Phlegmasia caerulea dolens and venous gangrene

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Phlegmasia caerulea dolens and venous gangrene are related clinical entities that arise due to acute massive thrombosis of the venous drainage of an extremity. While these venous disorders are rare, it is difficult to compute an exact incidence for PCD or venous gangrene. A spectrum of disorder exists, ranging from mild calf vein thrombosis through iliofemoral deep vein thrombosis to the severe conditions of PCD and venous gangrene which are threatening to both life and limb. The first description of PCD is attributed to Fabricius Hildanus in the sixteenth century, and the term was first used in 1938 by Grégoire to distinguish bischaemic forrow of venous thrombosis from the more common non-ischaemic entity, then called phleghmasia alba dolens. PCD is characterized by limb swelling, cyanosis and pain. It represents a reversible phase of ischaemic venous occlusion that may progress to venous gangrene in 40–60 per cent of cases. Venous gangrene is always preceded by PCD, starting distally and spreading proximally. Gangrene may involve skin and subcutaneous tissue, or muscle, or both, and so may threaten limb viability.

Pathophysiology

The fundamental process that occurs in PCD and venous gangrene is total or near-total thrombotic occlusion of venous drainage, including the microvascular collaterals. Single or multiple obstructions to the main veins of a limb have not been shown to produce any important obstruction to the venous circulation. In dogs, only division of all the veins at the root of the hind limb leads to changes consistent with those seen in venous gangrene. PCD is characterized by patency of a number of major or collateral veins at the root of an extremity, which accounts for the potential reversibility of the ischaemia. In venous gangrene there is complete obstruction to the venous outflow from the limb.

Obstruction to venous outflow leads to changes in the forces that govern inflow and outflow of fluid at both the arterial and venous end of the capillary. Under the normal Starling equilibrium, hydrostatic pressure drives fluid out of the capillary into the interstitium at the arterial end and fluid is reabsorbed at the venous end where colloid oncotic pressure exceeds hydrostatic pressure. When the venous outflow is occluded, hydrostatic pressure at the venous end of the capillary rises to exceed colloid oncotic pressure and interstitial oedema develops. The development of oedema pressure may reach 16 to 17 times the normal value within 6 h of occlusion. The development of oedema produces interstitial tissue pressures of 25–48 mmHg (normal pressure 0–10 mmHg) within 1–2 days. Shock develops as a consequence of loss of plasma. Experimentally, large volumes of fluid have been shown to be lost into the affected limb. Fluid loss into the interstitial spaces as great as 6–10 litres has been reported within 5–10 days of the onset of venous thrombosis.

There is debate over the mechanism of arterial insufficiency associated with PCD. A few case reports have described occlusive thrombosis of small peripheral arterioles in venous gangrene, but others have confirmed arterial patency by angiography and anatomical dissection at autopsy. Consequently, spasm has been mooted, although there is no supporting evidence for this theory. Periarterial sympathectomy and acetylcholine fail to produce any improvement in tissue perfusion. Neither decrease in blood flow nor change in arterial pulse amplitude suggestive of spasm has been demonstrated following experimental venous ligation and massive venous occlusion. It therefore seems likely that ischaemia results from collapse of small arteries when critical closing pressure is exceeded. Under normal conditions arteries remain open due to an equilibrium between pressure and tension in the vessel wall. Tissue pressure is close to zero and has little effect on transmural pressure. Once hydrostatic pressure in the vessel falls below a critical point, tension in the wall will cause collapse of the vessel. In PCD and venous gangrene, hydrostatic pressure falls due to hypotension and tissue pressure increases due to oedema. If hydrostatic pressure falls to 50 mmHg, arterial wall tension can overcome the transmural pressure of 10 mmHg, causing the vessel to collapse.
Aetiology

