Complications of Umbilical Artery Catheterization in a Model of Extreme Prematurity

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Abstract

Background—Umbilical artery catheter (UAC) use is common in the management of critically ill neonates; however, little information exists regarding the anatomic and vascular effects of UAC placement in premature newborns.

Methods and Results—Baboons were delivered at 125 d of gestation (term = 185 d), treated with surfactant, had UACs placed, and were ventilated for either 6 d or 14 d. Animals were assigned to short-term (6 d, n = 6) and long-term (14 d, n = 30) UAC placement. At necropsy, aortas were removed with UACs still in place. Histological examination of upper, middle, and lower aorta specimens stained with hematoxylin and eosin and immunolabelled to detect smooth muscle (α-actin) was done in a blinded manner. Controls were delivered at 125d, 140d, and 185d and the aortas acquired immediately after birth. None of the non-catheterized control animals (125 d, n = 4; 140 d, n = 5; 185 d, n = 5) had aortic vessel thrombi or vascular wall abnormalities. All 6 animals with short-term (6/6, 100%) and 18 animals with long-term (18/30, 60%) UAC placement displayed aortic thrombi and neointimal proliferation of the vascular wall. The majority (60%) of analyzed animals with UAC placement displaying neointimal hyperplasia were immunopositive for α-actin, indicating the presence of smooth muscle in these lesions.

Conclusion—Our findings suggest that both short- and long-term UAC use is associated with aortic wall pathological abnormalities compared to control animals. This study emphasizes the judicious use and early removal of UACs if possible in order to potentially prevent significant hemostatic and aortic wall vascular complications.
Keywords
aorta; baboon; infant; thrombosis

INTRODUCTION

Umbilical artery catheter (UAC) use is common in the management of critically ill neonates occurring in 10.8 to 64.4% of neonatal intensive care unit admissions, and 2% of all births.1 Indications for UACs include the need for blood gas or laboratory sample analysis, continuous blood pressure monitoring, exchange transfusions, and medication infusions.2,3 Complications associated with UAC use include infection, thrombosis, thromboembolism, umbilical artery rupture, aortic dissection, and aortic aneurysm formation.4–12

Neonatal thrombotic disease is rare, and is most commonly diagnosed in association with indwelling intravascular catheters.13 Schmidt reported an incidence of clinically apparent thrombi in Southern Ontario of 2.4 per 1000 NICU admissions.14 Other studies report incidences ranging between 4.7 to 95%, as demonstrated by aortography, 2-D abdominal ultrasonography, and postmortem examinations of infants with UACs.15–22 This variability in incidence can be partially explained by disparities in the selected timing and methods used for diagnosing thrombosis in these studies. Whether Doppler sonography, aortography, or postmortem examination is used to diagnose thrombosis affects reported incidence, as well as retrospective versus prospective analyses.23–25 Although neonatal arterial thrombosis associated with UACs is a relatively uncommon recognized complication in neonatal intensive care units (NICU), when it does occur, it has been associated with a 21% mortality rate.14

Thrombotic complications related to UAC placement include thrombosis in the abdominal aorta, renal failure, hypertension, septicemia and death. Studies have shown an increased risk for thrombi and infection in correlation to the duration the UAC is left in place.15,21,26 However, many infants with UACs have no apparent acute clinical complications and it remains unclear how common subclinical thrombotic lesions are in these infants. To study this, we performed a prospective blinded study investigating the effects of short-term (6 days) and long-term (14 days) UAC placement in immature non-human primates to assess how often thrombotic lesions are present. We also wanted to determine any correlation between clinical course and gross and histopathological aorta findings following necropsy in animals with UACs. Our findings suggest that both short-and long-term UAC use is associated with significant aortic vascular wall pathological abnormalities compared to control animals.

