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Positioning and complications of umbilical catheters

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GERDIEN DUBBINK-VERHEIJ

POSITIONING AND COMPLICATIONS OF UMBILICAL CATHETERS

Positioning and Complications of Umbilical Catheters

2019 G.H. Dubbink-Verheij, Leiden, the Netherlands

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Voor mijn ouders
En voor Hans, Mart, Nynke en Linde

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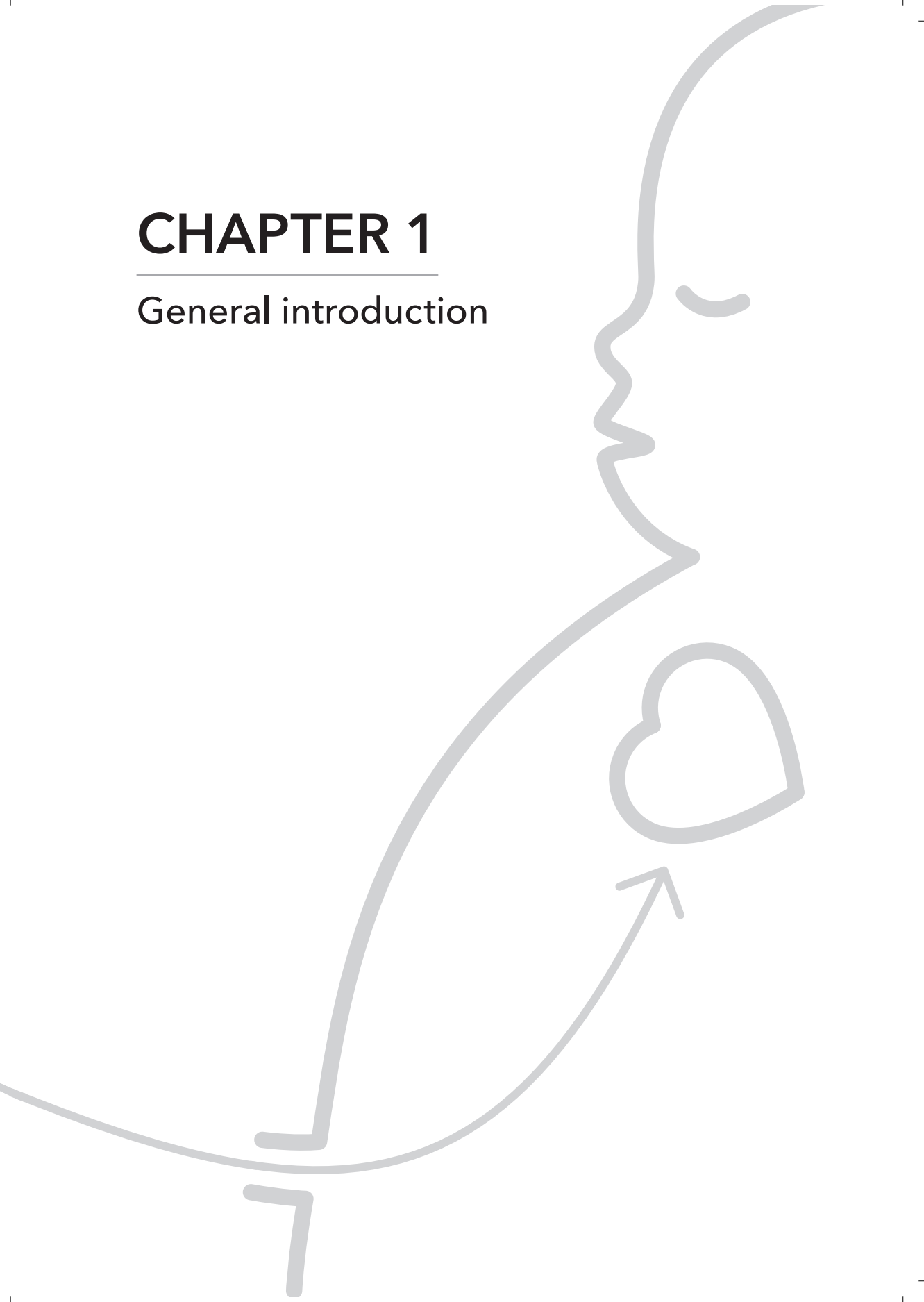
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CHAPTER 1

General introduction



HISTORICAL BACKGROUND AND INDICATIONS FOR UMBILICAL CATHETERIZATION

Umbilical vessel catheterization is one of the most common procedures performed in neonatal intensive care units (NICUs). The first report of the use of the umbilical vein as a route of intravascular access was published by Diamond in 1948.¹ Louis Diamond used umbilical catheters to treat hydropic neonates with severe haemolytic disease with exchange transfusions. Peripheral veins and arteries are difficult to enter; they are thin and fragile, and cannulas clog easily. Seeking an alternative, Diamond used new, thin-walled plastic catheters to perform exchange transfusions through the umbilical vein in 50 neonates and reported encouraging results. From then on, the use of umbilical venous catheters (UVCs) became common practice in NICUs all over the world.

Seventy years after Diamond's first report, UVCs are still used to perform exchange transfusions. They are also widely used for several other indications, as they provide more stable vascular access than peripheral cannulas. They are used for administration of medications, parenteral nutrition, vasoactive and hyperosmolar infusions, and for measurement of the central venous pressure.^{2, 3} The ease and speed of placing UVCs allows also utilisation of the umbilical venous route to infuse emergency medications during neonatal resuscitation.³ In addition, the UVC route is even used to perform invasive procedures such as atrial septostomies or as access for embolization of cranial arteriovenous malformations.²⁻⁵

The earliest reports of the use of umbilical artery catheters (UACs) were published later in 1962 when UACs were first used for frequent blood sampling, and in 1963 for performing angiocardiography in infants with congenital heart disease.⁶⁻⁹ The most important indications for UACs are currently frequent blood sampling and continuous monitoring of blood pressure.^{3, 10} Other less frequently used indications for UACs are exchange transfusion and infusion of fluids.^{3, 11} The use of UACs for interventional purposes such as catheterization of cerebral arteries in neonates with vein of Galen malformations and embolization of pulmonary sequestration has also been described.^{12, 13}

ANATOMY AND PHYSIOLOGY

The umbilical vein extends from the umbilicus to the liver, where it widens to form the umbilico-portal confluence, also called the umbilical vein recess, or portal sinus.¹⁴ This confluence connects to branches of the left portal vein and, superiorly, to the ductus venosus.^{15, 16} The ductus venosus is 2 cm long in a full-term infant.¹⁷ In lambs the ductus venosus leads through the liver to a thoracic part of the inferior vena cava (IVC).¹⁸ In humans, the inferior vena cava has no notable thoracic part. The ductus venosus merges

with the hepatic vein and the inferior vena cava just below the diaphragm into a vestibulum or recess, which connects to the right atrium just above the diaphragm. However, in the literature this recess is still called the inferior vena cava-right atrium (IVC-RA) junction.^{15, 19} UVCs are thus inserted through the umbilicus, umbilical vein, umbilico-portal confluence, ductus venosus and IVC-RA junction (Figure 1).

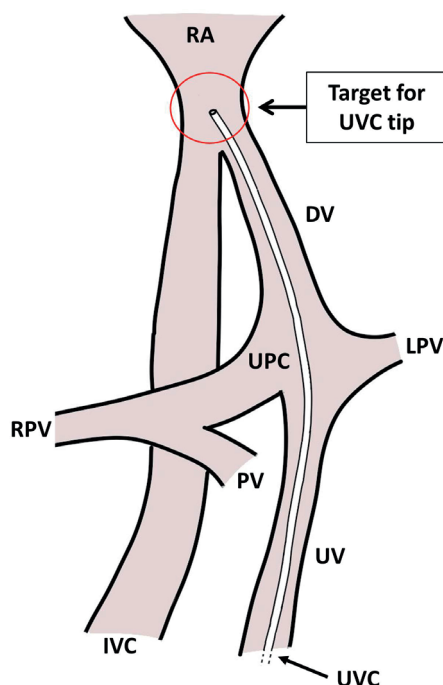


Figure 1. Schematic drawing of relevant anatomy for the umbilical venous catheter (UVC) route with target zone for the UVC tip indicated. RA: right atrium; DV: ductus venosus; UPC: umbilico-portal confluence; LPV: left portal vein; RPV: right portal vein; PV: portal vein; IVC: inferior vena cava; UV: umbilical vein; UVC: umbilical venous catheter;

Because vessel branches are abundant in the UVC route and catheters are usually introduced without radiological guidance, they can be misdirected before or after reaching the desired location. Malpositioned UVCs can enter the left or right portal vein, the splenic or mesenteric vein, superior vena cava or internal jugular vein, the right atrium or even the left atrium via the patent foramen ovale.^{16, 19-21} Alternatively, the catheter may enter the right ventricle via the tricuspid valve and even end up in the main, right or left pulmonary artery.¹⁶

After birth, the ductus venosus and umbilical vein become obliterated and form the ligamentum venosum of the liver and the ligamentum teres hepatis in the lower margin of the falciform ligament respectively.¹⁹ First, functional closure of the ductus venosus develops after abrupt decrease in blood flow and blood pressure in the portal sinus

following postpartum closure of the umbilical vein. Later on, permanent closure of the ductus venosus is caused by fibrotic transformation.²² Closure of the ductus venosus is completed in term infants before day 18 and in preterm infants before day 37 after birth.²³⁻²⁵ During this process, umbilical catheterization becomes increasingly difficult, although successful insertion of a UVC at 11 days after birth has been reported.²⁶

UACs are introduced through the umbilicus, pass caudally in one of the umbilical arteries, angulate above the bladder to enter the right or left internal iliac artery, then pass cranially into the common iliac artery and end up into the abdominal aorta (Figure 2).^{10, 21}

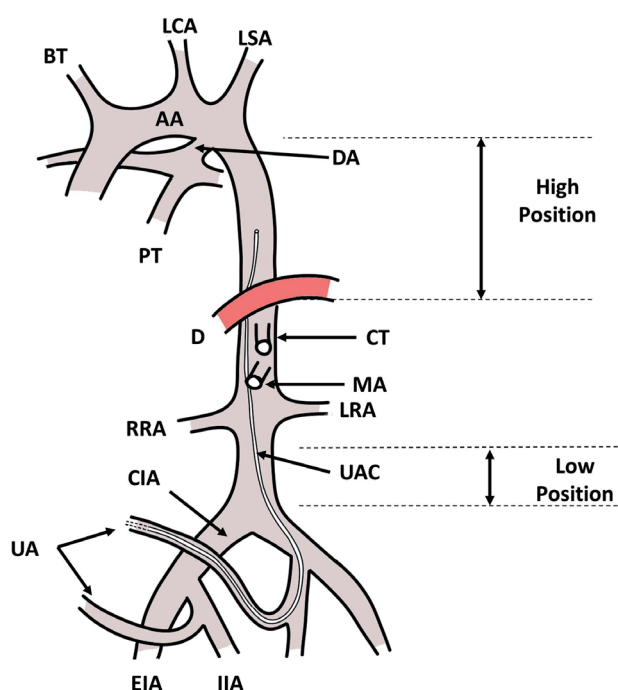


Figure 2. Schematic drawing of relevant anatomy for the umbilical artery catheter (UAC) route with low and high position indicated. DA: ductus arteriosus; PT: pulmonary trunk; AA: arcus aortae; BT: brachiocephalic trunk; LCA: left common carotid artery; LSA: left subclavian artery; D: diaphragm; CT: celiac trunk; MA: mesenteric artery; LRA: left renal artery; RRA: right renal artery; CIA: common iliac artery; IIA: internal iliac artery; EIA: external iliac artery; UA: umbilical artery; UAC: umbilical artery catheter;

In case of a too high position of a UAC the tip can be positioned in the ductus arteriosus, left subclavian artery or left ventricle.^{19, 26} Malposition of UACs can also occur in the truncus celiacus, inferior gluteal artery and renal artery.¹⁹ The umbilical arteries achieve functional closure within the first minutes of life. This process is initiated by localized constrictions leading to diminished blood flow, which eventually leads to irreversible closure and transformation of the distal part of the umbilical arteries into the medial um-

bilical ligaments.²⁷ The proximal part of the umbilical artery stays patent and transforms the superior vesical artery which supplies the bladder.²⁸ Despite functional closure the umbilical arteries can be dilated and cannulated in the first days of life.¹⁰

PROCEDURE AND POSITIONING OF UMBILICAL CATHETERS

Umbilical catheters must be inserted with aseptic technique with the infant draped and closely monitored. After disinfection of the umbilical stump and surrounding skin a cord ligature is placed around the base of the stump. This can be tightened when necessary to minimize blood loss. A scalpel is used to cut the umbilical cord approximately 0.5-2 cm above the abdominal wall. The umbilical vein and arteries are identified and dilated by a forceps if needed. The selected and prefilled catheters can then be introduced and advanced with gentle pressure to the desired depth.^{3, 29} After making sure the catheter draws blood and flushes, it is secured by sutures in the Wharton's jelly of the umbilical cord and taped to the abdomen of the infant³⁰ (see Figure 3 and 4).



Figure 3. Premature infant born with gestational age 25 3/7 weeks and birth weight 950 grams. Umbilical venous and artery catheters were placed about 2 hours after birth. The photo is published with parental permission.

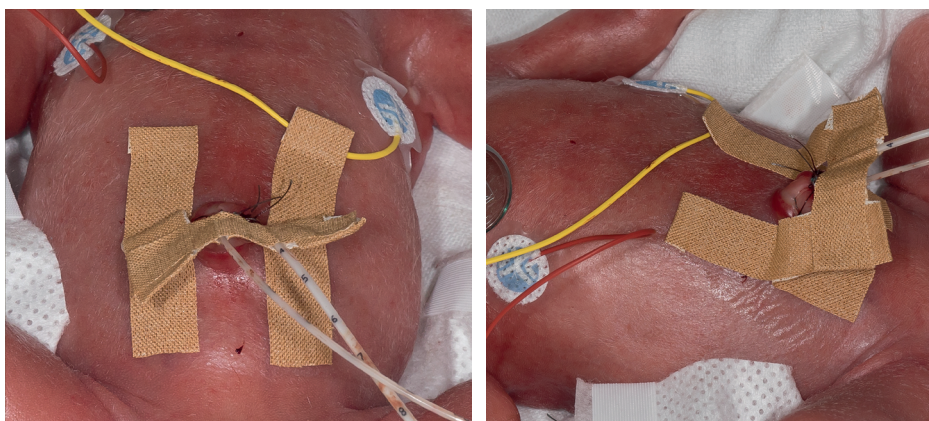


Figure 4. Umbilical catheters are secured by sutures in the Wharton's jelly of the umbilical cord and taped to the abdomen of the infant by a bridging technique. In this infant the umbilical venous catheter was malpositioned in the liver, pulled back to a low position (seen on photo) and shortly thereafter replaced by a peripherally inserted central catheter.

Positioning the UVC

The IVC-RA junction is generally considered the optimal location for the tip of the UVC.^{11, 19, 31-33} The distance from the entry point of the ductus venosus to the junction with the right atrium (the target zone for the UVC tip) is very small (4 to 11 mm) and is correlated with birth weight.^{34, 35} This hampers optimal positioning of UVCs, especially in very-low-birth-weight infants. After placement of the catheters in the correct position, migration of catheters is often observed. This migration - even of less than a centimetre - may lead to malposition due to the small length of the target zone.^{34, 36} The ductus venosus is also considered an acceptable location for the UVC tip, because at this point liquid will no longer flow into the liver.^{15, 32} In the past, some authors suggested or even advised position of the tip in the right atrium.^{19, 37, 38} Others aim for positioning at the IVC-RA junction, but also accept a position of the tip in the central right atrium.^{15, 35, 38} However, in the last decades, intracardiac positioning of the catheter-tip has become increasingly controversial. This position is associated with life-threatening pericardial tamponade and increases the risk of cardiac arrhythmias.^{39, 40} Positioning of UVCs in the heart must therefore be discouraged and efforts must be made to ensure accurate placement of UVCs at the IVC-RA junction and outside the heart.

Positioning the UAC

Two possible locations are described for correctly positioning the tip of UACs. UACs are either placed with the tip above or below the level of branching visceral arteries within the aorta. These two positions are generally called 'high' or 'low' position.^{11, 19, 41} High positioned UACs are placed with the tip in the descending aorta above the level of the diaphragm and below the left subclavian artery. Low UACs are placed with the tip above

the aortic bifurcation and below the renal arteries (see Figure 2). Nowadays high positioned UACs are generally preferred because of fewer clinically ischemic complications and, in all probability, a reduced incidence of aortic thrombosis.⁴²

QUESTIONS CONCERNING UMBILICAL CATHETERS

Placement of umbilical catheters is an important and valuable skill in the management of critically ill infants. Umbilical catheterization (UC) is taught to and performed by all residents in paediatric and neonatal care in The Netherlands and umbilical catheters are used in NICUs as well as in general paediatric departments. However, knowledge of positioning and prevention of malposition and complications of umbilical catheters is limited and many questions remain to be answered:

- What is the optimal method for achieving correct positioning of umbilical catheters?
- What is the optimal method for confirming correct position and detecting malposition of umbilical catheters?
- How often do complications during and after UC develop, and is it possible to prevent them?

These questions have led to the studies presented in this thesis. Performing UC in vulnerable infants brings with it the responsibility of balancing advantages against potential risks, and performing the procedure as safely as possible. Increased knowledge of positioning, use and complications of umbilical catheters is needed to reduce catheter-related complications and improve the outcome in this most vulnerable group of infants.

AIMS AND OUTLINE OF THE THESIS

The general aim of this thesis was to optimize positioning of umbilical catheters and to improve the use of these catheters, thus limiting complications.

The first aim of this thesis was to evaluate practices used in the NICU to achieve correct positioning of umbilical catheters. The accuracy of two commonly used methods to estimate the insertion length of umbilical catheters, the Dunn-method and the Shukla-method, was compared. The variations in the execution of the Dunn-method between caregivers in the Netherlands were examined. To predict the correct insertion length of UVCs, a new formula was developed and validated in a group of infants. Despite attempts to introduce and maintain catheter tips at the optimal position, migration of UVCs still occurs; this phenomenon was studied using serial ultrasonography.

The second aim of this thesis was to describe the complications associated with the placement and use of umbilical catheters. The duration of the procedure of UC was audited and during the procedure the temperature and cardiorespiratory status of the infant were studied. The literature about cardiac arrhythmias in relation to UC was reviewed and described, including two case reports of infants with this clinical picture at our department. Catheter-related thrombosis in infants with UVCs and with other central venous catheters (CVCs) was studied retrospectively and thrombosis in the umbilical venous route in infants with and without UVCs was also studied prospectively by serial ultrasonography. The incidence of central line-associated bloodstream infection in infants with UVCs, femoral venous catheters (FVCs) and peripherally inserted central catheters (PICCs) was determined.

Chapter 1 of the thesis is a general introduction to the subject.

Part I: Positioning of Umbilical Catheters

Chapter 2 is a questionnaire study examining the variations between paediatric professionals in the Netherlands in measuring the shoulder-umbilicus length. The shoulder-umbilicus length is necessary when using the Dunn-method to predict the insertion length of umbilical catheters.

Chapter 3 presents a study comparing the accuracy of two commonly used methods, the Dunn-method and the Shukla-method, to estimate the insertion length of umbilical catheters.

In **Chapter 4** a newly developed formula for predicting the correct insertion length for UVCs is presented and validated in a group of infants.

In **Chapter 5** the occurrence of migration of UVCs after correct positioning is described and the detection of malposition and migration of UVCs using ultrasonography is compared with the detection by chest X-rays.

Part II: Complications associated with Umbilical Catheterization

Chapter 6 describes the occurrence of hypothermia during UC and the duration of the procedure in relation to the temperature and cardiorespiratory status of the infant.

In **Chapter 7** two case report of patients with cardiac arrhythmias related to umbilical catheters are presented. In this chapter the literature about cardiac arrhythmias associated with UC is also reviewed.

Chapter 8 is a prospective study with serial ultrasound determining the incidence and location of thrombi after UC.

Chapter 9 is a report of the incidence of thrombosis in three different central venous catheters (UVCs, FVCs and PICCs) used in infants.

Chapter 10 is a descriptive cohort study comparing the incidence of bloodstream infection in UVCs with the same incidence in two other CVCs, namely FVCs and PICCs.

Part III: Review, General Discussion and Summaries

In **Chapter 11** the literature on the positioning of umbilical catheters and morbidity associated with UC, including the results and outcomes of the studies in the preceding chapters, is reviewed. Practical recommendations and future perspectives are provided.

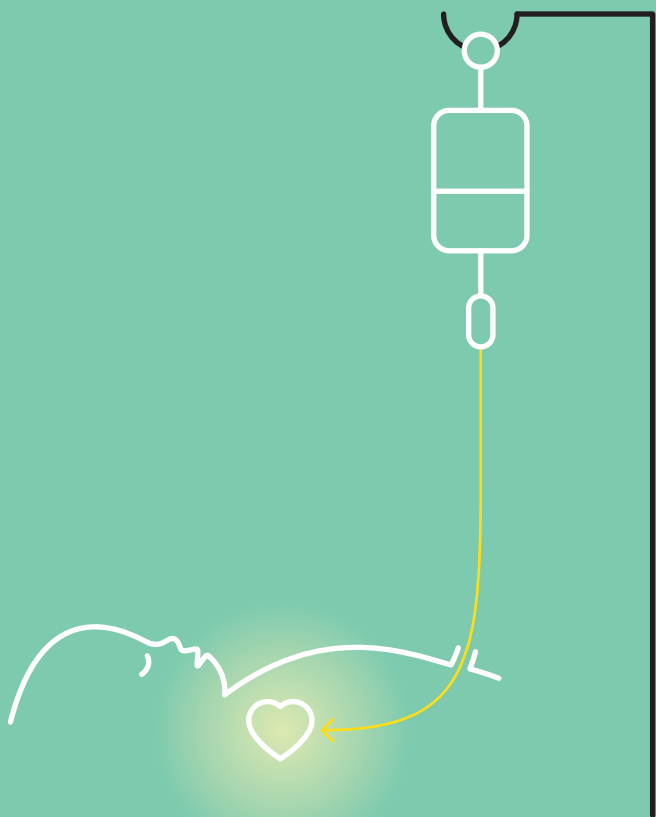
Chapter 12 and **13** contain the summary of this thesis in English (chapter 12) and Dutch (chapter 13).

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PART I

Positioning of Umbilical Catheters

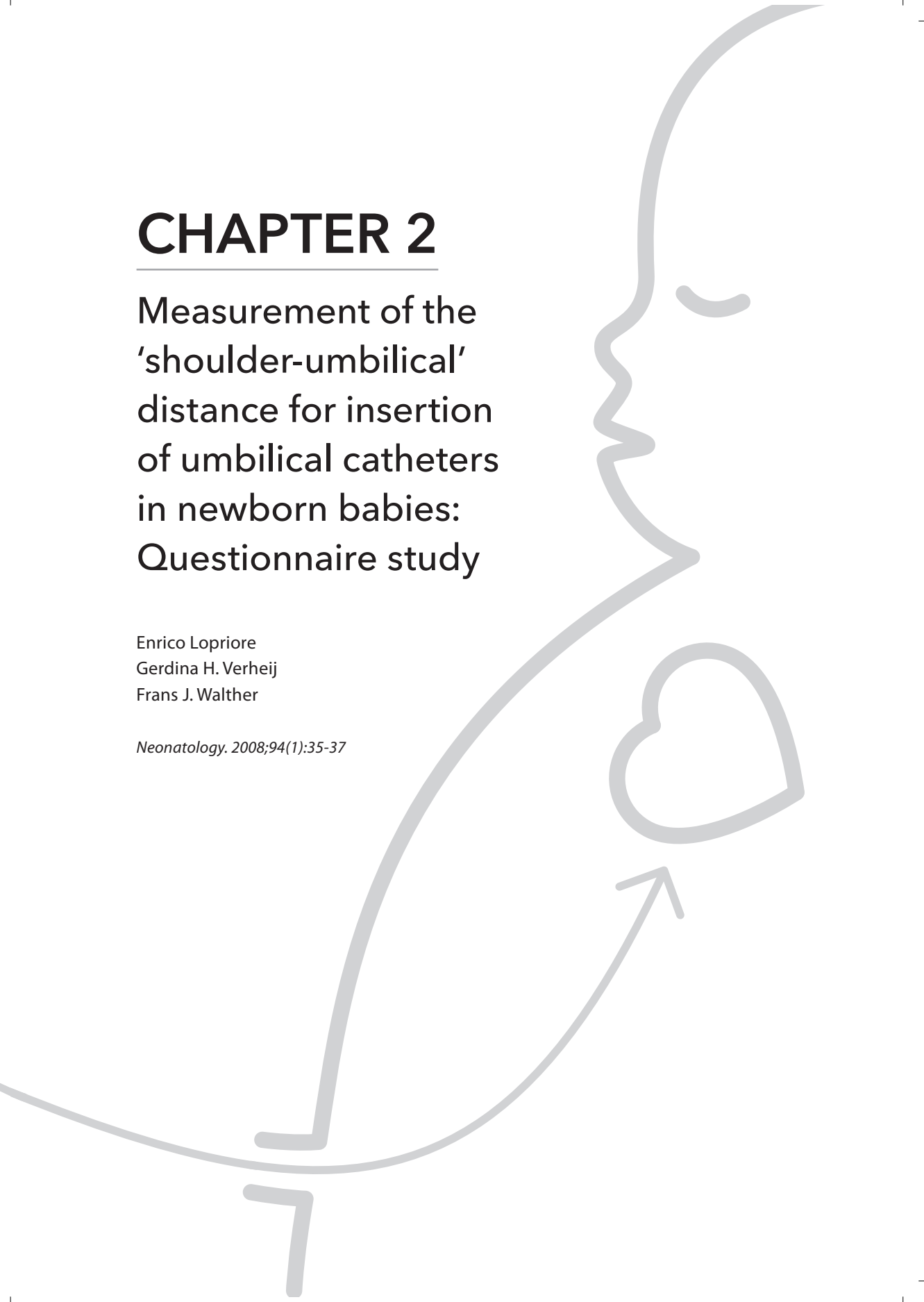


CHAPTER 2

Measurement of the 'shoulder-umbilical' distance for insertion of umbilical catheters in newborn babies: Questionnaire study

Enrico Lopriore
Gerdina H. Verheij
Frans J. Walther

Neonatology. 2008;94(1):35-37



ABSTRACT

Approximately 40 years ago, Dr. Peter Dunn introduced a simple method to determine the insertion length of umbilical catheters in neonates, by using the 'shoulder-umbilical' (S-U) length. Since then, various studies have reported a high rate of malposition of umbilical catheters. One of the possible reasons is that the method used to determine the S-U length varies among paediatric professionals. We performed a questionnaire study among 101 paediatric professionals in the Netherlands and found that the method used by the participants to measure the S-U length was highly inconsistent. Placement of an umbilical venous catheter in a too deep position may lead to potentially life-threatening complications. Therefore, uniformity in measurement is paramount for clinical and teaching purposes. Paediatric professionals using Dunn's definition to place umbilical catheters should adhere more strictly to the original description of the measurement of the S-U length.

INTRODUCTION

Placement of umbilical catheters is a common procedure in neonatal intensive care units. Umbilical venous catheters are required for fluid, medication and nutrition administration whereas umbilical arterial catheters are used for monitoring blood gases and blood pressure. The most common method used to estimate the correct insertion length of the catheters was described in 1966 by Dunn,¹ and requires the measurement of the 'shoulder-umbilical' (S-U) length in combination with the appropriate graph. However, various methods are currently being used to measure the S-U length, leading consequently to a different corresponding insertion-length of catheters. Incorrect measurement may lead to malposition of the umbilical catheters and potential complications such as thrombosis, pericardial or pleural effusions and arrhythmias.² The aim of this study was to examine the variations between paediatric professionals in various centres in the Netherlands in determining the S-U length.

PARTICIPANTS, METHODS, AND RESULTS

We developed a questionnaire in which the method used to measure the S-U had to be determined (Figure 1).

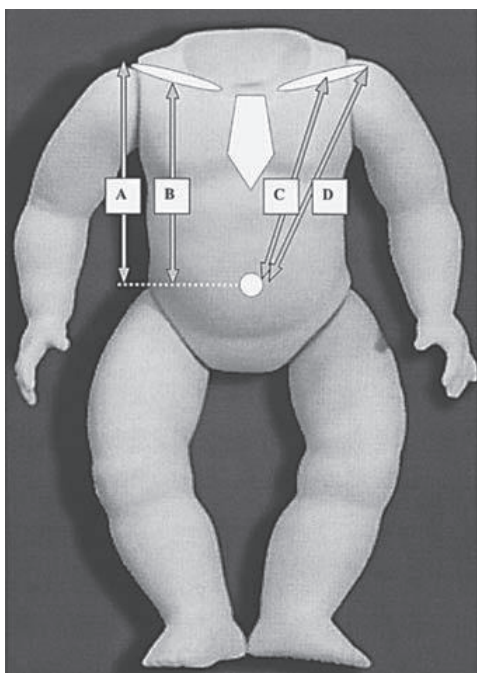


Figure 1. Measurement technique used to determine the S-U length.

The S-U length method of Peter Dunn is routinely used in all participating centres. We asked the participants to select which technique they used to determine the S-U length (A, B, C or D). The response rate was 69% (101/147). A total of 101 paediatric professionals (45 paediatric consultants and 56 paediatric senior house officers) from five university hospitals in the Netherlands and one general hospital participated in the study. Fourteen participants (14%) chose method A, 8 (8%) method B, 39 (39%) method C, and 40 (40%) method D. The technique used to determine the distance between shoulder and umbilicus varied greatly between the various centres and between the paediatric professionals within the same institution (Figure 2).

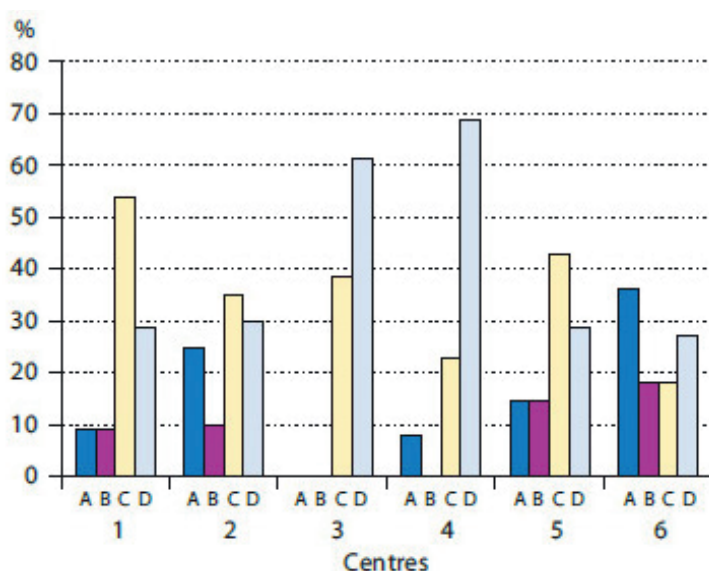


Figure 2. Technique (A, B, C or D) used in the 6 participating centres to determine the S-U length (centre 1 represents the general hospital; centres 2-6 represent the five university hospitals).

The technique used varied also between consultants and senior house officers. Seven consultants (16%) chose method A, 4 (9%) method B, 13 (29%) method C, and 21 (47%) method D. Seven senior house officers (13%) chose method A, 4 (7%) method B, 26 (46%) method C, and 19 (34%) method D. In the Netherlands, umbilical lines are usually put in by the senior house officers.

COMMENT

This study shows that the method used by paediatric professionals to measure the S-U length for placement of umbilical catheters is inconsistent. The S-U length was defined

by Dunn as 'the distance between the top of the shoulder over the lateral end of the clavicle and a point vertically beneath it that was level with the centre of the umbilicus', corresponding thus to option A.¹ The charts required to determine the distance at which the catheter should then be positioned are based on this original definition.¹ However, only 14% of participants report using this method. Most participants (40%) used method D.

According to the theorem of Pythagoras [http://en.wikipedia.org/wiki/Pythagorean_theorem], length measurement in method D is equivalent to the hypotenuse (the hypotenuse of a right triangle is the triangle's longest side; the side opposite the right angle) and results thus in a deeper insertion length. For a given term infant with a birth weight of 3.5 kg, the discrepancy in measure between method A and D is 1.5 cm (SU distance of 17 and 18.5 cm for methods A and D, respectively), which corresponds approximately to 1 vertebral body count on an anterior-posterior chest radiography. A mean difference of 1 vertebral body may result in malposition of an umbilical catheter.³ The study of Ades et al. shows that umbilical lines positioned using the S-U length method tend to overestimate the correct insertion length.³ Our data suggest that this incorrect positioning may partly be due to incorrect measurement of the S-U length. Placement of an umbilical venous catheter in a too deep position may lead to potential complications such as intracardiac thrombosis, myocardial perforation, pericardial effusion and arrhythmias.² Therefore, uniformity in measurement is paramount, not only for teaching purposes, but also for clinical reasons. However, even if the distance is measured more consistently, radiological investigations (chest radiography or echocardiography) after insertion to verify placement are still required. Nevertheless, paediatric professionals using Dunn's definition to place umbilical catheters should adhere more strictly to the original description of the measurement of the S-U length.