A relationship between malignancy and thromboembolic disorders has long been recognized\(^1\) and an underlying malignancy may be present in 20–40 per cent of patients\(^3,15,18\). True venous gangrene most often occurs in association with some form of malignant disease\(^18,21\). Often the tumour has not previously been detected\(^22\). Abnormalities of blood coagulation have been found in up to 95 per cent of patients with cancer, although clinically apparent thrombosis occurs in only 5–15 per cent\(^23,24\). In many instances where there is no apparent cause for thrombosis an underlying primary hypercoagulable state is found, such as intrinsic deficiencies of antithrombin III, proteins C or S, or plasminogen\(^25,26\). Lupus anticoagulant may be detected\(^27\). Recently, resistance to activated protein C has been demonstrated as a hereditary genetic defect that is frequently found in patients with recurrent venous thromboembolism\(^29,30\). Patients should be investigated for the presence of all these hypercoagulable states. PCD or venous gangrene may also occur in the following situations: after surgery or trauma, postpartum, in patients with a history of deep vein thrombosis, and in association with a variety of inflammatory conditions such as ulcerative colitis\(^31\), pneumonitis and gastroenteritis\(^31\). Prolonged immobility is a precipitating factor. PCD and venous gangrene have been reported as complications of severe mitral stenosis with heart failure\(^31\), after insertion of a vena cava filter\(^32\), and following intravenous drug abuse\(^33\). In approximately 10 per cent of cases no cause is found\(^3,17,19\).

Clinical features

Ischaemic venous thrombosis has been reported in patients ranging in age from 6 months to 87 years\(^17\). The highest incidence occurs in the fifth and sixth decades\(^18\). Women are affected more often than men\(^4\) in a ratio of 2:1. In the lower limb the left side is affected more often than the right\(^17,18\). This is believed to be the result of compression of the left iliac vein by the overlapping right iliac artery\(^34\). Symptoms of PCD are preceded by those of the commoner, non-ischaemic form of phlebothrombosis, phlegmasia alba dolens, in 50–60 per cent of cases\(^3,18\). Speed of onset is variable. Some cases are fulminant and can stimulate arterial occlusion, while others are more indolent and progress gradually from simple iliofemoral deep venous thrombosis to massive venous occlusion.

PCD is characterized clinically by the feature triad of swelling, pain and cyanosis; diagnosis is initially made on clinical grounds. Massive oedema develops rapidly, and the involved limb has a tense and firm quality. In a few instances oedema may extend to the trunk. Sequestration of plasma in the limb may be so intense as to produce cutaneous blebs or bullae. Pain is a constant feature and may begin over the femoral triangle, but it rapidly spreads to affect the whole limb. The pain is agonizing with a bursting quality, and may be difficult to control. Cyanosis is a striking feature, beginning distally, where it remains most intense, but spreading to involve the entire limb. Varying degrees of arterial hypotension, from mild to severe shock, have been reported in patients with PCD\(^25\). Arterial insufficiency may develop rapidly and arterial pulses diminish or disappear; excessive oedema may make palpation of pulses difficult and pedal pulses are palpable in only 17 per cent of patients. The femoral pulse is often weak and is absent in 9 per cent of patients\(^1\).

Venous gangrene develops in 40–60 per cent of patients with PCD\(^3,4\). Gangrene starts distally and progresses proximally; it usually occurs within 2 days of the development of arterial insufficiency, although in some cases it has occurred within hours of the loss of pulses. Superficial gangrene accounts for 10–20 per cent of cases of venous gangrene. In this state arterial pulses are usually present, in contrast to deep gangrene involving muscle when pulses are usually absent\(^3,18\).

The reported incidence of pulmonary embolism varies from 12 per cent\(^36\) to 40 per cent\(^3,57\) and the incidence is increased when tissue necrosis is present. In a series in which only patients with clinical, radiological and electrocardiographic evidence of pulmonary embolism were included, the incidence was 20 per cent\(^3\).