METHODS

Animal model

All animal studies were performed at the Southwest Foundation for Biomedical Research (SFBR) Primate Center in San Antonio, TX. The Institutional Animal Care and Use Committee at the SFBR approved all procedures. The premature baboon model has been
used for clinical research for several years. Details of animal care have been published elsewhere. To summarize, fetal baboons (Papio papiopio) were delivered at 125 ± 2 days of gestation (term = 185 days) by cesarean section. Animals were assigned to short-term (6 d, n = 6) and long-term (14 d, n = 30) UAC placement. At birth, the baboons were weighed, sedated, intubated, and given 4 ml/kg of surfactant (Survanta, courtesy of Ross Laboratories, Columbus, OH) before the initiation of ventilator support. Ventilation was provided for either 6 days (short-term UAC group) or 14 days (long-term UAC group). The animals were cared for in an intensive care setting with continual blood pressure, heart rate and pulse oximetry monitoring and frequent arterial blood gas sampling. To assess for intrauterine developmental changes that would occur during fetal development to term gestation, non-catheterized control animals (125 d gestational control, n = 4; 140 d gestational control, n = 5; 185 d gestational control, n = 5) aortas were studied.

Hypotension was defined as a transduced mean blood pressure <28 mm Hg accompanied by either increasing base deficit decreasing urine output, and was treated with volume boluses, pressors and hydrocortisone if indicated. As indices of severity of illness, oxygenation index (OI = mean airway pressure (cm/H2O) × FiO2 ×100/PaO2) and ventilation index (VI = peak inspiratory pressure × ventilator rate × PaCO2/1,000) were calculated. For nutritional management, parenteral nutrition was initiated at 24 hours of life with amino acids at 1.5 g/kg per day (Trophamine; B. Braun Medical, Irvine, CA), electrolytes, vitamins (Pediatric MVI [Astra, Westborough, MA] or Cernevit [Clintec, Deerfield, IL]), and trace elements (MTE-5; Fujisawa USA, Deerfield, IL). Amino acid intake was increased to 3.0 g/kg per day at 48 hours of life and l-cysteine (0.60 mmol/kg per day) was added at 72 hours of life. A 20% lipid emulsion (Intralipid; Pharmacia and Upjohn, Clayton, NC) was initiated on Day 2 at 1.5 g/kg per day and was increased to 3.0 g/kg per day by Day 5. Enteral nutrition was initiated usually at 96 hours of life. Primilac (Bio-Serv, Frenchtown, NJ) was given by intermittent gastric infusion at an initial volume of 10 ml/kg per day and advanced by 10–30 mL/kg per day, as tolerated.

**Patent Ductus Arteriosus**

Animals were monitored by clinical examination and echocardiography for evidence of patent ductus arteriosus. The technique for the echocardiographic examination of the preterm baboon has been described previously. Echocardiographic studies were performed at 1 and 6 h of age and at 24-h intervals, up to 1 d before necropsy.

**Umbilical Artery Catheterization**

All UACs were inserted once the baboons were placed under an open radiant warmer equipped with servocontrol mechanism. The umbilical stump was thoroughly cleaned with povidone-iodine solution and the field was draped in a sterile manner. Sterile umbilical cord string was placed snugly around the base of the cord to control bleeding. Slight tension was applied to the clamped umbilical cord and a pulsating umbilical artery was visualized. A horizontal incision was made approximately 1.5 cm above the junction of the skin and the umbilical cord using a 15 blade surgical scalpel. Upon nicking the selected artery, the arterial orifice was dilated with a vein pick, and a saline-filled No. 2.5 French end-holed radiopaque polyvinyl umbilical catheter was inserted (Argyle, Sherwood Medical, Ireland).
The catheter was inserted to a distance such that the tip was situated above the diaphragm in the descending thoracic aorta between the sixth and ninth thoracic vertebrae (high-lying). An anteroposterior chest/abdominal radiograph was performed immediately after insertion to confirm proper catheter placement and then the catheter was sutured in place. No antibiotic ointment was applied locally to the umbilical stump. Once the catheter was in place, it was connected to a sterile 3-way stopcock to a continuous infusion pump running ¼ normal saline with 0.5 units of heparin per 1 mL at 0.8 mL/hour.