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CHAPTER 3

Poor accuracy of methods currently used to determine umbilical catheter insertion length

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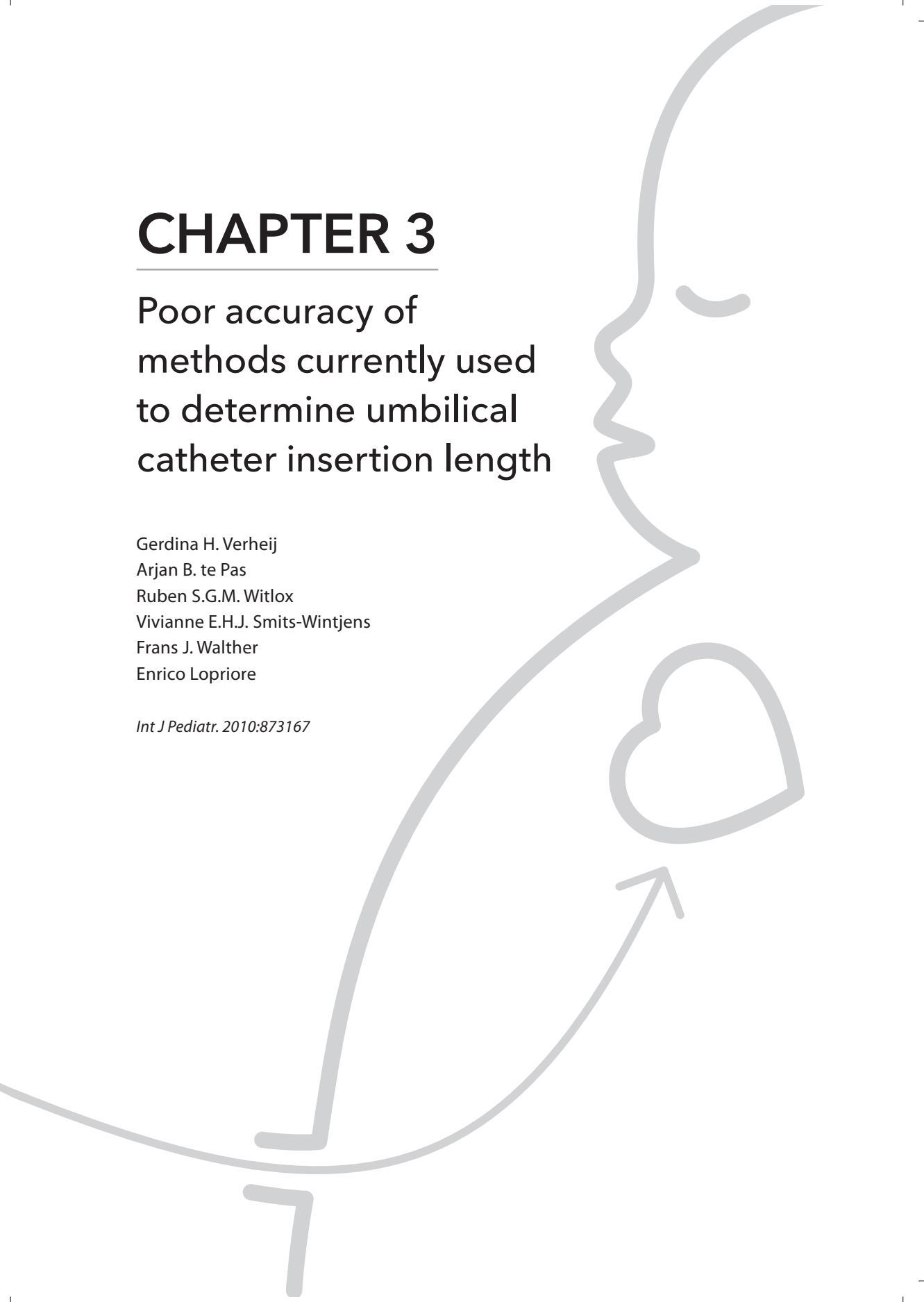
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Int J Pediatr. 2010;873167



ABSTRACT

This study compares the methods of Dunn and Shukla in determining the appropriate insertion length of umbilical catheters.

In July 2007 we changed our policy for umbilical catheter insertions from the method of Dunn to the method of Shukla. We report our percentage of inaccurate placement of umbilical-vein catheters (UVCs) and umbilical-artery catheters (UACs) before and after the change of policy.

In the Dunn-group, 41% (28/69) of UVCs were placed directly in the correct position against 24% (20/84) in the Shukla-group. The position of the catheter-tip of UVCs in the Dunn-group and the Shukla-group was too high in 57% (39/69) and 75% (63/84) of neonates, respectively. UACs in the Dunn-group were placed directly in the correct position in 63% (24/38) compared to the Shukla-group in 87% (39/45) of cases. The position of the catheter-tip of UACs in the Dunn-group and the Shukla-group was too high in 34% (13/38) and 13% (6/45) of neonates, respectively.

In conclusion, the Dunn-method is more accurate than the Shukla-method in predicting the insertion length for UVCs, whereas the Shukla-method is more accurate for UACs.

INTRODUCTION

Umbilical catheters are frequently required in the management of severely ill neonates. Umbilical-vein catheters (UVCs) can be used for intravenous administration of parenteral nutrition, hypertonic solutions, blood products, and medication. Umbilical-artery catheters (UACs) can be used for blood-sampling and continuous monitoring of blood pressure. However, the advantages of umbilical catheters must be carefully balanced against the potential risks. Several life-threatening complications have been associated with the use of umbilical catheters including catheter-related infections, intestinal necrosis, thrombosis, cardiac arrhythmias, myocardial perforation, and pleural and pericardial effusion.¹⁻⁸ Complications associated with umbilical catheterization may result from inappropriate positioning of the catheter. Accurate prediction of the insertion length of the catheter is therefore paramount, as well as confirmation of the position after insertion by chest X-ray or with ultrasound.^{9, 10}

Several formulas and graphs using various body measurements have been proposed to predict the correct position of umbilical catheters.^{2, 11-16} The two most widely used methods are Dunn¹⁴ and Shukla and Ferrara.¹⁵ The Dunn-method is based on the measurement of the shoulder-umbilicus length and uses nomograms to determine the insertion length of the catheters.¹⁴ Dunn examined 50 neonates at necropsy. 19 were stillborn and the remaining 31 had died during the first week of life. Their birth weight ranged from 680 to 4027 gram. The Shukla-method uses equations based on birth weight.¹⁵ Shukla retrospectively studied 43 neonates (mean birth weight 2037 [$\pm$ 1077] gram) with UACs and 10 (mean birth weight 2260 [$\pm$ 1144] gram) with UVCs. In a prospective study, Shukla inserted 25 UACs and 16 UVCs in 29 neonates using equations derived from the retrospective study. He found all catheter tips in acceptable positions. The accuracy of both methods to estimate the correct insertion length is not well known. Both methods have been developed based on a small group of neonates and have not been validated prospectively in larger groups of neonates.

We performed a study to compare the accuracy of both methods in determining the correct position of umbilical catheters.

PATIENTS AND METHODS

In this prospective observational study, we compared the position of umbilical catheters before and after implementation of the Shukla-method at our department, in July 2007.

In the first study period, from December 1st 2006 to June 1st 2007, the policy used to determine the insertion length of umbilical catheters was based on the Dunn-method. During this period two members of our group (GV and EL) observed that the

Dunn-method was often associated with a too high position and significant inter- and intra-observer variation.¹⁷ To avoid this variation-bias, the method of Shukla was implemented in our neonatal nursery and was used in the second study period from October 1st 2007 to April 1st 2008. During the two 6-month study periods, all neonates admitted to the Leiden University Medical Center who received umbilical catheters were included in the study. Parental consent was not necessary, because both the method of Dunn and Shukla are accepted methods to use for the positioning of umbilical catheters in the Netherlands. In accordance with Dutch legislation on retrospective observational studies, IRB approval was not required. Patients with fetal hydrops or major congenital abnormalities were excluded, because of possible interference with the calculated or measured insertion length of the catheters. We also excluded cases in which a UAC was mistakenly placed in the umbilical vein instead of an artery or a UVC was placed in an artery.

In the first study period, we measured the length from the tip of the neonate's shoulder to the umbilicus and used the nomograms of Dunn to determine the insertion length of the catheters. In the second study period we calculated the insertion length with the equations of Shukla. To calculate the depth for inserting a UAC we multiplied the neonate's weight in kilograms by 3 and added 9 cm. To calculate the depth for inserting a UVC we used the insertion length of the UAC, divided this number by 2, and added 1 cm.^{4, 14, 15}

We confirmed the depth of the catheter-tip using antero-posterior chest X-rays. The position was stated as the corresponding vertebra level. The primary outcome variable was the rate of UVCs and UACs ideally positioned on initial X-ray. Ideal position of the UVC was defined as the catheter-tip being visible between the 9th and 10th thoracic vertebrae on a chest X-ray.^{2, 18} The position of the UVC was considered too high if the tip of the catheter was higher than the 9th thoracic vertebra, and too low if the tip was below the 10th thoracic vertebra. Ideal position of the UAC was defined as the catheter-tip being visible between the 6th and 10th thoracic vertebrae.^{11, 16, 18, 19} The position of the UAC was considered too high if the tip of the catheter was higher than the 6th thoracic vertebra, and too low if the tip was below the 10th thoracic vertebra. Secondary outcomes were rates of too high and too low position and rate of complications. The following neonatal data were collected: success of insertion of catheters, gestational age at delivery, birth weight, gender, mortality, respiratory distress syndrome, mechanical ventilation, patent ductus arteriosus requiring medical treatment or surgical closure, necrotizing enterocolitis $\geq$ Bell stage II, culture-proven sepsis, and catheter-related complications such as thrombosis, cardiac arrhythmias, myocardial perforation, pleural and pericardial effusion. Ultrasound examination to rule out catheter-related complications (such as thrombosis) was not routinely performed in all neonates. Catheter-related complications were diagnosed only after clinical suspicion.

Statistical analysis

Results of categorical variables were compared using Fisher's exact test or Chi-square test as appropriate. Student's t test was used to compare normally distributed values between two groups. A p-value < .05 was considered to indicate a statistical significance. Analysis was performed using SPSS version 16 (SPSS, Inc., Chicago, Illinois, USA).

RESULTS

During the study period, 220 patients received either a UVC or a UAC, or both. Four patients were excluded due to fetal hydrops (n=2) and incorrect insertion of catheters (UVC in umbilical artery and UAC in umbilical vein) (n=2). The remaining 216 patients were included in the study, 97 patients in the Dunn-group and 119 patients in the Shukla-group. All patients received a UVC and 144/216 patients also received a UAC.

Table 1 shows the baseline characteristics of both groups.

Table 1. Baseline characteristics in Dunn-group versus Shukla-group.

	Dunn-group (N = 97)	Shukla-group (N = 119)	p-value
Male – n (%)	53 (55%)	68 (57%)	.78
Birth weight (grams)*	1997 ± 1223	1902 ± 988	.54
Gestational age at birth (weeks)*	32.3 ± 4.8	32.1 ± 4.6	.76
SGA – n (%)	10 (10%)	7 (6%)	.31
RDS – n (%)	31 (32%)	33 (28%)	.55
Mechanical ventilation – n (%)	57 (59%)	62 (52%)	.34
PDA – n (%)	18 (19%)	12 (10%)	.08
NEC – n (%)	3 (3%)	3 (3%)	1.0
Sepsis – n (%)	25 (26%)	24 (20%)	.33
Catheter-related thrombosis – n (%)	5 (5%)	3 (3%)	.47
Cardiac arrhythmia – n (%)	0 (0%)	1 (1%)	1.0
Mortality – n (%)	7 (7%)	9 (8%)	1.0
Successful UVC insertion – n (%)	69 (71%)	84 (71%)	1.0
Successful UVC insertion at first attempt – n/N (%)	63/97 (65%)	80/119 (67%)	.77
Successful UVC insertion at second attempt – n/N (%)	6/19 (32%)	4/25 (16%)	.46
Successful UAC insertion – n/N (%)	38/67(57%)	45/77(58%)	.78

SGA: small for gestational age; RDS: respiratory distress syndrome; PDA: persistent ductus arteriosus; NEC: necrotizing enterocolitis; UVC: umbilical-vein catheter; UAC: umbilical-artery catheter;

*Values are given as mean ± SD

Birth weight ranged from 575 to 6430 grams in the total group and gestational age from 25 to 42 weeks. Overall, UVCs were successfully introduced in 70% (153/220) of neonates

and UACs were placed successfully in 58% (83/144). In the other neonates the tip of the catheter could not be introduced in the vessel or (in UVCs) the tip was in the portal vein. If the tip of the UVC was in the portal vein, a second attempt to introduce a UVC next to the first UVC was made. This second attempt was successful in 23% (10/44) of cases. The vast majority of catheters (98%) were inserted by residents. We found no difference between the rate of successful and correct insertion between residents and experienced neonatologists. Figure 1 shows the percentages of UVCs and UACs placed correctly and incorrectly in the Dunn-group and Shukla-group.

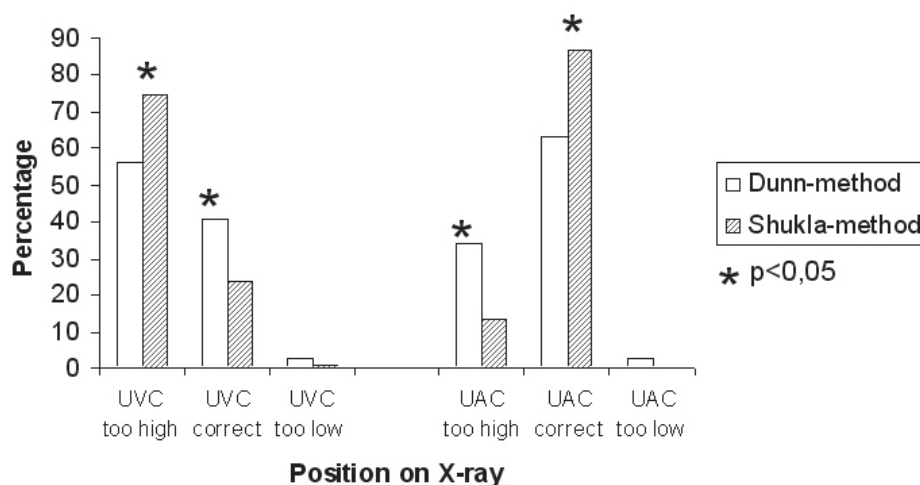


Figure 1. Positions of umbilical-artery catheters (UAC) and umbilical -vein catheters (UVC).

Positions of the tip of UVCs in the Dunn-group and Shukla-group ranged from the 4th to the 11th thoracic vertebrae on chest X-rays (Figure 2).

In the Dunn-group, 41% (28/69) of UVCs were placed directly in the correct position against 24% (20/84) in the Shukla-group ($p < .05$). UVCs placed according to the Dunn-method (57%, 39/69) were less often in a too high position (above the 9th thoracic vertebra) compared to UVCs placed according to the Shukla-method (75%, 63/84) ($p < .05$). In the Dunn-group 3% (2/69) of UVCs were placed too low and in the Shukla-group 1% (1/84) ($p = .45$). Catheter-tips of UVCs placed at two or more vertebrae higher than the 9th thoracic vertebra were found in 32% (22/69) in the Dunn-group and in 55% (46/84) in the Shukla-group ($p < .05$) (Figure 3).

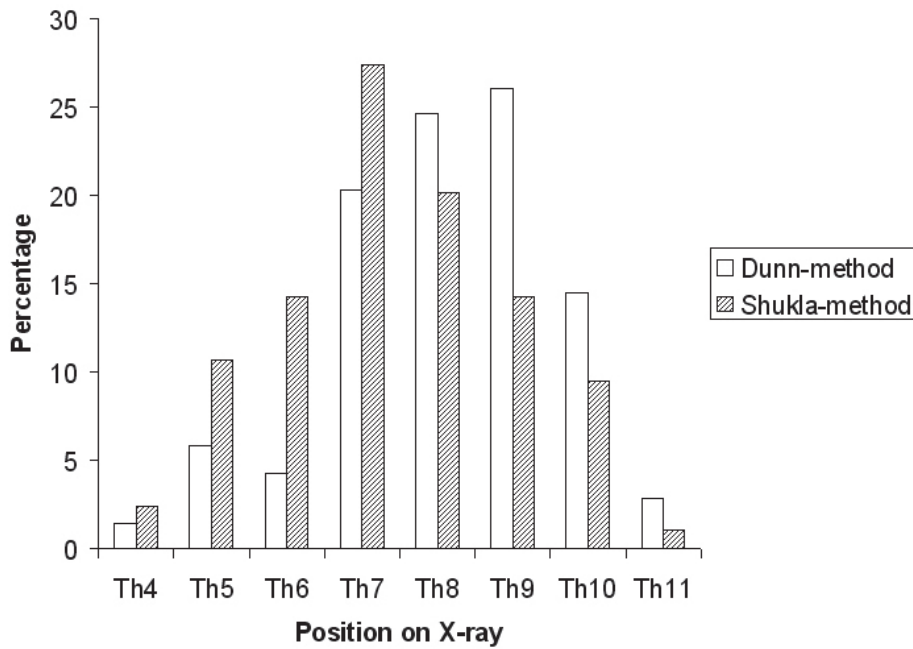


Figure 2. Positions of umbilical-vein catheters on X-ray.

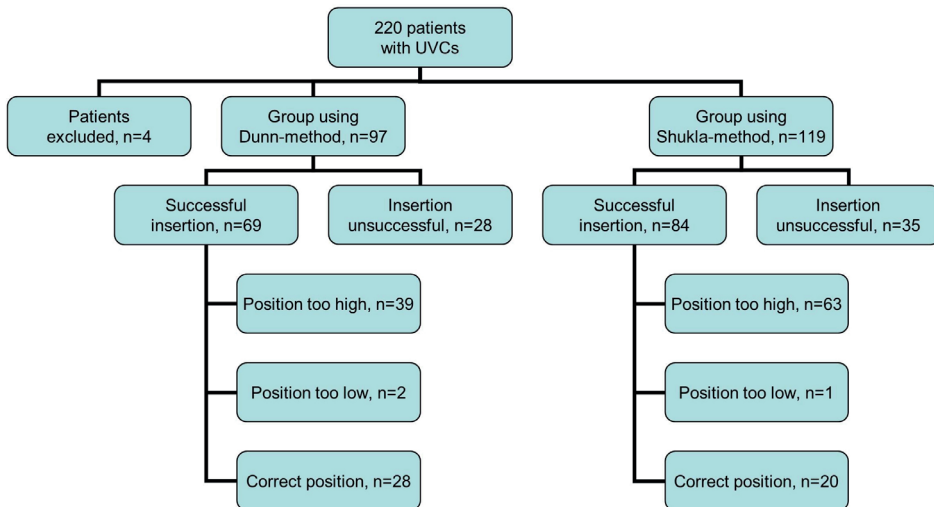


Figure 3. Flow-chart showing the position of the umbilical-vein catheters (UVCs) using the 2 different methods.

Positions of the tip of UACs in the Dunn-group and Shukla-group ranged from the 1st to the 11th thoracic vertebrae on chest X-rays (Figure 4).

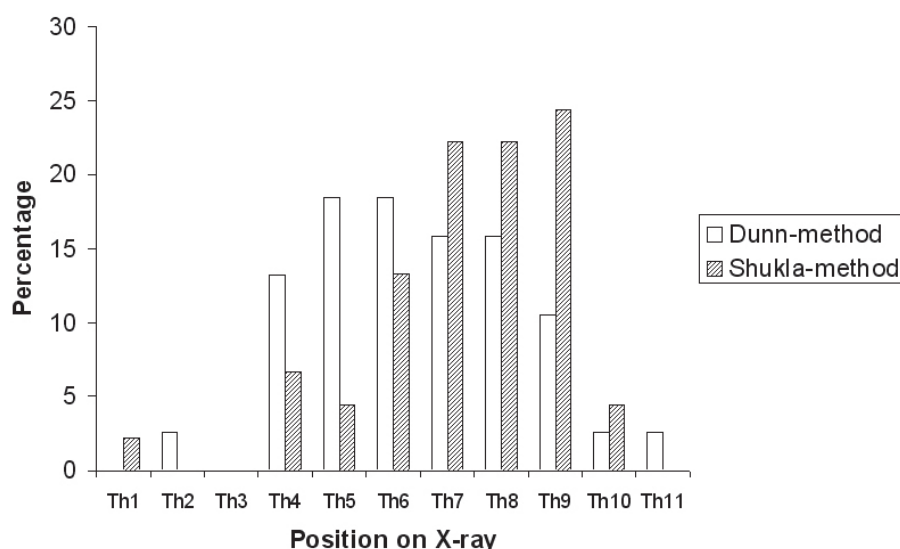


Figure 4. Positions of umbilical-artery catheters on X-ray.

UACs in the Dunn-group were placed directly in the correct position in 63% (24/38) compared to the Shukla-group in 87% (39/45) of cases ($p < .05$). The tip of UACs was placed too high in 34% (13/38) of cases in the Dunn-group and 13% (6/45) of cases in the Shukla-group ($p < .05$). One UAC in the Dunn-group was in a too low position (Figure 5).

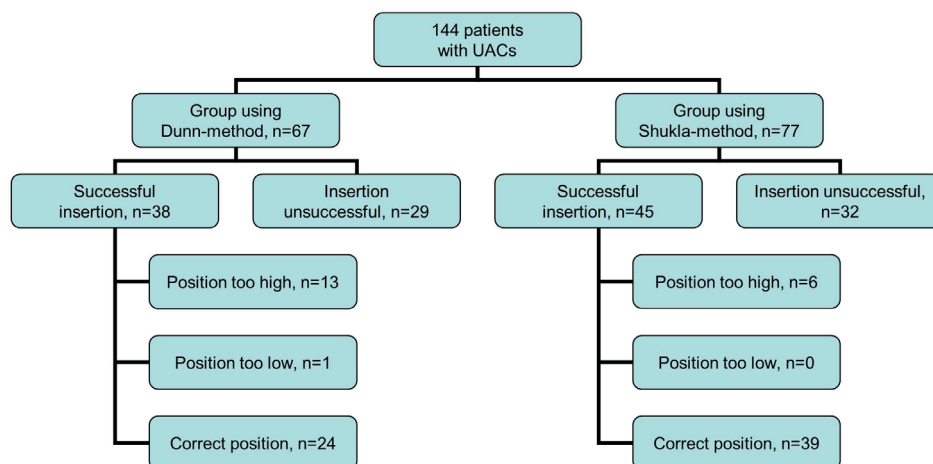


Figure 5. Flow-chart showing the position of the umbilical-artery catheters (UACs) using the 2 different methods.

One neonate in the Shukla-group developed a supraventricular tachycardia directly after umbilical catheterization. The chest X-ray showed malposition of the UVC-tip at

the 6th thoracic vertebra. Catheter-related thrombosis, diagnosed by ultrasonography, occurred in 5/97 (5%) of patients in the Dunn-group and 3/119 (3%) of patients in the Shukla-group. The thrombi were located in the right atrium or inferior vena cava. Myocardial perforation, pericardial or pleural effusion did not occur during the study period.

DISCUSSION

In this study, we assessed the accuracy of the two most commonly used methods to predict the appropriate insertion length of UVCs and UACs.^{2, 14, 15} We observed that the overall accuracy of both methods is poor and both methods lead to too high positions of umbilical catheters. Interestingly, the Dunn-method is more accurate than the Shukla-method in predicting the appropriate insertion length for UVCs, whereas the Shukla-method is more accurate for the placement of UACs. High-positioned venous catheters (with the tip in the right atrium or deeper) are associated with cardiac arrhythmias, intra-cardiac thrombosis, pleural and pericardial effusions and myocardial perforation and need to be avoided.^{3, 5-8, 20}

Thrombosis related to the catheter occurred in 8/216 (4%) in the total study group. Since ultrasonography to detect or rule out thrombosis was not routinely performed, data on the rate of catheter-related thrombi presented in this study should be interpreted with care as under-reporting cannot be ruled out.

The high rate of a too high position of UVCs observed in this study can be due to several reasons. Both Dunn and Shukla accepted in their original research a position of the UVC-tip in the right atrium,^{14, 15} but this position is now considered to be too high.²¹ The optimal position for UVCs is at the junction of the inferior vena cava and the right atrium.^{9, 21} This will correspond to the catheter-tip being visible between the 9th and 10th thoracic vertebrae on a chest X-ray, although positioning at the level of the 8th thoracic vertebra may also be adequate in some patients.⁹ Also, both methods were developed based on a small sample size (n = 50 in the Dunn-study and n = 29 in the prospective part of the Shukla-study) and have not been validated prospectively in larger groups of neonates.^{14, 15} In addition, the Dunn-method is limited by inter-observer variation.¹⁷

Our findings are in agreement with the results from a recent randomized controlled trial reported by Wright et al,¹¹ in which they report that placement of UACs using the Dunn-method leads to a too high position in many neonates. The aim of this trial was to establish the validity of a newly derived formula [(4 x birth weight) + 7 cm] compared to the Dunn-method. Wright et al. showed that the use of this formula significantly reduced the rate of UACs placed too high. In 3% (1/35) of neonates in which the new formula was used the UAC was too high, against 49% (19/39) in the control group in which the Dunn-method was used (p < .0001). Whether this new formula is more accurate than the

Shukla-method has not been studied and requires further investigation. Moreover, only very low birth weight infants were included (< 1500 gram), limiting the applicability of this new formula to this subgroup.¹¹

A major disadvantage of Wright's formula is the high rate (11%) of catheters positioned too low, which is of concern given the association with gut ischemia and thrombosis of renal and mesenteric arteries.²¹ Ideally, UACs should either be placed in a high position (between the 6th and 10th thoracic vertebrae) or in a low position (between the 3rd and 5th lumbal vertebrae).^{11, 19, 22, 23} A recent Cochrane systematic review suggests that high positioning of UACs is associated with less ischemic complications.²⁴

Shukla and Ferrara verified their own formulas and found all catheter-tips in acceptable positions, but they only verified 26 UACs and 16 UVCs.¹⁵ Weaver and Ahlgren based their equation to predict the insertion length of UACs on measurement of the heel-to-crown length of the neonate and reported in 39 of 40 cases the catheter-tip was at the desired level.¹⁶ Heel-to-crown length, however, is difficult to measure and this method is not widely used.

Although our study is limited by the non-randomized, nonblinded design, the catheters were inserted by almost 20 doctors and most of them were unaware of the advantages or disadvantages of both methods (in terms of accuracy). Another limitation is related to the confirmation of catheter position with X-ray. Whether radiography is the ideal diagnostic tool to determine the correct position of UVCs and UACs is controversial. Some authors advocate bedside real-time ultrasonography as the gold standard in verifying the position of umbilical catheters.⁹

CONCLUSION

Although the method of Dunn is more accurate than the method of Shukla for determining the appropriate insertion length of UVCs, the Shukla-method is superior for determining the appropriate insertion length of UACs. However, it would not be practical to combine two different methods for the insertion of umbilical catheters, which may even lead to confusion and mistakes. Ideally, new and more reliable formulas should be developed for determining the correct insertion length of UVCs as well as UACs. These formulas should be validated in large studies of neonates including a wide range of gestational age and birth weight.

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CHAPTER 4

Revised formula to determine the insertion length of umbilical vein catheters

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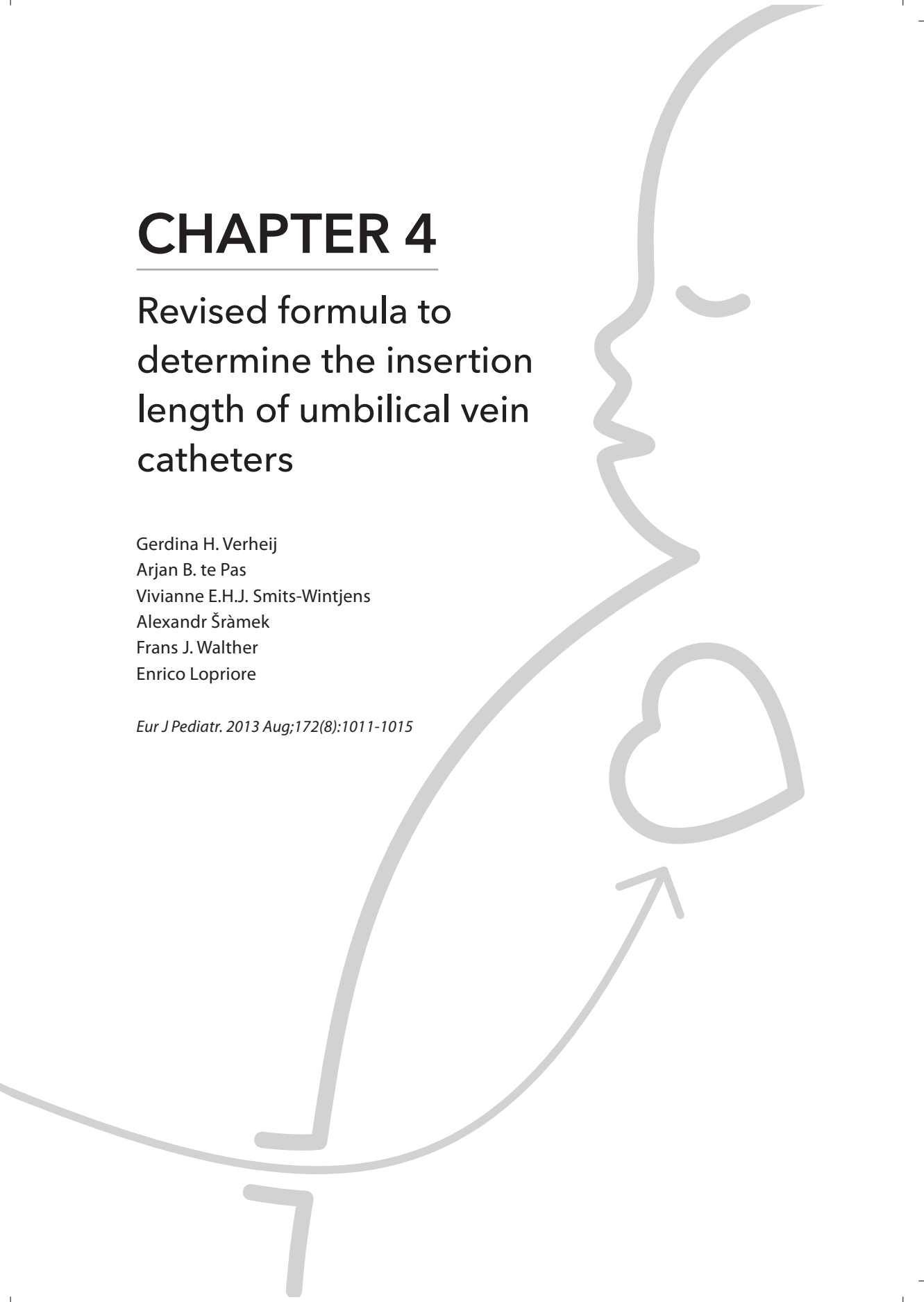
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ABSTRACT

The method of Shukla is commonly used to predict the insertion length of umbilical vein catheters (UVCs) but often leads to over-insertion. Malposition of UVCs can lead to complications. In this study, we compared the formula of Shukla, i.e., $(3 \times \text{birth weight in kg} + 9)/2 + 1\text{cm}$ with a revised formula, i.e., $(3 \times \text{birth weight in kg} + 9)/2\text{cm}$ in determining the insertion length of UVCs. A cohort where the revised formula was used for UVC placement (revised group) was compared with a historical cohort using the conventional formula (Shukla group). We evaluated the position of UVCs stated as the corresponding vertebra level with a radiograph of the infant's chest and abdomen immediately after insertion in both groups. Positioning of the catheter-tip above the ninth or below the tenth thoracic vertebra was considered too high or too low, respectively. Median position of 93 UVCs placed according to Shukla was lower (seventh thoracic vertebra, interquartile range (IQR) 6-9) when compared to 92 UVCs placed according to the revised formula (eighth thoracic vertebra (IQR 7-9)). UVCs were more often over-inserted using the Shukla formula (73%) when compared to the revised formula (54%). One UVC in the Shukla-group (1%) and two UVCs in the revised group (2%) were placed too low ($p=\text{NS}$).

Conclusion: The revised formula reduces the rate of over-insertion of UVCs without increasing the rate of inadequate lower positioning.

