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Symmetrical peripheral gangrene: association with noradrenaline administration

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Abstract. The syndrome of symmetrical peripheral gangrene is characterised by distal ischaemic damage in two or more extremities, without large vessel obstruction. Four patients with bilateral pedal ischaemia are described and their haemodynamic profiles presented. In all four cases the syndrome developed in association with noradrenaline administration, sepsis and DIC, despite a high cardiac output and a low calculated systemic vascular resistance index. Early treatment with epoprostenol was instituted in the final case and was successful.

Key words: Gangrene – Disseminated intravascular coagulation – Epoprostenol

The syndrome of symmetrical peripheral gangrene is characterised by distal ischaemic damage in two or more extremities, without large vessel obstruction. This condition was first reported by Jonathan Hutchinson in 1891 [1]. He described a man who had lost the extreme tips of all his toes and the borders of both his ears whilst the ends of his fingers were gangrenous. He concluded that "Perhaps the most probable conjecture was that in some way the central organ of the circulation had been enfeebled" [1]. Since then it has become clear that this syndrome is associated not only with low cardiac output states but with numerous other medical conditions including disseminated intravascular coagulation (DIC) [2], sepsis [3], frostbite and the administration of vasoactive drugs [4].

Although symmetrical peripheral gangrene is uncommon, we have recently encountered several cases, possibly related to the use of noradrenaline in patients with hyperdynamic septic shock. Four cases of symmetrical peripheral gangrene are reported in whom noradrenaline may have precipitated or exacerbated digital ischaemia.

Case reports

Case 1

A 44-year-old male caucasian was brought to the Accident and Emergency department in extremis with pneumonia. He was deeply cyanosed with a systolic arterial blood pressure of 60 mmHg. He was resuscitated and ventilated, and then transferred to the intensive care unit (ICU). Antibiotic therapy with cefuroxime and erythromycin was commenced. Despite ventilatory support with 100% oxygen and 5 cm H_2O of positive end expiratory pressure (PEEP), he remained hypoxaemic with a PaO_2 of 7.9 kPa (59 mmHg). By 2 h after admission to the ICU, he suffered an asystolic cardiac arrest from which he was quickly resuscitated. A thermistor-tipped pulmonary artery flotation catheter was inserted. His cardiac index (CI) was 4.3 l/min/m^2, systemic vascular resistance index (SVRI) 615 dyne : s/cm^5 : m^2 and pulmonary capillary wedge pressure (PCWP) 13 mmHg. At this time he was receiving 13 μg/kg/min of dobutamine, 0.66 μg/kg/min of noradrenaline and 3 μg/kg/min of dopamine. Dobutamine was adjusted in order to increase oxygen delivery (D_{O2}) to greater than 600 ml/min/m^2, and the dose of noradrenaline was increased in a stepwise fashion to achieve a mean arterial pressure (MAP) of 80 mmHg. He had a coagulopathy with prolongation of the prothrombin time (PT) to 35 s (normal range – 10–13 s) and the partial thromboplastin time (PTT) to 54 s (normal range – 24–36 s). The thrombin time (TT) was 13 s (normal range – 12–17 s), the fibrinogen level was 1.4 g/l (normal range – 1.8–4.7 g/l) and fibrin degradation products (FDP_s) were >10 μg/ml but <40 μg/ml (normal range <10 μg/ml). His platelet count at this time was 31×10^9/l (normal range – $150–450 \times 10^9$/l). Blood cultures identified Type B *Haemophilus influenzae* and the antibiotic regimen was changed to cefotaxime 2 g q.i.d.

On the third day of admission his toes became dusky. At that time he was receiving 4 μg/kg/min of noradrenaline. His CI was 5.7 l/min/m^2, SVRI was 988 dyne·s/cm^5·m^2, MAP was 81 mmHg and urine output was >30 ml/h. The peripheral temperature recorded from the dorsum of his foot had decreased from 33.7 to 28.1 °C over the hours preceding the development of digital ischaemia, whilst his core temperature remained at 39.0 °C. The dose of noradrenaline was progressively reduced to 0.8 μg/kg/min over the ensuing days but all his toes remained ischaemic and eventually became black and gangrenous despite the presence of pedal and tibial pulses in both feet at all times. His fingers were unaffected. Renal function remained satisfactory throughout with adequate urine output and creatinine clearance.

