Vascular compromise in newborn infants

D T Gault

With improved neonatal resuscitation techniques a number of infants are now surviving only to develop vascular problems secondary to intravascular catheterisation, repeated venepuncture, or arterial blood sampling. Spontaneous thromboses are also more common in early life than in later childhood.1 2 Guidelines for the prevention, diagnosis, and treatment of blocked vessels in adult patients are not automatically applicable to the newborn. The size of the delicate vessels, the immature haemostatic mechanism, and the background of relative polycythaemia pose special problems. Thromboembolic vessel obstruction may result in death or irreversible damage to an organ or limb. In addition to blockage of peripheral vessels,14 thrombosis of the cerebral,1 pulmonary,6 7 coronary,8 9 renal,10 and mesenteric arteries,11 is reported in the neonate. Peripheral artery occlusion usually presents with a cold, pulseless, mottled, and discoloured limb. Obstruction of the central veins or arteries may be more difficult to recognise. Renal vein thrombosis, for example, does not always present with haematuria and an enlarged kidney, and thrombosis of the aorta may not disclose itself with congestive cardiac failure and ischaemia of the lower limbs.1

Incidence

The incidence of thrombosis in the newborn appears to be increasing.12 This may be due to more widespread use of intravascular catheters, prolongation of life in very ill infants, or a more careful analysis of necropsy material where previously the diagnosis of vessel thrombosis was missed.1 The diagnosis of thrombosis may not be made unless the necropsy examination of infants revealed thrombotic complications of umbilical vein catheterisation in between 20 and 61% of cases, although in some of them the infusia of a hyperosmolar solution may have been a factor.13 14 Umbilical artery cannulae have also been shown frequently to cause thrombosis both on necropsy studies15 16 and on aortography.17 Of course, not all the reported thromboses would have led to ischaemic damage. In some cases the vessel is only partially occluded and in others an adequate collateral circulation exists. In a large series of 4000 patients with umbilical artery catheters, only 1% developed actual clinical symptoms of thrombosis.18

The placement of vascular catheters carries a potential risk no matter which vessel is involved. Neonatal thrombosis has been described in association with radial,19 femoral,20 pulmonary,21 and temporal artery22 lines, as well as with catheters into the jugular23 or femoral24 veins. Thrombi are also found when catheters are not used. A review of consecutive necropsies revealed a 4.5% incidence of thrombosis in uncatheterised cases, and an 11% incidence when intravascular catheters were used.25 Even temporary catheterisation can cause problems. In a prospective study of children undergoing cardiac catheterisation, 3.6% developed clinical symptoms of femoral artery thrombosis.26 An extensive literature review of 1045 cannulations of the radial artery in newborn infants showed that 6% of cases suffered transient ischaemia and 0.5% had permanent ischaemic damage.27 Even temporary occlusion after radial artery cannulation has been reported.28 The incidence of vessel occlusion without ischaemic changes, however, is as high as 63%,28 and in such cases, an adequate collateral circulation exists. Flow in the blocked vessel is often restored several days after catheter removal. The propensity to develop thrombosis is related to size of the infant. The risk of vessel obstruction after cardiac catheterisation is highest in infants of less than 10 kg.29 30

Aetiology

The cause of thrombosis in the neonatal period is often uncertain but some key factors bear special mention. It is mainly sick children who are affected. In one early series, 80% of cases were associated with infection. One factor here may be the growth of small endocardial vegetations which dislodge to occlude distant vessels.4 Emboli may also derive from cardiac thrombi secondary to fibrillation and anomalous valves.4 Some maternal factors are important. Both venous thrombosis and peripheral gangrene have been reported in the infants of diabetic mothers.32–34 Venous emboli may pass through the foramen ovale to enter the arterial circulation.34

Thrombus formation in fetal placental veins is unusual in a normal pregnancy, but occurs quite often in maternal hypertension.35 Chorionic thrombi may embolise to fetal vessels and have been linked to the presence of pulmonary and portal venous emboli.35 In cases of initial twin pregnancy with subsequent fetus papyraceous of one, fragments of thromboplastic material may pass through vascular shunts to the circulation of the live fetus,36 to present as local ischaemic damage due to thrombosis.37–38 It is estimated that 32% of pregnancies which
are twin at 10 weeks lead to singleton deliveries.\textsuperscript{39} Thrombi may also form within a patent ductus, particularly when there is an aneurysmal dilatation,\textsuperscript{40} and resulting emboli can cause peripheral vessel occlusion.\textsuperscript{4}

Virchow postulated three major factors contributing to the formation of thrombi: abnormalities of the vessel wall, disturbances of blood flow, and changes in blood coagulability.\textsuperscript{41} This provides a convenient framework within which to examine how neonatal thrombi may form.