INTRODUCTION

Umbilical vein catheters (UVCs) are frequently required in the management of ill neonates for intravenous administration of parenteral nutrition, hypertonic solutions, blood products, and medication. However, the advantages of UVCs must be carefully balanced against the potential risks. Several life-threatening complications have been associated with the use of UVCs including catheter-related infections, thrombosis, intestinal perforation, hepatic necrosis, cardiac arrhythmias, myocardial perforation, and pericardial effusion.¹⁻⁶ Complications associated with umbilical catheterization often result from inappropriate positioning of the catheter.^{1,7,8} Accurate prediction of the insertion length of the catheter is therefore paramount, as well as confirmation of the position after insertion by chest X-ray or with ultrasound.⁹⁻¹¹

Several formulas and graphs using various body measurements have been proposed to predict the correct position of umbilical catheters.^{2, 12, 13} One of the most common used methods is the formula of Shukla.¹³ This method uses equations based on the birth weight of the neonate. In a recent study, we found that the Shukla method was frequently associated with over-insertion of UVCs.¹⁴ This prompted us to revise the formula and stopped adding 1 cm to the equation as suggested by Anderson et al. (see video).² The aim of this study is to investigate whether this revised formula led to a reduction in over-inserted UVCs.

PATIENTS AND METHODS

In this prospective observational study, we compared the position of UVCs before and after implementation of the method with the revised formula in July 2011. In the first study period, from October 2007 to April 2008, the policy used to determine the insertion length of umbilical catheters was based on the formula of Shukla, i.e., $(3 \times \text{birth weight in kg} + 9)/2 + 1 \text{ cm}$. Following a recent study performed at our center showing a high rate of over-insertion of UVCs when using the Shukla formula,¹⁴ we changed our management guidelines (in July 2011) and used a revised formula.² The difference with the Shukla formula is that the revised formula does not include the addition of 1 cm to the equation. The revised formula is $(3 \times \text{birth weight in kg} + 9)/2 \text{ cm}$. In the second study period, from August 2011 to April 2012, we included UVCs placed using the revised formula.

We evaluated the catheter-tip position with an antero-posterior radiograph of the infant's chest and abdomen directly after insertion and stated the position as the corresponding vertebral level. Lateral radiographs were not routinely made. The position of

the catheter tip was recorded prospectively in a dedicated database during both study periods.

The primary outcome was the rate of UVCs correctly positioned on initial X-ray. A catheter tip visible between the ninth and tenth thoracic vertebra was defined as correct. The position of the UVC was considered too high if the tip of the catheter was higher than the ninth thoracic vertebra and too low if the tip was below the tenth thoracic vertebra.

Patients with fetal hydrops or major congenital abnormalities were excluded because of possible interference with the calculated insertion length of the catheters. We also excluded cases where UVC and umbilical artery catheter were interchanged by mistake.

The following neonatal data were collected: gestational age at birth, birth weight, gender, success of insertion of catheters and catheter-related complications such as thrombosis, cardiac arrhythmias, myocardial perforation, pleural and pericardial effusion. Ultrasound examination to rule out catheter-related complications (such as thrombosis) was not routinely performed in all neonates. Catheter-related complications were diagnosed only after clinical suspicion.

Parental consent was not required for this study because both calculation methods were standard practice in the time periods. In accordance with Dutch legislation on retrospective observational studies, IRB approval was not required.

Statistical analysis

We calculated a priori that group sizes of at least 88 infants with UVCs were required to demonstrate a 20% reduction in outcome (UVC positioned too high) (55% versus 75%) with 0.05 significance and a power of 80%, by two-tailed analysis. Results of categorical variables were compared using Fisher's exact test or Chi-Square test as appropriate. Mann-Whitney test was used to compare not normally distributed values between groups. Statistical significance was assumed at $p < 0.05$. Analysis was performed using SPSS version 17.0 (SPSS, Inc., Chigaco, IL, USA).

RESULTS

During the first study period in 143 infants, UVCs were placed using the Shukla formula. Four patients were excluded due to fetal hydrops ($n=3$) and incorrect insertion of the catheter (UVC in the umbilical artery) ($n=1$). In 93/139 infants (67%), a UVC was successfully introduced. In the other 46 infants (33%), the tip of the UVC could not be introduced through the umbilical cord, or the tip was in the left or right portal vein.

During the second study period, 125 patients received a UVC using the revised formula. All patients were included. A UVC was successfully introduced in 92/125 patients (74%). Table 1 shows the baseline characteristics of both groups.

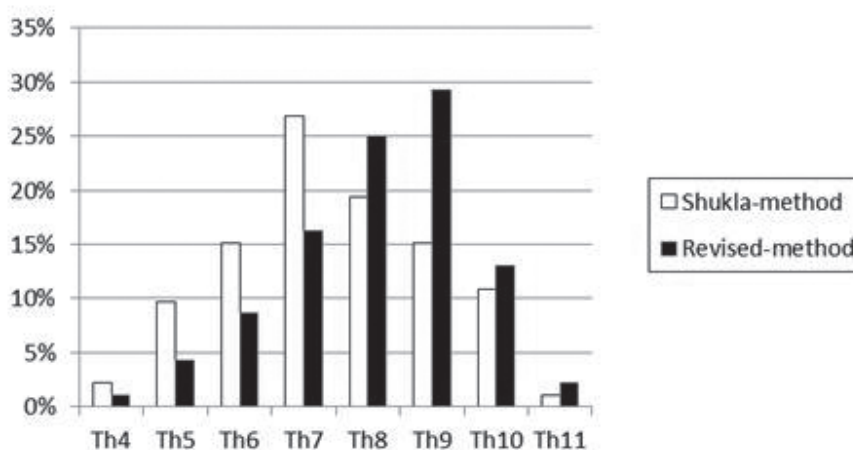
Table 1. Baseline characteristics in Shukla group versus revised group.

	Shukla group (n=139)	revised group (n=125)	p-value
Male, n (%)	74 (53)	70 (56)	0.65
Birth weight (grams) ^a	1,560 (642-4,450)	1,525 (494-4,4760)	0.42
Gestational age at birth (weeks) ^a	31 (24-41)	31 (24-41)	0.58
Small for gestational age, n (%)	3 (2.2)	4 (3.2)	0.60
Successful UVC insertion, n (%)	93 (67)	92 (74)	0.24
Successful UVC insertion at first attempt, n/N (%)	89/139 (64)	90/125 (72)	0.17
Successful UVC insertion at second attempt, n/N (%)	4/28 (14)	2/7 (29)	0.37

UVC umbilical vein catheter;

^aValues are given as median (ranges)

Overall, positions of 185 UVCs were analyzed: 93 in the Shukla group and 92 in the revised group. Positions of the tip of UVCs ranged from the 4th to the 11th thoracic vertebra on chest X-rays (Figure 1).

**Figure 1.** Position of the catheter tip on chest X-ray in relation to the corresponding vertebral body. UVC=Umbilical-vein catheter.

Median (IQR) position of the UVCs using the Shukla formula was higher than when using the revised formula (seventh (6-9) thoracic vertebra versus eighth (7-9) thoracic vertebra ($p<0.01$)).

In the Shukla group, 26% (24/93) of UVCs were placed directly in the correct position versus 43% (40/92) in the revised group ($p<0.05$) (Figure 2). The rate of over-insertion was higher in the Shukla group when compared to the revised group (73% (68/93) versus 54% (50/92)), respectively ($p<0.01$) (Figure 2). In the Shukla group, 1% (1/93) of UVCs were placed too low versus 2% (2/92) in the revised group ($p=NS$) (Figure 2).

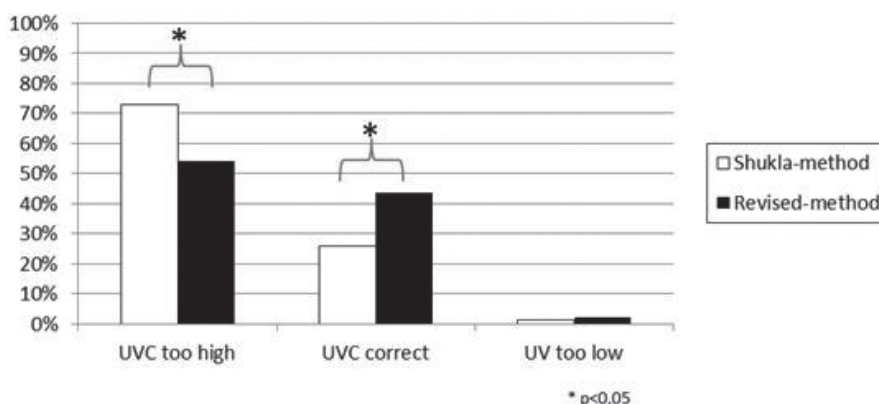


Figure 2. Rates of correct and incorrect positioning of UVCs on chest X-ray in the two groups. UVC=Umbilical-vein catheter; *p<0.05.

The rate of over-insertion in infants with a gestational age below 28 weeks was 68% (25/37) versus 63% (93/148) of infants with gestational age of 28 weeks and older. This difference was not statistically significant.

One infant in the Shukla group developed a supraventricular tachycardia directly after umbilical catheterization. The chest X-ray showed malposition of the UVC tip at the level of the sixth thoracic vertebra. In the revised group, one infant developed pericardial effusion with imminent cardiac tamponade and was treated by pericardial puncture. The chest X-ray showed the UVC tip only at the tenth thoracic vertebra level and ultrasonography showed the tip was at the junction between the inferior vena cava and the right atrium.

DISCUSSION

This study shows that the revised formula leads to less over-insertion of UVCs compared to the formula of Shukla, without increasing the risk of more UVCs being placed too low.

The two most commonly used methods to predict the accurate depth of UVCs are the method of Dunn (based on measurement of the shoulder-umbilicus length)¹² and the method of Shukla.¹³ Both methods were published several decades ago based on small studies with a limited group of infants. Several studies have shown that the two methods are not accurate in predicting optimal positioning of umbilical lines. Ades et al. reported that almost all catheters placed using the Dunn method and the Shukla method required adjustment after insertion.¹⁵ In a recent study, we reported that the overall accuracy of both methods was poor and that they lead to a high rate of over-insertion.¹⁴ Malposition and manipulation to adjust the position of UVCs is associated with complications.⁷

However, as shown in several studies and in one case with imminent tamponade in this study, correct positioning does not warrant uneventful catheterization.^{16, 17} Our study was not powered to detect a difference in rates of clinical complications. Nevertheless, the revised formula has the potential to reduce the rate of complications due to the reduction of over-insertion.

In our total study group, UVCs were successfully introduced in 70% of neonates, which is slightly lower compared to other reports (range 73%-92%).¹⁸⁻²⁰ This study led to more awareness in our department that effort should be undertaken to aim for a higher percentage of successful introduction of UVCs.

The ideal location for the catheter-tip is at the junction between the inferior vena cava and the right atrium (IVC/RA).^{19, 21, 22} Position of UVCs may be evaluated either with thoraco-abdominal X-ray or with ultrasound. Controversies persist regarding the optimal diagnostic management to determine the correct position of the tip of umbilical catheters in neonates. Some authors advocate bedside real-time ultrasonography as the gold standard in verifying the position of umbilical catheters.^{9, 15, 22, 23} The practical advantage of ultrasonography is that it allows to determine directly the correct position of the catheter, even before it is secured at the desired position. The disadvantage of ultrasound is that it requires qualified practitioners being able to perform the examination during or directly after placement of the UVC at any moment of the day (and night). Due to this limitation most centers (including ours) are forced to use chest and abdomen radiography to assess the catheter-tip position.^{1, 2, 8, 10, 16, 17, 20} However, there is no international consensus on the correct position of UVCs on X-rays. In this study, we defined the ideal position of the UVC when the catheter-tip was visible at or between the ninth or tenth thoracic vertebra. Some authors advocate that the tip should be positioned at, or just above the diaphragm on chest X-ray, while others advise that the tip should be between the eighth and ninth thoracic vertebra or between the eighth to tenth vertebra.^{10, 18, 19, 22} Alternatively, other authors recommend that the tip should lie at least 0.5 cm outside the cardiac line on chest X-ray in small infants or 1.0 cm in larger infants.²⁴

These discrepancies are mainly due to the fact that it is difficult to relate anatomical structures (for example, the IVC/RA junction) to the projection of vertebral bodies on chest X-ray because of the variability of these structures in relation to bony landmarks. Greenberg et al. correlated the position shown by ultrasonography to the nearest vertebral body on X-ray.²³ UVCs positioned at the eighth and ninth thoracic vertebra on X-ray were positioned at the IVC/RA junction in 90% of cases. UVCs positioned below the tenth thoracic vertebra were all in the liver proximal to the ductus venosus.²³ Based on their results, the authors suggested that the correct position for the catheter tip on chest X-ray should be the eighth and ninth thoracic vertebra (when ultrasonography is not available). Ades et al. found poor correlation between thoracic level on X-ray and position of the tip at ultrasonography. Catheter-tips at the IVC-RA junction and IVC were

located at thoracic vertebral bodies 6 to 11.¹⁵ Recently, Michel et al. also compared ultrasonography with radiography and found that the median level for adequately placed catheters (with the tip at the IVC-RA junction or thoracic portion of vena cava inferior) was the seventh thoracic vertebra (range 4-10). However, almost the same range was found with positions of intracardiac catheter-tips, which were placed at thoracic vertebral levels four to nine. The authors concluded that a position of the tip between the eighth and ninth thoracic vertebra lacks precision and advised that ultrasonography should replace X-rays for determining tip position.⁹

Whether an intracardiac position of the catheter tip should be considered inadequate is also controversial. Some authors suggest or even advise position of the tip in the right atrium.^{10, 15, 25} However, this should not be recommended, as this position is associated with life-threatening pericardial tamponade.^{7, 26}

Care should be taken when interpreting our results due to the methodological limitations of our study related to the nonrandomized and nonblinded study design. In addition, the catheter position was not confirmed with ultrasonography. However, the formulas used in this study were intended for calculating correct placement of catheters, accepting the IVC-RA junction as the right location using a chest X-ray.

In conclusion, use of the revised formula leads to less over-insertion of UVCs compared to the formula of Shukla. More studies, preferably using also bedside real-time ultrasonography, are needed to validate these findings. However, when X-rays are used, the variable position of vertebra should be accounted for. The location of the catheter tip in relation to the diaphragm and cardiac line is also important. Given the limited reliability of chest X-ray in determining the correct position of UVCs, ultrasonography should become one of the routine skills of all caregivers in neonatal wards involved in the placement of umbilical catheters.

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CHAPTER 5

Inadvertent migration of umbilical venous catheters often leads to malposition

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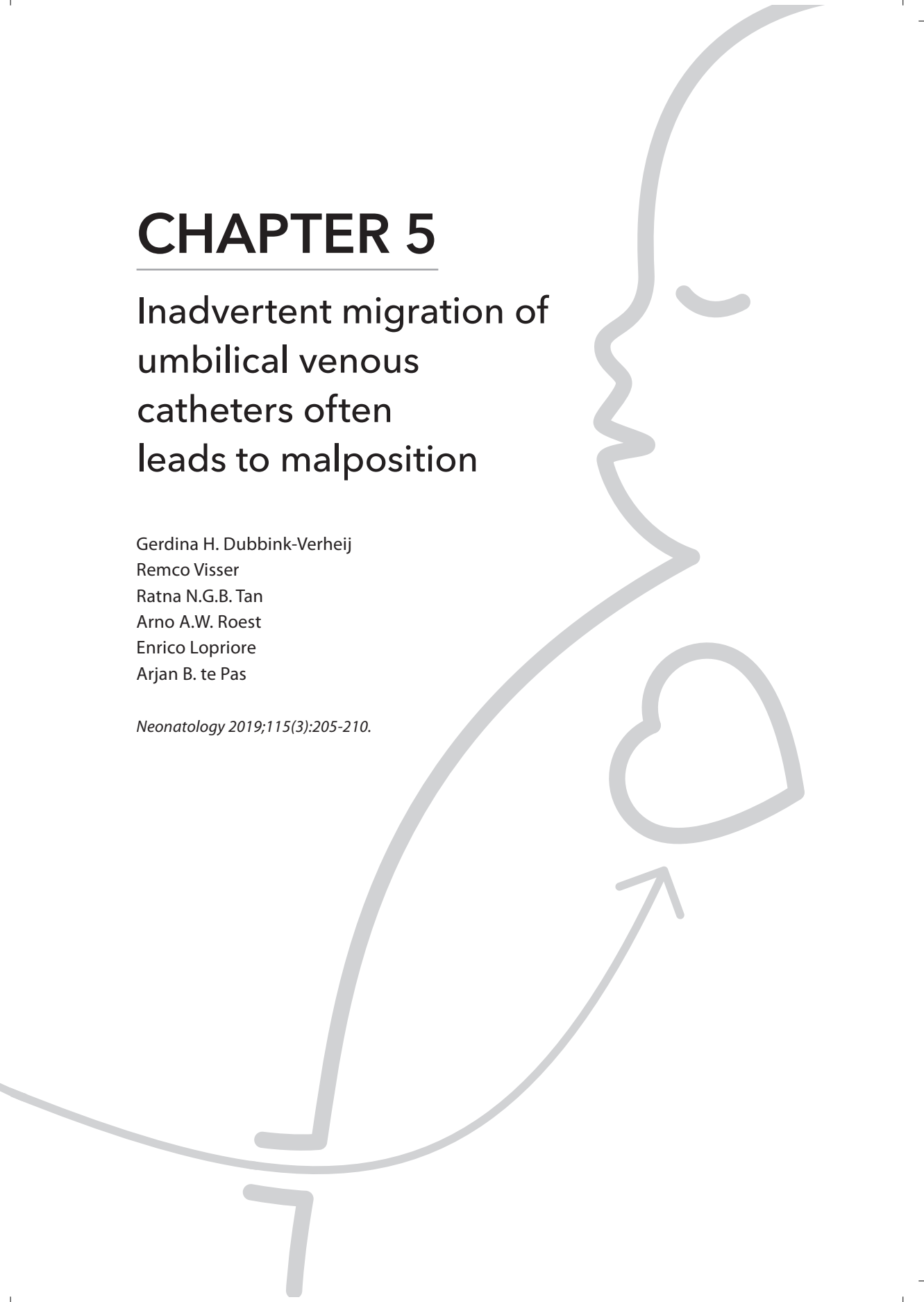
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ABSTRACT

Background

Migration of umbilical venous catheters (UVCs) has been described anecdotally.

Objectives

The aim of this paper was to investigate migration of UVCs using ultrasonography (US).

Methods

In a prospective observational study, the position of UVCs was determined using serial US within 24 hours, at midweek, and at the end of the week after umbilical catheterization. Migration was recorded in distance and direction. Malposition was defined as a position of the UVC in the heart (right atrium or more distal along the UVC-route), umbilico-portal confluence, or in the umbilical vein. UVC position determined by US was compared with chest X-rays (CXR) when these were performed for standard care within the same time period of 1 h.

Results

Migration of UVCs was detected with US in 25/40 infants (63%) in 32 occasions, leading to malposition in 17/25 (68%) infants. UVCs migrated inwards in 18/32 (56%), leading to position within the heart in 17/18 occasions. Most migrations occurred before Day 3 (21/32 [66%]). When a CXR was taken at the same time as US was performed (30 occasions), the assessment of the catheter-tip position differed in 23% of the occasions. When malposition was detected by US, this was detected on routinely performed CXRs in 11% of the occasions.

Conclusions

UVCs often migrate following insertion, often leading to malposition. Awareness for this is needed, and US is a feasible alternative for detecting malposition compared to CXRs and avoids additional radiation. Re-evaluation of the position of UVCs at least once, but within 24 h after placement, is recommended.

INTRODUCTION

Umbilical venous catheters (UVCs) are frequently used in sick infants for intravenous access. UVCs are relatively easy to insert and may be used for a longer period in comparison to peripheral intravenous cannulas. Catheters are introduced in the umbilical vein to reach the umbilicoportal confluence, passing the ductus venosus to reach the junction between the inferior vena cava and right atrium (IVC-RA-junction) (Figure 1). The ideal location for the UVC tip is between the insertion of the ductus venosus in the IVC and the IVC-RA-junction.¹⁻⁴ It is important to prevent malposition as this may lead to complications, such as hepatic necrosis, thrombosis, and cardiac arrhythmias.^{1, 4-10}

Migration of UVCs was regularly observed on our neonatal intensive care unit (NICU) on chest X-rays (CXRs) in the following days after placement, despite fixation of the catheter with stitches in the umbilical cord and adhesive plasters to the abdominal wall. Although there are several reports on the placement and location of UVCs, there is little data on the occurrence of migration after placement, and how often this leads to malposition. Gupta et al. reported that on CXR 46% of UVCs migrate into the cardiothymic silhouette requiring repositioning within 24 h after placement.¹¹ Although CXR is still a commonly used imaging modality for determination of UVC position, it is not a very accurate method to estimate the location of the UVC and migration leading to malposition can be overlooked.¹² Ultrasonography (US) is more accurate and increasingly advocated for this purpose.¹³

The aim of our study was to describe the migration of UVCs using US.

METHODS

Study design and patient population

We conducted a prospective observational study at the NICU of the Leiden University Medical Center from October 1, 2016 until October 1, 2017. All infants who had a UVC inserted were eligible for the study.

Umbilical catheterization and assessment of position

According to our protocol, UVCs were placed in all neonates born at a gestational age <28 weeks or with a birth weight <1,000 g and in all other neonates that needed mechanical ventilation or circulatory support by inotropes. Other indications for a UVC at our unit are difficulties to get intravenous access and the need for an exchange transfusion. To determine the depth of the UVCs the revised formula of Shukla was used.¹⁴ The technique used for umbilical catheterization is described and demonstrated by Anderson et al.,⁵ aiming for the position of the UVC tip at the IVC-RA-junction. The UVC

(4-, 5-, or 8-French catheter; Vygon, France) was sutured in place to the umbilical cord and taped to the infant's abdomen. An anteroposterior CXR was routinely performed to determine the position of the UVC directly after catheterization.

Serial US was performed at the day of placement of the UVC (Day 1), during midweek, and at the end of week 1 after placement (or sooner when UVC was removed). The exact day depended on the presence of a caregiver skilled in US. Furthermore, in case of a catheter dwell time of >7 days, an extra US was performed at the day of removal. When CXR was also performed on the day an US was planned, US was performed within the same time period of 1 h.

The position of the catheter tip was determined by US, and the distance between the catheter tip and the IVC-RA-junction was measured. The ultrasonographer was blinded to the result of the CXR at the time of performing US. US was performed by skilled neonatologists or pediatric cardiologists. The correct position of the UVC on ultrasound scan was defined as a UVC with the catheter tip in the ductus venosus or at the IVC-RA-junction^{3,4} (Figure 1).

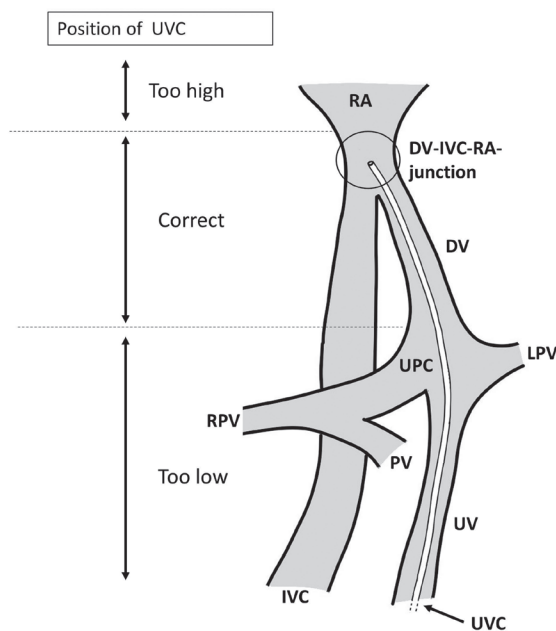


Figure 1. Relevant anatomy for the UVC route with too high, correct, and too low locations for the UVC indicated. RA, right atrium; DV, ductus venosus; UPC, umbilicoportal confluence; LPV, left portal vein; RPV, right portal vein; PV, portal vein; IVC, inferior vena cava; UV, umbilical vein; UVC, umbilical venous catheter;

Malposition was defined as the catheter tip in the heart, in the umbilicoportal confluence or umbilical vein. The position was defined too high when the UVC tip was in the heart (RA or more distal along the UVC-route). The position was defined too low when

the UVC tip was in the umbilicoportal confluence or umbilical vein. Infants with UVCs positioned too low or UVCs with the catheter tip in branches of the portal vein were excluded, and the UVC was removed within one h after insertion.

The correct position of the UVC on CXR according to the vertebral level method was defined as a UVC with the catheter tip projecting on the ninth or tenth thoracic vertebral level. The position was defined too low when the catheter tip projected below the tenth thoracic vertebral level and too high projecting above the ninth thoracic vertebral level. One of the researchers (G.H.D.-V.) reviewed all CXRs.

US was performed with a Toshiba Aplio 400 or Aplio i700 machine (Toshiba Medical Systems Europe B.V., The Netherlands) with multi-frequency transducers. Standard two-dimensional gray scale ultrasound images were acquired from at least subcostal, abdominal and apical four-chamber views, with parasternal short-axis views as needed, and were stored in digital format. To achieve better visualization of the exact position of the catheter tip, a saline solution (max 1 mL) was injected in the catheter as a contrast medium when deemed necessary.

When the UVC tip was too high, the UVC was repositioned directly after CXR or US if deemed necessary. All repositioning actions, including their distance, were recorded. Standard repeat examinations to document final position of the UVC after repositioning were not made.

Migration of the UVC on US was defined by one of the following two criteria: criterion 1 was fulfilled when the catheter tip was positioned in another anatomical structure than on prior US or than expected after repositioning. Criterion 2 was fulfilled when the distance between the catheter tip and the IVC-RA-junction differed >0.5 cm from this distance on prior US or >0.5 cm from the expected distance after repositioning.

Outcome measures

The primary outcome was the proportion of migration of UVCs after placement detected on US. Secondary outcomes were the time point when migration was detected, the proportion of malposition, and the location. We also compared the detection of migration and malposition of UVCs by US with CXRs when one was taken.

Data collection and statistical analysis

Data collected included gestational age, birth weight, mode of respiratory support, weight at subsequent ultrasound scans, date and time of UVC placement and removal, timing of all CXRs and ultrasound scans, position of the catheter tip on CXR and US, and inward and outward migration. The baseline characteristics of each infant and clinical data needed were retrieved from the electronic patient dossier Metavision (iMD-soft, Leiden, The Netherlands).

Data are given as median with interquartile range (IQR) or range for continuous data, and number (percentage) for dichotomous data where appropriate. The Chi-square test was used to compare the incidence of migration in different periods and groups, and the Kruskal-Wallis test was employed in case of more than two groups. P-values <0.05 were considered statistically significant. Statistical analyses were performed with IBM SPSS Statistics version 23.0 (IBM Software, Armonk, NY, USA).

RESULTS

During the study period, umbilical catheterization was performed in 143/629 infants, of whom 103 infants were excluded because consent could not be obtained or a skilled ultrasonographer was not available. In total, 40 infants were included with median gestational age of 27 weeks (range 24-41) and a birth weight of 1,053 g (range 600-3,925). Respiratory support was given in 36/40 (90%) infants, of whom 12/40 (30%) received mechanical ventilation and 24/40 (60%) received continuous positive airway pressure at the moment of catheterization. UVCs were placed in 30 infants on the day of birth (Day 1), in 9 infants on Day 2 and in 1 on Day 3 after birth. The median dwelling time of the UVC was 7 days (IQR 5-8). US was performed on Day 1 and on median Day 3 (IQR 3-3), 7 (IQR 6-7) and 8 (IQR 8-10).

Migration

Serial US detected migration in 25/40 (63%) infants. In 17/25 (68%) infants, this led to malposition (Figure 2).

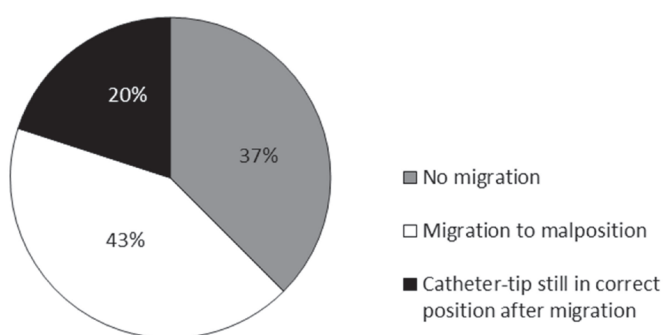


Figure 2. Migration of umbilical venous catheters (UVCs) in 40 infants.

Migration occurred twice in 7 infants, leading to 32 migrations in 25 infants. In 7/32 (22%) occasions, criterion 1 of migration was fulfilled (the UVC tip migrated to another anatomical structure), in 5/32 (16%) occasions, criterion 2 was fulfilled (the UVC tip mi-

grated over a distance >0.5 cm) and in 20/32 (63%) occasions, both criteria were fulfilled. In 15/32 (47%) occasions, the UVC tip even moved over a distance >1 cm. In 18/32 (56%) occasions, UVCs migrated inwards, which led to the catheter tip in the heart in 17/18 (94%) occasions. In 14/32 (44%) occasions, UVCs migrated outwards, which led to a catheter-tip that was too low in 2/14 (14%) occasions. In 19 occasions with migration detected by US (in 17 infants), the UVC was migrated to an incorrect position, whereas 2 out of these 19 occasions (11%) were detected by routinely performed CXRs.

In 38 infants the first US was performed within the first 24 h after UVC placement, in 21/38 infants within one h after placement, and in 17/38 infants 9 h (median) after placement (IQR3-14). The first US showed that the catheter tip was in correct position in 5/38 (13%) infants and positioned too high in 32/38 infants (84%). Five out of 32 UVCs positioned too high were accepted by the caregiver without repositioning (protocol not followed). The other 27/32 UVCs that were positioned too high were repositioned directly after US. In 1 infant the exact position of the UVC tip could not be determined due to limited visualization by US. In the infants with US performed within one h after placement, the incidence of migration on the following ultrasound scan was higher (17/21 [81%]) than in the infants with the first US performed later (median 9 h) after UVC placement (7/17 [41%]) ($p=0.01$). The occurrence of migration observed during midweek and the end of the week was not different ($p=0.06$), although there is a trend towards a higher migration rate during midweek (Table 1).

Table 1. Migration of umbilical venous catheters

	Day 3 (n=37)	Day 7 (n=24)	Day 8 (n=11)
No migration	16 (43)	15 (63)	9 (82)
Migration	21 (57)	9 (38)	2 (18)
Inward, too high	11	5	1
Inward, still correct	1	-	-
Outward, too low	2	-	-
Outward, still correct	7	4	1

Data are represented as number (percentage).

Time expressed in days of umbilical venous catheterization. Day 1: insertion day, Day 3(IQR 3-3), Day 7(IQR 6-7), Day 8 (IQR 8-10).

In 30 occasions, a CXR and US was performed within the same period. Positioning was different when assessed with CXR compared to US in 7/30 (23%) occasions and 2/21 (10%) malpositions were missed on CXR (Table 2).

Table 2. Chest X-ray (CXR) versus ultrasonography (US) for the position of the umbilical venous catheter tip

	Malposition on US	Correct position on US	Total
Malposition on CXR	19	5	24
Correct position on CXR	2	4	6
Total	21	9	30

Data are represented as numbers.

In 6/40 infants intracardiac thrombosis was detected by US. In 4 of these infants, inward migration of the UVC was observed. None of these 4 infants needed antithrombotic treatment. No cardiac arrhythmias were observed in the study population.

DISCUSSION

In this prospective study, we observed that UVCs often migrate (63%) in the days after placement, despite securing them in the correct position. This often led to malpositions of the catheter. Most UVCs migrated inwards to a position in the heart, which is potentially dangerous. Outward migration was also seen, but in most of these cases, the migrated UVC was still in acceptable position. These findings imply that caregivers should be more aware of the possibility of catheter migration, and the position should be rechecked in the days after placement.

Migration of UVCs has been reported anecdotally.¹⁵⁻¹⁷ Case reports described UVC-related complications such as pericardial effusion, left atrial thrombosis and intrahepatic hematoma in infants with a migrated UVC at the time of detection of the complication.^{15,16} Gupta et al. reported that 36% of UVCs migrated into the cardiothymic silhouette on CXRs within 1 h after insertion, and 23% after 24 h.¹¹ Franta et al. very recently performed a prospective study using serial US.¹⁸ During the inclusion period of our study, they reported a migration incidence of 50% and, despite adjustments of the UVC position if needed, malposition re-occurred in 23-62% on the different scans. Catheter migration in this study was defined as a change in catheter location from optimum position to malposition or from one malpositioned site to another. In our study, we assessed a UVC with the catheter tip still in correct position as migrated as well if it migrated to another anatomical structure or over a distance of at least 0.5 cm. Only including migration of UVCs that result in malpositions, our migration rate would be 42%, thus comparable to the migration rate in the study of Franta et al.¹⁸

Although we calculated the insertion length of the UVC by a revised formula of Shukla to avoid positioning that is too high,¹⁴ the 13% correctly positioned UVCs in our population was disappointing. Studies, including previous studies at our department and studies using the same formula, reported variable success in correct positions (14-56%).^{14,19-23}

Caregivers probably prefer (intentionally or not) to insert UVCs rather too high than too low, thus adding some length to the calculated length. This may contribute to the large proportion of too high positioned UVCs in our and other studies.