He remained persistently hypoxaemic despite ventilatory support with 100% oxygen and PEEP of up to 20 cmH_2O. He eventually deteriorated and died 11 days after ICU admission from intractable hypotension and failure of oxygenation.

Case 2

A 29-year-old man was admitted for antegrade insertion of a double-J stent to relieve obstruction in his left ureter. He had previously undergone cystectomy and ileal loop urinary diversion because of a neuropathic bladder. He suffered from recurrent urinary tract infections and had developed stenosis in the upper left ureter.

On this admission, he was found to have urinary tract colonisation with a gentamicin resistant strain of *Pseudomonas*. Antibiotic cover with ciprofloxacin 200 mg and ceftazidime 1 g was given intravenously prior to surgery. During the procedure, the left renal vein was inadvertently punctured by a guide wire and the nephroscope. A nephrostomy tube was used to tamponade the puncture in the renal vein and the procedure was abandoned. Arterial blood pressure and heart rate remained stable throughout the procedure, but postoperatively he became hypotensive and pyrexial. His systolic blood pressure fell to 60 mmHg and core temperature rose to 41 °C. He was transferred to the intensive care unit where he was resuscitated with blood and colloidal solutions. Over the next 4 h a massive transfusion proved inadequate to keep pace with continuing blood loss and he was therefore returned to the operating theatre. At surgery bleeding from the left renal vein could not be controlled, a left nephrectomy was therefore performed and he was then returned to the intensive care unit.

Overnight he continued bleeding and he was returned to the operating theatre in the morning for packing of the renal bed. A coagulopathy had developed with a PT of 31 s, PTT of 75 s and TT of 18 s. His fibrinogen level was 1.4 g/l and the FDPs were more than 40 but less than 80 μg/ml. His platelet count at this time was 46×10^9/l. Postoperatively he remained hypotensive with a MAP < 50 mmHg despite a CVP of 10 mmHg. A pulmonary artery flotation catheter was inserted and revealed a PCWP of 16 mmHg, CI of 6.56/min/m^2, and SVRI of 427 dyne·s/cm^5·m^2. A noradrenaline infusion was commenced initially at a rate of 0.1 μg/kg/min to maintain his MAP at 80 mmHg.

By day 3, he had received 100 units of blood, 24 units of platelets, 30 units of fresh frozen plasma and 12 units of cryoprecipitate. His haemoglobin was 11 g/dl, platelets 59×10^9/l, and coagulation had improved (PT 27 s, PTT 57 s, TT 13 s, FDPs >10<40 μg/ml, fibrinogen 1.6 g/l). Blood cultures had yielded *Streptococcus faecalis* and gentamicin was administered according to measured levels.

By day 4, he was in established multiple organ failure with adult respiratory distress syndrome (ARDS), renal failure requiring continuous arterio-venous haemodialysis and increasing dependence on noradrenaline to maintain an adequate arterial blood pressure.

On day 7 he developed a blue discoloration of all his toes. The dose of noradrenaline he was receiving at that time was 10 μg/kg/min in order to maintain a mean arterial pressure of around 80 mmHg. His CI was 7.6 l/min/m^2, SVRI 617 dyne·s/cm^5·m^2, D_{O2} 1056 ml/min/m^2 and V_{O2} 266 ml/min/m^2. His core temperature was 37.0 °C and the peripheral temperature measured at the dorsum of his left foot was 28.3 °C. Over the next 3 days, he remained persistently vasodilated despite a noradrenaline infusion of 10–12 μg/kg/min to maintain a mean arterial blood pressure of 70–80 mmHg. His toes remained ischaemic and his pedal pulses could not be felt.

On day 10, he suffered an asystolic cardiac arrest from which he could not be resuscitated.

