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PATHOPHYSIOLOGY, CAUSES AND PHARMACOLOGICAL STUDY OF ARTERIAL THROMBOSIS

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ABSTRACT

Arterial thrombosis is the formation of blood clots in the deep veins. It commonly affects the deep leg veins or the deep veins of the pelvis. It is a potentially dangerous condition that can lead to preventable morbidity and mortality. Arterial thrombosis affects 0.1% of persons per year. The approach to making a diagnosis currently involves an algorithm combining pretest probability, D-dimer testing, and compression ultra sonography. This will guide further investigations if necessary. Prophylaxis is both mechanical and pharmacological. The goals of treatment are to prevent extension of thrombi, recurrence of thrombi, pulmonary embolism and also prevention of complications.DVT is a potentially dangerous condition with risk factors. The mainstay of treatment is anticoagulant therapy. Low-molecular-weight heparin, unfractionated heparin, and vitamin K antagonists have been the treatment of choice. Currently anticoagulants specifically targeting components of the common pathway have been recommended for prophylaxis. These include Fondaparinux, a selective indirect factor Xa inhibitor and the new oral selective direct Thrombin inhibitors (Dabigatran) and selective factor Xa inhibitors (Rivaroxaban and Apixaban). Others are currently undergoing trials. Thrombolytics and vena caval filters are very rarely indicated in special circumstances.

KEYWORDS: *Deep vein thrombosis, pulmonary embolism, venous thromboembolism, prevention, Treatment.*

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INTRODUCTION

Acute limb ischemia is defined as a sudden decrease in limb perfusion that causes a potential threat to limb viability. The threatened limb may manifest as ischemic rest pain or the development of tissue loss (ulcers, gangrene).The clinical presentation depends upon the aetiology and whether the patient has underlying peripheral artery disease. Patients who present later than two weeks after the onset of the acute event are considered to have chronic limb ischemia[1]. The treatment of acute arterial occlusion remains a challenge for vascular specialists. Surgical thromboembolectomy and bypass grafting were important for therapy for several years. Consequently, thrombolytic therapy and percutaneous transluminal angioplasty (PTA) are treatment options for selected patients. Despite these advances, the morbidity, mortality and limb loss rates from acute lower extremity ischemia remain high. Thus, early diagnosis and rapid initiation of therapy are important to solve the ischemic extremity.

ETIOLOGY AND CAUSES

Acute arterial occlusion occurs due to an embolus from proximal source lodging into a more distal vessel, acute thrombosis of a stent or graft and dissection of an artery or direct trauma to an artery. Arterial embolism is an abrupt interruption of blood flow to an organ or body part due to a clot. An embolus is a blood clot or a component of plaque that acts like a clot. Embolus is the process in which more than one clot or piece of plaque. When the clot moving from one site to another site in the body is called an embolism. An arterial embolism is caused by one or more clots. The clots are stuck in an artery and block the blood flow. Due to blockade of an artery, starvation of oxygen supply occurs to the tissues, which can leads to damage or death of cells occurs in tissue (necrosis).Arterial emboli usually occur in the legs and feet. Few may occur in the brain, causing a stroke or in the heart causing a heart attack. Less common sites include the kidneys, intestine and eyes. An Atrial fibrillation is a major risk factor for arterial embolism. The risk of an embolism increases when factors that contribute to form clots are increased. Other risk factors include injury or damage to an artery wall and situations that increase blood clotting. One more condition is that posses a high risk for embolization is mitral stenosis. Usually an embolus is formed due to hardening in the aorta and other large blood vessels. These clots can break loose and flow down to the legs and feet. Paradoxical embolization occurs when a clot in a vein enters the right side of the heart and passes through a hole into the left side. The clot can move towards an artery and block the blood flow to the brain and other organs. If a clot associates the arteries supplying blood flow to the lungs is called a pulmonary embolus.