Involvement of the upper limb is rare. Haimovic\(^18\) reported arm involvement in only 4 per cent of patients with PCD, in contrast to venous gangrene which was associated with a 19 per cent incidence of upper limb thrombosis. Patients with upper limb ischaemic venous thrombosis usually have at least two of the following three features: (1) haemodynamic compromise due to poor cardiac output; (2) thrombosis of central veins (subclavian or axillary), often due to intravenous central venous catheters; (3) occlusion of peripheral veins\(^38,39\). Treatment and outcome are similar to those for the lower limb.

Contrast venography, which has been widely used to confirm the diagnosis and assess the extent of venous thrombosis, is generally regarded as the ‘gold standard’ investigation. However, venography may not be technically possible and is uninterpretable in 20–25 per cent of patients\(^39,40\). It is invasive, costly, and precipitates thrombosis in 2–3 per cent of normal cases\(^41\). Complete occlusion results in non-visualization of the deep venous system, and ascending venography is therefore of little diagnostic value in the assessment of PCD. In contrast to ascending venography, descending venography provides improved images of the iliofemoral system. However, it is almost always impossible to obtain descending venograms via the ipsilateral femoral vein. Although descending venography may be possible via the contralateral femoral vein, involvement of the inferior vena cava frequently prevents this; descending venography via the upper limb is then the technique of choice.

Non-invasive assessment of thrombosis using continuous-wave or complex Doppler ultrasonography provides a rapid and accurate method of assessment\(^42,43\). A review of studies assessing duplex ultrasonography against contrast venography in the diagnosis of proximal deep venous thrombosis reported a sensitivity of 93 per cent and specificity of 98 per cent for ultrasonography\(^44\). Ultrasonographic methods can be used at the bedside, avoiding transfer of severely ill patients to the radiology department.

Treatment

Many treatments have been advocated for PCD and venous gangrene, including sympathectomy, hot packs, sympatholitics, antivasospastic drugs, phenylbutazone, hyaluronidase, fibrinolysin and steroids, all to little effect. Some consider PCD as representing a terminal event in which efforts at therapeutic intervention are futile. Following progression of PCD to venous gangrene, therapeutic intervention is even less likely to be...
Successful treatment is aimed at preventing propagation of thrombus and reducing venous hypertension, so preserving tissue viability. Initial management involves correction of hypotension by intravenous administration of fluids to improve tissue perfusion as far as possible. Bed rest and elevation of the affected limb in PCD encourages venous drainage through venous channels that remain patent; elevation is an important aspect of early management. The leg must be elevated high in the air, not merely laid on a pillow. Large foam wedges may be used, or the affected limb may be suspended from a high frame at the foot of the bed in the manner of gallows traction. Failure to achieve adequate elevation may account for progression to venous gangrene.

Definitive management thereafter involves three forms of treatment: anticoagulation, thrombectomy or thrombolysis, in any combination. Anticoagulation, fluid resuscitation and adequate elevation allow successful treatment in a significant proportion of patients with PCD. An immediate intravenous bolus dose of heparin, 10000–15000 units, is recommended, followed by a continuous infusion to maintain the activated partial thromboplastin time at twice the control value. If symptoms fail to resolve by 6–12 h, additional measures such as thrombolysis or thrombectomy are required. A marked contrast is seen in response to treatment between patients with uncomplicated PCD and those with venous gangrene. The combined results for cases reported from 1967 to 1985 (38 patients with 45 affected lower limbs) suggest that heparin is beneficial in all cases of uncomplicated PCD and in none of venous gangrene. Heparin should remain the initial treatment of choice for uncomplicated PCD as it requires only intravenous cannulation and has fewer side-effects than thrombolysis. However, heparin-induced thrombocytopenia can develop, which requires coumarin anticoagulation to be substituted for heparin.