(1) ABNORMALITIES OF THE VESSEL WALL
If during birth a limb is trapped between the fetal head and the maternal pelvis, damage to the intima of a major vessel sufficient to precipitate thrombosis may occur.\textsuperscript{42} Birth trauma may explain some cases of limb ischaemia but thrombosis has also been seen after caesarean section.\textsuperscript{43} in association, for example, with amniotic construction bands\textsuperscript{43} and entrapment by the umbilical cord.\textsuperscript{42}

External pressure on the vessel wall due to a compartment syndrome has been reported to cause vessel obstruction and digital ischaemia; fasciotomy was beneficial.\textsuperscript{44} Even drugs extravasated into the subcutaneous tissues during emergency neonatal reconstruction can obstruct the venous return of an upper limb, and removal of the offending material by aspiration using blunt cannulae can restore the circulation (D T Gault, personal observation).

Thrombosis of femoral vessels leading to amputation after venepuncture has been reported.\textsuperscript{45} Intentional and inadvertent arterial puncture is also known to cause arterial thrombosis,\textsuperscript{46} especially if a substance which irritates the vessel intima is infused.\textsuperscript{47} Even a vasculitis in a newborn infant has presented with peripheral gangrene.\textsuperscript{48}

Intravascular catheters can act as a nidus for fibrin and platelets, may damage the endothelium of the vessel wall, may partially occlude a vessel, and may precipitate vasospasm. Neonatal monitoring with umbilical artery catheters, introduced in 1962,\textsuperscript{49} is now commonplace and is associated with the majority of catheter related thrombosis. The risk is greatest when hyperosmolar solutions are infused.\textsuperscript{50}

(2) FLOW
Hyperviscosity of the blood is reported in 1–5\% of neonates.\textsuperscript{50–52} Blood viscosity is a function of plasma viscosity and packed cell volume. In newborn infants, a venous packed cell volume greater than 0.65 is considered to be indicative of hyperviscosity; a small rise in packed cell volume above 0.70 results in a considerable increase in blood viscosity.\textsuperscript{52} Delayed cord clamping can increase packed cell volume by permitting the placental blood to be transferred to the infant. Hyperviscosity is also related to the deformability and aggregability of the red blood cells—those of a newborn infant are larger and less deformable than in older children and are associated with increased platelet adhesion.\textsuperscript{53}

Increased blood viscosity is noted in the infants of smokers\textsuperscript{54} and diabetic mothers\textsuperscript{55} where sluggish maternal circulation may cause compensatory polycythaemia in the fetal blood. Small for dates babies are also prone to polycythaemia and in them this may be a response to chronic hypoxia as a result of placental insufficiency.\textsuperscript{56} Hyperviscosity adversely affects blood flow leading to a relative local hypoxia and acidosis which may prematurely trigger the coagulation system.\textsuperscript{57} Peripheral gangrene in a term infant with polycythaemia has been reported.\textsuperscript{57}

The risk of arterial and venous thrombosis is high in dehydrated infants, usually those with neonatal diarrhoea.\textsuperscript{4 33 51–65} The newborn have little reserve to cope with dehydration, and an extracellular fluid volume deficit rapidly leads to a low flow state that could aggravate a tendency to thrombosis.\textsuperscript{46}

(3) COAGULATION
It is currently thought that damage to the vessel wall and disturbances of blood flow are more directly implicated in neonatal thrombosis than the peculiarities of neonatal haemostasis and fibrinolysis.\textsuperscript{1} In a healthy infant both the coagulation and fibrinolytic systems are immature but in balance. Inherited deficiencies of antithrombin III\textsuperscript{57} and protein C\textsuperscript{53} have been reported in neonates and were associated with fatal thrombosis.