PATHOPHYSIOLOGY

EMBOLIC VESSEL OCCLUSION

The majority of arterial emboli arise in the left heart where they form the structural and functional abnormalities. Most other emboli originate in arteries. In general, emboli that originate more proximally in relation to the heart have more potential targets available to them. Thus clots originating in the aortic arch can potentially embolize to any arterial branch in the body. Atherosclerotic plaque formed in more distal arteries such as the carotids are embolize to the brain causing strokes or transient ischemic attacks (TIA's), while plaques in the infra-renal aorta are far more likely to cause lower extremity ischemia. Retrograde embolization may occasionally occur during the late diastolic flow reversal seen with decreased heart rates. This process is believed to allow large descending aortic plaques to cause strokes [2].The ultimate probability of an embolus reaching any specific arterial bed is determined by the relative amount of blood flow that bed receives and the anatomy of the arterial branches supplying that area. [3] Larger emboli tend to lodge at points of acute narrowing such as arterial bifurcations or areas of luminal stenosis, whereas smaller emboli may travel distally to lodge in tiny arterioles [4]Although arterial embolic disease shares many features with arterial thrombosis, there are important distinctions. Differentiating an acute embolic event from an acute thrombotic event is in fact one of the conundrums faced by medical practitioners. Both processes typically affect individuals with risk factors for heart disease and peripheral arterial disease. [5]Some situations such as limb ischemia, making the correct diagnosis early may allow for expedited care. However, individuals with embolic ischemia usually do not have time to build collateral circulation and therefore often present with more sudden and severe symptoms such as threatened limb loss [6].

SYMPTOMS

SYMPTOMS OF AN ARTERIAL EMBOLISM IN THE ARMS OR LEGS MAY INCLUDE

Cold arm or leg
Decreased or no pulse in an arm or leg
Fingers or hands feel cool
Lack of movement in the arm or leg
Muscle pain in the affected area
Muscle spasm in the affected area
Numbness and tingling in the arm or leg
Pale colour of the arm or leg (pallor)
Weakness of an arm or leg[7]

EXAMS AND TESTS

TESTS TO DIAGNOSE ARTERIAL EMBOLISM

Angiography of the affected extremity or organ
Doppler ultrasound exam of an extremity
Duplex Doppler ultrasound exam of extremity
Echocardiogram
MRI of the arm or leg
Myocardial contrast echocardiography (MCE)
Plethysmography
Transcranial Doppler exam of arteries to the brain
Transesophageal echocardiography (TEE)
This disease may also affect the results of the following tests:
Euglobulin lysis time (ELT)

Factor VIII assay
Isotope study of the affected organ
Plasminogen activator inhibitor-1 (PAI-1) activity
Platelet aggregation test
Tissue-type plasminogen activator (t-PA) levels [8-11].

TREATMENT

Arterial embolism requires prompt treatment at a hospital. The goals of treatment are to control symptoms and to improve the interrupted blood flow to the affected area of the body. The cause of the clot, if found, should be treated to prevent further problems [12].

MEDICATIONS INCLUDE

- Anticoagulants (such as warfarin or heparin) can prevent new clots from forming
- Antiplatelet medications (such as aspirin or clopidogrel) can prevent new clots from forming
- Painkillers given through a vein (by IV)
- Thrombolytic(such as strepto- kinase) can dissolve clots[13]

SOME PEOPLE NEED SURGERY. PROCEDURES INCLUDE

- Bypass of the artery (arterial bypass) to create a second source of blood supply
- Clot removal through a balloon catheter placed into the affected artery or through open surgery on the artery (embolectomy)
- Opening of the artery with a balloon catheter (angioplasty) with or without a stent

POSSIBLE COMPLICATIONS

- Acute MI
- Infection in the affected tissue
- Septic shock
- Stroke (CVA)
- Temporary or permanent decrease or loss of other organ functions
- Temporary or permanent kidney failure
- Tissue death (necrosis) and gangrene
- Transient ischemic attack (TIA)

METHODS OF THERAPY SYSTEMIC INTRAVENOUS INFUSION

Intravenous administration of a thrombolytic agent through a peripheral vein. It must be recognized that high-dose intra-arterial infusions will elevate the systemic action of the agent. Therefore “systemic infusion” refers to the site of infusion, not to the patients’ response to the plasminogen activator. Systemic intravenous infusion for limb artery occlusion was investigated in the 1960s and 1970s but has been almost completely abandoned[14].

REGIONAL INTRA-ARTERIAL INFUSION

With the use of nonselective intra arterial catheter, directly infuse the thrombolytic agent, the catheter is placed proximal to the occluded vessel. With selective intra-arterial infusion, the distal end of the intra-arterial catheter should keep within the occluded artery, but its tip is proximal to the thrombus. The results with intra arterial thrombolytic therapy improved as procedural difficulties were overcome and gradual changes in infusion methods were introduced.

GUIDE WIRE TRAVERSAL TEST

A guide wire is passed through the length of the thrombus before the initiation of prolonged infusion with the catheter fixed in the proximal thrombus. Whenever a nonhydrophilic guide wire is passed, initial successful lysis of “acute” thrombi will occur.