The first thrombectomy for PCD was performed by Leriche and Geisendorf in 1939. This operation has been recommended as both a first-line and a secondary treatment following failure of anticoagulation. Thrombectomy was enthusiastically advocated in the 1960s as the most logical treatment of PCD. It removes the massive venous occlusion at the root of the extremity that is the fundamental underlying cause of the condition. Thrombectomy is aimed also at preventing propagation of the thrombosis and subsequent gangrene, preventing pulmonary embolism, and avoiding serious postphlebitic sequelae. Early descriptions of thrombectomy for simple iliofemoral thrombosis claimed an 85 per cent patency rate if done within 10 days of the onset of thrombosis and reported normal legs with minimal or no oedema in 81 per cent of survivors. However, higher rates of rethrombosis have been reported in thrombectomy for PCD. A 5-year follow-up in patients with good early results discovered 94 per cent with significant oedema and stasis still requiring compression stockings. Two-thirds of postoperative deaths resulted from pulmonary embolism. While thrombectomy offers a treatment that can provide rapid relief of venous and compartmental hypertension, patients may be too ill to undergo general anaesthesia for the procedure. Thrombectomy fails to clear thrombus distally from small venous channels and consequently yields poor results in patients with venous gangrene. It does not prevent future venous stasis due to valvular incompetence. For these reasons thrombectomy is now recommended only for patients in whom anticoagulation therapy has failed or is contraindicated, or for those with impending venous gangrene. Thrombectomy combined with adjunctive regional thrombolysis may improve results. Fasciotomy has been used alone or in conjunction with thrombectomy in a small number of patients, with indifferent results. Theoretically it offers advantages in reducing compartmental pressures, but prolonged wound healing and risk of infection have prevented this technique playing much part in the treatment of PCD or venous gangrene.

Thrombolysis offers an attractive alternative method of treatment for both PCD and venous gangrene. Thrombolytic agents can be delivered into the occluding thrombus, allowing lysis in both major veins and smaller venous channels inaccessible to surgery, while preserving patency of existing venous collateral pathways. These potential advantages may be outweighed by contraindications to thrombolysis. When strict inclusion criteria were applied for treatment of uncomplicated deep venous thrombosis by thrombolysis, only 7 per cent of 209 patients had no contraindication to the use of lytic agents. Descriptions of the use of thrombolysis as first-line treatment for PCD and venous gangrene are largely confined to individuals treated using streptokinase administered systemically or urokinase delivered via transvenous catheters into the affected limb. Successful resolution of symptoms is described but it is difficult to draw any wider conclusions. Thrombolysis has more frequently been used as a secondary measure following failure of anticoagulation. Weaver et al. published results of one centre's experience with PCD (16 patients and 17 limbs), combined with the results of 12 further literature reports involving 38 patients and 45 limbs. Good results (two of two limbs), defined as survival without major amputation, were noted in the treatment of uncomplicated PCD with thrombolysis following failure of anticoagulation. In venous gangrene, thrombolytic treatment was less successful (three of five limbs). Heparin anticoagulation alone was successful in 12 of 12 limbs with uncomplicated PCD, but failed in all 12 limbs with venous gangrene. Thrombectomy was successful in 11 of 12 limbs with PCD, but gave poor results in venous gangrene, with failure in six of nine limbs treated. The remaining limbs either received unspecified anticoagulation or no treatment. These results are reflected in a later series from the same centre, but again the numbers involved were small. Thrombolytic treatment for uncomplicated deep venous thrombosis produces poorer clearance of occluding than of non-occluding thrombosis; only 14 per cent of occluded segments had 50–100 per cent lysis.

Use of low-dose intra-arterial thrombolysis has recently been reported as an alternative to intravenous treatment. Patients with PCD usually have systemic hypotension and a compromised circulation through the affected limb; this reduces the effective dose of lytic agent reaching the capillary system when delivered intravenously as systemic thrombolysis. Intra-arterial thrombolysis delivers the lytic agent to the capillary system and peripheral veins where it is most needed, and tissue plasminogen activator has proven successful in three patients.