**Pathology Methods**

At 6 days (short-term UAC group, 131 d corrected gestational age) and 14 days (long-term UAC group, 139 d corrected gestational age), before the planned necropsy, each animal was ventilated with 100% oxygen for 5 minutes (for the purpose of performing post-mortem pressure volume studies), and deep anesthesia was induced by the slow infusion of pentobarbital to decrease blood pressure by 50%. The endotracheal tube was clamped to allow for adsorption atelectasis, and after 2 minutes the heart was stopped with additional pentobarbital. The chest was opened and the aorta was identified. A circumferential suture tie was placed around the proximal aorta above the level of the 7th thoracic vertebrae. The umbilical artery was dissected until the iliac artery containing the umbilical artery catheter could be visualized and a circumferential suture tie was placed around the distal portion of this vessel. These suture ties served to hold the UAC in place. Following this the aorta was transected superior to the proximal suture tie and inferior to the distal iliac suture tie. The aorta was then dissected away from the surrounding connective tissue using a blunt forceps. Each aorta with its internal iliac branch containing the UAC was then placed in an individual container of 10 percent formaldehyde.

Gross examination of the all aorta specimens was done in a blinded manner. Transverse 2 mm sections were taken at the most proximal region of the descending aorta below the superior suture tie (“upper” aorta segment), the region below the superior mesenteric artery (“middle” aorta segment), and the region above where the common iliac arteries bifurcated (“lower” aorta segment). Following this, a vertical incision along the length of the aortic vessel sections that remained (lying between the upper and middle removed sections and the middle and lower removed sections) was made using a scalpel and the vessels were gently splayed open. This technique allowed for direct visualization of the internal aorta wall, the identification of any postmortem thrombi, the presence of a fibrin sheath or cast, or the presence of an aneurysm. Since postmortem thrombi may represent stagnant blood that formed thrombi following necropsy and not reflect actual organized thrombotic lesions, we only considered thrombi seen histologically as representing true thrombotic lesions.

**Histology and Immunohistochemistry**

Aorta tissues were paraffin-embedded and 5-μm sections were stained with hematoxylin and eosin or processed for immunohistochemistry. Automated immunolabelling (Ventana Systems, AZ) of slide mounted sections was performed. Slides were dewaxed, rehydrated, and incubated using a commercial primary antibody. Immunolabelling of smooth muscle α-actin was performed with a mouse anti-human monoclonal primary antibody (clone 1A4, DAKO, CA) followed by a biotinylated secondary antibody, and subsequent alkaline...
phosphatase detection (Ventana Systems, AZ). Negative (no primary) controls were performed and all examinations were blinded. For the purpose of this study, we applied the term “lesion” to any thickened intimal area or an area that had a thrombus in the aorta lumen seen microscopically.

Pulmonary histopathologic slide comparisons between the control, short-term UAC, and long-term UAC groups were performed blindly by two of the authors (JC and RM) to assess for the presence of pathologic changes related to airway injury (e.g., large, simplified alveolar structures, dysmorphic capillary configurations and variable interstitial cellularity and/or fibroproliferation) and thrombi.

**Statistics**

Data are presented as mean ± SD. Between-group differences were compared by analysis of variance, unpaired Student’s t-test, or the Mann-Whitney rank sum test where appropriate. Statistical results were generated using Statview (SAS Institute, San Francisco, CA) software.

**RESULTS**

There were no statistical differences between the two UAC groups in birthweight (short-term UAC = 386±50 g, long-term UAC = 381±42 g), sex (% male: short-term UAC = 50%, 3/6; long-term UAC = 50%, 15/30), or gestation (short-term UAC = 125±2 d; long-term UAC = 125±2 d) (Table 1). The 125 d, 140 d, and 185 d gestation control animals had respective birth weights of 353±24, 479±108, and 946±196 and respective sex (% male) of 75% (3/4), 80% (4/5), and 40% (2/5).

PDA was demonstrated by echocardiogram in all 6 (100%) of short-term and 26 of 30 (87%) of long-term UAC animals. PDA was closed with indomethacin in 4 of 6 (67%) short-term and with ibuprofen in 2 of 30 (6.7%) long-term UAC animals. Oxygenation index and ventilation index measurements, done to assess severity of respiratory illness, were not significantly different between the short- and long-term UAC animal groups.