Case 3

A 35-year-old female caucasian was admitted following seven episodes of haemetemesis. She had a history of heavy alcohol consumption and was found to be bleeding from oesophageal varices. Her haemoglobin on admission was 4.5 g/dl. A Sengstaken-Blakemore tube was passed and intermittent positive pressure ventilation was commenced because of increasing respiratory distress. She was also commenced on dopamine at 3 μg/kg/min. She continued to bleed despite intravenous vasopressin, (20 iu/h for 6 h), and 22 h after admission her oesophageal varices were injected with ethanolamine. Subsequently, the bleeding stopped and the vasopressin was discontinued. At this point she had received in total 24 units of blood, 8 units of fresh frozen plasma, and 10 units of platelets. Her haemoglobin was 11.8 g/dl, her platelet count was 21×10^9/l. The clotting screen demonstrated a PT of 17 s, PTT of 60 s, TT of 10 s, fibrinogen level of 0.6 g/l and FDP_s between 320 and 640 μg/ml. Over the next few days she developed ARDS. On day 4, after an initial improvement, her condition again deteriorated, she became hypotensive and was unresponsive to volume replacement. A pulmonary artery flow directed catheter was inserted and her haemoynamic profile was as follows: PCWP – 16 mmHg, CI – 3.9 l/min/m^2, MAP – 54 mmHg, SVRI – 1100 dyne·s/cm^5·m^2, D_{O2} – 760 ml/min/m^2. Blood cultures were later found to grow *Escherichia coli*. She was commenced on antibiotics and started on noradrenaline at a dose of 0.1 μg/kg/min to maintain her MAP at 80 mmHg which she required for 36 h. Later on the same day it was noted that her toes had become cold and dusky though all pedal pulses were present. At this point her central temperature was 38 °C and her peripheral temperature recorded from the dorsum of her foot was 30.5 °C. Although her clinical condition began to improve her toes became increasingly ischaemic despite discontinuing the noradrenaline infusion. On day 8, it was noted that her left calf was distended and bilateral venograms showed evidence of thrombosis in the left femoral vein. She was commenced on intravenous heparin. Her respiratory function gradually improved and she was weaned from the ventilator. She was discharged to the general ward 21 days after admission and 3 weeks later was discharged home. The distal portions of her right and left toes finally became necrotic and self-amputated.

Case 4

A previously fit and active 79-year-old man developed gas gangrene of his perineal region following haemorrhoidectomy. He was confused and mildly pyrexial but normotensive prior to surgery. He was treated with antibiotics immediately preoperatively and then underwent an extensive resection of his perineum and a defunctioning colostomy. On admission to the intensive care unit he was mechanically ventilated, a pulmonary artery flow directed cathether was inserted, low dose dopamine was commenced and he was transfused with blood and colloidal solutions to an optimal left atrial filling pressure. At that time his MAP was 80 mmHg, his PCWP was 16 mmHg, CI was 3.74 l/min/m^2 and his SVRI was 1524 dyne·s/cm^5·m^2.

Over the next few hours he became increasingly pyrexial and his MAP fell to 65 mmHg. His PCWP was 15 mmHg, CI was 4.31 l/min/m^2, SVRI was 1161 dyne·s/cm^5·m^2, D_{O2} was 714 ml/min/m^2 and his V_{O2} was 140 ml/min/m^2. Noradrenaline was commenced at 0.1 μg/kg/min in order to maintain a MAP of around 80 mmHg.

Over the following 24 h he remained haemodynamically stable but the gas gangrene spread to both groins and extended into the perineal region. He therefore underwent further extensive resection of necrotic tissue and at this time it was noted that his rectum had also become necrotic.

Later on the second day his feet, particularly the heels and toes, became ischaemic though all pedal pulses were present. At this time his peripheral temperature was 33 °C and his central temperature was 38.5 °C. His urine output was >30 ml/h and his creatinine clearance 67 ml/min. He was receiving noradrenaline at 0.2 μg/kg/min. His PCWP was 20 mmHg, CI was 3.13 l/min/m^2, SVRI was 1720 dyne·s/cm^5·m^2, D_{O2} was 583 ml/min/m^2 and V_{O2} was 147 ml/min/m^2. At this time his platelet count was 91×10^9/l and his coagulation screen showed a PT of 22 s, a PTT of 62 s, TT of 8 s, a fibrinogen level of 2.5 g/l and FDPs of >20<40 μg/ml. Although blood cultures were negative, coliforms were grown from necrotic tissue. It was decided to treat him with low dose epoprostenol (a naturally occurring prostaglandin, a congener of prostacyclin) at 5 ng/kg/min. Within 30 min there was almost complete resolution of the peripheral ischaemia apart from a very small area on the tip of one toe. One hour following the commencement of epoprostenol his MAP was 72 mmHg, peripheral temperature was 33.8 °C, PCWP was 14 mmHg, CI was 3.6 l/min/m^2, SVRI was 1408 dyne·s/cm^5·m^2, D_{O2} was 612 ml/min/m^2 and his V_{O2} was 141 ml/min/m^2. Over the following days his condition remained stable. He had occasional periods of hypotension related to sepsis but it was possible to discontinue both the noradrenaline and the epoprostenol. There was no further extension of the perineal gangrene and his feet remained well perfused with complete