The risk of pulmonary embolus in PCD is high and this may be increased by thrombolysis. Lysis may cause clot fragmentation and manipulation of venous catheters may dislodge thrombus. The placement of a permanent or removable vena caval filter has, therefore, been advocated.
before starting thrombolysis. Further indications for vena cava filters include contraindication to anticoagulation, inadequate thrombectomy and post-traumatic PCD.

**Prognosis**

PCD and venous gangrene remain life- and limb-threatening conditions. In the presence of an underlying malignancy or concomitant disease, response is poor to the severe physiological disturbance of massive thrombosis. The mortality rate is reported as 20-40 per cent.

Amputation for PCD and venous gangrene is necessary in 20-50 per cent of patients. However, there is conflicting evidence about the extent of amputation required. Brockman and Vasko found that tissue loss was so severe that 43 (61 per cent) of 71 patients undergoing amputation required an above-knee and 17 per cent a below-knee procedure. Haimovici, however, stressed the fact that many of the lesions of venous gangrene are superficial, in contrast to the deep tissue necrosis of pure arterial ischaemia. He reported that 60 per cent of survivors of venous gangrene required only minor amputation (toes, fingers or transmetatarsal) or debridement and skin grafting. The mortality rate among amputees was 22 per cent overall, and 66 per cent in those who underwent above-knee amputation. Timing of the operation was marked as a crucial factor in that for arterial disease. In arterial disease, deep tissues are invariably compromised and delay in interventional treatment or amputation results in myonecrosis with systemic consequences. Amputation in venous gangrene should be delayed as long as possible while aggressive treatment is pursued to allow venous channels to reopen, limb swelling to subside and the extent of tissue loss to be determined. Allowing swelling to reduce prevents the serious wound problems that arise following amputation of a grossly swollen limb. If amputation is delayed, all that may be required is superficial debridement or minor resection, which should be as conservative as possible.

Information on postphlebitic sequelae in PCD and venous gangrene is limited; their extent has not been formally evaluated. In published series to 1965, 102 (36.6 per cent) of 279 patients reported some form of postphlebitic problem, ranging from mild oedema to full-blown postphlebitic limb. This undoubtedly underestimates the full impact of PCD, as the majority of reports make no comment on this complication while others describe long-term sequelae in 60 per cent of patients.

**Conclusions**

PCD and venous gangrene are rare conditions and so the individual surgeon encounters them only a few times in a career. This situation accounts for the disparate nature of the accumulated literature on the subject, and the lack of long-term follow-up and consensus on best treatment. Lack of information on thrombolysis in the treatment of PCD and venous gangrene is disappointing, given its theoretical benefits. The wealth of experience of the use of thrombolysis for arterial thrombosis has not been fully equated in venous, but the relative rarity of the latter. Intra-arterial thrombolysis represents an encouraging development among the treatment options and merits further research.

What remains certain is that mortality and morbidity rates are high, and the threat to life and limb is considerably greater in patients with venous gangrene than in those with PCD. Treatment of the reversible phase of venous ischaemia in PCD offers a greater chance of success whether by anticoagulation, thrombectomy or thrombolysis. When venous gangrene occurs, the results of treatment are universally dismal and amputation rates high. Indeed, amputation may offer the only option if the patient is to survive. Choice of management and extent of treatment have to be carefully balanced in the one-third of patients with venous gangrene who have an underlying malignancy.

The best management for PCD is elevation, fluid resuscitation and anticoagulation with heparin, but further experience with thrombolysis may prove this to be the best first-line management. Currently, thrombolysis and thrombectomy are generally reserved for treatment following failure of anticoagulation or impending venous gangrene.

PCD and venous gangrene represent as serious a threat to life and limb now as they did 30 years ago. Treatment options have remained largely unchanged, unproven or only moderately successful.

**References**