INTRATHROMBUS INFUSION

The thrombolytic agent is delivered by an intra-arterial catheter fixed within the thrombus. This can distribute the drug and maximize the concentration of the drug within the thrombus and directly pass the agent to the locality of thrombus bound plasminogen. The inability to fix a catheter in the proximal thrombus is predictive of failure of lysis.During this process, a catheter is positioned in the most of the distal part of the thrombus. It is back down proximally as the thrombolytic agent is delivered along the entire length of the thrombus.

INFUSION METHODS

Stepwise infusion involved in the placing the tip of the catheter within the proximal thrombus and infusing a fixed dose of lytic agent over a short duration of time. As the thrombus diffuses, the catheter is advanced and the process can be repeat until the thrombus is dissolved. This method is intensive and requires the patient to be the angiography during the entire treatment. Continuous infusion refers to the conventional infusing, the lytic agent using a constant infusion pump. This is the standard process used for catheter-directed intrathrombus infusion.

CURRENT STRATEGIES

Present therapeutic strategies for the treatment of arterial thrombosis are based on receptor system. Collage is designated as the primary platelet agonist. While agonist is capable of activating platelets, including the activation of the receptor function of GP IIb-IIIa for the binding of fibrinogen and von Willebrand factor (VWF) to initiate platelet aggregation, stable aggregation of platelets are developed by two autocrine factors generated upon platelet stimulation: Adenosine Di phosphate (ADP), released from platelet dense bodies and Thromboxane A2 (TXA2), generated by the sequential actions of COX-1 and Thromboxane Synthase on the arachidonic acid. This is released from membrane phospholipids. GP IIb-IIIa antagonists (Eptifibatide, Abciximab, Tirofiban).

- P2Y12 inhibitors (clopidogrel, ticlopidine)],
- To block the generation of the agonists {e.g. the Cox-1 inhibitor aspirin and Factor Xa (FXa) inhibitors [low molecular weight (LMW) heparins]}, or
- To antagonize the agonist itself (e.g. thrombin inhibitors (standard heparin, direct thrombin inhibitors)].

ASPIRIN

The clinical successes achieved by the current therapies to treat arterial thrombosis have been remarkable.

Aspirin was the most widely used drug. The trend toward the widespread use of this drug to block arterial thrombosis was first indicated by the findings of the ISIS-2 trial which demonstrated that aspirin reduced mortality from acute MI to a rate that is similar to that of the thrombolytic agent, streptokinase [15].The data from multiple trials summarized by the Antiplatelets Trialist's Collaboration found a 25% relative risk reduction by aspirin of vascular death, MI or stroke, vs. placebo which led to the widespread adoption of aspirin as standard therapy for primary and secondary prevention of arterial ischemia. This collaboration also reviewed the clinical trials using aspirin to show that low-dose aspirin (75–150 mg daily) is effective for long-term use. While the half-life of aspirin in humans is relatively short (· 20 min), its effect persists for the lifetime of an affected platelet in circulation as the drug acetylates Cox-1 at serine-529, located at the active site of the enzyme [16].

THIENOPYRIDINES

The second most widely used of the antiplatelet drugs for chronic use are thienopyridines targeting P2Y12. This class of drugs are clopidogrel, and its precursors are ticlopidine, act via irreversible inhibition of the platelet P2Y12 receptor. The four antithrombotic drug classes include: (1) Thrombin inhibitors; (2) GP IIb-IIIa antagonists; (3) P2Y12 antagonists; and (4) inhibition of TXA2 production[17].

TICLOPIDINE

Ticlopidine has been shown to be efficacious in conditions such as claudication, unstable angina, and cerebrovascular disease[18]. However, the incidence of neutropenia associated with ticlopidine led to the development of a second-generation thienopyridine, clopidogrel, with increased potency and fewer side-effects. In the CAPRIE trial, clopidogrel was shown to be more efficacious than aspirin, particularly in high-risk patients (diabetics and those with a history of prior revascularization). Subsequently, the cure study demonstrated that patients with unstable angina or non-ST segment elevation MI received a 20% relative risk reduction if they were randomized to clopidogrel plus aspirin vs. placebo plus aspirin.

GP IIB-IIIA ANTAGONISTS

The GP IIb-IIIa antagonists are designed to bind to the integrin on unstimulated platelets and on platelets after stimulation. GP IIb-IIIa is an attractive antiplatelet target, on the · final common pathway mediating platelet aggregation irrespective of the agonist used to induce platelet activation, platelet specific, and responsible for a variety of aggregation dependent platelet functions including those in coagulation, inflammation, fibrinolysis and vascular cell proliferation[19]. Early trials of the LMW heparin enoxaparin in unstable angina and non-Q wave MI patients demonstrated improved efficacy over standard heparin and the drug has emerged as the most commonly used LMW heparin[20]. Fondaparinux, a synthetic penta saccharide, also utilizes the ant thrombin III binding region of heparin and has been found to be an appropriate anticoagulant for prevention of deep vein thrombosis in orthopedic surgery.Unlike enoxaparin, which inhibits both thrombin and FXa, fondaparinux acts only as an indirect FXa inhibitor.