Poor lower extremity perfusion (detected clinically) following UAC placement occurred in 2 of 6 (33%) of short-term and 4 of 30 (13%) of long-term UAC animals. These 6 animals initially presented clinically with black toes, which progressed to black, cold legs bilaterally with 5 of 6 (83%) animals requiring inotropic support for hypotension. None of the short-term animals, but 3 of 4 (75%) long-term animals with black lower extremities died, one on DOL 3 and two on DOL 12. All 6 (100%) of short-term and 15 of 30 (50%) of long-term UAC animals required inotropic support for hypotension. No significant differences were seen between groups except for mean arterial blood pressure on DOL 2.5 (6d > 14d, P < 0.05 by ANOVA). Hypertension was not demonstrated in any of the animals.

Gross examination of the aorta specimens demonstrated no aortic wall or iliac artery aneurysms in non-catheterized control (125 d, n = 4; 140 d, n = 5; 185 d, n = 5), short-term or long-term catheterized animals. Postmortem thrombi were noted in 3 (3/14, 21%) non-catheterized control animals with thrombus seen in the iliac artery of one 140 d animal and
in the aorta of two 185 d animals. A fibrin sheath along the UAC was noted in 3 (3/6, 50%) of short-term and 18 (18/30, 60%) of long-term catheterized animals. Gross postmortem thrombi were seen in none of the short-term and 9 (9/30, 30%) of the long-term UAC animals, with 6 animals displaying thrombi in the aorta (6/9, 67%) and 3 animals displaying thrombi isolated to the iliac arteries (3/9, 33%). There were no statistically significant differences in the number of gross postmortem thrombi seen between the non-catheterized control, short-term UAC and long-term UAC placement animals groups. There were also no significant differences in the number of UACs with fibrin sheaths seen between the short-term and the long-term UAC placement animals groups.

Histologically, none of the non-catheterized control animals (125 d, n = 4; 140 d, n = 5; 185 d, n = 5) had aortic vessel thrombi or vascular wall abnormalities. All 6 animals with short-term UAC (6/6, 100%) and 18 animals with long-term (18/30, 60%) UAC placement displayed aortic thrombi and neointimal proliferation of the vascular wall (Figures 1 and 2). Two of 36 (5.6%) UAC animals, both long-term UAC animals, had suspected sepsis; both of these animals demonstrated thrombi on histologic examination of their aorta specimens.

The majority (60%) of analyzed animals with UAC placement displaying neointimal hyperplasia were immunopositive for α-actin, indicating the presence of smooth muscle in these lesions (Figure 3). There was no correlation between the presence of histopathological aortic vascular wall thrombi and the severity of histopathological abnormalities seen on lung tissues sections from necropsy specimens.

**DISCUSSION**

The primary goal of our analysis of non-human primate fetal aortas was to investigate the effects of UAC placement in an animal model that closely mimics a human 26-week gestation. The majority of animals subjected to UAC placement developed aortic thrombi with thrombus formation detected in 80% of aortic sections analyzed histologically (24 of 36 animals with UAC placement). These finding suggest that UAC placement for durations of 6 and 14 days may result in aortic vascular wall injuries. Although some animals had obvious clinical evidence of UAC-induced complications, such as decreased lower limb perfusion with subsequent development of black, necrotic limbs, the majority of animals with evidence of gross and microscopic lesions were clinically asymptomatic. It is not clear why 33% (12 of 36) of the animals with UAC placement did not demonstrate histologic thrombotic lesions in their aortic sections. Further research on factors that predispose or protect these animals from developing aortic wall thrombotic lesions related to UAC placement is needed.

There was a discrepancy between postmortem thrombi seen on gross examination and organized thrombotic lesions of the aorta and iliac arteries demonstrated histologically. Three control animals had postmortem thrombi seen grossly, but not histologically, whereas none of the short-term UAC placement animals had postmortem thrombi seen grossly, but 100% (6/6) demonstrated thrombotic lesions histologically. In the long-term UAC group animals, postmortem thrombi were seen grossly in 30% (9 of 30) of animals and histologically in 60% (18 of 30) of animals, with correlation between gross postmortem
thrombi and histological thrombi occurring in 20% (6 of 30) of animals. These findings support the need to analyze the aorta and iliac vessels histologically, since postmortem thrombi likely reflect stagnant blood that formed thrombi following necropsy and not actual organized thrombotic lesions.