In all above mentioned studies the position of the catheter tip is determined by interpreting CXRs. There is limited data demonstrating that US is superior for determining the position of the UVC when compared to CXR.^{10, 12, 13, 18, 24, 25} Although other authors report poor correlation between the thoracic level by CXR and catheter location by US,^{10, 12, 13, 18, 24, 25} we found agreement between CXR and US in 23/30 imaging pairs. However, comparison of US and CXR in determining UVC position was not the primary goal of this study, and conclusions about the accuracy of both modalities cannot be drawn. Moreover, to limit the burden of radiation to the infant, CXRs are not serially performed at our NICU. During the study period, only 2 out of 19 occasions with malposition due to migration this was detected by routinely performed CXRs.

To prevent migration of UVCs and possible subsequent complications of malposition, knowledge of causes and risk factors for this phenomenon is critical. Abdominal girth variation is suggested as a possible cause of UVC migration.^{15, 18} Some authors speculate abdominal distension will lead to outward migration.¹⁸ Following this theory, weight loss of the infant could lead to inward migration due to a smaller abdominal diameter. Others explain inward migration of the UVC by downward movement of the IVC-RA junction caused by lung expansion and diaphragmatic descent, resulting in an upward movement of the catheter tip.¹⁶ Other risk factors for migration have been suggested, such as birth weight, weight and postnatal age at insertion, and changes in the ventilation mode.^{11, 18} Although we documented ventilation mode and weight loss, our study group was too small to investigate the relation of these factors with UVC migration.

We did not perform a standard CXR or US to confirm a correct position of the UVC after repositioning. However, in cases of repositioning after US, subsequent migration of the UVC was assessed based on the expected location of the UVC tip after pulling back the catheter. For repositioning, we measured the distance between the UVC tip and IVC-RA-junction and recorded the distance and direction of all repositioning actions.

The high proportion of inward migration in our study is concerning. The location of the UVC tip in the heart is associated with life-threatening complications, such as cardiac arrhythmias, pericardial effusion and cardiac tamponade.⁴ In only 1/40 infants we could not visualize the UVC tip by US. To improve the detection of migration and malposition of UVCs, US is a valuable and feasible tool, as it mostly takes only a few minutes and avoids additional exposure to radiation.^{17, 24} Our study showed that inadvertent migration occurs frequently between placement of the UVC and Day 3. We speculate that most migration takes place during the first hours after placement, as migration (after initial US and repositioning, if needed) was observed more frequently in infants with the initial US performed within 1 h of the first CXR (thus, shortly after catheterization)

compared to infants with initial US performed later (median 9 h). It is possible that we underestimated the occurrence of migration, as this could have been missed when US was not performed within an h. It is likely that performing only one US 24 h after the initial placement could detect most migrations and thus prevent complications.

In conclusion, UVCs frequently migrate inadvertently during the first hours and days following insertion. Part of the UVCs migrate to malposition, especially in the heart. We recommend re-evaluating the position of the catheter at least at one time point, but within 24 h after placement. This could be done by repeating CXR. However, to avoid additional radiation, US would be preferred. Incorporating US in daily practice at the NICU will detect migration of UVCs better and possibly prevent subsequent complications.

Acknowledgement

We would like to thank Hans Dubbink for his valuable support in manufacturing Figure 1 of this article.

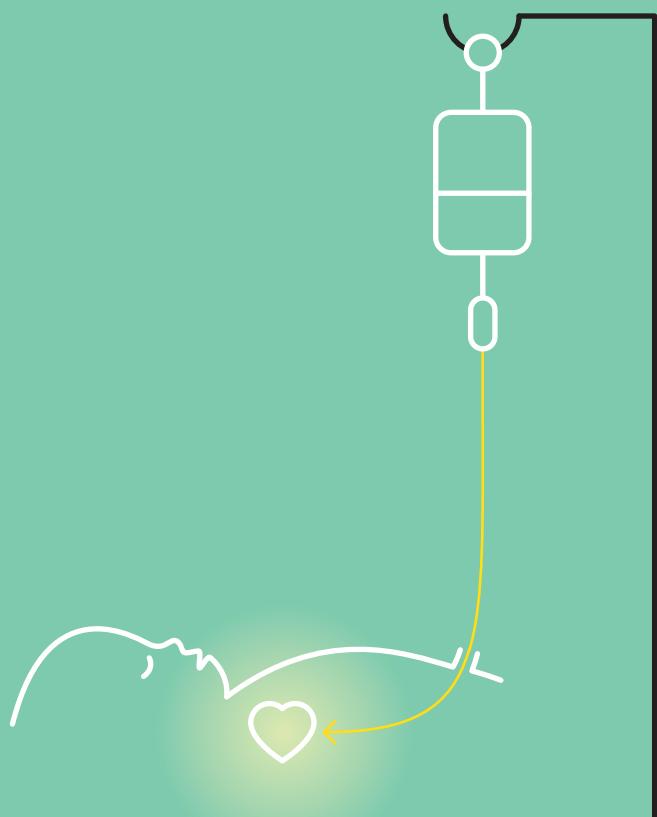
Statement of Ethics

The study was approved by the hospital institutional review board. Written informed consent was obtained from the parents of participating infants.

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PART II

Complications associated with Umbilical Catheterization

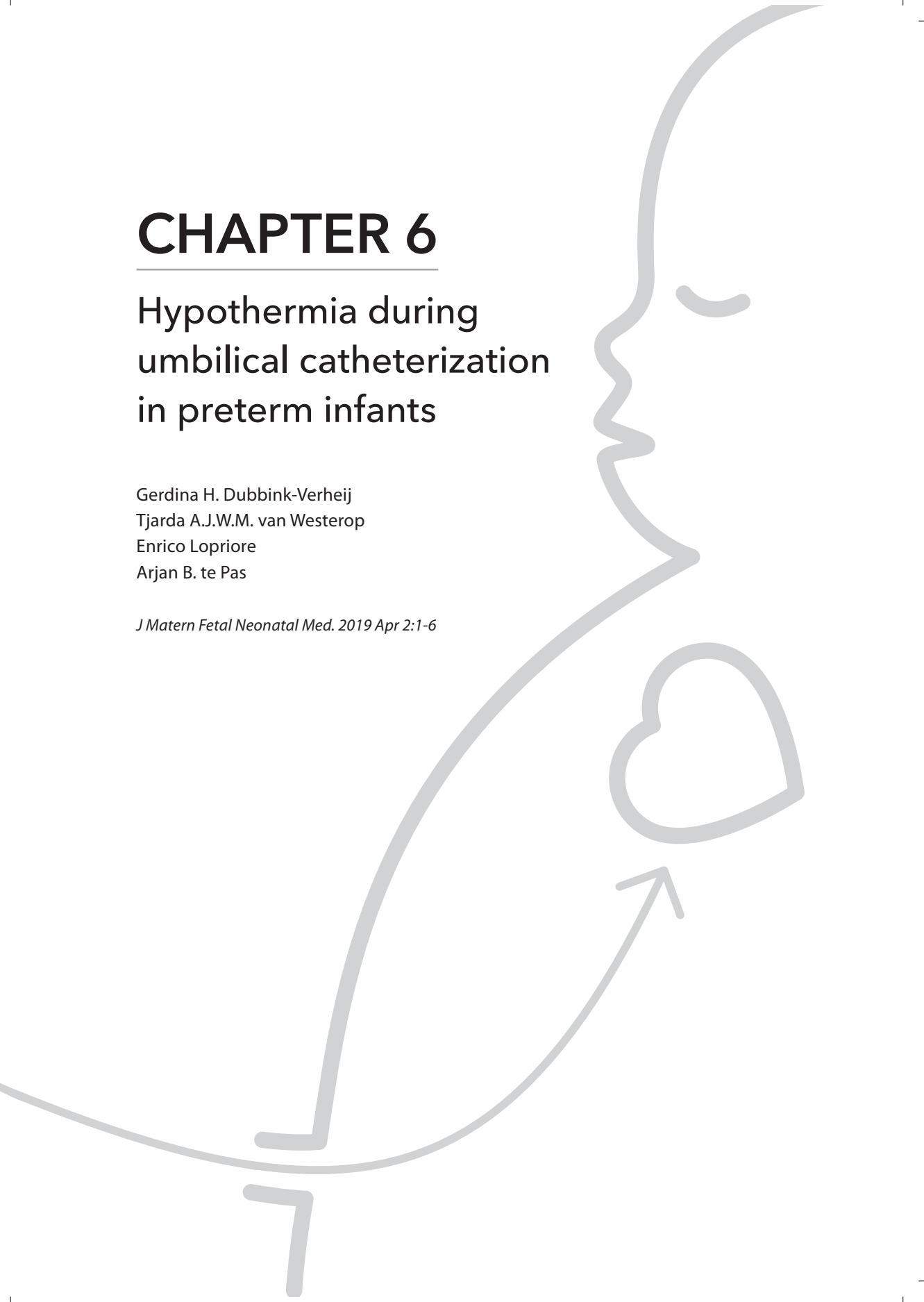


CHAPTER 6

Hypothermia during umbilical catheterization in preterm infants

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ABSTRACT

Objective

To describe the effect of umbilical catheterization (UC) on skin temperature and cardio-respiratory status in preterm infants.

Materials and methods

In a prospective observational study of infants < 32 weeks of gestation the duration of UC, course of skin temperature, and cardiorespiratory status were registered. Hypothermia was defined as a temperature below 36.5°C.

Results

UC was performed in 55 infants with a median (range) gestational age of 28 weeks (24-31) and birth weight of 1120 g (625-2091). Mean (SD) temperature first decreased 0.6 (0.6)°C during UC followed by a rise of 0.4 (0.4)°C after reaching the minimal temperature. Hypothermia already existed in 69% (38/55) of the infants before start of UC, which increased to 89% (49/55) during UC ($p=0.001$). Duration of UC was not associated with the development of hypothermia during the procedure ($p=0.48$). Heart rate (mean(SD)) significantly increased (162 (17) vs 152 (15); $p<0.001$) and there was a trend toward an increase in supplemental oxygen (mean(SD)) (0.31 (0.17) vs 0.28 (0.13); $p=0.78$), but both changes were only temporary.

Conclusion

Hypothermia was frequent in preterm infants before start of UC and increased during UC. Postponing UC until the infant has a normal temperature should be considered.

INTRODUCTION

Preterm infants treated in neonatal intensive care units (NICUs) are at increased risk of hypothermia due to increased evaporative heat loss, associated with a large skin-air temperature gradient.¹ Hypothermia present at admission is associated with increased neonatal mortality and morbidity.²⁻⁷ Reducing the risk of hypothermia in the delivery room is therefore of paramount importance and can be achieved using several preventive measures. However, procedures performed in the NICU may also cause or contribute to the development of hypothermia, especially in preterm infants. Although umbilical catheterization (UC) is commonly performed soon after admission to the NICU, little is known about the effect of this procedure on body temperature.

Complications of preterm birth, such as respiratory distress syndrome (RDS), are most likely to occur in the first hours after birth. During these hours, hypothermia can worsen the cardiorespiratory condition of preterm infants. This is because the combination of the procedure and hypothermia can increase the energy demand on the infant, leading to exhaustion.^{1, 8} When UC causes hypothermia or worsens existing hypothermia, the necessity of placing umbilical catheters soon after birth should always be weighed against the risk.

To audit our current practice in preventing hypothermia we evaluated the effect of the UC procedure on skin temperature and cardiorespiratory status.

MATERIALS AND METHODS

We conducted a prospective observational study in preterm infants to evaluate the course of skin temperature during UC. The study was performed at the NICU of the Leiden University Medical Center, a tertiary care center in the Netherlands. All infants born with a gestational age below 32 weeks who received an umbilical (venous and/or arterial) catheter during the study period of December 1st 2015 to September 30th 2016 were eligible for the study. Only infants with no missing temperature values were included. This observational study was reviewed by the Ethics Review Committee of the LUMC. In concordance with Dutch laws and guidelines, a statement of no objection against execution of the study was issued by the Ethics Review Committee.

The procedure of umbilical catheterization was performed with the infant lying on the base of the open incubator. Measures to prevent hypothermia followed the local protocol and included the following:

- 1) the materials needed for catheterization were prepared before opening the incubator,
- 2) an infant radiant warmer or heat lamp was placed above the infant,

- 3) at least 80% of the body of the infant was covered with a sterile surgical cloth drape with a small central aperture, and
- 4) infants with a gestational age below 26 weeks – and some others, when the caregiver considered it necessary - were covered with an extra plastic isolation blanket with a central aperture underneath the sterile drape to conserve heat.

The procedure was performed by caregivers with different level of expertise (residents, nurse practitioners, nurse practitioners in training, neonatologists or neonatal fellows). Inexperienced residents and nurse practitioners were supervised by a neonatologist or neonatal fellow.

The duration of the UC procedure was recorded. Starting time was defined as the moment the incubator was opened, and end of the procedure was defined as the moment the incubator was closed again. After the procedure an anteroposterior chest X-ray was performed to determine the position of the catheter(s). We also recorded the time the chest X-ray was made and the first time the umbilical catheter was used for medication or nutrition. Dates and times were reported by the assisting nurse or the performing caregiver. Hypothermia was defined as a skin temperature below 36.5°C, with 36-36.5°C as mild, 32-36°C as moderate, and below 32°C as severe hypothermia.⁹

The following items of the procedure were recorded for every infant: type of umbilical catheter (venous catheter and/or artery catheter), malposition of the catheter, level of experience of the caregiver, and whether other procedures were performed during the time the incubator was open. Gestational age, birth weight, Apgar score, and ventilatory state (including fraction of inspired oxygen and peak inspiratory pressure), were also documented, as well as mortality, intraventricular hemorrhage (IVH) grade 2 or more,¹⁰ and RDS defined as the need for surfactant administration.

During UC, heart rate was measured using a Phillips IntelliVue monitor, and skin temperature was measured using a Phillips temperature sensor (Phillips Healthcare Nederland, Eindhoven, The Netherlands) attached with an adhesive hydrogel skin pad (Care-for-me, Dräger, Lübeck, Germany). The ventilatory state of the infant was measured by the ventilator Avea (CareFusion, Houten, The Netherlands)). Heart rate, skin temperature, and ventilatory state were collected from start of the procedure until the catheter was used. Baseline characteristics of each infant and clinical data needed were distracted from the electronic patient dossier Metavision (iMD-soft, Leiden, The Netherlands).

Statistical Analysis

Statistical analysis was performed with IBM SPSS Statistics version 23 (IBM Software, Armonk, NY, United States). Data are given as median or mean with standard deviation (SD) or interquartile range (IQR) unless otherwise indicated. Temperature, heart rate and oxygen at the start and during catheterization were compared with the paired samples

t-test. Association between the duration of the procedure and the occurrence of hypothermia, temperature decrease, heart rate increase, and increase in supplemental oxygen was determined using a Wald chi-square test. Association between the experience of the performing caregiver and the duration of the procedure was determined using a Kruskal-Wallis test. A Mann-Whitney U test was used to compare the duration of insertion of an umbilical venous catheter only with duration of insertion of both umbilical catheters. A McNemar test was used to compare the proportion of hypothermia before and during catheterization. P-values below 0.05 were considered significant.

RESULTS

Patient characteristics

During the study period UC was performed in 100 infants, of which 58 were born below 32 weeks of gestation. In 3 infants the temperature values during the procedure were not available. The remaining 55 infants were included in this study: their characteristics are shown in Table 1. 11% of these 55 infants were born below 26 weeks of gestation.

Table 1. Patient characteristics

Patient characteristics (N=55)	
Gestational age (weeks)	28 (24 – 31)
Birth weight (g)	1120 (625 – 2091)
Apgar score at 5 min	8 (0 – 10)
Mortality, n (%)	1 (2)
IVH $\geq$ grade 2, n (%)	10 (18)
RDS, n (%)	53 (96)
Mechanical ventilation during catheterization, n (%)	14 (25)

Data are represented as median (range) unless otherwise specified. IVH: intraventricular hemorrhage, RDS: respiratory distress syndrome.

UC was started at median (IQR) 157 (85–335) minutes after birth. We attempted to place an umbilical venous catheter (UVC) in all infants and, in addition, an umbilical-artery catheter (UAC) in 48/55 (87%). The procedure was successful in 40/55 (73%) of UVCs and in 36/48 (75%) of UACs. No additional interventions were performed on any infants during the UC procedure, with one exception when acute care for another infant had to be performed by the same caregiver during the period the incubator was open to allow for UC.

Duration of umbilical catheter procedure

The median (IQR) duration of the UC procedure was 30 (24-44) minutes. There was no difference in duration when a UVC alone was placed or both a UVC and a UAC (43 (15-50) vs 30 (25-41) minutes; $p=0.78$). The duration from start of the procedure until the catheter was used (including waiting time for the chest X-ray to be performed and time needed to reposition catheters if necessary) was 74 (57-110) minutes.

There was a trend toward decrease in duration of UC when the level of experience of caregivers was higher ($p=0.06$; Table 2).

Table 2. Duration of umbilical catheterization

Performing caregiver	Number of catheterizations	Duration of umbilical catheterization
Resident	30	35 (30-46)
Nurse practitioner	1	23 (-)
Nurse practitioner in training	1	40 (-)
Neonatologist or fellow	16	25.5 (15-32)
Supervised inexperienced caregiver	7	43 (26-50)

Duration is represented as median (IQR) in minutes.

Effect of umbilical catheterization on infant temperature, heart rate and need for oxygen

The mean (SD) skin temperature at the start of UC was 36.1°C (0.7) and decreased significantly to a minimal temperature of 35.5°C (0.7) during the procedure ($p<0.001$), leading to a mean decrease of -0.6°C (0.6) (Table 3).

Table 3. Temperature values and hypothermia during umbilical catheterization

	N=55
Temperature at start of UC	36.1 (0.69)
Minimal temperature during UC	35.5 (0.70)
Temperature decrease during UC	0.6 (0.6)
Hypothermia during UC	49/55 (89)
Mild	9/49 (18)
Moderate	40/49 (82)
Severe	0/49 (0)

Data are represented as mean (SD) or n/N (%). UC umbilical catheterization.

This decrease was followed by an increase of 0.4°C (0.4) to a temperature of 35.9°C (0.7) at the end of the procedure. Hypothermia occurred in 49/55 (89%; Table 3) infants during the procedure (mild 9, moderate 40, severe 0). In 38/55 (69%) hypothermia already existed before the start of the procedure and in 11/55 (20%) hypothermia was new and developed during the procedure ($p=0.001$; Figure 1).

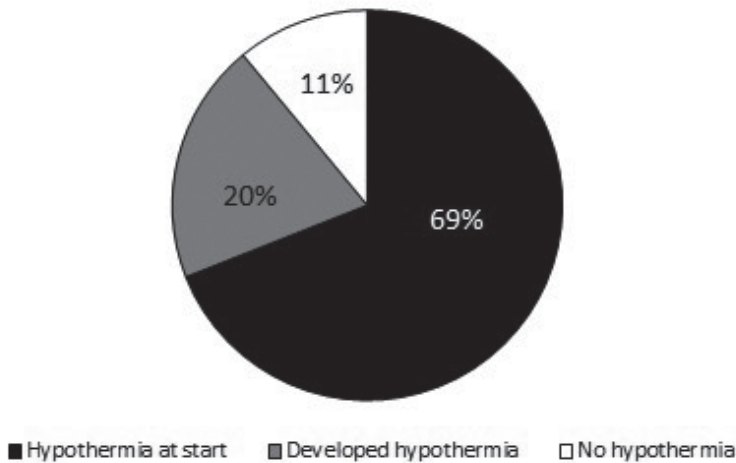


Figure 1. Incidence of hypothermia at start and during umbilical catheterization

When hypothermia already existed, the temperature decreased further during the procedure with a mean (SD) of -0.5°C (0.5). 13/16 (81%) infants with mild hypothermia at the start developed moderate hypothermia during the procedure. No differences were found between temperature at the start of UC, temperature decrease and minimal temperature during UC, and hypothermia before and during UC in infants born below 26 weeks compared to infants born at 26 weeks and older.

The course of temperature during the first 40 minutes of umbilical catheterization is shown in figure 2. The lowest temperature value was reached at a different time point in each infant. Figure 2 includes mean temperatures of 55 infants at $t=0$ minutes and of 22 infants at $t=40$ minutes, because in 33 infants duration of the procedure was <40 minutes.

The duration of UC was not associated with temperature decrease ($p=0.87$) or with the development of hypothermia during the procedure ($p=0.48$).

Mean (SD) heart rate at the start of UC was 152 (15) beats/min, maximum heart rate 162 (17) ($p<0.001$) and heart rate at end of UC was 149 (17) beats/min ($p=0.20$). Mean (SD) supplemental oxygen at start of UC was 0.28 (0.13), maximal supplemental oxygen during UC was 0.31 (0.17) ($p=0.06$), and supplemental oxygen at end of UC was 0.28 (0.13) ($p=0.78$). The duration of UC was not associated with increase in heart rate ($p=0.10$) or increase in supplemental oxygen ($p=0.97$).

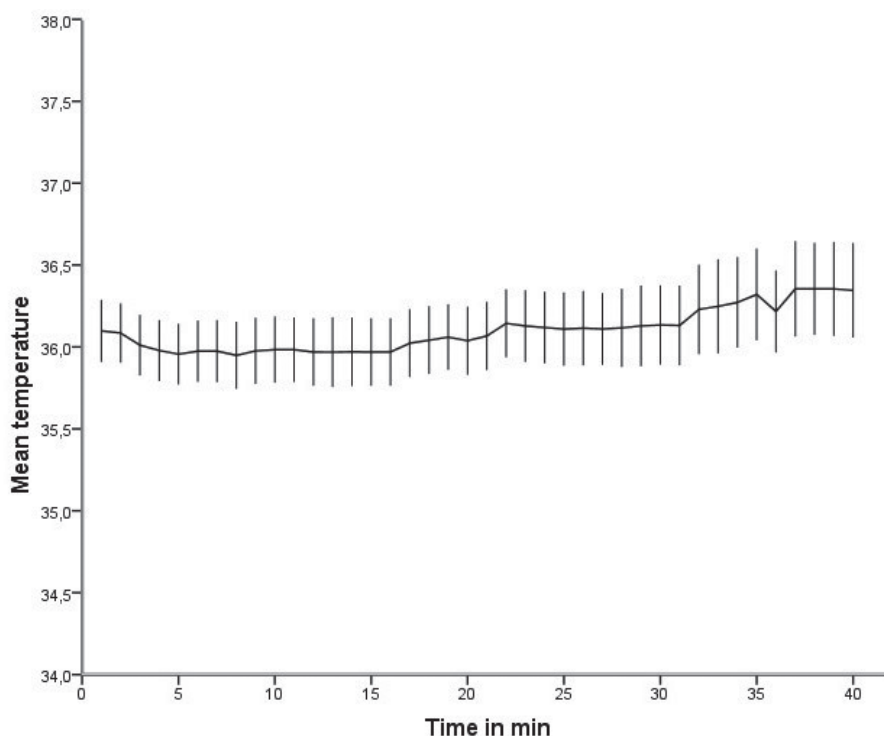


Figure 2. Course of temperature during first 40 minutes of umbilical catheterization. At $t=0$ $n=55$, at $t=40$ $n=22$. Error bars represent 95% confidence interval.

DISCUSSION

During UC in preterm infants, body temperature temporarily decreases and heart rate temporarily increases with a trend toward a temporary increase in supplemental oxygen. In this study hypothermia occurred in 89% of infants during UC. A large proportion of these infants was already hypothermic before the procedure (78%), suggesting that not all infants had been rewarmed adequately before UC was started. No association was found between the duration of the procedure and the development of hypothermia.

To our knowledge, this study is the first to investigate development of hypothermia during UC. Although Fleming et al. report that the temperature at the start and end of UC did not differ in their study, they do not report the temperature during the procedure itself.¹¹ Ghyselen et al. investigated the temperature decrease during the insertion of another central venous catheter, which is a peripherally inserted central catheter (PICC).¹² Their study showed that the temperature of infants undergoing this procedure without

a wrapping bag generally dropped to hypothermic levels. However, a polyethylene bag was effective in maintaining the temperature at a normal level.

Dongara et al. investigated the duration of insertion of 72 PICCs and 72 UVCs after randomization for the type of catheter.¹³ The mean time needed for PICC insertion was 34.1 min (SD 34.7) and 28.3 min (SD 17.2) for UVC insertion. These durations are comparable with the median duration of 30 min we needed to perform UC. In our study there was a trend toward a longer duration when inserting a UVC only, compared with a UVC and a UAC during the same procedure. However, only 7 infants were given a UVC alone. This group is therefore too small to accurately represent all procedures with only a UVC. Fleming et al. investigated whether bedside ultrasonography would be a more efficient and accurate method for determining umbilical catheter position compared with chest X-ray.¹¹ The mean time to usage of the catheter was 75 min in 15 infants with ultrasound-guided placement and 139 min in 16 infants with confirmation of position by chest X-ray after standard placement. Despite waiting for confirmation of the position by chest X-ray in our study group, the median duration of 74 min from the start of the procedure to use of the UVC is only a few minutes longer than the duration reported in the ultrasound-guided group of Fleming et al.¹¹

Our study has some limitations. The skin temperature of the infants was measured, possibly not giving a reliable reflection of the core temperature. However, in infants with birth weight <2001 g moderate to strong correlation ($r=0.50-0.77$) was described by Helder et al. with a 0.27°C (0.03-0.51) lower skin temperature (measured at the abdomen as in our department) compared with rectal temperature.¹⁴ Performing caregivers were informed about the registration of the duration of the procedure, possibly leading to a feeling of time pressure and shorter procedures during the study period. The duration from the end of the procedure until use of the catheter is variable, due to different levels of urgency for use of the catheter or logistical reasons causing delay. These reasons were not structurally registered. Another limitation of this study is that variations in temperature, heart rate and oxygen during UC were not compared with the same variations in a control group of preterm infants without catheterization. We therefore cannot rule out the possibility of comparable variations in preterm infants without UC. However, we expect these parameters, especially skin temperature, to be more stable in infants kept in their incubator without undergoing procedures.

During UC 20% of infants developed hypothermia. To prevent its harmful effects, all efforts were made to keep the temperature of the infant stable during catheterization. This can be achieved by the use of warm gel mattresses and auxiliary heat lamps, and by closing the incubator as soon as the procedure is finished.¹ Wrapping preterm infants in a plastic bag after birth can also prevent hypothermia.¹⁵ Wrapping the infant in a plastic bag with a hole at the level of the umbilicus during the procedure of UC may also be helpful to keep the temperature stable. The use of measures to prevent heat loss in our

population is likely to have limited the decrease in temperature and to have led to the rewarming of the infant during the procedure, as shown in figure 2. However, these measures could not prevent a drop in temperature during the first minutes of the procedure. This drop frequently caused or worsened hypothermia in infants. Tsai et al. report that insertion of a PICC was associated with higher rates of catheter-related complications when the procedure lasted longer than 60 min, compared with instances when it was shorter than 30 min.¹⁶ Limiting the time needed to perform UC may also have beneficial effects. However, we found no correlation between the duration of the procedure and the development of hypothermia or temperature decrease. We generally observed a drop in temperature at the beginning of the procedure. However, the temperature was stabilizing and sometimes rising again in the latter part of the procedure, indicating that a longer duration will not necessarily lead to ongoing temperature decrease. Limiting the duration of the procedure may be more challenging in institutions where trainees perform catheterizations. In our study a trend towards longer duration of the procedure when performed by less experienced caregivers was observed.

Hypothermia shortly after birth is a frequently observed problem in preterm infants and needs to be avoided. Although UC was performed a median of 2 h and 37 min after birth in our study, 69% of infants were still hypothermic at the moment the procedure started. To achieve intravenous administration of glucose and amino acids within the first hour of life, performing UC during the first 'golden hour' of neonatal preterm life is advocated.^{17, 18} However, as shown in this study, UC may lead to inadequate rewarming of infants who are already hypothermic after birth. For hypothermic infants, we suggest considering postponing the procedure of UC until the infant has a normal temperature if it is possible to give the infant alternative intravenous access during waiting time that can be inserted more quickly. In these cases, UC is not essential and may even be a harmful step in the first hour(s) of life.

In conclusion, hypothermia is a common condition in infants. It develops during UC in one in five very preterm infants catheterized after birth. In even more infants, however, hypothermia is already present at the start of the procedure, and frequently worsens temporarily during catheterization. Efforts have to be made to prevent the development of hypothermia during catheterization. Moreover, the rewarming of infants after birth needs to be optimized and time should be allowed for this in order to limit the presence of hypothermia after birth even before undergoing procedures at the NICU.

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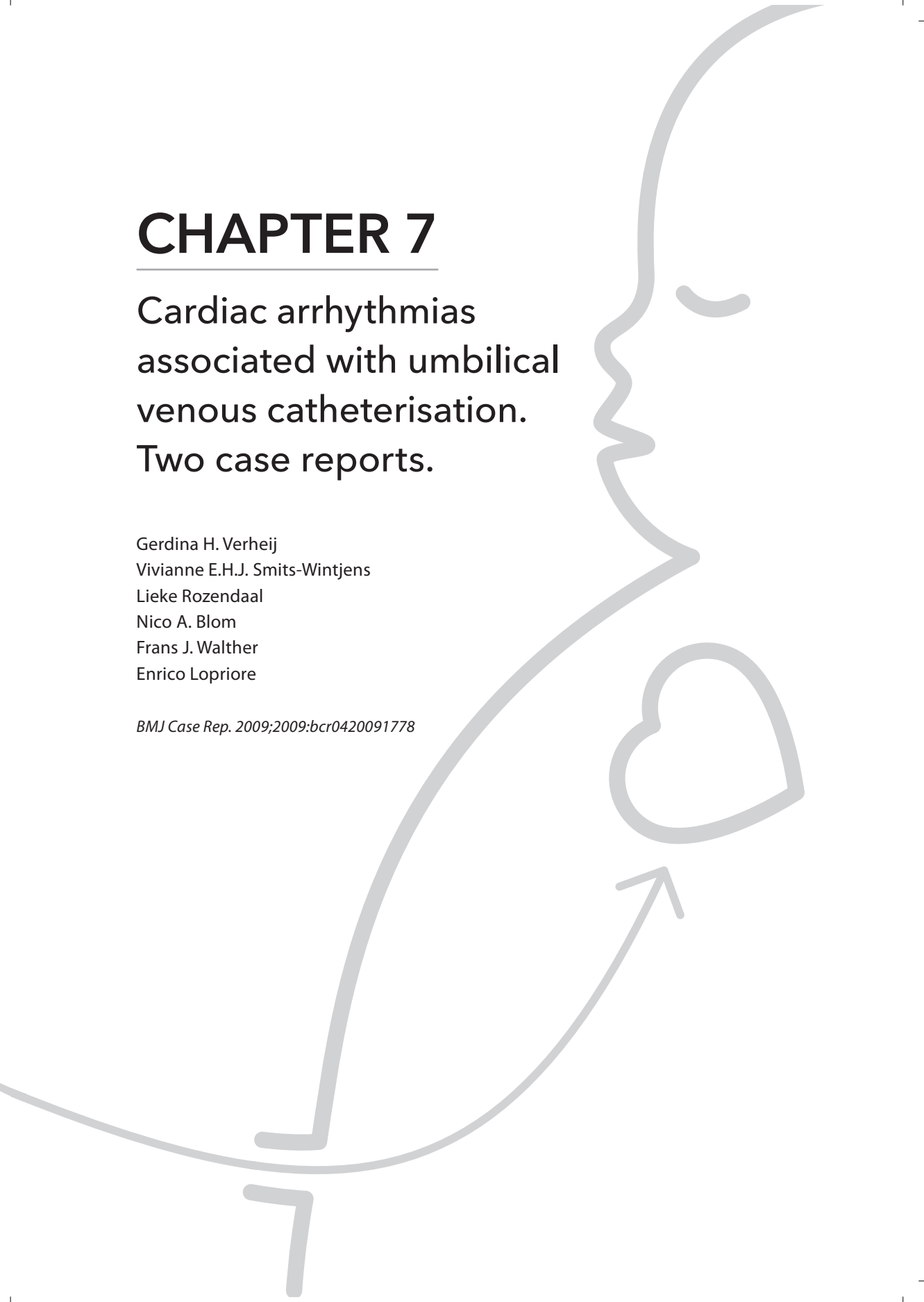


CHAPTER 7

Cardiac arrhythmias
associated with umbilical
venous catheterisation.
Two case reports.