**Treatment**
Neonatal intensive care units are likely to encounter vascular compromise and should formulate a treatment policy. Even when arterial occlusion does not cause irreversible ischaemia, the affected extremities may suffer retarded growth.\textsuperscript{64–68} The small calibre of the vessels, their tendency to spasm, and reports of re-thrombosis after surgery have in the past curbed enthusiasm for a surgical solution. However, with recent advances in microsurgical techniques, some success has been recorded.

**HEPARIN**
The newborn infant appears to require a proportionally larger amount of heparin than an adult to achieve an adequate therapeutic effect and as the half life is short, continuous infusion is the best method of treatment.\textsuperscript{67} A 50 unit/kg bolus followed by 20 units/kg/hour has been shown to resolve femoral artery thrombosis after cardiac catheterisation in 43\% to 80\% of cases.\textsuperscript{67–69} McDonald and Hathaway showed that a mean dose of 27 units/kg/hour was required to give plasma heparin concentrations in the therapeutic range (0.3–0.5 units/ml) and they reported good results in 14 out of 15 babies studied.\textsuperscript{60}

**THROMBOLYSIS**
Thrombolytic treatment has been shown to be effective and safe in a paediatric population.\textsuperscript{52 61 70} Two thrombolytic agents, streptokinase and urokinase, are widely used to activate plasminogen which is converted to the
proteolytic enzyme plasmin, capable of dissolving fibrin clots. Administered systematically, these drugs can treat both arterial and venous thromboses, but there is a risk of haemorrhage, especially in preterm babies who already run a high risk of intracranial haemorrhage. Clots less than five days old are more susceptible to thrombolysis, but chronic obstructions have also been treated. A loading dose of 10 000 units/kg of streptokinase and then 1000 units/kg/hour is recommended. The treatment is then adjusted to reduce fibrinogen concentrations to low doses (1-0 to 1-4 g/l). If little response is noted, streptokinase can be increased to 2000 units/kg/hour. Streptokinase is made from the streptococcus, and may be affected by the presence of antistreptococcal antibodies; urokinase is considered by some to be preferable as it is non-antigenic. A loading dose of 4000 units/kg of urokinase followed by 4000 units/kg/hour has been commonly used but some authors have doubled the loading dose or the hourly infusion rate.

The fibrinolytic mechanism is not fully developed at birth, and a bias of the haemostatic mechanism towards fibrin formation has been reported. Like heparin, a higher concentration of the plasminogen activator may be required for successful thrombolysis in the newborn and premature infant relative to older children and adults. Corrigan et al showed that 11 times the amount of urokinase was required to achieve levels of activity seen in adults.

Many authors have reported success with thrombolytic treatment. In heparin resistant femoral thrombosis, thrombolysis was successful in excess of 85% of cases. Thrombolysis has been recommended as the first line treatment for thrombosis, with thrombectomy reserved for those that do not respond. Local administration at the site of the blockage using a catheter permits lower doses to be used. Selective treatment with 50 units/kg/hour of streptokinase has shown good results in children.

SURGERY
Thrombectomy in very young infants is prone to reclotting but despite this, useful limb salvage is often achieved. The passage of a Fogarty catheter down a small vessel may fissure the intima, and even mobilising a vessel has been reported to cause thrombosis in this age group. Flanigan et al noted that very small (2-3 French gauge) Fogarty catheters could not enter the femoral arteries of a neonate. Clots may, however, be removed by aspiration using a small plastic catheter with a blunt end. Both success and failure of thrombectomy is recorded.

The femoral and brachial-arteries in neonates are of a similar size to the digital vessels in adults where microsurgical replantation surgery is now routine. Even when thrombectomy from such vessels does not restore all pulses, the limb is often salvaged and the surgery may well improve access to the collateral circulation. In one recent case where persistent rethrombosis beset a surgical reconstruction in a preterm infant, the limb was salvaged using postoperative thrombolytic treatment. Surgery to salvage a failed trial of thrombolysis, and thrombolysis to improve the results of surgery may yet provide the most comprehensive treatment option. Even when a limb is viable after a thrombosis, there may be later growth discrepancy. Surgery, when the child is older, has been described to improve limb blood flow and equalise limb length.

Complications
Vascular occlusion can precipitate distal ischaemic damage and necrosis, but even when an adequate collateral circulation develops, a variety of late complications can occur. In the upper limb, contractures and stunted forearm bone growth have been reported. Damage to the femoral artery after cardiac catheterisation has also caused reduced leg growth and some children have even gone on to develop claudication.