The published literature on neonatal thrombotic disease is limited, especially concerning well-designed international and multi-institutional studies. Schmidt and Andrew, in a prospective study from the Canadian registry over a 3.5-year time period, in which 25 Canadian and 58 international institutions participated voluntarily, reported 97 cases of radiologically confirmed venous or arterial thrombosis (the total denominator of cases from the participating centers was not reported so the overall incidence of arterial thromboses in this study is not known). There were 33 cases of arterial thrombosis with 12 cases of aortic thrombosis, and 16 cases of iliac and femoral artery thrombosis. The median gestational age was 36 weeks with a birth weight of 2700 grams with the majority of arterial thromboses diagnosed by Doppler ultrasound. As supported by their report, clinically diagnosed arterial thromboses in neonates are rare. However, our current study shows that subclinical histopathological arterial thromboses in non-human primate fetal aortas are common with both short and long-term UAC duration. Our animals were more immature and smaller compared to the subjects reported in the Canadian registry study, so our finding may not apply to more mature and larger infants. Although ELBW infants are at risk for arterial thromboses, since the majority of these infants have UACs placed, the incidence of histopathological arterial thromboses in this population is not known.

From a gestational age standpoint, premature baboons in our study mimic human 26-week gestation infants, however the mean weights of the premature baboons in our study (386±50 g, 6 d group; 381 ± 42 g, 14 d group) are lower than the mean weights of human 26-week gestation infants (~936 g, 50th percentile). It is not clear if this weight discrepancy predisposed premature baboons with UACs in our study to increased thrombosis formation. Smaller premature baboons with UACs may have an increased proclivity for thrombosis formation since aortic blood flow will likely be reduced in these animals due to increased vascular resistance related to the smaller aorta lumen diameter. This decreased aorta lumen diameter may have resulted in an increased number of thrombotic lesions in our study compared to what may actually occur in premature infants with UACs at a similar gestational age.

Existing literature has demonstrated that the probability of developing aortic thrombus in situ with a UAC in place increases proportionally to duration of placement. The incidence of thrombotic lesions have been reported as 16% within 1 day, 32% within 7 days, 56% within 14 days, and 80% within 21 days of UAC placement. Our study demonstrated that 100% of animals with short-term (6 days) and 60% with long-term (14 days) placement had histologic aortic thromboses. We had a small number of short-term animals in our study, so it is possible the incidence of thrombosis would be different if a larger population was studied. The higher incidence of thrombotic lesions in the short-term group compared to the long-term group may be explained by the occurrence of natural thrombolysis leading to clot dissolution over time.
Although coagulation profile studies in premature baboons are not well established, clotting in adult baboons is similar to that of humans. The baboon has been shown to have comparable concentrations of Factors VIII, IX, XI, and the baboon’s platelets function in the same manner as human platelets. The coagulation status of 5 year-old healthy male baboons has been shown to comparable to human reference ranges with few exceptions including elevated thrombin/antithrombin complex and fibrinopeptide A and lower plasminogen activity. The timing and mechanisms involved in thrombotic clearance may differ between premature baboons and infants, which may limit extrapolation of our findings to premature infants. Further studies investigating differences in fibrinolysis between premature baboons and infants are needed.

Another limitation of our study is that we did not evaluate animals with UACs at time intervals other than 6 and 14 days, so we cannot determine if there is a specific duration of UAC use that appears to be safer in regards to thrombosis development. We did not attempt to correlate thrombotic lesions detected by US Doppler with thrombotic lesions detected by gross and histopathological examination, which may be helpful information clinically. Also, because we did not examine every segment along the entire length of the proximal aorta to the distal internal iliac arteries histologically, we may not have detected all possible thrombotic lesions. Since we did not conduct long-term studies, the natural development, progression, or resolution of thrombotic lesions over time in the presence of UACs is still unclear and requires further investigation.

Aorta specimens in our study were analyzed for the presence of neointimal formation as a marker of vascular wall injury, with the majority (60%) of analyzed specimens exhibiting the presence of smooth muscle based on immunohistochemistry. Platelets, associated with thrombotic lesions, may stimulate proliferation and migration of vascular smooth muscle cells (SMC). As the damaged vascular wall is reconstituted, neointima forms, in which SMC’s migrate from the media to the intima where they multiple, then synthesize and deposit extracellular matrix. This neointimal formation was seen in 58% of aortic sections of UAC-exposed animals. Our study cannot predict whether or not future vessel remodeling will result in a return to pre-injury vessel architecture, persistence or a chronic progression of SMC invasion into the aorta lumen. Treatment with cyclooxygenase inhibitors may cause inhibition of platelet aggregation, which could have prevented thrombus formation and altered vascular SMC proliferation and migration in our study. However, there did not appear to be an inverse relationship between animals treated for PDA with non-selective cyclooxygenase inhibitors and the presence of thrombi and neointimal formation. On the contrary, all 4 of the short-term UAC animals treated with indomethacin developed thrombotic lesions.