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ABSTRACT

Umbilical venous catheters (UVCs) are commonly used in the management of severely ill neonates. Several life-threatening complications have been described, including catheter-related infections, myocardial perforation, pericardial effusion and cardiac arrhythmias. This report describes two neonates with cardiac arrhythmias due to umbilical venous catheterisation. One neonate had a supraventricular tachycardia requiring treatment with intravenous adenosine administration. Another neonate had an atrial flutter and was managed successfully with synchronized cardioversion. The primary cause of cardiac arrhythmias after umbilical venous catheterisation is inappropriate position of the UVC within the heart and the first step to treat them should be to pull back or even remove the catheter.

Cardiac arrhythmia is a rare but potentially severe complication of umbilical venous catheterisation in neonates.

INTRODUCTION

Umbilical venous catheters (UVCs) are commonly used in the management of severely ill neonates for intravenous administration of parenteral nutrition, hypertonic solutions, blood products and medication. However, the advantages of UVCs must be carefully balanced against the potential risks. Several life-threatening complications have been associated with the use of UVCs, including catheter-related infections, thrombosis, myocardial perforation, pleural and pericardial effusion.¹⁻⁶

Cardiac arrhythmias by indwelling atrial lines, such as UVCs, have also been described in neonates.⁷⁻¹⁰ In the perinatal period paroxysmal supraventricular tachycardia (SVT) and atrial flutter are the most common types of tachyarrhythmias, usually in the absence of structural heart disease. The onset of atrial flutter and paroxysmal supraventricular tachycardia has also been reported secondary to umbilical (or jugular) venous catheterization.^{6, 11-14} The aetiology of these tachyarrhythmias in each case was inappropriate placement of the venous catheter within the heart.

Although most neonatal textbooks report on the risk of arrhythmias after umbilical venous catheterisation, not much is known about the underlying pathophysiological mechanism and the incidence of this complication.^{6, 10} Moreover, the clinical course of cardiac arrhythmias due to placement of UVCs has not well been studied. Establishing the risks associated with any medical procedure is crucial.

We describe two neonates with cardiac arrhythmias associated with umbilical venous catheterisation and discuss the management of these sometimes acute life-threatening situations.

CASE NO. 1

A 3750 g male infant was born at 41 weeks of gestation in a secondary care center. Because of perinatal asphyxia the child was intubated, mechanically ventilated and transported to our hospital. Apgar scores were 2, 5 and 8 at 1, 5 and 10 minutes, respectively. Umbilical cord arterial pH was 6.9 with a base excess of -11.8 mmol/l. On admission to our neonatal nursery, the infant had a normal heart rate (119 beats/min) and a normal blood pressure (54/46 mm Hg). Physical examination showed no major congenital malformations, normal heart sounds, no heart murmur, equal pulses on all extremities and no hepatosplenomegaly. Laboratory investigations, including serum electrolytes, showed no abnormalities.

On day 1, the infant developed seizures and was treated successfully with phenobarbital (20 mg/kg). An electro-encephalogram on day 2 did not show epileptic activity. Cranial ultrasound examinations on day 1, 2 and 5 were normal. There was no cerebral edema.

Umbilical venous and arterial catheters were placed on day 1. Insertion length was determined by using the method from Shukla.¹⁵ Directly after catheterisation, the infant developed a tachycardia of 300 beats/min and the diagnosis of SVT was confirmed by electrocardiogram (ECG). The ECG showed a regular narrow QRS complex tachycardia with retrograde p waves buried within the T waves indicating the presence of an atrio-ventricular reentry tachycardia (Figure 1).

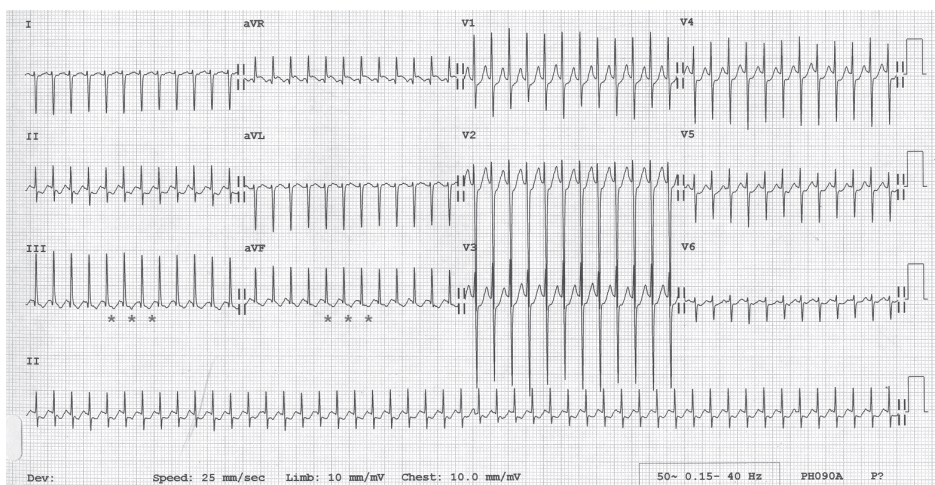


Figure 1. Supraventricular tachycardia of case no. 1. The ECG shows narrow QRS complex tachycardia of 300 beats/min with retrograde p waves (stars) within the T waves suggestive for atrioventricular re-entrant tachycardia.

The catheters were pulled back 1 cm, but the tachycardia persisted. Placement of an ice pack on the infant's face failed to decrease the infant's heart rate. Intravenous adenosine (0.1 mg/kg) was given without success. A second dose of adenosine (0.2 mg/kg intravenous) converted the heart rhythm to a normal sinus rhythm. A chest X-ray showed malposition of the venous catheter tip at the sixth thoracic vertebra. The catheter was subsequently pulled back 2 cm. After repositioning of the catheter, SVT reoccurred. Administration of a third dose of adenosine (0.2 mg/kg intravenous) converted the heart rate to a normal sinus rhythm. Further clinical course was uncomplicated, without other episodes of tachycardia. The catheters were removed 2 days later.

CASE NO. 2

A 1564 g male infant was born at 28 weeks of gestation at our centre and admitted to our neonatal nursery. Apgar scores were 8, 9 and 9 at 1, 5 and 10 minutes, respectively. On admission the infant had a sinus rhythm with a normal heart rate (146 beats/min)

and blood pressure (47/28 mm Hg). On physical examination slight groaning and sub-costal retractions were found, with normal heart sounds and without heart murmur. Pulses were felt equally on all extremities and no hepatosplenomegaly was detected. Laboratory investigations, including serum electrolytes, showed no abnormalities.

Umbilical venous catheterisation was performed. Insertion length was determined by using the method from Dunn.¹⁶ Directly after introduction of the catheter the infant developed a tachycardia (heart rate up to 240 beats/min). Placement of an ice pack on the infant's face resulted in a short bradycardia, but after a few seconds tachycardia re-occurred. Due to suspicion of malposition of the UVC, the catheter was pulled back 1 cm, but tachycardia persisted. A chest X-ray showed malposition of the catheter tip localized at the seventh thoracic vertebra. The catheter was pulled back 2 cm, but normalization of the heart rhythm did not occur. Intravenous adenosine was given four times (0.1, 0.1, 0.2 and 0.4 mg/kg, respectively) without success of converting to sinus rhythm. The ECG performed during adenosine administration revealed an atrial flutter (Figure 2).

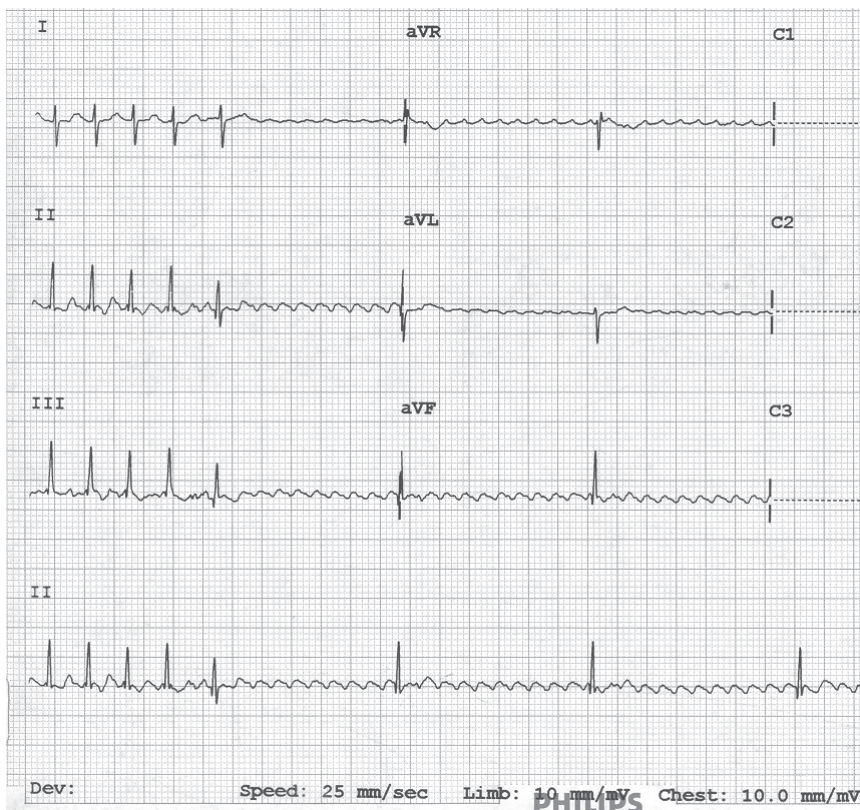


Figure 2. Atrial flutter of case no.2. Intravenous adenosine for a supraventricular tachycardia (see left) resulted in transient atrioventricular blockade unmasking an atrial flutter of 450 beats/min.

Echocardiography was performed and showed no anatomical abnormalities. The tip of the catheter was in the inferior venal cava (just below the junction with the right atrium). Subsequently synchronized cardioversion was performed with 2 J and converted the heart rhythm to a normal sinus rhythm. During tachycardia the infant remained hemodynamically stable. Further clinical course was unremarkable and episodes of tachycardia did not reoccur. The UVC was removed 1 week later.

DISCUSSION

Umbilical venous catheterisation is an often essential routine procedure in the neonatal period. UVCs provide an easy and secure access route for continuous intravenous administration of fluids and medication. However, several complications associated with the use of UVCs have been described, including cardiac arrhythmias. This study shows that the incidence of cardiac arrhythmias after umbilical venous catheterisation is low (0.4%). Nevertheless, cardiac arrhythmias may be life-threatening and require prompt medical treatment.

Several cases of cardiac arrhythmias (mostly atrial flutter) after UVC placement have been reported in the literature (Table 1).

Table 1. Literature review of cases with arrhythmia related to placement of an umbilical venous catheter (UVC).

Author (year)	Cases (n)	Position of UVC	Arrhythmia	Treatment
Egan et al (1971)	3	Right atrium (n=2), left atrium (n=1)	Atrial arrhythmia (n=1) Bigeminy rhythm (n=1) Prolonged sinus bradycardia (n=1)	Catheter withdrawal (n=3)
Dunnigan et al (1985)	3	Right atrium (n=3)	Atrial flutter (n=3)	Transoesophageal pacing (n=3)
Leroy et al (2002)	1	Left atrium	Atrial flutter	Transoesophageal pacing
Sinha et al (2005)	1	Fifth thoracic vertebra	Atrial flutter	Synchronised cardioversion
This study (2008)	2	Sixth thoracic vertebra (n=1) Seventh thoracic vertebra (n=1)	Supraventricular tachycardia (n=1) Atrial flutter (n=1)	Adenosine (n=1) Synchronised cardioversion (n=1)

In four cases, heart rhythm was converted to normal sinus rhythm by transoesophageal pacing,^{12, 14} in another case successful treatment was achieved with synchronized cardioversion.¹¹ In three cases with a cardiac arrhythmia related to a catheter with the tip in the heart, the arrhythmia reverted to normal sinus rhythm after removing the catheter.⁶

The primary cause of cardiac arrhythmias after umbilical venous catheterisation is inappropriate position of the UVC within the heart.^{6, 14} Intracardiac catheters may cause mechanically induced premature atrial beats that can be the initiating trigger for atrial flutter or even SVT in the presence of an accessory atrioventricular myocardial pathway as shown in the first case.

Radiographic investigations are therefore mandatory to ensure that the catheter is correctly positioned. The optimal position for catheters is at the junction of the inferior venal cava and the right atrium.¹⁶ This will correspond to the catheter tip being visible between the ninth and tenth thoracic vertebra on a chest X-ray, although positioning at the level of the eighth thoracic vertebra may also be adequate in some patients.¹⁷ Malposition has been defined as either a catheter tip above the eighth thoracic vertebra or a position below the tenth thoracic vertebra. Some authors suggested that position of the catheter tip should ideally be asserted with echocardiography instead of chest X-ray.^{17, 18}

Two methods are commonly used to determine the correct insertion length of UVCs. The Dunn method is based on the measurement of the shoulder-umbilicus length.¹⁶ This method is hampered by several important limitations, including interobserver variation.¹⁹ The second method, from Shukla et al uses equations based on the birth weight of the neonate.¹⁵ Importantly, both methods have been developed based on a small group of infants (range 10-50 infants) and have not been validated prospectively in larger groups of neonates. Whether the estimation of the insertion length based on these methods is accurate is not known. In both our reported cases, the catheter position was too deep.

The optimal management of neonates with cardiac arrhythmias secondary to umbilical venous catheterisation has not well been studied. As arrhythmias are usually due to malposition of the catheter, the first step should be to pull back or even remove the catheter. However, in both our cases pulling back was not successful and in the first case even induced another episode of tachycardia. As most of the newborns with SVT have atrioventricular re-entry tachycardia,²⁰ the next step should aim to stop the re-entry loop by inducing a vagal response, initially by placing an ice pack on the child's face.^{10, 20} If tachycardia persists, administration of adenosine, an endogenous purine nucleoside, is relatively safe and effective. Adenosine impairs atrioventricular nodal conduction and thereby terminates re-entrant SVTs.²¹ Adenosine has a very short half-life of less than 15 s because of rapid metabolism by adenosine deaminase.²² It must be administered within seconds as an intravenous bolus and will terminate 85-93 % of SVTs caused by a re-entry mechanism.²¹ Termination of the tachycardia will occur within 20 s of injection.^{21, 22} Because of the short half-life of adenosine possible side-effects are transient and thus acceptable. Side-effects include transient disturbance of respiration, flushing, nausea, headache, short bradycardia and very short complete atrioventricular block.²²

The starting dose of adenosine in infants is controversial. Some advocate a starting dose of 0.05 mg/kg,²¹⁻²³ but this is effective in less than 10 % of infants. Infants tend to need a higher dose to terminate the tachycardia than older children and this may be explained by the difference in weight to body surface area ratio.²⁴ One danger of a starting dose that is too low is that parents and physicians lose confidence in what is a very effective drug. More recent literature advocates a starting dose of 0.1 mg/kg or even higher.^{20, 24} In our first patient three doses of adenosine (cumulative dose of 0.5 mg/kg) were necessary to treat the patient successfully. Cardiac arrhythmia in our second patient was not caused by a re-entry tachycardia but by an atrial flutter which explains the lack of effect of adenosine. Administration of adenosine does not terminate tachycardias of atrial origin, such as atrial flutter. However, by producing a transient atrioventricular block, adenosine administration may help detect atrial flutter.^{10, 21, 22} Treatment of an atrial flutter requires synchronized cardioversion or transoesophageal atrial pacing.

In conclusion, this case reports show that cardiac arrhythmia can be the result of intra-cardiac position of a UVC. Given the potential severity of this complication, physicians involved in the care of neonates should be aware of this risk and be familiar with its diagnosis and management.

LEARNING POINTS

- Cardiac arrhythmia is a rare but potentially severe complication of umbilical venous catheterisation in neonates.
- The primary cause of cardiac arrhythmias after catheterisation is inappropriate position of the umbilical venous catheter within the heart.
- The first step to treat cardiac arrhythmias should be to pull back or even remove the catheter.
- As most of the newborns with SVT have atrioventricular re-entry tachycardia, the next step should aim to stop the re-entry loop by inducing a vagal response, initially by placing an ice pack on the child's face. If tachycardia persists, administration of adenosine, an endogenous purine nucleoside, is relatively safe and effective.

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CHAPTER 8

Thrombosis after umbilical venous catheterization: prospective study with serial ultrasound

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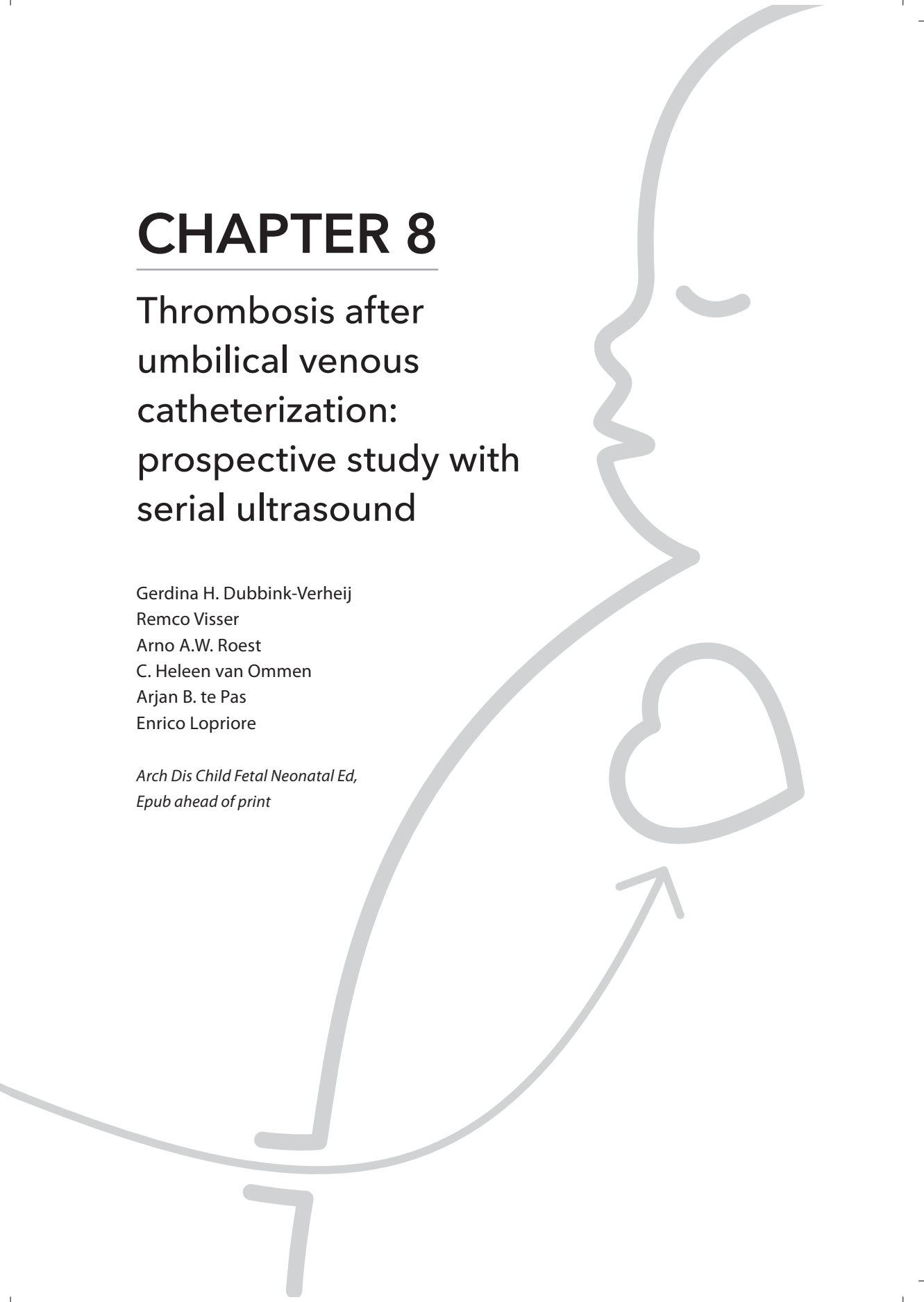
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ABSTRACT

Background

Umbilical venous catheters (UVCs) are associated with thrombus formation. Most studies on thrombosis in infants with UVCs focus on only one part of the route, and none assessed a control-group of infants without UVCs.

Objective

To determine the incidence and location of thrombi in infants after umbilical catheterization, and compare this with a control-group of infants without umbilical catheters.

Design

Prospective observational study with serial ultrasonography of the UVC route from the umbilico-portal confluence to the heart. Ultrasonography was performed until day 14 after catheterization in cases and day 14 after birth in controls.

Results

Thrombi in the UVC route were detected in 75% (30/40) of infants with UVCs in the study-group, whereas no thrombi were detected in the control-group of infants without UVCs (0/20) ($p < 0.001$). Six thrombi (20%) were located in the right atrium. Most of these were also partly present in the ductus venosus. Six thrombi (20%) were located in the ductus venosus only, and in 12 infants (40%) the thrombus was at least partly located in the umbilico-portal confluence. Thrombi persisted after UVC removal in 25/30 cases. Two infants with thrombotic events were treated with low-molecular-weight heparin and resolution was found. In the other 23 infants managed expectantly, 2 died due to necrotizing enterocolitis, 1 was lost to follow-up and in 20 spontaneous regression was seen.

Conclusions

Thrombotic events occur frequently in infants after umbilical catheterization. Most thrombi were asymptomatic and regressed spontaneously with expectant management. Routine screening for thrombi in UVCs is therefore not advised.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Umbilical venous catheters are associated with thrombus formation.
- The incidence of thrombosis in infants without umbilical venous catheters is unclear.

WHAT THIS STUDY ADDS

- Most infants have thrombosis in the umbilical venous catheter route after umbilical venous catheterization.
- Thrombosis in the umbilical venous catheter route in infants without umbilical venous catheters is not detected.
- Routine screening for thrombi in umbilical venous catheters does not seem necessary as most are asymptomatic and regress spontaneously.

INTRODUCTION

Umbilical catheters are frequently required for the management of critically ill infants. Umbilical venous catheters (UVCs) are used for intravenous administration of parenteral nutrition and medication. These catheters are relatively easy to insert, and may be used for a longer period as compared to peripheral iv access. However, the advantages of UVCs should be balanced against the potential risks. Central venous catheterization is reported to be the most common cause of neonatal thrombosis.^{1,2} Catheter-associated thrombosis may be asymptomatic but may also result in thrombocytopenia, infection, pulmonary embolus, liver necrosis and, occasionally, even death.³⁻⁵ Reported incidence of UVC-related thrombosis varies greatly from 2.2% to 43% due to differences in study design and methodology.⁶⁻¹³ UVCs are introduced in the umbilical vein to reach the umbilico-portal confluence, and subsequently pass the ductus venosus to reach the junction between the inferior vena cava (IVC) and right atrium, which is the ideal location for the UVC tip.^{5,14} The tip of UVCs is positioned too high when it is located in the right atrium or passing through the patent foramen ovale, within the left atrium or pulmonary vein.¹⁵ Too low positioned UVCs have their tip in or below the umbilico-portal confluence or are malpositioned, for example in the portal vein. Thrombus formation may occur in all parts of this UVC route. Most studies on thrombosis in infants with UVCs focus on only one part of the route, such as the liver or heart, not determining the incidence of thrombus formation in all locations together.⁶⁻¹¹ None of these studies investigated the occurrence of thrombosis in the UVC route in infants without UVCs.

The aim of this study was to determine the incidence and location of thrombi in infants after umbilical catheterization with ultrasonography in the entire UVC route and to investigate if thrombosis in this route exists in infants without umbilical catheters.

METHODS

We conducted a prospective observational study at the neonatal intensive care unit of the Leiden University Medical Center, a tertiary care center in The Netherlands. The study was approved by the hospital system institutional review board. Written informed consent was obtained from the parents of participating infants.

Infants of all gestational ages were considered for enrollment in the study-group if a UVC was inserted. Infants were included from October 1st 2016 until October 1st 2017. We aimed for a convenience sample of 40 infants with and without UVCs during this period.

Umbilical catheterization was performed according to local protocol. Estimated insertion length of the UVC was calculated based on the revised formula of Shukla.¹⁶ An antero-posterior chest X-ray was routinely performed in all cases to determine

the position of the catheter. Within an hour after catheterization, the position of the catheter-tip was determined by ultrasonography as well, and the presence and location of a thrombus was noted. Ultrasonography was performed by skilled neonatologists or pediatric cardiologists. Correct position of the UVC was defined as a UVC with the catheter-tip in the ductus venosus or at the junction of the ductus venosus and IVC/right atrium by ultrasonography (see Figure 1). Only infants with UVCs in the correct route with the catheter-tip having passed the umbilico-portal confluence could be included in the study. Infants with UVCs positioned too low or with the catheter-tip in blood vessels in the liver were excluded, because these UVCs were removed within one hour after insertion. These patients were also not eligible for the control-group. UVCs that were positioned too high were pulled back to the correct position after ultrasonography. Ultrasound scans were repeated on day 3, 7 and 14 after catheterization. Additional ultrasound scans were performed on the day of catheter removal. During the study period of one year infants without an indication for a UVC were considered for enrolment in the control-group. Matching cases and controls according to gestational age and birth weight was not possible as all infants below 28 weeks routinely receive umbilical catheters in our department. In the control-group ultrasonography was scheduled within 24 hours after birth, on day 7 and on day 14. In both groups in case of discharge of the patient before day 14 an ultrasound scan was performed within 24 hours preceding discharge. In case of non-availability of a skilled professional to perform ultrasonography, the examination was performed one or two days before or after the scheduled day.

Ultrasonography was performed with a Toshiba Aplio 400 or Aplio i700 machine (Toshiba Medical Systems Europe B.V., the Netherlands) with multi-frequency transducers. Standard two-dimensional gray scale images were acquired from at least subcostal, abdominal and apical four-chamber views, sometimes extended with parasternal short-axis views and were stored in digital format. The heart, IVC, ductus venosus and umbilico-portal confluence were visualized and screened for the presence of thrombi. A thrombus was defined as an echo dense structure within the heart or vessels or around the catheter observed in two dimensions. Except for thrombi in the ductus venosus, thrombi were classified as obstructive or non-obstructive based on the presence or absence of flow around the thrombus. Thrombi in the right atrium were classified as filling more or less than 50% of the atrium. Flow in the ductus venosus ceases within the first minutes to days independent of the presence or absence of a UVC.¹⁷ Thus, flow was not used as a discriminating factor to assess thrombi in the ductus venosus.

Decisions to remove the UVC were made by the attending physician. Decisions to treat thrombi were based on the Dutch national guideline concerning catheter-related thrombosis in neonates.¹⁸ This guideline advises a 'watch and wait' approach in most cases. If thrombi cause complete obstruction of blood flow or rapidly progress without treatment, treatment with low-molecular-weight heparin (LMWH) is advised, as well as

in thrombi filling >50% of the right atrium. Thrombolysis is only advised in cases with high risk of organ- or life-threatening consequences.¹⁸ Follow-up of thrombi after day 14 was performed if considered clinically indicated according to the attending physician.

All above data were recorded. Baseline characteristics of each infant, and clinical data, including gestational age, birth weight, duration of hospital admission, mortality, date and time of UVC placement and removal, timing of ultrasound scans, peripherally inserted central catheter (PICC) insertion after UVC placement, position of catheter-tip and presence and location of thrombosis, were extracted from the electronic patient dossier Metavision (iMD-soft, Leiden, The Netherlands). Presence and timing of necrotizing enterocolitis stage 2a or higher,¹⁹ culture-proven sepsis and thrombocytopenia (defined as a platelet count $\leq 150 \times 10^9/L$) and treatment of thrombi were also recorded.

Statistical analysis

Data are given as median with range unless otherwise mentioned. Incidences of thrombosis were compared with the Chi-square test. The student's t-test for parametric and the Mann-Whitney U test for non-parametric data were used for comparisons of continuous variables. P-values below 0.05 were considered significant. All statistical analyses were performed with IBM SPSS Statistics version 23.0 (IBM Software, Armonk, NY, United States).

RESULTS

Patient characteristics

We included 40 infants in the study-group of infants with UVCs and 20 infants in the control-group without UVCs. Patient characteristics in both groups are given in Table 1.

Table 1 – Patient characteristics of infants with UVC (study-group) and infants without UVC (control-group)

Variable	Study-group (n=40)	Control-group (n=20)	p-value
Gestational age at birth (weeks)	27 (24-41)	29 (27-41)	0.06
Birth weight (grams)	1052.5 (600-3925)	1464.5 (1020-3300)	0.07
SGA, n (%)	6 (15)	0 (0)	0.07
Duration of hospital admission (days)	18.5 (3-102)	13 (3-44)	0.04
PICC received after UVC, n (%)	12 (30)	3 (15)	0.21
NEC, n (%)	5 (12.5)	1 (5)	0.36
Culture-proven sepsis, n (%)	11 (27.5)	2 (10)	0.12
Mortality, n (%)	4 (10)	1 (5)	0.51

Data are represented as median (range) unless otherwise specified. P-values <0.05 were considered significant. Significant p-values are depicted in **bold**. UVC: umbilical venous catheter. SGA: small-for-gestational-age, defined as a birth weight adjusted for gestational age below the 10th centile according to growth curves for Dutch neonates.²⁹ PICC: peripherally inserted central catheter. NEC: necrotizing enterocolitis stage 2a or higher.¹⁹

Four patients in the study-group died, due to necrotizing enterocolitis (n=2) and pulmonary bleeding (n=2), and one patient died in the control-group due to necrotizing enterocolitis (n=1).

Incidence of thrombosis

Thrombi in the UVC route were detected in 75% (30/40) of cases in the study-group, whereas no thrombi were detected in the control-group (0/20) ($p<0.001$). Thrombi were first detected by ultrasonography in 14/30 cases (47%) at day 3-5, 12/30 (40%) at day 6-8, and 4/30 (13%) between day 9 and 15 (median day 6). Thrombi were detected in 9/30 cases after UVC removal, in 4/30 cases at the day of UVC removal and in 17/30 cases before UVC removal. In none of the cases thrombosis was the reason for UVC removal. Thrombi were detected in different parts of the UVC route (Figure 1).

Six thrombi (20%) were located in the right atrium. Five of these thrombi were also partly present in the ductus venosus and one was located along the entire route including ductus venosus and umbilico-portal confluence as well. All right atrial thrombi filled less than half of the atrium and the two thrombi located at the junction of ductus venosus and IVC/right atrium were non-obstructive as well. Six thrombi (20%) were located in the ductus venosus only and in 12 infants (40%) thrombi were at least partly located in the umbilico-portal confluence.

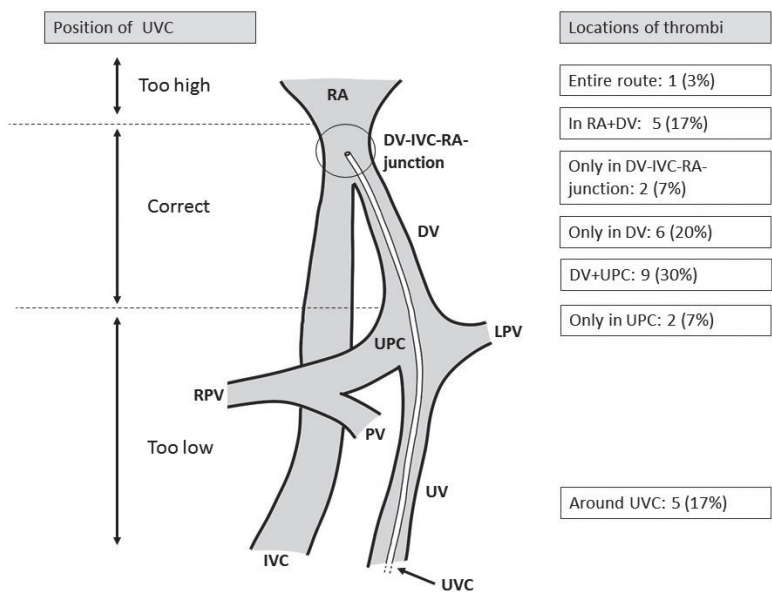


Figure 1. Locations of the 30 detected thrombi, n (%). RA: right atrium, DV: ductus venosus; UPC: umbilico-portal confluence, LPV: left portal vein, RPV: right portal vein, PV: portal vein, IVC: inferior vena cava, UV: umbilical vein, UVC: umbilical venous catheter.

Other aspects

Ultrasound data for study-group and control-group are given in Table 2.

Table 2. Ultrasound data in study-group and control-group.

	Study-group (n=40)	Control-group (n=20)
Follow-up duration after UVC insertion (days, median, range)	14 (2-16)	-
Follow-up duration after birth (days, median, range)	-	13 (1-17)
Position of UVC at initial ultrasound		
Correct	5 (13)	-
Too high	33 (83)	-
Not to determine	1 (3)	-

UVC: umbilical venous catheter.