reversal of the ischaemia. He remained on the intensive care unit for 16 days and after discharge to the general ward underwent multiple grafting procedures to his perineal region. He has now been discharged home fully mobile.

Discussion

Symmetrical peripheral gangrene has long been recognised as a complication of low cardiac output. In 1938 Fishberg suggested that this condition was a result of impaired peripheral perfusion caused by a reduction in cardiac output exacerbated by intense reflex vasoconstriction [5]. This explanation is supported by pathological studies which have consistently failed to demonstrate either thrombosis or emboli within the peripheral vessels of such patients. It is also supported by studies which have shown closure of small blood vessels when the intraluminal pressure falls below a critical value [6] and zero flow through human digital arteries at perfusion pressures of between 36 mmHg to 60 mmHg [7].

Haematological abnormalities and infection have also been associated with the development of this syndrome [2, 3]. In particular, DIC can produce localised gangrene, purpura, purpura fulminans and ecchymosis. The classical gun metal grey, symmetrical, well-demarcated acrocyanosis which relentlessly progresses to necrosis of the extremities is also part of the clinical syndrome of sepsis and DIC. In these cases the skin may remain warm and as a rule the peripheral pulses are palpable. The ischaemia may be due to sludging of platelet and fibrin thrombi within the microcirculation. Many infectious agents have been shown to trigger DIC and it has been observed that when DIC occurs in the presence of infection, hypotension is invariably present [8] thereby exacerbating poor peripheral blood flow.

Peripheral gangrene has also been reported following administration of various vasoactive drugs such as vasopressin [9] and dopamine [4] as well as classically following ergot ingestion [10]. It is also likely to occur following the administration of noradrenaline. This has been attributed to their vasospastic effects which may be more intense in the digital vascular beds than in the larger systemic vessels. The use of noradrenaline, a potent vasopressor with predominantly α-adreno receptor stimulatory effects, has in recent years been reappraised and has increased particularly in patients with hyperdynamic septic shock. This has been partly due to its success at reversing hypotension unresponsive to other adrenergic agents [11] and also because of its potential beneficial effects on renal function in such cases [12].

At the time of appearance of the peripheral gangrene in all cases, cardiac output was normal or elevated, although they all had previously suffered periods of hypotension during which time digital blood flow may have been reduced. Case 1 had also suffered a cardiac arrest however the features of the syndrome did not occur until some days after this initial collapse. All the patients also had well documented evidence of infection as well as having features of DIC. The triad of prolonged partial thromboplastin time, thrombocytopaenia, and hypofibrinogenaemia is highly reliable if not pathognomonic of DIC.

Peripheral gangrene occurs more frequently in patients with pre-existing vascular disorders such as Raynaud's syndrome, diabetes, atherosclerosis and those who have suffered prior cold injury. None of our patients fell into any of these categories, although patient 1 was a heavy smoker and patient 4 was elderly.

In the cases reported here it is difficult to say whether the shock, DIC, sepsis or the administration of vasoactive drugs was the major contributor to the peripheral gangrene. Although any one of these alone might not have been sufficient, gangrene may be precipitated when these occur in combination and care should be taken when a vasoconstrictor drug such as noradrenaline is being administered. The potential risks of using vasoconstrictors in these circumstances is supported by experimental work demonstrating that gangrene can be induced in animals with intravascular coagulation by the administration of noradrenaline [13] suggesting that the thrombotic complications of DIC are more likely to occur in the presence of vascoconstriction. A characteristic feature of this generalised Schwartzman reaction is the development of bilateral renal cortical necrosis. Neither of the two patients who died had a post mortem however cases 2, 3 and 4 did maintain satisfactory renal function throughout their illness.