It is not known if thrombotic lesions and neointimal hyperplasia occurring in the neonatal period contributes to future cardiovascular disease. UAC placement may result in endothelial disruption and collagen exposure. Removal of the vascular endothelium results in immediate platelet and white blood cell deposition with intimal hyperplasia developing after days to weeks at the site of injury. Chidi et al demonstrated a consistent relationship between degree of intimal injury and duration of catheterization in rabbits. The presence of the catheter, in situ, was enough to start the process of local fibrin formation. Further
long-term studies need to be done to determine if aorta vessel injury secondary to UAC placement in the neonatal period contributes to the future impairment of adult aortic compliance and/or is an associated risk for high blood pressure.

CONCLUSION

Our findings suggest that both short- and long-term UAC use is associated with significant aortic vascular wall histopathological abnormalities compared to control animals. It is prudent that physicians judiciously place UACs and remove them as early as possible in order to hopefully circumvent known and potential short- and long-term complications associated with these catheters. Long-term studies of patients exposed to UAC placement as neonates are needed to further elucidate this potential contributor to the development of adult disease.

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Figure 1.
Photomicrographs of hematoxylin and eosin-stained aorta sections. Non-catheterized controls (left column) are compared to indwelling UAC animals (right columns). Panels: A) Middle aorta, 125 d gestational control animal; B) Upper aorta, 6 d animal; C) Middle aorta 6 d animal; D) Lower aorta, 140 d gestational control animal; E) Lower aorta, 14 d animal; F) Middle aorta, 14 d animal. All images represent × 4 mag.
Figure 2.
Photomicrographs of hematoxylin and eosin-stained aorta sections from 6 d & 14 d UAC animals displaying neointimal hyperplasia and thrombus formations adjacent to the internal elastic lamina (IEL). Panels: A) Lower aorta, 14 d animal (× 4); B) Lower aorta, 14 d animal (× 20); C) Middle aorta, 6 d animal (× 20); D) Middle aorta, 14d animal (× 4).
Figure 3.
Photomicrographs of aorta and iliac arteries from 14 d UAC animals. Sections were immunolabelled with an α-actin primary antibody to label smooth muscle (red). Tissues exhibit neointimal hyperplasia and thrombus formations adjacent to the internal elastic lamina (IEL). Panels: A) Lower aorta (× 4); B) Lower aorta (× 20); C) Lower aorta (× 4); D) Right iliac artery (× 4).
Table 1
Characteristics of immature baboons with umbilical artery catheter placement after delivery.

| Characteristics       | 6 d UAC group (n = 6) | 14 d UAC group (n = 30) |
|-----------------------|-----------------------|--------------------------|
| Gestational age (days)| 125 ± 2               | 125 ± 2                  |
| Birth weight (grams)  | 386 ± 50              | 381 ± 42                 |
| Sex (male)            | 50% (3/6)             | 50% (15/30)              |
| PDA                   | 100% (6/6)            | 87% (26/30)              |
| Sepsis                | 0                     | 5.6% (2/36)              |
| NEC                   | 0                     | 0                        |
| Inotropic support     | 100% (6/6)            | 50% (15/30)†             |
| Poor LE perfusion     | 33% (2/6)             | 13% (4/30)               |
| Early death           | 0                     | 10% (3/30)               |
| Aorta thromboses *    | 100% (6/6)            | 60% (18/30)              |

Abbreviations: UAC, umbilical artery catheter; PDA, patent ductus arteriosus; NEC, necrotizing enterocolitis; LE, lower extremity.

* Diagnosed histologically following necropsy.
† P < 0.05 by Student t-test. Data are presented as mean ± S.D. or percent as indicated.