At initial ultrasound 5/40 UVCs (13%) were in correct position, 2/40 (5%) were placed with tips in the left atrium, and 31/40 (78%) in the right atrium. In one UVC the exact position of the tip could not be determined due to limited visualization of the catheter by ultrasonography and in one ultrasonography was not performed directly after catheterization. Thrombus data of these cases are included in the analysis. Thrombocytopenia was seen in 6/40 infants with UVCs (15%) and in 2/20 controls (10%) ($p=0.59$) during admission. One infant with thrombocytopenia in the UVC-group had no thrombus in the UVC route. In 3 infants with thrombocytopenia, this was observed before and in 2 after detection of the thrombus. In 4 cases, thrombocytopenia was interpreted by the attending physician as a possible symptom of thrombosis. Two infants with thrombi had persistent catheter-related sepsis with *Staphylococcus aureus*. No other symptoms of thrombosis, such as loss of UVC patency were noted.

Follow-up of infants with catheter-related thrombi

Four of the 30 detected thrombi were visualized around the catheter and could not be visualized anymore after removal of the catheter. One infant with a thrombus around the UVC was lost to follow-up. The other 25 thrombi persisted after removal of the catheter. Two of 25 patients were treated with LMWH with resolution of the thrombus as a result. One, with thrombus formation in ductus venosus and umbilico-portal confluence, was treated because a thrombus in both venae iliacae communes developed after placement of another central venous catheter (CVC) and the other because progression of a thrombus in right atrium and ductus venosus during expectative management. All other patients were managed expectantly.

Two of the 25 patients with thrombi died during the neonatal period due to necrotizing enterocolitis. In 12/25 patients follow-up was considered not necessary, as the thrombi regressed spontaneously during the study period or were located in the ductus venosus (a non-functional structure after birth). The remaining 9/25 patients were discharged

home without treatment with persisting thrombi in right atrium and/or umbilico-portal confluence. Thrombi in these 9 cases were non-obstructive, filled less than 50% of the right atrium and were stable during hospital admission. One of these 9 cases was lost to follow-up. At ultrasound follow-up in the outpatient department within one year after term age, the other 8 thrombi all regressed and disappeared spontaneously.

DISCUSSION

In this study, thrombosis in the UVC route was detected with screening by ultrasonography in 75% of infants after umbilical catheterization, whereas no thrombi were demonstrated in the investigated location in infants without UVCs. This result emphasizes that CVCs play an important role in the aetiology of neonatal thrombosis.²⁰ Studies described that thrombus formation in the UVC route could lead to thrombocytopenia, persistent sepsis, liver damage, portal hypertension, symptoms of right heart failure and pulmonary embolism.²¹⁻²³

We prospectively screened the complete route of the UVC from the umbilico-portal confluence up to and including the heart, whereas previous studies mainly focused on one or two parts of this route. This might explain the higher incidence of UVC-related thrombosis (75%) when compared to previous reports (2.2-43%).⁶⁻¹³ The incidence of thrombi located only in the umbilico-portal confluence in this study was 30% (12/40), which is comparable to the incidence reported in previous studies. However, the incidence of thrombi located in the right atrium, IVC and ductus venosus was much higher, 58% (23/40) when compared to previous reports (10-30%).^{6,8} The use of novel ultrasound machines with higher sensitivity to detect thrombi compared with the equipment used in the past, may possibly explain the higher incidence of thrombi compared with older studies. Methodological differences related to the use of different ultrasound screening programs or differences in the screened population may be an explanation as well. Suggested risk factors for catheter-related thrombosis, such as being small-for-gestational-age, dwelling time of the UVC, and the use of parenteral nutrition could differ in our population compared to others and be of influence on the incidence of thrombosis.²² However, the sample size of our group is too small to confirm the influence of risk factors.

Neonatal thrombosis is in 89-94% of cases catheter related, but reliable data on thrombosis in infants without catheters, especially in the UVC route, are not available.^{2,20} The ductus venosus is a fetal structure that after birth closes permanent with fibrotic transformation into the ligamentum venosum. Some authors suggest thrombus formation contributes to this process as well.^{17,24} However, we did not observe this in our study. Hence, although our control-group was just a small group of infants, the thrombotic incidence of 0% in this group is an important finding.

Neonates are at increased risk of thrombosis due to small vessel diameters and disruption of haemostatic balance by numerous acquired and prothrombotic disorders.^{5, 21, 22, 25} Intravascular catheters can cause thrombosis by damaging the epithelium and introducing a foreign thrombogenic surface.⁵ In clinically unstable infants at increased risk of thrombosis, CVCs are needed to provide optimal neonatal care. The umbilical vein was for decades an obvious possibility for catheterization and, in many cases, the first choice to get intravenous access in infants. The high incidence of thrombosis in infants with UVCs demonstrated in this study suggest that our policy on use of UVCs needs to be reconsidered. However, CVCs are frequently needed in sick infants and other types of central catheters than UVCs are associated with thrombosis as well. Replacement of the UVC by another type of catheter may not necessarily lead to less complications.^{6, 13, 22, 26, 27}

Management of UVC-related thrombi is based on expert opinion guidelines and the impact of these thrombi on outcome is not clear.^{20-22, 26, 28} As shown in our study, spontaneous resolution of UVC-related thrombi detected by screening is likely to occur. Therefore, a 'watch and wait' approach in asymptomatic thrombi detected by screening with ultrasonography may be justified.²⁶ However, it is unclear how many infants with catheter-related thrombi will develop long-term consequences later in childhood. To determine the natural history, and possible consequences of catheter-related thrombosis a larger prospective study is needed. Currently, a prospective study in neonates with thrombi is being performed in the Netherlands (the Neoclot study).¹⁸ Because clinical implications of thrombi are not clear yet, and most thrombi detected by screening disappear spontaneously, routine screening apart from research settings cannot be advised. This is also confirmed by Haddad et al, who report that the majority of catheter-related thrombi they detected was stable and detection led infrequently to changes in patient management.²⁸

Care should be taken when interpreting the results of our study due to several limitations, including the relatively small number of patients. In addition, we excluded infants with UVCs positioned too low or malpositioned with catheter-tips in veins in the liver, because these catheters were removed shortly after catheterization and not used. It would have been interesting to know the incidence of thrombi in this separate group, with catheters being in situ for a very short period.

In conclusion, our study demonstrates that thrombi are frequently detected after umbilical catheterization by ultrasonography. Most thrombi are asymptomatic and disappear without treatment. Thus, routine screening for thrombi in UVCs is not advised. However, given the high risk of thrombus formation in UVCs, these catheters should be used with caution and removed promptly if the clinical indication is no longer present.

Acknowledgement

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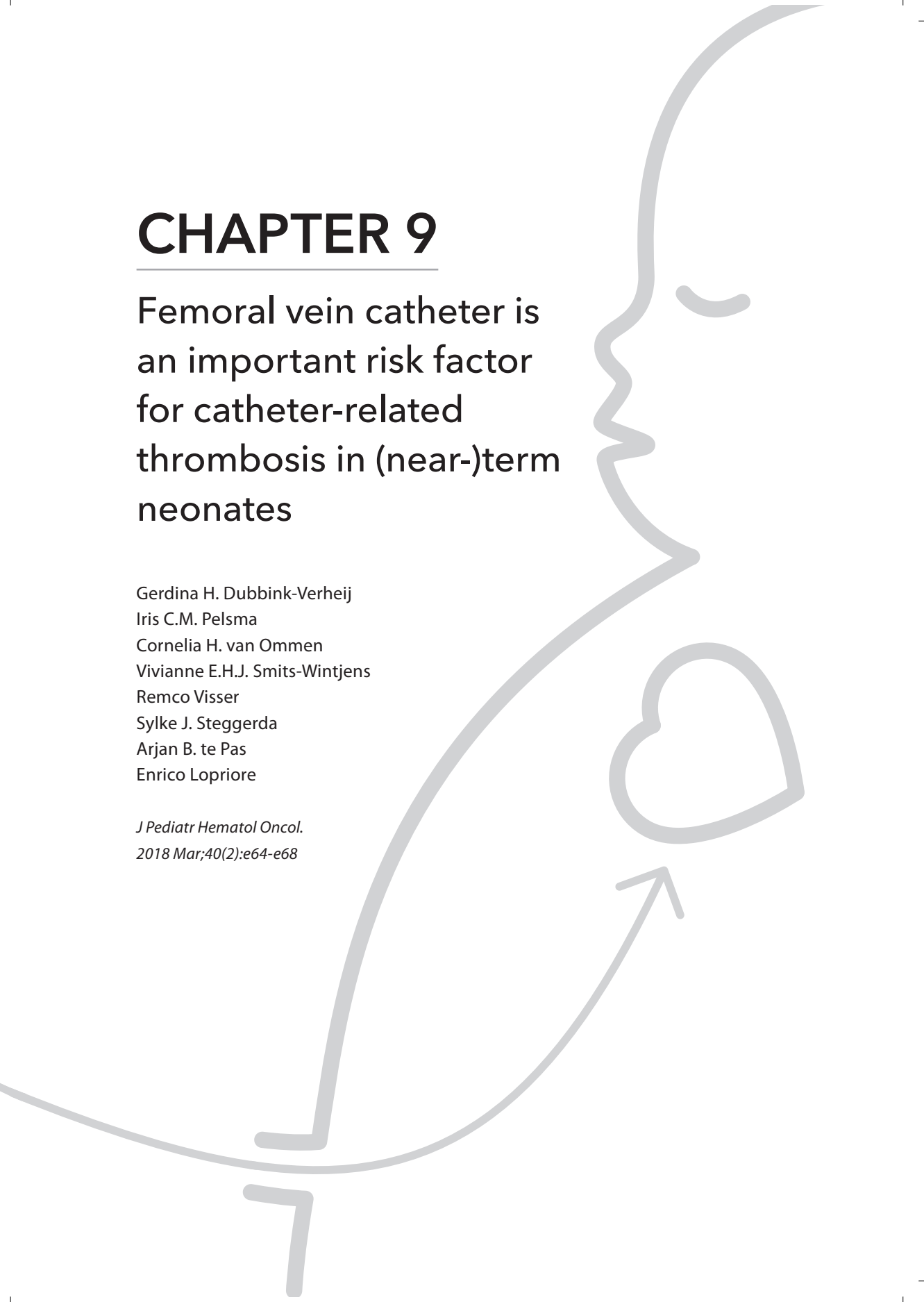


CHAPTER 9

Femoral vein catheter is
an important risk factor
for catheter-related
thrombosis in (near-)term
neonates

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ABSTRACT

Central venous catheters (CVCs) in neonates are associated with an increased risk of thrombosis. Most reports focus on umbilical venous catheters (UVCs) and peripherally inserted central catheters (PICCs), while limited data is available on femoral venous catheters (FVCs). We performed a retrospective cohort study in all neonates (gestational age ≥ 34 weeks) with CVCs. Primary outcome was the occurrence of thrombosis in CVCs. Secondary outcomes were possible risk factors for thrombosis, the thrombotic incidence in FVCs, UVCs and PICCs and clinical aspects of thrombosis in these groups.

552 neonates received a total of 656 catheters, including 407 (62%) UVCs, 185 (28%) PICCs and 64 (10%) FVCs. Thrombosis was detected in 14 cases, yielding an overall incidence of 2.1% or 3.6 events per 1000 catheter days. FVC was significantly associated with the occurrence of thrombosis when compared with UVC ($p=0.02$; odds ratio 3.8; 95% confidence interval 1.2-12.0) and PICC ($p=0.01$; odds ratio 8.2; 95% confidence interval 1.6-41.7). The incidence of thrombosis was higher in FVCs than in UVCs and PICCs, that is, 7.8% (5/64), 1.7% (7/407) and 1.1% (2/185), respectively ($p<0.01$). The number of thrombotic events per 1000 catheter days was 12.3 in FVCs, 3.2 in UVCs and 1.5 in PICCs ($p<0.05$).

We concluded thrombosis occurs more frequently in FVCs than in other CVCs.

INTRODUCTION

Central venous catheters (CVCs) are frequently used in critically ill neonates admitted to the neonatal intensive care unit (NICU). CVCs provide stable vascular access and are used for the administration of drugs, parenteral nutrition and vasoactive and/or hyperosmolar infusions. However, central venous catheterization is also reported to be the most common cause of neonatal thrombosis.^{1,2} Reported incidence of catheter-related thrombosis varies from 0.7% to 43% depending on the type of catheter and the time and method of diagnosis.³⁻¹⁰ Catheter-associated thrombosis may be asymptomatic but may also result in thrombocytopenia, infection and compromised venous flow due to partial or total vessel occlusion.

Most CVCs used in the NICU are umbilical venous catheters (UVCs) and peripherally inserted central catheters (PICCs).¹¹ Femoral venous catheters (FVCs) are less often used and less well studied in neonates.¹²

In this study, we evaluated the incidence, risk factors and clinical aspects of catheter-associated thrombosis in a cohort of (near-)term neonates with CVCs.

METHODS

Design

A descriptive retrospective cohort study design was used. The study was conducted at the NICU of the Leiden University Medical Center (LUMC), a tertiary care center in The Netherlands. The study was approved by the hospital system institutional review board.

Patient characteristics

All consecutive neonates admitted from January 1, 2006 until June 30, 2013 to our NICU and born at or after 34 weeks of gestation were included. Neonates with a lower gestational age were not included because FVCs are not placed in those patients at our NICU. The medical charts of all neonates were reviewed for neonates with catheter placement during admission. Neonates with their catheters being removed within 12 hours after placement and neonates with missing data on occurrence of thrombosis or catheter use were excluded.

The presence of thrombosis detected on Doppler ultrasound was recorded. A thrombus was defined as a persistent echo-dense structure observed in two dimensions within the heart, a vessel or on the tip of the catheter. Flow was measured to evaluate for obstruction caused by the thrombus. Ultrasound of the catheter was not performed routinely in all neonates with catheters, but only when symptoms of thrombi were present, that is, persistent thrombocytopenia, persistent positive blood cultures or clinical

signs of thrombosis, for example, a swollen, red leg or arm. Catheter thrombosis was defined as a thrombus in the route of a CVC in a neonate who had had recent catheterization in that route. In case of detection of a thrombus in a neonate who had received >1 catheter, the thrombus was allocated to the catheter that was or had been in situ at the thrombus location. Primary outcome was the occurrence of catheter thrombosis in CVCs. Secondary outcomes were possible risk factors for thrombosis, the number of thrombotic events per 1000 catheter days in FVCs, UVCs and PICCs, and clinical aspects of thrombosis in the different groups. Follow-up of patients with thrombotic events was conducted at the pediatric outpatient clinic of the LUMC.

Data collection

The following neonatal data were recorded, including gestational age at birth, birth weight, sex, presence of respiratory distress syndrome or congenital heart disease (CHD), mortality, duration of hospital admission, and occurrence of thrombosis. Small for gestational age was defined as a birth weight adjusted for gestational age below the 10th centile according to growth curves for Dutch neonates.¹³ To search for risk factors for thrombosis type of catheter, the number of catheters placed, prophylactic heparin treatment during catheter use, central line-associated bloodstream infection (CLABSI) including type of causative microorganism, and administration of parenteral nutrition during catheter dwell time were also recorded. Age at catheter insertion and removal, number of catheter days, indication for catheter removal, thrombocytopenia (defined as platelet counts $< 150 \times 10^9$), and number of platelet infusions were recorded according to catheter group. Removal of the catheter was recorded either as elective or nonelective. A nonelective removal was defined as removal of the catheter because of a complication and before the completion of therapy for which the catheter was placed. CLABSI was defined as the presence of a positive blood culture in a clinically ill neonate with a catheter in place for >2 days or with a catheter which was in place for > 2 days and was removed within 48 hours before the clinical onset of sepsis.

Characteristics of thrombotic events including age at detection and days after catheter insertion of thrombotic event, location of thrombus, rationale for detection of the thrombus, size of the thrombus, complications associated with the thrombotic event, and management of thrombosis were recorded according to catheter group.

Statistical analysis

Data are given as median with range unless otherwise mentioned. For continuous variables the Kruskal-Wallis test was used. Post-hoc comparisons were performed using Mann-Whitney U test. For categorical variables, initial and post-hoc comparisons were performed using the Chi square or Fisher exact test, as appropriate. Upon initial testing, p-values below 0.05 were considered significant. In post-hoc testing, we applied a Bonfer-

roni adjustment to the alpha values to control for type 1 errors. In these comparisons p-values below 0.017 (0.05/3) were considered significant. Univariate logistic regression analysis was performed to analyse factors contributing to thrombosis. A Poisson model with the log of the catheter days as offset was used to perform this regression analysis. Gestational age, sex, birth weight, type and amount of catheters placed, use of prophylactic heparin, parenteral nutrition during catheter dwell time, CLABSI events, and length of hospital admission were univariately analyzed to search for possible risk factors. All statistical analyses were performed using SPSS 20 (IBM Software, Armonk, NY, United States).

RESULTS

Patient characteristics

A total of 2986 neonates born at ≥ 34 weeks' gestation were admitted to our NICU during the study period, of which 21% ($n = 628$) received ≥ 1 CVCs. We excluded 76 neonates because of removal of the catheter within 12 hours ($n=73$) or because of missing data ($n=3$).

The remaining 552 neonates received 656 CVCs, including 407 (62%) UVCs, 185 (28%) PICCs and 64 (10%) FVCs. In the total group, 466 neonates received 1 CVC. The remaining neonates received 2 ($n=71$), 3 ($n=12$) or 4 ($n=3$) CVCs. Baseline patient characteristics are given in Table 1.

Table 1. Baseline patient characteristics for the total population and per catheter type.

Variable	Total population (n=552)	FVC (n=64)	UVC (n=407)	PICC (n=185)	p-value	FVC vs. UVC	FVC vs. PICC	UVC vs. PICC
Gestational age at birth (weeks)	38 (34-42)	39 (34-42)	38 (34-42)	38 (34-42)	0.03	0.007	0.04	0.84
Birth weight (grams)	3155 (807-6430)	3411 (1742-4700)	3115 (1130-6430)	3020 (807-4900)	0.001	0.002	<0.001	0.12
Male sex, % (n)	56 (309)	58 (37)	54 (220)	57 (105)	0.75			
SGA, % (n)	13 (74)	5 (3)	14 (55)	17 (31)	0.05			
RDS, % (n)	19 (105)	17 (11)	21 (85)	15 (27)	0.18			
CHD, % (n)	18 (102)	42 (27)	13 (54)	32 (59)	<0.001	<0.001	0.135	<0.001
Mortality < 1 month, % (n)	8 (42)	6 (4)	8 (33)	8 (14)	0.21			
Duration of hospital admission (days)	8 (1-62)	11 (2-53)	8 (1-49)	13 (2-62)	<0.001	<0.001	0.18	<0.001

Data are represented as median (range) unless otherwise specified. Upon initial testing, p -values <0.05 were considered significant. Post-hoc testing was significant if p -values were <0.017 . Significant p -values are depicted in **bold**. CHD indicates cyanotic congenital heart disease; FVC, femoral venous catheter; PICC, peripherally inserted central catheter; RDS, respiratory distress syndrome, defined as the need for mechanical ventilation and surfactant; SGA, small for gestational age, defined as a birth weight adjusted for gestational age below the 10th centile, according to growth curves for Dutch neonates;¹³ UVC, umbilical venous catheter.

Neonates with FVCs had a higher gestational age at birth and a higher birth weight compared with neonates with other types of catheters.

Incidence and risk factors for thrombotic events

A total of 14 cases (2.1%) of catheter thrombosis were found during the placement of 656 catheters or 3895 catheter days, which resulted in an overall rate of 3.6 thrombotic events per 1000 catheter days. The yearly occurrence of thrombosis was stable during the study period. Figure 1 depicts the incidence of thrombosis in the different catheter groups.

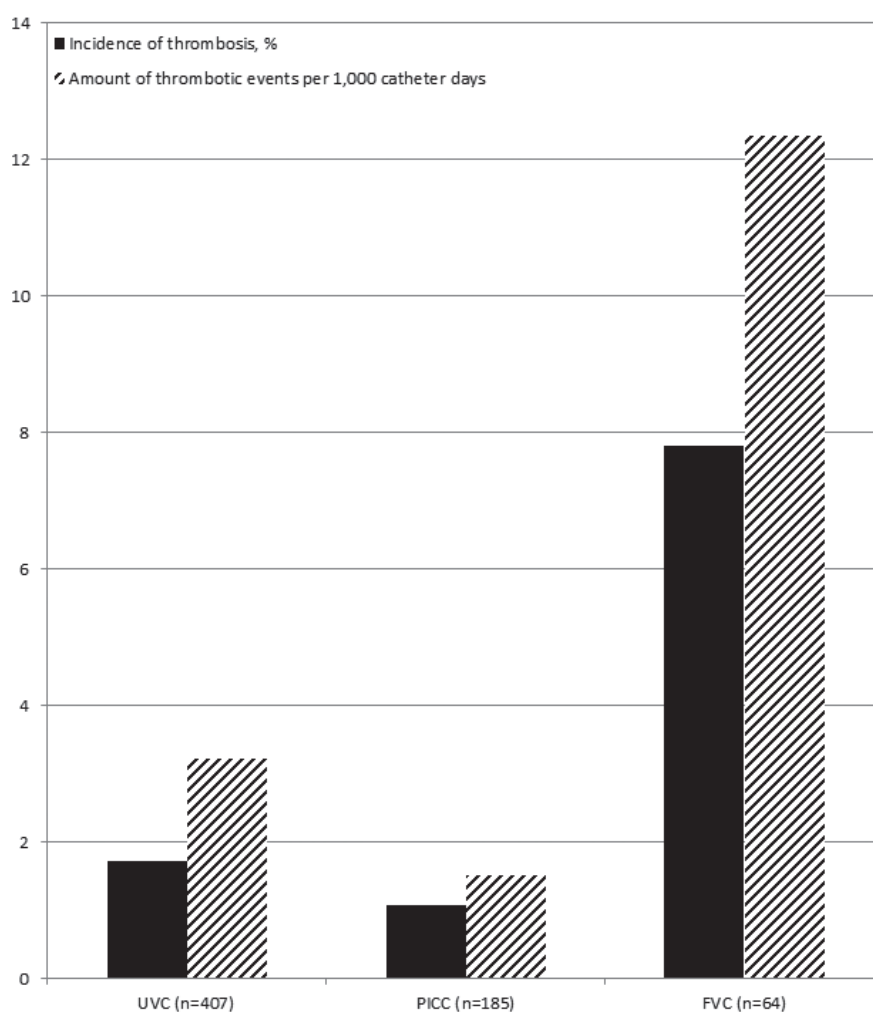


Figure 1. Incidence of thrombosis. FVC indicates femoral venous catheter; PICC, peripherally inserted central catheter; UVC, umbilical venous catheter.

The occurrence of thrombosis in the FVC group (7.8%) was higher than in the UVC group (1.7%) and in the PICC group (1.1%) ($p=0.004$ and $p=0.005$ respectively, with Bonferroni correction). The thrombosis rate per 1000 catheter days varied from 12.3 in FVCs to 3.2 in UVCs ($p=0.02$) and 1.5 in PICCs ($p=0.01$).

On univariate regression analysis, FVC was significantly associated with the occurrence of thrombosis when compared with UVC ($p=0.02$; odds ratio (OR), 3.8; 95% confidence interval (CI), 1.2-12.0) and PICC ($p=0.01$; OR, 8.2; 95% CI, 1.6-41.7). Other factors included in the risk model, such as gestational age, birth weight, male sex, amount of catheters placed, prophylactic heparin treatment, use of the catheter for parenteral nutrition, CLABSI, and length of hospital admission, were not significantly associated with thrombosis. Table 2 shows the results of this analysis, including ORs and 95% CIs.

Table 2. Analysis of potential risk factors for thrombosis.

Variables	Thrombosis (N=14)	No thrombosis (N=642)	p-value	Univariate Odds Ratio (95% CI)
Gestational age (wk)	38 (35-41)	38 (34-42)	0.87	1.02 per week increment (0.81-1.29)
Birth weight (g)	3230 (1575-4750)	3125 (807-6430)	0.42	1.03 for each 100-g increase (0.96-1.10)
Male	11/362 (3)	351/362 (97)	0.07	3.20 (0.89-11.5)
Female	3/294 (1)	291/294 (99)	-	-
No. of catheters placed	1 (1-3)	1 (1-4)	0.77	1.11 (0.56-2.19)
Type of catheter				
FVC	5/64 (8)	59/64 (92)	-	-
UVC	7/407 (2)	400/407 (98)	0.02	0.26 (0.08-0.83)
PICC	2/185 (1)	183/185 (99)	0.01	0.12 (0.02-0.63)
Prophylactic heparin treatment, yes	7/270 (3)	263/270 (97)	0.71	1.22 (0.43-3.47)
Prophylactic heparin treatment, no	7/386 (2)	379/386 (98)	-	-
Parenteral nutrition, yes	10/290 (3)	280/290 (97)	0.19	2.17 (0.68-6.91)
Parenteral nutrition, no	4/366 (1)	362/366 (99)	-	-
CLABSI event, yes	2/35 (6)	33/35 (94)	0.25	2.39 (0.54-10.68)
CLABSI event, no	12/621 (2)	609/621 (98)		
Length of hospital admission (d)	16 (7-35)	9 (1-62)	0.66	1.01 (0.97-1.05)

Data are presented as median (range) or n/N (%). Odds ratios and their associated 95% CI are shown. P-values < 0.05 were considered significant. Significant p-values are depicted in **bold**. CI indicates confidence interval; CLABSI, central line-associated bloodstream infection; FVC, femoral venous catheter; PICC, peripherally inserted central catheter; UVC, umbilical venous catheter.

Catheter characteristics

Catheter characteristics are shown in Table 3.

Median length of catheter dwell time was 5 days in UVCs and 6 days in PICCs and FVCs. Age at catheter insertion and catheter removal and percentage of parenteral nutrition during catheter dwell time varied significantly between catheter location groups.

Indications for catheter removal varied between catheter location groups. Catheters were still in situ at discharge from our department in 28% (181/656) of cases. Follow-up information of infants with these catheters after discharge was not known. Elective removal of the catheter was performed in 38% (251/656) of cases because the catheter was no longer needed. Sepsis (15%; 32/220; $p < 0.05$) and local infiltration (18%; 39/220; $p < 0.001$) were more frequently observed as the cause of nonelective removal in UVCs compared with the other catheters. In FVCs, thrombosis (8%; 3/40; $p < 0.05$) was more often than in the other catheter groups the reason for catheter removal and, in PICCs, catheter occlusion (18%; 26/145; $p < 0.01$) occurred more often than in the other catheter groups.

Table 3. Catheter characteristics according to catheter type.

Variable	FVC (N=64)	UVC (N=407)	PICC (N=185)	p-value	FVC vs. UVC	FVC vs. PICC	UVC vs. PICC
Total no. catheter days	405	2166	1324				
No. catheter days	6 (1-19)	5 (1-22)	6 (1-31)	0.001	0.051	0.696	0.001
Age at catheter insertion (d)	4.5 (1-50)	1 (1-13)	5 (1-39)	<0.001	<0.001	0.407	<0.001
Age at catheter removal (d)	10 (3-55)	6 (1-22)	12 (2-45)	<0.001	<0.001	0.355	<0.001
Parenteral nutrition during catheter dwell time, % (n)	50.0 (32)	38.3 (156)	55.1 (102)	<0.001	0.076	0.478	<0.001

Data are represented as median (range) unless otherwise specified. Upon initial testing, p -values < 0.05 were considered significant. Post-hoc testing was significant if p -values were < 0.017 . Significant p -values are depicted in **bold**. FVC, indicates femoral venous catheter; PICC, peripherally inserted central catheter; UVC, umbilical venous catheter.

Clinical aspects and follow-up of thrombi

Characteristics of thrombotic events are presented in Table 4.

Thrombi in cases with FVCs were more likely to totally disrupt the blood flow compared with thrombi in cases with UVCs (4/5 vs. 0/7; $p = 0.02$; $p = 0.007$ with Bonferroni correction). Occurrence of thrombocytopenia was not statistically different between the different catheter groups and between neonates with and without thrombi.

Eleven neonates were treated with low-molecular-weight heparin (eg, tinzaparin/fraxiparin/nadroparin). Treatment duration ranged from 16 to 90 days. Thrombectomy and treatment with thrombolytic agents were not used in this study population.

In 7 of 14 neonates (50%), the thrombus resolved within the first 3 months after diagnosis or within 1 year in 4 other cases of thrombi (29%). In 2 thrombi cases, no follow-up with ultrasound was performed, and in 1 case of thrombus, follow-up ultrasound was nonconclusive.

Table 4. Characteristics of thrombotic events according to catheter type.

Variable		UVC (N=7)	PICC (N=2)	FVC (N=5)
Size of thrombus, n (%)	Small: normal flow	6 (86)	-	-
	Partial obstruction	1 (14)	1 (50)	20 (1)
	Total obstruction	-	1 (50)	80 (4)
Reason for thrombus finding, n (%)	Accidentally	1 (14)	-	-
	Thrombocytopenia	6 (86)	2 (100)	40 (2)
	Clinical Signs	-	-	60 (3)
Location of thrombus, n (%)	Vena cava inferior	1 (14)	1 (50)	-
	Right atrium	4 (57)	-	-
	Vena femoralis	-	-	60 (3)
	Vena iliaca	-	1 (50)	20 (1)
	Vena porta	1 (14)	-	-
	Line tip	-	-	20 (1)
	Ductus venosus	1 (14)	-	-
Days after catheter insertion at thrombosis, median (range)		8 (3-18)	9.5 (7-12)	6 (4-9)
Age at time of thrombosis, median (range) (d)		9 (8-18)	11.5 (7-16)	11 (5-16)

FVC indicates femoral venous catheter; PICC, peripherally inserted central catheter; UVC, umbilical venous catheter.

In 1 patient who had a thrombus in the vena iliaca after FVC placement, a difference in length between the two legs was observed during outpatient follow-up at the age of 4 months and persisted until the age of 6 years.

DISCUSSION

The overall incidence of clinical thrombosis in our cohort of term and near-term neonates with CVCs was 2.1%. We found a higher incidence of thrombosis in FVCs (7.8%) compared with UVCs (1.7%) and PICCs (1.1%). This is the first single-center study comparing the incidences of thrombosis in 3 of the most widely used CVC types in a large cohort of neonates. In the vast majority of cases, neonatal thrombosis is caused by the presence of CVCs.^{2,3} The incidence of catheter-associated thrombosis in neonates varies greatly in the literature. This variation is mainly due to methodological differences between the studies. Clinical studies have reported incidences of thrombosis ranging from 0.7 to 43%.³⁻¹⁰ The highest incidences of thrombosis in neonates are found when systematical ultrasound screening is performed and in autopsy studies the detection of thrombosis is even higher.¹⁴ Our incidence is within the range of incidences reported in most previous studies, however, neonates were not screened routinely for thrombotic events, and ultrasound examination was performed only when suspicion of thrombosis

was raised based on clinical symptoms. This may have led to an underestimation of the real thrombotic incidence in this population.

Only a few studies compared the risk of thrombosis in the different catheter types used in neonates. Tanke et al report a higher incidence of thrombus formation in infants with umbilical catheters in comparison with infants with subclavian catheters (13%, 25/193 in the total group), but the difference was not significant.⁷ Park et al conclude in a review that the site of insertion of the catheter does not affect the incidence of CVC-related thrombosis.⁶ This conclusion was based on comparisons between UVCs and PICCs (2%, 4/198 versus 0/178),¹⁵ femoral and jugular catheters (2.1%, 1/64 versus 1.6%, 1/64)¹⁶ and PICCs in subclavian and jugular veins (1.9%, 2/107 versus 0.8%, 1/129).¹⁷ Murai reports a lower incidence of thrombosis in FVCs compared with our study.¹⁶ The incidence in the study of Murai is closer to the incidence of thrombosis in UVCs reported in our study. The author suggests that the low incidence in his study may be due to the relatively short duration of catheter use. However, FVCs in our study were also used for a similar short duration. Differences in the reported incidences between studies can be caused by several factors including methodological differences, differences in definitions and criteria, and differences in population. We used other sizes of catheters than that reported by Murai, and we possibly have more children with CHDs in our population.

Neonatal thrombosis is usually thought to be the result of a combination of risk factors. The most important risk factor is central venous catheterization.¹⁸ Catheters may lead to thrombus formation in neonates by damage to the vessel wall, disruption of blood flow in small vessel diameters, infusion of hyperosmolar substances and thrombogenic catheter materials.¹⁹

We identified an association between FVCs and the occurrence of thrombosis compared with other catheter types. Hypothetically, the higher thrombotic risk in our FVC population may not be due to the type of catheter but to other clinical factors, such as the underlying illness itself. As shown in our study, the population of neonates receiving UVCs or PICCs differed from the population receiving FVCs. Neonates who receive a FVC in our department were generally very ill, with either CHD (27/64; 42%), sometimes requiring therapeutic cardiac catheterization, or with severe respiratory or neurological problems. In a study limited to neonates with single ventricle heart lesions, Aiyagari et al also report a high incidence of thrombosis in neonates who had an initial FVC (42%) and also in neonates with initial UVCs (11%).⁸ Murai reports a low incidence of thrombosis, however, in his study, the presence of CHD was not reported.¹⁶ Moreover, in FVCs, signs of thrombosis may be more easily detected than in the other catheters, resulting in a bigger difference in incidences than the difference that would have been detected by systematic screening.