Prevention
Catheter related vascular occlusion is likely to be influenced by the type of catheter, its placement, and the concomitant use of heparin. The use of smaller catheters for cardiac catheterisation has decreased the incidence of femoral artery thrombosis. Heparin as a 100 unit/kg bolus at the time of catheterisation has also reduced the incidence of thrombosis in these children. Low dose heparin (1–2 units/ml in infusions) has been shown to prolong umbilical artery catheter patency, but may not affect the thrombosis rate.

Silastic catheters are less thrombogenic than standard polyvinyl chloride catheters and end hole catheters are less thrombogenic than side hole catheters. The use of thromboresistant umbilical artery catheters (heparin bonded to the surface polyurethane) failed to reduce the incidence of complications significantly. The thrombosis rate is not affected by a change in the placement of the catheter tip, either at the seventh thoracic or fourth lumbar segment.

Conclusion
Vascular compromise in a neonate was first described in 1828 and of the first 52 cases of ischaemic extremities, 17 died and 17 lost limbs. Much better results are now obtained. Early recognition of the problem with prompt instigation of thrombolytic treatment has become the mainstay of treatment. Good results of surgical thrombectomy are also now recorded, and once again, early referral is essential. While rethrombosis after surgery may occur, the unconventional combination of surgery and subsequent thrombolytic treatment has salvaged limbs in very difficult circumstances.

Commentary

Severe examples of ischaemic limb damage, especially those culminating in amputation, have probably become less common as a result of increased vigilance for early signs of ischaemia, better catheters and related equipment, and improved skills of the operators. None the less, the rising population of extremely preterm babies are a vulnerable group and fear of retinopathy may lead to determined attempts at arterial oxygen monitoring by sampling through an arterial catheter or by repeated arterial puncture. A range of physical signs may be observed which suggest limb ischaemia including mottling, blue discoloration, blanching, poor capillary refilling, coolness, and poor pulses. Often these signs are transient but sometimes they progress to frank gangrene with a demarcation line.

Mr Gault’s informative and well referenced paper indicates the spectrum of treatments available, including the scope for surgery. A major difficulty for paediatricians is that there is still insufficient information derived from clinical studies to decide the appropriate management in individual circumstances, especially in extremely small babies. When signs of limb ischaemia are first observed we usually do not know whether they are due to reversible arterial ‘spasm’, thrombosis, or embolism. Dextran, heparin, streptokinase, and urokinase have risks in very small ill babies. Neonatal care is about balancing risks but we are hampered if neither the risks nor the benefits are understood. Finally, most paediatricians won’t have ready access to a surgeon with experience in microsurgery—such experience that there is being embodied in single case reports. Faced with these uncertainties the best approach is firstly to avoid unnecessary harm. A perceived risk of retinopathy is no reason to strive for arterial access at all costs. When invasion of arterial territory is contemplated there is always room for considering the alternative monitoring strategies. It would seem sensible to correct polycythaemia, hypovolaemia, and hypotension before arterial catheterisation, bearing in mind that these factors predispose to vascular compromise. Hyperosmolar solutions should not be infused through arterial catheters, and increased vigilance is required in babies receiving vasopressor drugs. The catheter should be promptly removed if signs of ischaemia, including early blanching, develop. It should not be replaced at the same site even if the signs regress.

The litigation implications of vascular compromise should be acknowledged. Medical and nursing staff must be protected from blame when there was no negligence; but we must also protect a patient’s right to compensation where the standard of care was unreasonable. Accurate documentation in the medical and nursing records of events in relation to arterial catheterisation is a basis for the fair assessment of claims.

Arterial catheterisation, including unsuccessful attempts, should be noted and the time recorded. The same applies to arterial punctures—timed information on the blood gas chart is acceptable provided the site of the arterial sample is given. When an arterial catheter is in use a measurement of the adequacy of the circulation in the appropriate limb should be recorded at hourly intervals in the intensive care chart—for example, ‘warm and pink’. Signs consistent with ischaemia should be recorded and timed. If, as a result, a catheter is removed then the time of removal must be noted. The progression or regression of ischaemic signs should be recorded along with the timing of any treatments.

In practice, a careful attitude towards documentation usually goes hand in hand with clinical vigilance and against this background avoidable vascular compromise is less likely to occur.
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