prevention of VTE remains to be defined, but it is a cheap, well-known, widely available, more secure therapy, with extended benefits in the primary prevention of atherothrombotic events when anticoagulation is contraindicated. Finally, a highly debated and controversial topic is the role of statins in VTE. The potential beneficial effect is based on the antithrombotic role mediated by the decrease in platelet activation, up-regulation of thrombomodulin expression by the endothelial cells, increased susceptibility of fibrin to lysis, as well as on the anti-inflammatory role focused on reducing tissue factor, C-reactive protein, IL-6 and IL-8, MCP-1 expression (47). A secondary analysis in the JUPITER trial supports the benefit of rosuvastatin 20 mg/day in decreasing by 43% the risk of symptomatic VTE in healthy subjects. Two recent meta-analyses admit the benefit of statins in primary prevention of VTE, but at a much lower level (about 11%). The need to adjust data related to selected population, objec-
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tive, associated therapy, age, statin type, etc. account for the attenuated optimistic results of previous studies (48,49). The only way to clarify the role in primary VTE prevention is to initiate a randomized prospective trial, with venous thrombosis as primary end-point (50). Recently, information about the beneficial effect of statins has been supplemented with data on secondary prevention. Two recent Danish studies state a reduction by about 50% in the rate of recurrent VTE associated with a 30% reduction in the incidence of CVE and the relationship is dose dependent but not influenced by antivitamin K therapy. As with the primary prevention, the results need to be clarified by prospective randomized placebo-controlled trials (51, 52).

Evidence from clinical studied suggest that a new integrated approach should be applied to patients with venous or arterial thrombosis. An individualized attitude based on comprehensive assessment of total prothrombotic burden is required in order to provide a more efficient antithrombotic prevention.

REFERENCES

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