Thrombi in neonates with FVCs in our study were more likely to totally occlude the blood vessel. This may lead to severe complications, such as necrosis of the leg. In

UVCs the risk of thrombosis was lower and thrombi were generally smaller, but most of these thrombi were located in the right atrium. Although these thrombi were nonocclusive, other severe consequences, such as pulmonary thromboembolism, have been reported.^{20, 21}

The results found in our study should be interpreted with care because of the retrospective study design. The risk of thrombosis depends on multiple factors, and we could not correct for all these factors in our study. Possibly the risk of thrombosis depends, besides the type, also on the size of the catheter used, and we did not record the sizes of the catheters in our study.

In conclusion, our data show that term and near-term neonates with FVCs have a higher risk of thrombosis compared with neonates with UVCs and PICCs. Thrombi in neonates with FVCs were more likely to totally occlude the blood vessel. Although our conclusions are hampered by several methodological limitations, we suggest that caregivers should be aware of a possible increased risk for thrombosis in term and near-term neonates with FVCs and use these catheters with increased caution.

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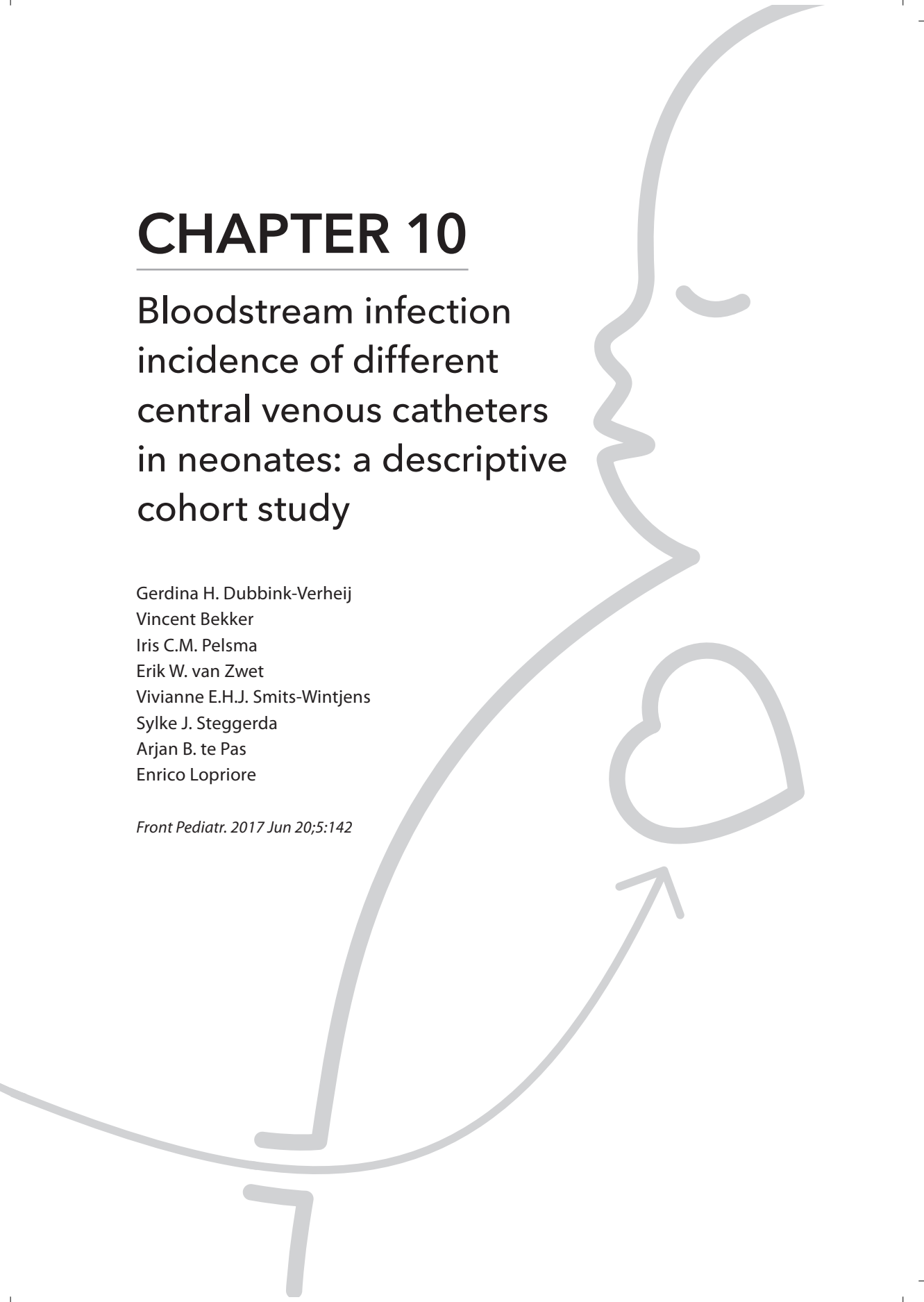


CHAPTER 10

Bloodstream infection incidence of different central venous catheters in neonates: a descriptive cohort study

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ABSTRACT

Central venous catheters (CVCs) in neonates are associated with a risk of central line-associated bloodstream infections (CLABSI). Most reports on the incidence of CLABSI in neonates focus on umbilical venous catheters (UVCs) and peripherally inserted central catheters (PICCs). We evaluated the incidence and risk factors for CLABSI in a cohort of neonates with femoral venous catheters (FVCs), UVCs and PICCs, with a gestational age ≥ 34 weeks born between January 1, 2006 and June 30th, 2013. We included 2,986 neonates with a total of 656 catheters. The CLABSI incidence rate varied from 12.3 per 1,000 catheter days in FVCs to 10.6 per 1,000 catheter days in UVCs and 5.3 per 1,000 catheter days in PICCs. In a Kaplan-Meier survival analysis we did not find a difference in CLABSI risk between the catheter types ($p=0.29$). The following factors were independently associated with an increased risk of CLABSI: parenteral nutrition [hazard ratio (HR) 2.60, 95% Confidence Interval (CI) 1.25-5.41], male gender (HR 2.63, 95% CI 1.17-5.90), and higher birth weight (HR 1.04, 95% CI 1.002-1.09), whereas antibiotic treatment at birth (HR 0.25, 95% CI 0.12-0.52) was associated with a decreased risk.

Conclusion: In our cohort, we did not find a difference between the CLABSI incidence in FVCs, PICCs and UVCs. Occurrence of CLABSI is associated with parenteral nutrition, male gender and higher birth weight. Antibiotic treatment at birth was associated with a decreased risk of CLABSI.

INTRODUCTION

Central venous catheters (CVCs) are frequently used in critically ill neonates admitted to the neonatal intensive care unit (NICU). The most common central venous catheters in the NICU are umbilical venous catheters (UVCs) and peripherally inserted central catheters (PICCs).¹ Femoral venous catheters (FVCs) are less often used and less well studied in neonatal populations.²

Although CVCs in neonates have many benefits, they have also important disadvantages. CVC use has been associated with an increased risk for developing hospital-acquired bloodstream infections, also termed central line-associated bloodstream infections (CLABSI).^{3,4}

Bloodstream infections in neonates are associated with longer stay in the hospital, unfavorable outcome and mortality.⁵ Risk reduction of these infections is important to improve the outcome of neonates.

Bloodstream infections in neonates have been studied extensively,⁶ but little is known about the influence of the type of catheter used on the CLABSI incidence. Only a few studies compared the risk of CLABSI between the different types of catheters, mostly in small and heterogeneous cohorts of neonates.^{3,7-12}

In this study, we evaluate the incidence of and potential risk factors associated with CLABSI comparing FVCs, UVCs and PICCs in a cohort of term and late preterm neonates.

MATERIALS AND METHODS

Design

A descriptive cohort study design was used. The study was conducted at the NICU of the Leiden University Medical Center (LUMC), a tertiary care center in The Netherlands. The study was approved by the hospital system institutional review board. Written informed consent was deemed not necessary because the study participants were anonymized.

Patient characteristics

From January 1, 2006 until June 30, 2013 2,986 neonates of 34 or more weeks' gestation were admitted to our NICU. The threshold of 34 weeks gestational age was chosen because FVCs are not placed in neonates of lower gestational ages at our NICU. The medical charts of all neonates were reviewed to select neonates with catheter placement during admission. According to our protocol, CVCs were placed in all neonates that needed mechanical ventilation or circulatory support by inotropes. Other indications for a CVC at our unit are difficulties to get intravenous access and the need for an exchange transfusion. There were no protocol changes regarding the indication for CVCs during the

study period. We excluded neonates with their catheters being removed within 12 hours after placement and neonates with missing data on CLABSI occurrence or catheter use.

Data collection

Gestational age at birth, birth weight, and gender were recorded. In addition, respiratory distress syndrome (RDS), defined as the need for mechanical ventilation and surfactant, administration of parenteral nutrition during catheter dwell time, type of CVC, age at catheter insertion, duration of catheter dwell time, use of antibiotics during the first 24 h after birth, prophylactic heparin treatment during catheter use, indication for catheter removal, proven sepsis, and CLABSI including type of causative microorganism were recorded. Small for gestational age was defined as a birth weight adjusted for gestational age below the 10th centile according to growth curves for Dutch neonates.¹³ The choice to use a specific CVC type was left to the discretion of the care-giver. In general the first days after birth, a UVC was the first catheter to choose. In case of failure to place a UVC, and in older neonates a PICC or FVC was inserted. UVCs were placed in high position.

Proven sepsis was defined by a positive blood culture in the presence of clinical signs suggestive of infection. A positive blood culture without symptoms in the neonate was considered as contamination. CLABSI was defined as proven sepsis occurring with a catheter in place for more than 2 days or with a catheter which was in place for more than 2 days and was removed within 48 h before the clinical onset of sepsis. The incidence of CLABSI was measured as the percentage of CLABSI in the group and as CLABSI events per 1,000 catheter-days.

Removal of the catheter was recorded either as elective or non-elective. A non-elective removal was defined as an unresolvable complication leading to removal of the catheter prior to the completion of therapy for which the catheter was placed.

Statistical analysis

Data are given as median with range unless otherwise mentioned. For comparison of continuous variables, the Kruskal-Wallis test was used. Post hoc comparisons were performed using Mann-Whitney U test. For initial and post hoc comparisons of categorical variables, we performed the Chi square or Fisher's exact test where appropriate. Upon initial testing, p-values below 0.05 were considered significant. In post hoc testing, we applied a Bonferroni adjustment to the alpha values to control for Type 1 errors. In this comparisons, p-values below 0.017 (0.05/3) were significant. To estimate survival or duration of stay of the different types of catheters, the Kaplan-Meier method was used. An event was defined as the occurrence of a central line infection. Patients were censored after removal of the central line or at transfer to another hospital. Cox regression analysis was performed to analyze risk factors contributing to time to CLABSI. We chose to analyze gestational age, gender, birth weight, RDS, type and amount of catheters

placed, use of prophylactic heparin, use of antibiotics during the first 24 h after birth, and parenteral nutrition during catheter dwell time to search for possible risk factors. If p-values were below 0.20 in a univariate analysis, these variables were analyzed using a multivariate Cox regression model in which p-values below 0.05 were considered statistically significant. All statistical analyses were performed using SPSS 20 (IBM Software, Armonk, NY, United States).

RESULTS

Patient characteristics

A total of 2,986 neonates born at 34 or more weeks gestation were admitted to our NICU during the study period, of which in 21% ($n = 628$) one or more CVCs were placed. A total of 76 neonates were excluded because their catheter was removed within 12 h ($n=73$) and data could not be retrieved ($n=3$).

In the remaining 552 neonates, 656 CVCs were placed, including 407 (62%) UVCs, 185 (28%) PICCs and 64 (10%) FVCs. In 466 neonates one CVC was placed. The remaining neonates had two ($n=71$), three ($n=12$) or four ($n=3$) CVCs. In 19 neonates, two catheters were in place simultaneously during a period of more than 1 day. Baseline patient characteristics are given in Table 1.

Table 1 – Baseline patient characteristics for the total population and per catheter type.

Variable	Total population (n=552)	Femoral venous catheter (FVC) (n=64)	Umbilical venous catheter (UVC) (n=407)	Peripherally inserted central catheter (PICC) (n=185)	p-value	FVC vs UVC	FVC vs PICC	UVC vs PICC
Gestational age at birth (weeks)	38 (34-42)	39 (34-42)	38 (34-42)	38 (34-42)	0.03	0.007	0.04	0.84
Birth weight (g)	3155 (807-6430)	3411 (1742-4700)	3115 (1130-6430)	3020 (807-4900)	0.001	0.002	<0.001	0.12
Male gender, % (n)	56 (309)	58 (37)	54 (220)	57 (105)	0.75			
SGA, % (n)	13 (74)	5 (3)	14 (55)	17 (31)	0.05			
RDS, % (n)	19 (105)	17 (11)	21 (85)	15 (27)	0.18			
CHD, % (n)	18 (102)	42 (27)	13 (54)	32 (59)	<0.001	<0.001	0.135	<0.001
Asphyxia, % (n)	9 (48)	9 (6)	10 (39)	5 (9)	0.15			
PDA, % (n)	1 (5)	2 (1)	0.7 (3)	1 (2)	0.78			
Pneumothorax, % (n)	4 (23)	5 (3)	4 (18)	5 (9)	0.96			
Mortality < 1 month, % (n)	8 (42)	6 (4)	8 (33)	8 (14)	0.21			
Duration of hospitalization (days)	8 (1-62)	11 (2-53)	8 (1-49)	13 (2-62)	<0.001	<0.001	0.18	<0.001

Data are represented as median (range) unless otherwise specified. Upon initial testing, *p*-values <0.05 were considered significant. Post-hoc testing was significant if *p*-values were <0.017. Significant *p*-values are depicted in bold. SGA: small for gestational age, defined as a birth weight adjusted for gestational age below the 10th centile according to growth curves for Dutch neonates;¹³ RDS: respiratory distress syndrome, defined as the need for mechanical ventilation and surfactant; CHD: cyanotic congenital heart disease; Asphyxia: asphyxia for which therapeutic cooling was indicated; PDA: persistent ductus arteriosus needing treatment (conservative or surgical).

Neonates with FVCs had a higher gestational age at birth and a higher birth weight compared to neonates with other types of catheters. The percentage of neonates with congenital heart disease was also different in the three catheter groups.

Catheter characteristics and duration of stay of the catheter

Catheter characteristics are shown in Table 2.

Median length of catheter dwell time varied from 5 days in UVCs to 6 days in PICC, whereas median length of FVC dwell time was not significantly different from both other catheter types. Age at catheter insertion and catheter removal, percentage of parenteral nutrition during catheter dwell time, and percentage of antibiotic treatment within 24 h post-partum varied significantly between catheter location groups.

Indications for catheter removal varied between catheter location groups (see Table S1 in Supplementary Material).

Table 2. Catheter characteristics by catheter type.

Variable	Femoral venous catheter (FVC) (n=64)	Umbilical venous catheter (UVC) (n=407)	Peripherally inserted central catheter (PICC) (n=185)	p-value	FVC vs UVC	FVC vs PICC	UVC vs PICC
Total amount of catheter-days	405	2166	1324				
Amount of catheter-days	6 (1-19)	5 (1-22)	6 (1-31)	0.001	0.051	0.696	0.001
Age at catheter insertion	4.5 (1-50)	1 (1-13)	5 (1-39)	<0.001	<0.001	0.407	<0.001
Age at catheter removal	10 (3-55)	6 (1-22)	12 (2-45)	<0.001	<0.001	0.355	<0.001
Antibiotic treatment within 24 h post-partum, % (n)	54.7 (35)	59.7 (243)	45.9 (85)	0.008	0.448	0.228	0.002
Parenteral nutrition during catheter dwell time, % (n)	50.0 (32)	38.3 (156)	55.1 (102)	<0.001	0.076	0.478	<0.001

Data are represented as median (range) unless otherwise specified. For continuous variables, Kruskal-Wallis test was used. Post hoc analysis was performed using Mann-Whitney U test. For categorical variables, initial and post hoc analysis was performed using the Chi-square or Fisher's exact test. Upon initial testing, *p*-values below 0.05 were considered significant. Post hoc testing was significant if *p*-values were below 0.017. Significant *p*-values are depicted in bold.

Table S1. Indications for catheter removal.

Reason for catheter removal	FVC (n=64)	UVC (n=407)	PICC (n=185)
Suspected sepsis	4	32	7
Phlebitis	1	0	10
Local infiltration	1	39	7
Leakage	4	15	6
Occlusion	4	4	26
Thrombosis	3	3	2
Malposition	1	32	11
Unknown	1	3	8
No longer needed	24	187	40
Still in situ at discharge	21	92	68

FVC: femoral venous catheter; UVC: umbilical venous catheter; PICC: peripherally inserted central catheter;

Catheters were still in situ at discharge of our department in 28% (181/656) of cases. Follow-up of indications for catheter removal in these infants after discharge was not known. Elective removal of the catheter was performed in 38% (251/656) of cases because they were no longer needed. The remaining 224 catheters with elective removals in our hospital were analyzed. Sepsis (25%; 32/128; $p<0.05$) and local infiltration (31%; 39/128; $p<0.001$) were more frequently observed as the cause of non-elective removal in UVCs compared to the other catheters. In FVCs, thrombosis (16%; 3/19; $p<0.05$) was more often the reason for catheter removal than in the other catheter groups. Catheter occlusion (34%; 26/77; $p<0.001$) occurred more frequently in PICCs than in the other catheter groups.

Estimated survival of the three types of catheters regarding CLABSI occurrence is shown in Figure 1. Occurrence of CLABSI did not differ significantly between the three catheter groups ($p=0.286$).

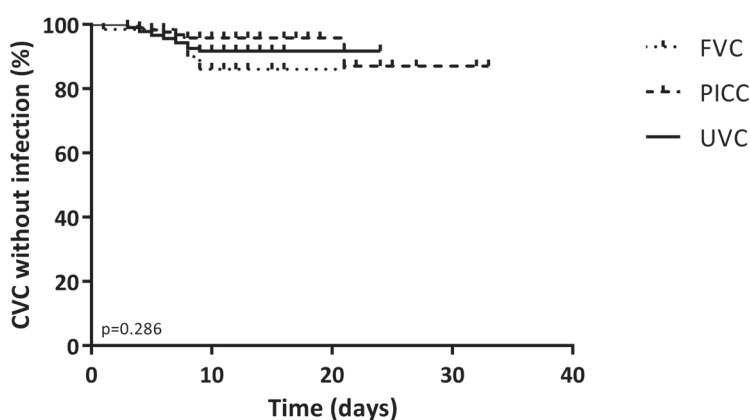


Figure 1. Kaplan Meier curve of the duration of stay for all catheters by catheter type. The primary end point was the occurrence of a central line-associated bloodstream infection event. Data were censored at elective removal and at patients who were lost to follow-up. p-Values below 0.05 were considered significant.

Incidence of and risk factors for central-line associated blood stream infections

In this study, 35 cases (5.3%) of CLABSI were found during the use of 656 catheters or 3,895 catheter-days, which resulted in an overall incidence rate of 9.0 per 1,000 catheter-days. Figure 2 depicts the risks and incidences of CLABSI in the different catheter groups.

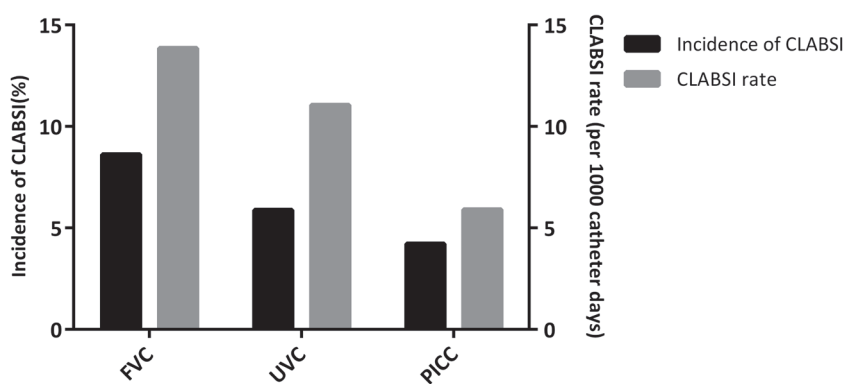


Figure 2. Incidence of central line-associated bloodstream infection (CLABSI) events by catheter type.

The risk of CLABSI varied from 4% (7/185) in the PICC group to 8% (5/64) in the FVC group, although differences between the catheter groups were not statistically significant.

cant ($p=0.42$). The CLABSI incidence rate varied from 12.3 per 1,000 catheter days in FVCs to 10.6 per 1,000 catheter days in UVCs and 5.3 per 1,000 catheter days in PICCs.

Coagulase-negative Staphylococci (CoNS; 51%) and *Staphylococcus aureus* (23%) were the most prominent causative organisms of CLABSI. All five CLABSI in the FVC-group were caused by CoNS. In the UVC-group, 9 of 23 septic episodes were caused by CoNS (39%), 7 by *S. aureus* (30%), 1 by *E. coli* (4%), 1 by *Bacillus species* (4%), 1 by *Streptococcus agalactiae* (4%) and the other 4 by multiple organisms or unspecified (17%). In the PICC-group, four of seven septic episodes were caused by CoNS (57%), one by *S. aureus* (14%), one by *E. coli* (14%), and 1 by multiple organisms.

On univariate Cox regression analysis, four variables were possibly associated with CLABSI (p -values <0.20). To test the hypothesis that the location of catheter was associated with the risk of CLABSI, we set up a multivariate Cox regression model with location of catheter as dependent variable and all four variables with p -values <0.20 in univariate analysis as independent variables. Male gender [hazard ratio (HR) 2.63], higher birth weight (per 100 g; HR 1.04) and parenteral nutrition during catheter use (HR 2.60) were identified as risk factors. Early antibiotic treatment (HR 0.25) was found to be inversely associated. Table 3 shows these factors including HRs, 95% confidence intervals, and p -values. Location of catheter, gestational age at birth, RDS, amount of catheters placed, and prophylactic heparin treatment were not significantly associated with CLABSI.

Table 3. Multivariate Cox regression analysis for CLABSI events.

Risk factors		CLABSI (n=35)	No CLABSI (n=621)	Hazard ratio (HR)	95% confidence interval lower	Upper	p-Value
Birth weight (g, HR per 100 grams)		3340 (2120-5290)	3125 (807-6430)	1.04	1.002	1.09	0.04
Gender (male), % (n)		77 (27)	54 (335)	2.63	1.17	5.90	0.02
Location of catheter, % (n)	Femoral venous catheter	14 (5)	10 (59)				
	Umbilical venous catheter	66 (23)	62 (384)	1.17	0.44	3.09	0.76
	Peripherally inserted central catheter	20 (7)	29 (178)	0.45	0.14	1.43	0.18
Antibiotic treatment within 24 h post-partum, % (n)		40 (14)	56 (349)	0.25	0.12	0.52	<0.001
Parenteral nutrition during catheter dwell time, % (n)		63 (22)	43 (268)	2.60	1.25	5.41	0.01

Four variables with p -values <0.20 in univariate analysis and location of catheter were included in this multivariate Cox regression model. Data are presented as median (range) unless otherwise specified. HRs including 95% confidence intervals (95% CI) are shown. p -Values below 0.05 were considered significant. Significant p -values are depicted in bold.

DISCUSSION

The overall incidence of CLABSI in our cohort of neonates (≥ 34 weeks of gestation) with central venous catheters was 9.0 per 1,000 catheter-days. We did not find a difference in CLABSI risk between FVCs, PICCs and UVCs.

The reported incidences of CLABSI in neonates admitted to NICUs vary from 0.8 to 18.1 per 1,000 catheter days.^{3, 10, 14-19} Variation in reported incidences is probably due to methodological differences between the studies including different cohort characteristics, but may also be attributable to differences in actions to prevent the development of CLABSI between the departments, such as emphasizing hand hygiene, avoidance of certain medications, and using bundles of care. We report the CLABSI incidence in our cohort of neonates born at 34 or more weeks of gestation, while most studies about this topic focus on the total NICU population or only extremely premature infants. The National Healthcare Safety Network (NHSN) reports CLABSI incidences for different birth weight categories separately with a pooled mean varying from 0.8 CLABSI per 1,000 catheter-days in infants >2500 g to 2.3 CLABSI per 1,000 catheter-days in infants ≤ 750 g.²⁰ Despite excluding the preterm and primarily smaller infants with the highest risk for infection, the CLABSI incidence in our cohort was high compared to the reported incidence in infants >2500 g. Low gestational age and hygiene are important factors influencing the incidence of CLABSI. Studies have shown that education of medical staff about hygiene, new disinfectant methods, and the use of specific care bundles for catheter placement can reduce the incidence of CLABSI.^{15, 17, 21, 22} During the last years we introduced several evidence-based strategies to reduce the incidence of CLABSI in our NICU. The effect of these actions needs to be evaluated in the future. One contributing factor for the high CLABSI incidence reported in this study might be that the definition of CLABSI used in this study is different from the more strict Center of Disease Control (CDC) criteria used in most other studies. These criteria require at least two positive blood cultures in case of common commensals to fulfill the criteria of CLABSI.²³ We used a definition requiring only one positive blood culture in an infant with clinical sepsis. The amount of blood taken from neonates at our department is restricted. Only 1 ml per sample is taken, and blood cultures are usually not repeated when the neonate recovers with antibiotic treatment. Use of the CDC criteria with at least two positive blood cultures would have shown a lower CLABSI incidence, but most likely would have underestimated the true incidence.

In our study, differences in CLABSI incidence between the different catheter types were not significant. The literature is conflicting on what type of CVCs carries the highest infection rate. Shalabi et al. and Arnts et al. found no difference in risk of CLABSI between UVCs and PICCs in neonates born <30 weeks of gestation and in the total NICU population, respectively.^{7, 8} Other authors compared the risk of CLABSI in infants with three

different catheter types, in particular UVCs, PICCs and other central catheters, including FVCs.^{3,9,10} Yumani et al. advocated that UVCs carry the highest infection rate,¹⁰ yet Chien et al. pointed to a higher risk of CLABSI in PICCs and Broviacs compared to UVCs.³ Tsai et al. reported a higher risk of CLABSI in infants with birth weight <1,500 g with FVCs compared to infants with PICCs.¹¹ Most studies that compared catheter types include smaller numbers of term and late preterm infants, and they usually analyze FVCs in a group with other catheters. The only study that compared FVCs with other catheters (UVCs) as a separate catheter type in term infants found a non-significantly higher risk in the FVC-group, but their cohort only comprised 19 FVCs.¹² It has been suggested previously that femoral catheterization increases the risk of infection, because of proximity to the groin.^{2,24} However, if this would be the case, we would have expected mostly gram-negative micro-organisms as causative organisms for CLABSI in the FVC-group, whereas only gram-positive micro-organisms (CoNS) were found.

To date, UVCs and PICCs have not been compared to FVCs to this extent before, which is one of the strengths of this study. In addition, this is the largest study to date comparing not only the rates of CLABSI in UVCs and PICCs but also in FVCs in a cohort of term and late preterm neonates.

However, our results have to be interpreted with caution because of the observational study design. As shown in our study, the population of neonates with UVCs or PICCs differed from the population with FVCs. A high proportion of neonates who have a FVC in our department have congenital heart disease (27/64; 42%) sometimes needing therapeutic cardiac catheterization. Hypothetically, different CLABSI incidences in the catheter groups may not be due to the type of catheter, but may be confounded by other clinical factors such as the underlying clinical condition itself.

Our data supports the findings that administration of parenteral nutrition during use of a catheter results in a higher risk of CLABSI, probably due to the lipid constituents in the fluid as found in other studies.²⁵⁻²⁷ By Cox regression higher birth weight was an independent risk factor for catheter infection, but with a HR of 1.04 this association is weak and seems not clinically relevant. It is in contrast with other reports with higher CLABSI incidences in neonates with lower birth weight.^{20,28} However, these studies are performed in populations of neonates with very low birth weight or the total neonatal population in contrast with our cohort of only late preterm and term neonates. We could not find an association between birth weight and CLABSI incidence in a cohort comparable to our cohort. Male gender was associated with a higher risk of CLABSI. The observational study design may lead to bias by indication and it is, therefore, not possible to prove causality. Male gender is associated with a higher neonatal morbidity and mortality hence boys will probably have more or other types of catheters placed which may lead to a higher CLABSI incidence.^{29,30}

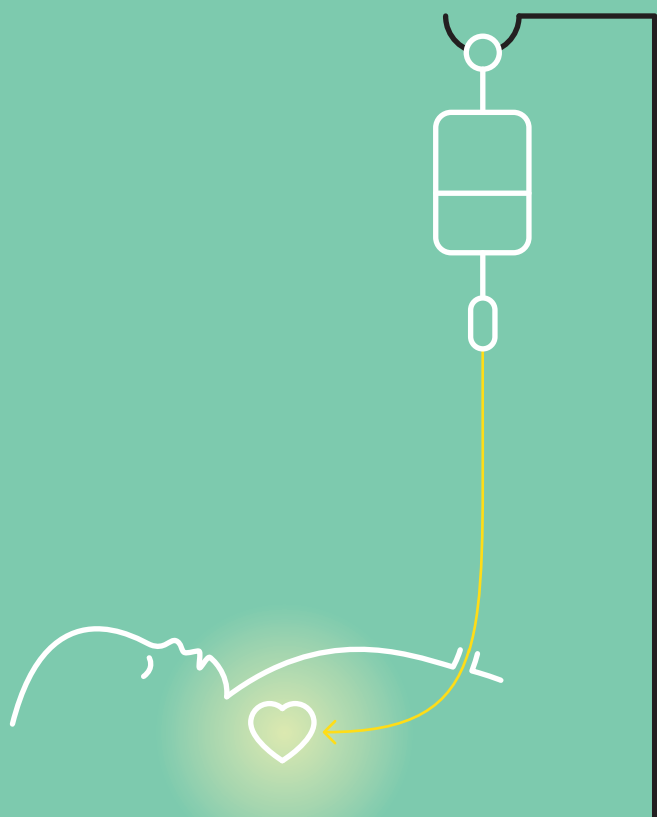
In our department treatment with antibiotics during the first 24 h after birth is associated with a lower risk of CLABSI. We could not find this association in prior studies. Antibiotics in the study population were started routinely in neonates with gestational ages below 35 weeks with no clear cause of the prematurity and in the presence of risk factors for infection. In neonates of all gestational ages, antibiotics are started in the presence of risk factors for infection and clinical signs of infection. According to the unit protocol Amoxicillin and Gentamycin are given for 48 h in case of negative cultures. In 12/552 cases (2.2%), culture-proven early onset sepsis was diagnosed, with 11/12 (92%) *Streptococcus agalactiae* as causative organism. Patients who are treated with antibiotics early have a different microbiome,³¹ and we speculated that they could carry less microorganisms on their skin, decreasing the risk of CLABSI. However, this does not mean that we can promote the use of early antibiotics, because this would, by selection of microorganisms, lead to a larger proportion of resistant causative organisms, although the total number of CLABSI could be lower.³²

In summary, CLABSI remain a problem in the NICU. We did not demonstrate a significant difference in CLABSI risk between three catheter types in the NICU. Several studies conducted on how to decrease the incidence of CLABSI have recently shown that proper education of medical staff, the use of specific care bundles, and standardization of protocols can prevent CLABSI.^{15, 21, 22, 33} More extensive follow-up studies are needed to determine the actual incidences of CLABSI in neonates of all gestational ages, which factors genuinely affect the risk of CLABSI and what methods are the most effective for preventing these events.