FONDAPARINUX

Venous thromboembolism prevention trials have been demonstrated that Fondaparinux has a superior efficacy than Enoxaparin. The present clinical trials of Fondaparinux in coronary disease patients will show if the concept of attaining superior efficacy by inhibition of FXa alone, can be accomplished in arterial settings. Arterial thrombosis developed at sites of mechanically disrupted atherosclerotic plaque, is triggered by a multitude of highly thrombogenic materials (eg.fibrillar collagen and tissue factor). This is the result of complex interrelations between coagulation and platelets orchestrated by local rheological conditions. An emerging strategy in the treatment of arterial thrombosis is the combination of antithrombotic provides greater therapeutic benefit than provided by drugs used singly.

COMBINATION OF ASPIRIN & CLOPIDOGREL

Accordingly, the combination aspirin-plus-clopidogrel is rapidly becoming the new standard of care for the management of patients with non-ST segment elevation ACS and in patients undergoing a PCI. In support of this trend, the CURE study demonstrated that aspirin-plus-clopidogrel caused a 20% relative risk reduction of vascular death, MI, and stroke compared with aspirin-plus-placebo .The dual antiplatelet therapy (aspirinplus-clopidogrel) was also more effective and safer than a combination aspirin-plus-warfarin in coronary artery stenting [21].The remarkable efficacy of the dual anti-platelet therapy has prompted the initiation of several clinical trials in indications as diverse as atrial fibrillation, peripheral arterial disease, peripheral arterial bypass surgery, secondary and highrisk primary prevention, acute ST-segment elevation MI and heart failure [22].Although anticoagulants were routinely used in the development of antiplatelet agents, analysis of these data shows that these combinations often provided a clinical benefit that was greater than anticipated. We and others have used thrombosis models to evaluate synergisms between various pathways. Because TXA2 and ADP activate different pathways, it was anticipated that combinations of inhibitors of the two pathways would confer a Treating arterial thrombosis 1579-2005 International Society on Thrombosis and Haemostasis greater protection against thrombotic events. However, rather than an additive effect, the two drugs used together were synergistic [23].

CLOPIDOGREL

The primary limitation of clopidogrel is that this drug demonstrates weak and somewhat variable inhibition of P2Y12. Following a 600-mg loading dose of clopidogrel, the extent of inhibition of ADP-induced aggregation varied from 33% to 78% in healthy individuals, at 6 hr post-dosing[24]. This effect is further exaggerated in patients undergoing PCI or stent placement [25].The antithrombotic effect of clopidogrel is likely to be dependent on a number of factors including but not limited to variations in P450s, polymorphisms of the P2Y12 receptor and receptor signalling pathways. Measurements of platelet aggregation and markers of platelet activation show that clopidogrel resistance is detected in 31% of the patients on day 5 and 15% of the

patients on day 30 of the treatment regimen. A prospective study of PCI patients with non-ST segment elevation MI showed that up to 25% of the patients were resistant to clopidogrel.

SUMMARY& CONCLUSION

Acute arterial thrombosis is the major cause for most cases of myocardial infarction and of about 80% of strokes causing death in the developed world. Venous thromboembolism is the third leading cause of cardiovascular associated death. The pathogenic changes that occur in the blood vessel wall and in the blood itself resulting in thrombosis are not fully understood. Understanding these processes is crucial for developing safer and more effective antithrombotic drugs. According to the National Heart, Lung, and Blood Institute (NHLBI) convened a working group (WG) to develop a research agenda to enhance understanding and effectiveness of antithrombotic therapy The working group (WG) demonstrate that the factors should be affect with the efficacy, safety, and predictability of antithrombotic therapies. Optimization of antithrombotic therapy is important and improves upon present interventions, and individually tailors therapy to increase efficacy and safety and to avoid failure. The clinical applicability and cost effectiveness of individually tailored antithrombotic therapy based on functional and genetic testing. The WG characterized and discussed the challenges for antithrombotic therapy in four steps, such as therapeutic strategies, antithrombotic agents, pharmacology and pharmacogenetics. Overall, the WG identified and prioritized the most pressing clinical needs to focus future research and translational efforts.

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CONFLICT OF INTEREST

Conflict of interest declared none.

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