Treatment of established symmetrical peripheral gangrene is generally unsatisfactory. Numerous therapeutic manoeuvres have been advocated including the intravenous administration of phentolamine, trimetaphan, nitroprusside and heparin, as well as sympathetic blockade. Although treatment is rarely successful, in a recently reported case of upper limb ischaemia associated with pneumococcal sepsis, ischaemia was reversed by sympathetic blockade [3]. Unfortunately in our patients with pedal ischaemia sympathetic blockade would not have been advisable since the resultant vasodilatation might have precipitated further hypotension and all four would have been at risk of haemorrhagic complications. Another report claims that the combination of epoprostenol and tissue plasminogen activator may minimise tissue loss in symmetrical peripheral gangrene [14]. Epoprostenol is a potent platelet inhibitor and vasodilator. In case 4 reported here, early acrocyanosis appeared to be reversed by the administration of epoprostenol.

In conclusion, symmetrical peripheral gangrene is a cutaneous marker of severe underlying disease. The apparent rarity of this complication suggests that it is produced only by a specific combination of predisposing events. Unfortunately, predicting the development of this complication in patients without peripheral vascular disease or embolic disorders is difficult since pedal pulses may be present, the skin may remain warm, cardiac output may be normal or high and it is clear from our experience that the whole-body calculated systemic vascular resistance does not reflect the intense vasoconstriction in the digital vascular bed. Finally, once ischaemia does develop, it appears difficult to prevent its relentless course to gangrene although the early use of epoprostenol may be of some benefit.

References

1. Hutchinson J (1891) Severe symmetrical gangrene of the extremities. Br Med J 2:8–9
2. Molos MA, Hall JC (1985) Symmetrical peripheral gangrene and disseminated intravascular coagulation. Arch Dermatol 121: 1057–1061
3. Johansen K, Murphy T, Pavlin E, Ledbetter D (1991) Digital ischaemia complicating pneumoccocal sepsis: reversal with sympathetic blockade. Crit Care Med 19:114–116
4. Winkler MJ, Trunkey D (1981) Dopamine gangrene: association with disseminated intravascular coagulation. Am J Surg 142:588–591
5. Fishberg AM (1938) Redistribution of blood in heart failure. J Clin Invest 17:510
6. Nichol J, Girling F, Jerrard W, Claxton EB, Burton AC (1951) Fundamental instability of the small blood vessels and critical closing pressures in vascular beds. Am J Physiol 164:330–344
7. Roddie IC, Shepherd JT (1957) Evidence for critical closure of digital resistance vessels with reduced transmural pressure and passive dilatation with increased venous pressure. J Physiol 136:498–506
8. Corrigan JJ, Ray WL, May N (1968) Changes in the blood coagulation system associated with septicaemia. N Engl J Med 279:851–856
9. Twiford TW, Granmayeh M, Tucker MJ (1978) Gangrene of the feet associated with mesenteric intraarterial vasopressin. Am J Roentgenol 130:558–560
10. Kempczinski RF, Buckley CJ, Darling RC (1976) Vascular insufficiency secondary to ergotism. Surgery 79:597–600
11. Meadows D, Edwards JD, Wilkins RG, Nightingale P (1988) Reversal of intractable septic shock with norepinephrine therapy. Crit Care Med 16:663–666
12. Desjars P, Pinaud M, Potel G, Tasseau F, Touze MD (1987) A reappraisal of norepinephrine therapy in human septic shock. Crit Care Med 15:134–137
13. McKay DG, Latour JG, Lopez AM (1971) Production of the generalised Schwartzmann reaction by activated Hageman factor and α-adrenergic stimulation. Thromb Diath Haemorrh 26:71–76
14. Denning DW, Gilliland L, Hewlett A, Hughes LO, Reid CDL (1986) Peripheral symmetrical gangrene successfully treated with epoprostenol and tissue plasminogen activator. Lancet II: 1401–1402

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