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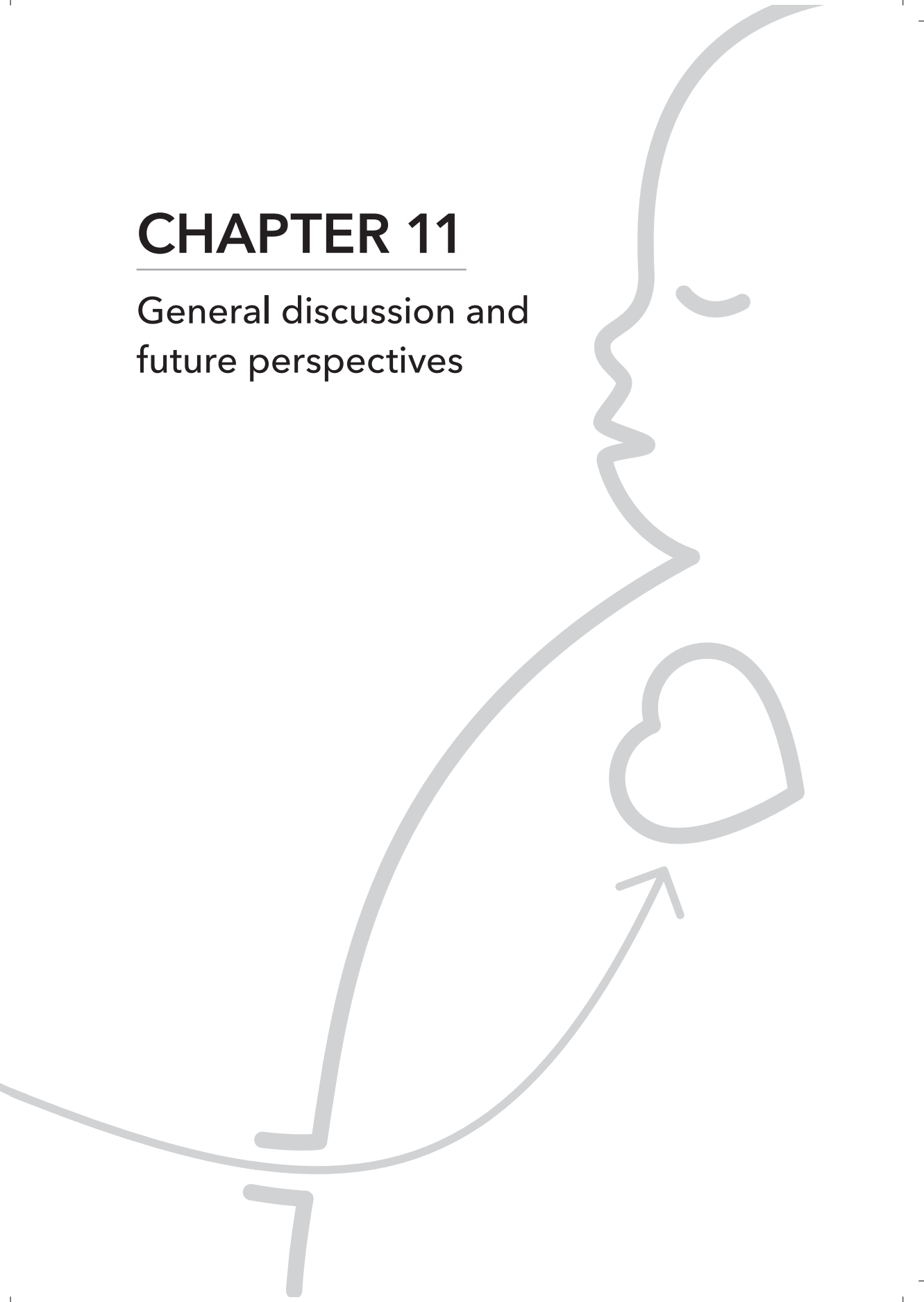
PART III

Review, General Discussion and Summaries



CHAPTER 11

General discussion and
future perspectives



Umbilical catheterization (UC) is a procedure frequently performed on neonates with cardiorespiratory instability.¹ While performing the procedure, caregivers often neglect to take the possibility of complications into account, although many different - even potentially devastating - complications are described in the literature.²⁻⁵ In particular the risk increases when the catheter is positioned incorrectly,⁵⁻⁷ and for this reason avoiding malposition is essential.

The aim of the research described in this thesis was to optimize the positioning of umbilical catheters and thus decrease the risk of complications. Many methods are currently used to ensure that umbilical catheters are positioned correctly, but considerable uncertainty still exists about their accuracy and feasibility. There are a large number of complications associated with the use of umbilical catheters, both frequent and rare. We chose to focus on cardiac arrhythmia, bloodstream infection, and thrombosis in relation to umbilical venous catheters (UVCs), and on hypothermia in relation to the procedure of UC.

In the conclusion of this chapter we weigh up the risks and benefits of the use of UVCs and discuss future research perspectives.

A) METHODS TO PREDICT CORRECT INSERTION LENGTH OF UMBILICAL CATHETERS

The ideal anatomical location for the tip of a UVC is the junction of the inferior vena cava and right atrium (IVC-RA junction),⁸⁻¹³ and the ductus venosus is also generally considered to be correct.^{6, 11} For umbilical-artery catheters (UACs) the ideal anatomical location for the tip is in the descending aorta above the level of the diaphragm and below the left subclavian artery.^{8, 9, 14, 15} Several formulas and graphs based on various body measurements have been proposed to predict the insertion length of umbilical catheters (see Figure 1 and 2).¹⁶⁻²⁹ The methods used for UVCs are presented in Table 1 and the methods for UACs in Table 2.

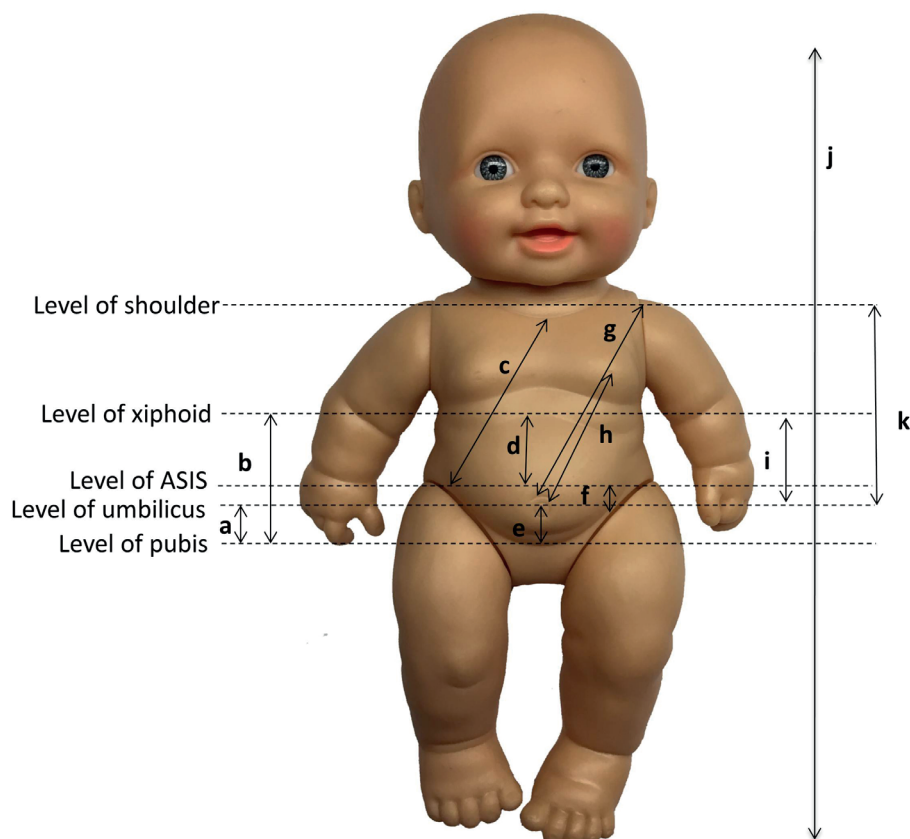


Figure 1. Different body measurements used in different methods to predict the insertion length of umbilical catheters, anterior view. a: umbilicus to symphysis pubis; b: xiphoid to pubis; c: suprasternal notch to superior iliac spine; d: xiphoid to anterior superior iliac spine (ASIS); e: umbilicus to pubis; f: umbilicus to ASIS; g: umbilicus to acromioclavicular joint; h: umbilicus to nipple; i: umbilicus to xiphisternum; j: total body length or heel-to-crown length; k: shoulder-umbilicus length;

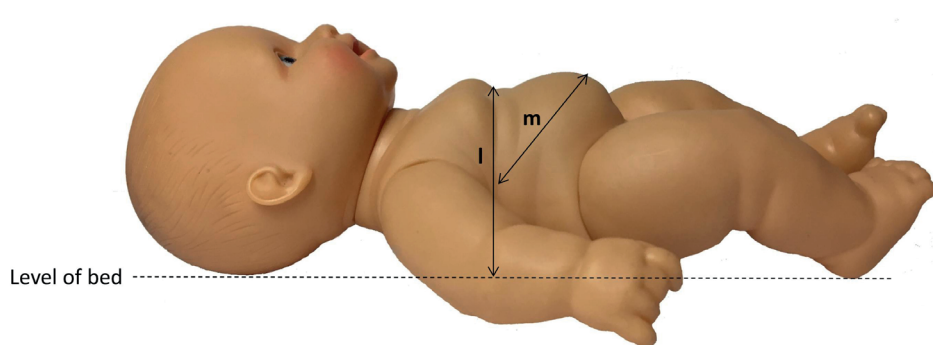


Figure 2. Different body measurements used in different methods to predict the insertion length of umbilical catheters, lateral view. l: xiphoid to bed distance; m: umbilicus to mid-xiphoid to bed distance;

Table 1. Methods to estimate umbilical venous catheter insertion length^{16, 17, 22-25}

Author (year)	Short description
Dunn (1966)	Nomogram based on shoulder-umbilicus length (k)
Shukla (1986)	$(3 \times \text{weight (kg)} + 9) / 2 + 1$
Vali (2010)	Measurement from the umbilicus to the mid-xiphoid-to-bed distance on the lateral aspect of the abdomen (l,m)
Gomella (2013)	Distance from umbilicus to xiphisternum + 1 cm (i)
Verheij (2013)	$(3 \times \text{weight (kg)} + 9) / 2$
Gupta (2015)	Distance from umbilicus to nipple - 1 cm (h)

The letters between brackets refer to the relevant body measurements shown in Figure 1 and 2.

Table 2. Methods to estimate umbilical artery catheter insertion length^{16-22, 25-29}

Author (year)	Short description
Dunn (1966)	Nomogram based on shoulder-umbilicus length (k)
Weaver&Ahlgren (1971)	$0.33 \times \text{heel-crown length (j)}$
Rosenfeld (1980)	Nomogram based on total body length (j)
Pollack (1981)	Shoulder-umbilicus length + weight to the nearest higher 0.5 kg (kg)
Shukla (1986)	$(3 \times \text{weight (kg)} + 9)$
Rubin (1986)	Distance from xiphoid to pubis + distance from pubis to umbilicus (b,e)
Lin (1989)	For 1000 g infant, insertion length is 10 cm. Add 1 cm for each additional 250 g. Above 2250 g, insertion length is 15 cm.
Sritipsukho (2007)	Distance from suprasternal notch to superior iliac spine (c)
Wright (2008)	$4 \times \text{weight (kg)} + 7$
Vali (2010)	$1.1 \times (\text{distance from xiphoid to anterior superior iliac spine} + \text{distance from umbilicus to anterior superior iliac spine}) + 1.6$ (d,f)
Gupta (2015)	Distance from umbilicus to nipple minus 1 plus twice the distance from umbilicus to symphysis pubis (h,e)
RWH (Lean) (2018)	Distance from umbilicus to acromioclavicular joint (g)

RWH, The Royal Women's Hospital; The letters between brackets refer to the relevant body measurements shown in Figure 1.

The two most widely used methods are Dunn¹⁶ and Shukla.¹⁷ The Dunn method is based on measurement of the shoulder-umbilicus length (S-U length), and uses nomograms to determine the insertion length of the catheter.¹⁶ Dunn defined the S-U length as 'the distance between the top of the shoulder over the lateral end of the clavicle and a point vertically beneath it that was level with the centre of the umbilicus'. However, as reported in our questionnaire (**Chapter 2**), only 14% of the neonatal caregivers in The Netherlands measured the S-U length correctly according to this definition.³⁰ Most respondents measured the S-U length as the distance between the top of the shoulder over the lateral end of the clavicle and the centre of the umbilicus. Following Pythagoras's theorem, measuring the S-U length in this way will lead to a deeper insertion length, and increases the possibility of a malposition of the catheter. A study by

Ades et al. showed that Dunn's method often led to overestimation of insertion length of umbilical catheters.³¹ We observed that this overestimation may be partly due to incorrect measurement of the S-U length. Moreover, obtaining accurate body measurements may be difficult because of the increased flexor tone of the infant. It is also possible that caregivers do not take the time to accurately interpret the graphs needed to correlate their measurements with the positioning of umbilical catheters.

The use of equations based on birth weight, such as those developed by Shukla, may be more accurate since these methods are based solely on calculations without the need for measurement and interpretation.¹⁷ Shukla tested these equations in a prospective study and concluded that all catheter tips were in acceptable positions. They aimed to position the tip in the inferior vena cava or right atrium, however, which is no longer recommended practice.^{5,32}

In **Chapter 3** of this thesis we assessed the accuracy of both the Dunn and Shukla methods to predict the appropriate insertion length of UACs and UVCs.³³ The overall accuracy of both methods is poor, frequently leading to umbilical catheters being positioned too high. For UACs, the Shukla method was more accurate in determining the correct insertion length and is therefore advisable. For UVCs, the Dunn method produced better results. Combining these two different methods, however, may lead to confusion and mistakes. We therefore revised Shukla's method for UVCs and validated this in a group of 92 infants (**Chapter 4**).²⁴ The use of this revised formula reduced the rate of over-insertion of UVCs without increasing the risk of more UVCs being placed too low. This revised formula $[(\text{birth weight} \times 3 + 9)/2]$ has the potential to reduce the rate of complications by reducing over-insertion. The formula is a derivative of Shukla's formula used to predict the insertion length of UACs $[\text{birth weight} \times 3 + 9]$. An additional advantage of these formulas is that they are easy to remember, and the simplicity minimizes the risk of miscalculation.

The Dunn, Shukla, and other methods have been compared in earlier studies (see Table 3 and 4).^{25, 34-37} Different conclusions were drawn, probably due to the variations in study design.

Table 3. Comparison of methods used to predict the correct insertion length of umbilical venous catheters
24, 25, 33-36

Author (year)	Methods compared	Ideal position of UVC on X-ray	Conclusion
Verheij (2010)	Dunn, Shukla	Th9-Th10	Dunn most accurate
Verheij (2013)	Shukla, revised Shukla	Th9-Th10	Revised Shukla most accurate
Kieran (2015)	Dunn, Shukla	Th9-Th10	No difference
Gupta (2015)	Shukla, Gupta	At diaphragm $\pm$ 0.5 cm	Gupta most accurate
Mutlu (2017)	Dunn, Shukla, revised Shukla	Th9-Th10	No difference, trend to Shukla most accurate
Lean (2019)	Dunn, Shukla, Vali, Gomella, revised Shukla	At or up to 1 cm above diaphragm on lateral X-ray	Gomella highest predicted success rate, Shukla most practical (highest rate of either correct or high position)

UVC: Umbilical venous catheter

Table 4. Comparison of methods used to predict the correct insertion length of umbilical artery catheters
19, 25, 29, 33, 34, 37-39

Author (year)	Methods compared	Ideal position of UAC on X-ray	Conclusion
Rosenfeld (1981)	Dunn, Rosenfeld	L3-L5	Rosenfeld most accurate
Wright (2008)	Dunn, Wright	Th6-Th10	Wright most accurate (in VLBW infants)
Verheij (2010)	Dunn, Shukla	Th6-Th10	Shukla most accurate
Kumar (2012)	Shukla, Wright	Th6-Th10	No accurate formula for all gestational age groups. Wright less repositioning in VLBW infants.
Kieran (2015)	Dunn, Shukla	Th6-Th10	Shukla most accurate
Min (2015)	Dunn, Wright	Th6-Th10	Wright most accurate
Gupta (2015)	Gupta, Shukla, Wright	Th6-Th10	Gupta most accurate
Lean (2018)	Dunn, Shukla, Wright, Weaver&Ahlgren, Sritipsukho, Rosenfeld, Pollack, Rubin, Lin, Vali, RWH guideline	Th6-Th10	RWH guideline, Weaver&Ahlgren, Sritipsukho highest predicted success rates

UAC: Umbilical artery catheter; RWH: The Royal Women's Hospital

These different conclusions emphasize the unreliability of formulas and body measurements to predict the insertion length of umbilical catheters. Body proportions are not exactly the same in all infants or groups of infants; each person is unique. This is probably the most important reason why no one universal method can correctly predict the insertion length of catheters in all infants. Until now, no method or formula has been proven to reliably predict the correct insertion length of umbilical catheters in different gestational age and birth weight groups. However, the need for an estimation method remains and choices have to be made about which method to use in clinical practice.

Some methods use one or more body measurements in combination with calculations.^{18, 22, 23, 27} However, we have demonstrated (**Chapter 2**) that body parts can easily be measured inaccurately and thus lead to inaccurate estimates.³⁰ The use of different measurements or patient parameters for UVC and UAC, e.g. shoulder-umbilical length for UVC and birth weight for UAC, can also easily lead to confusion. In a busy department and in situations where acute care is needed, methods based on different body measurements and complex calculations may be too demanding and possibly lead to miscalculations or misinterpretations. We therefore recommend the use of a simple method without complex body measurements or combined calculations.

In order to ensure that the inserted part of the UVC remains sterile, UVCs that have been positioned too low should not simply be repositioned. Instead, they must be removed and the procedure must start again.³⁶ When a UVC is positioned too high it can easily be pulled back into the correct position, although even a short period of this malposition increases the risk of complications such as cardiac arrhythmias and intracardiac thrombosis.

A catheter placed too high may cause complications, but it can be repositioned; a catheter placed too low, however, must be completely removed. For this reason, most caregivers would rather accept the risk of placing the catheter too high, and prefer a method or formula with the smallest risk that the UVC could be placed too low. This is why Lean et al. recommend the Shukla method for UVCs, although Gomella's method had the highest predicted success rate in their study.³⁶ In our department, the revised Shukla formula is still recommended in our guidelines for estimating the insertion length of UVCs as this method leads to less over-insertion (**Chapter 4**). However, in practice, caregivers are anxious about UVCs being placed too low and frequently add a little length (approximately 1 cm) to the estimate during insertion, thus unintentionally reintroducing Shukla's original formula. In these situations caregivers should be especially aware of signs of the catheter-tip entering the right atrium, such as arrhythmia, and immediately pull the catheter back to prevent complications.

Practical recommendations for the positioning of umbilical catheters

- Use a method based on the same body measurement or patient parameter to predict the insertion length of both the UVC and the UAC.
- Use a simple method.
- Keep to the definition described by the author of the method and transmit this definition clearly to new colleagues.
- Whatever method is chosen, be alert to signs that the UVC or UAC may have been placed too high during catheterization and, if necessary, pull the catheter back immediately.

B) METHODS TO CONFIRM THE CORRECT POSITION OF UMBILICAL CATHETERS

Checking the position of the tip of umbilical catheters after placement is strongly recommended to prevent malpositioning. Despite attempts to position catheter tips in the appropriate location, they are often positioned too low or too high along the catheter route or are malpositioned in vessels branching off the catheter route.^{9,40-42} In the past a radiographic examination - an anteroposterior and lateral thoraco-abdominal X-ray - was used to confirm the correct position of umbilical catheters and differentiate between umbilical artery and venous catheters.^{2,3,40,43} More recently the value of the lateral view has been called into question, and it is now only recommended by some authors when the catheter position is still unclear after the routine anteroposterior radiograph.^{6,44} The diaphragm, the cardiothymic silhouette, and the thoracic vertebrae are used as landmarks to determine the umbilical catheter position (Figure 3). For UVCs, the position of the tip should project above the diaphragm, outside the cardiothymic silhouette and at the level of the eighth to ninth or ninth to tenth thoracic vertebra.^{2,4,8,31,45} Interpretation

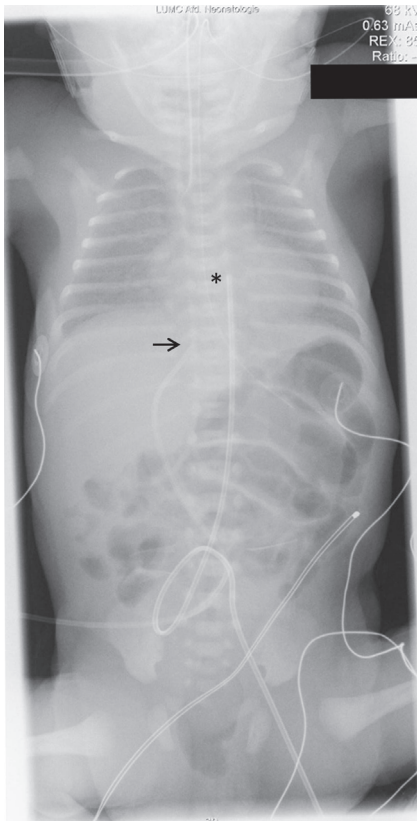


Figure 3. Anteroposterior thoraco-abdominal X-ray to determine position of umbilical catheters. The tip of the umbilical venous catheter (arrow) projects in between 9th and 10th thoracic vertebra, outside the cardiothymic silhouette, just below the diaphragm. The tip of the umbilical artery catheter (asterisk) projects just above 7th thoracic vertebra. Both catheters were accepted for use.

of radiographs including position of the catheter tip relative to the cardiac silhouette, appear to be more sensitive and accurate in assessing the position of the UVC tip than interpretation of radiographs relying solely on vertebral level.⁴⁶

UACs in a high position are accepted when the tip is seen at the level of the fifth or sixth to ninth or tenth thoracic vertebra, and in low position when the tip is between the third and fourth or fifth lumbar vertebra.^{3, 4, 9, 10} For UACs the use of bony landmarks on chest X-ray to map the location of the catheter tip with respect to vascular structures appears to be satisfactory.^{8, 47} However, the desired location of the IVC-RA junction for UVCs is frequently inconsistent with these landmarks on radiographs.^{8, 31, 48} Other methods have therefore been researched to give a more reliable representation of the real location of the UVC tip.

Correct positioning of the UVC can also be achieved by advancing the catheter until the electrocardiogram (ECG) has tall P-waves and QRS-complexes and then withdrawing the catheter until the P-wave returns to normal size.^{49, 50} However, the effectiveness and feasibility of this technique has not been studied extensively in larger groups of patients and ECG guidance is not yet commonly used in UC. Moreover, using this method involves deliberately introducing the catheter too high in order to induce ECG changes, and this carries a risk of complications.

The most promising method to check the position of umbilical catheters is ultrasonography (Figure 4).

The first report of the use of ultrasonography to localize intravascular catheters in children, including umbilical catheters, was published in 1981.⁵¹ One year later George et al. confirmed that using ultrasonography to establish the position of UVCs is simple and rapid, delivers no ionizing radiation, and is superior to radiographic examination in localizing UVC tips.⁴⁷ Later authors have also compared ultrasonography and radiographic examination. Most reported low correlation between thoracic level of the UVC tip and catheter location by radiographs and recommend ultrasonography,^{31, 48, 52-58} although one more recent study found high agreement between radiographs and ultrasonography.¹³

In **Chapter 5** of this thesis we also compared ultrasonography and chest X-rays as methods of detecting malposition and migration of UVCs, although this was not the primary aim of the study.⁵⁹ We found disagreement concerning position in 23% of imaging pairs. When the UVC passes through the ductus venosus, it travels in both a caudocranial and anteroposterior direction. Measurements taken on digitalised anteroposterior chest X-rays represent the distance in only one plane and this may lead to misinterpretation of the tip position.⁴⁶ With ultrasonography it is possible to perform dynamic views of the catheter tip from different angles, thus leading to more accurate tip localization.¹³ Other advantages are quicker, clearer results and prevention of additional exposure

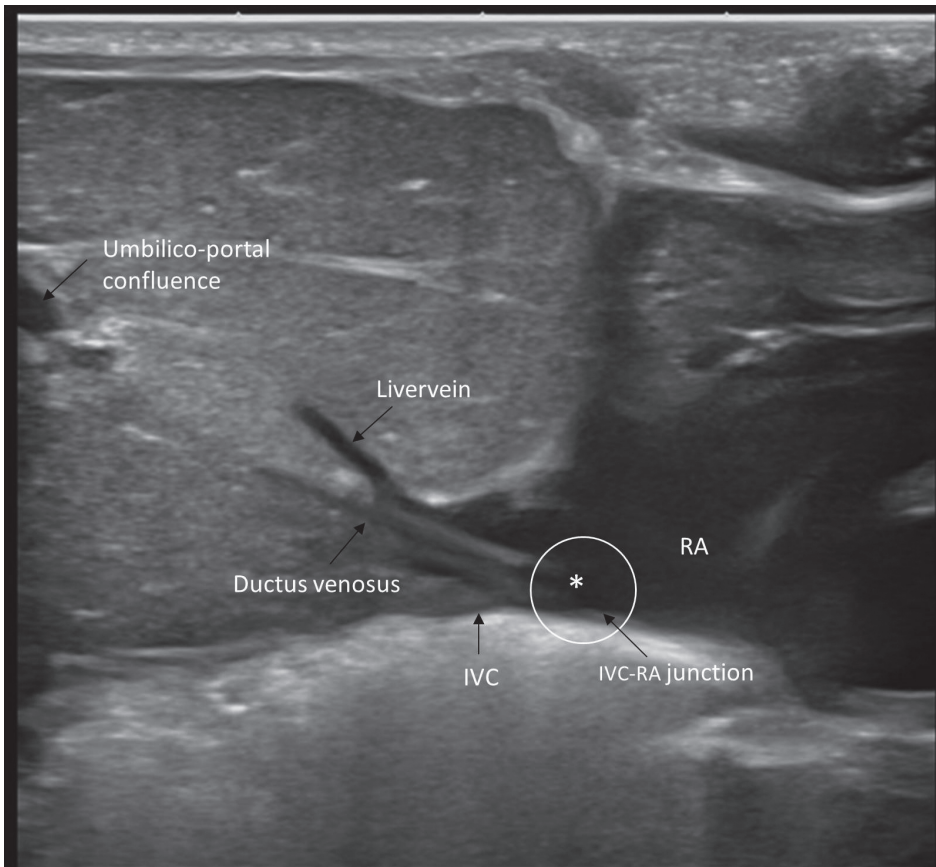


Figure 4. Ultrasound image of an umbilical venous catheter with correct position of the tip (asterisk). The tip of the catheter is localized at the junction of the inferior vena cava (IVC) and right atrium (RA).

to radiation.^{13, 55, 60} Ultrasonography can be used to evaluate and guide UVC position immediately, unlike an X-ray.⁶¹ Ultrasonography during UC decreased the time needed to place the catheter, the number of manipulations of the catheter, and the number of X-rays; it may also limit the risk of complications.⁶¹

Ultrasonography may be used during or directly after catheterization and also when the catheter is in place, to follow the UVC tip position over time.¹³ In **Chapter 5** we reported migration of UVCs in 63% of infants. Migration of UVCs is also described in other studies, most of which reported the highest amount of migration in the first two or three days after placement, in agreement with our own observations.^{54, 59, 62, 63} We found that migration frequently led to malposition.⁵⁹ To detect migration, especially migration leading to a potentially dangerous position in the heart, we now recommend confirming the position of UVCs with ultrasonography at least once, preferably 24-48 hours after placement. Few studies showed that neonatal caregivers are, after training, able to

interpret UVC tip position with high accuracy rates when compared with cardiologists or radiologists.^{13, 58} Ideally, UVC tip position should be checked daily in every infant, but incorporating daily ultrasonography into care at the Neonatal Intensive Care Unit (NICU) has several practical and logistical implications. Firstly, it requires some investment of time to train the clinicians to reliably detect the position of the catheter tip using ultrasound examination. Secondly, trained clinicians need to be available 24 hours a day and 7 days a week. Despite the logistical challenges, the use of frequent ultrasonography in infants with UVCs could prevent complications caused by the malposition of catheters and improve care in this vulnerable population. Efforts should therefore be made to achieve these goals.

UAC tips can be detected more reliably than UVC tips using chest X-rays. Similarly to Fleming et al.,⁶¹ we found during the study periods that UAC tips can easily be detected with ultrasonography as well. The reliability and feasibility of ultrasonography for localizing UAC tips in comparison with chest X-rays is still unclear as no comparative studies have been performed. However, we hypothesize that, in an infant with both arterial and venous umbilical catheters inserted, ultrasonography will detect both catheter tips, making a chest X-ray obsolete.

Practical recommendations for determination of the position of umbilical catheters

- Use ultrasonography as first choice modality to determine the umbilical catheter tip position.
- If equipment is available but clinical experience is lacking: invest in training for neonatal clinicians to learn the technique of checking the umbilical catheter tip position using ultrasonography.
- If ultrasonography is not feasible: use anteroposterior thoraco-abdominal X-ray, including assessment of the catheter tip in relation to vertebral level, diaphragm and cardiothymic silhouette to determine tip position. If in doubt, add lateral X-ray.
- Re-evaluate the UVC tip position when in place, preferably using ultrasonography, and at least once 24-48 hours after placement.

C) COMPLICATIONS ASSOCIATED WITH UMBILICAL CATHETERIZATION

Despite efforts to achieve and maintain the correct position of umbilical catheters, complications during and after UC cannot be totally avoided. In this thesis, we have described the occurrence of several possible complications of umbilical venous catheterization, including hypothermia (**Chapter 6**), cardiac arrhythmias (**Chapter 7**), thrombosis (**Chapters 8 and 9**) and bloodstream infection (**Chapter 10**). Most complications are not only related to UVCs but also to other central venous catheters (CVCs), such as femoral

venous catheters (FVCs) and peripherally inserted central catheters (PICCs). In **Chapter 9** and **Chapter 10** of this thesis we therefore compared the incidences of thrombosis and bloodstream infection between UVCs, FVCs and PICCs.

Hypothermia

Hypothermia in infants is associated with increased neonatal mortality and morbidity and must be avoided.⁶⁴⁻⁶⁹ During the first 'golden hour' of premature life, procedures such as UC are performed to stabilize the infant as soon as possible.^{70, 71} However, these procedures may cause or contribute to the development of hypothermia. As described in **Chapter 6** of this thesis, hypothermia already existed in 69% of infants in our NICU before the start of UC, and increased to 89% during the procedure. To our knowledge, no other studies investigate the whole course of the temperature of infants during UC. In our study a decrease in temperature was observed at the start, with temperature stabilizing and sometimes rising again in the latter part of the procedure. This is the most likely explanation why the duration of the procedure was not associated with temperature decrease or hypothermia.

The high proportion of infants with hypothermia at the start of UC in our department is alarming, and it is important to optimize the prevention of heat loss after birth. Performing UC in these hypothermic infants may lead to inadequate rewarming and may even decrease their temperature further. We recommend postponing this procedure until the infant's temperature is normal, unless it is impossible to give the infant alternative, more quickly inserted, intravenous access during waiting time. In hypothermic infants, UC is not essential and may even be a harmful step in the first 'golden hour' of life.

Practical recommendations concerning hypothermia

- Verify the temperature of the infant before the start of UC.
- In case of hypothermia: give alternative (temporary) intravenous access and postpone UC, even during the 'golden hour', until the infant is rewarmed.
- During UC: measure skin temperature continuously and take measures to prevent hypothermia during the procedure.

Cardiac arrhythmias

Cardiac arrhythmias are a known complication of UVCs.^{1, 4, 5} Mechanical irritation of the atrium or mechanically induced premature atrial beats may be the initiating triggers for atrial flutter or for supraventricular tachycardia (SVT) in the presence of an accessory atrioventricular myocardial pathway.^{72, 73} In infants without UVCs a newly developed tachyarrhythmia is usually caused by a SVT, and atrial flutter is almost exclusively observed in fetal life or immediately after birth.⁷⁴ However, in **Chapter 7** we described that in 6 out of 10 cases of cardiac arrhythmias related to UVCs the cause of the arrhythmia

was an atrial flutter.⁷² Atrial flutter is therefore a more prominent cause of tachyarrhythmia in infants with UVCs than in those without. Awareness of the possible types of arrhythmia is necessary, because distinction of the type is critical to guiding treatment.

In all cases described in our literature review, the UVC was assessed as too high by chest X-ray or ultrasonography. Not much is known about the incidence of cardiac arrhythmias related to UVCs. After the publication of our case study, three other case reports of a SVT (n=2) and atrium flutter (n=1) were published.^{73, 75, 76} In one of these cases the arrhythmia developed 30 hours after placement of the UVC and migration of the catheter to malposition was demonstrated.⁷⁵ Interestingly, in the last case multiple doses of adenosine were not successful in treating the SVT until the catheter was withdrawn. All cases emphasize the risk of UVCs positioned with the tip in the heart and the importance of evaluation and re-evaluation of UVC position as is also discussed in **Chapter 5** of this thesis.⁵⁹

Practical recommendations concerning cardiac arrhythmias

- Prevent the UVC being positioned too high or limit its duration as much as possible.
- The first step to treat cardiac arrhythmias in an infant with a UVC should be to pull back or even remove the UVC.
- If pulling back the catheter is not successful: use the normal treatment according to the type of arrhythmia (vagal response and adenosine in SVT, synchronized cardioversion or transoesophageal pacing in atrial flutter).

Thrombosis

The most common risk factor for neonatal thrombosis is catheterization of the central veins or arteries.^{77, 78} In the study described in **Chapter 8** we prospectively screened for thrombi along the entire UVC route and detected a high incidence of 75%. The incidence of thrombosis reported in the literature is lower than in our study and varies greatly from 2.2% to 43%.⁷⁹⁻⁸⁶ The lower reported incidences in previous studies may be due to the retrospective study design or the fact that only one part of the UVC route was evaluated. We assessed the presence of thrombi along the whole UVC route and found thrombi in a wide variety of locations, including umbilico-portal confluence, ductus venosus, junction of ductus venosus and inferior vena cava/right atrium and right atrium (Figure 5).

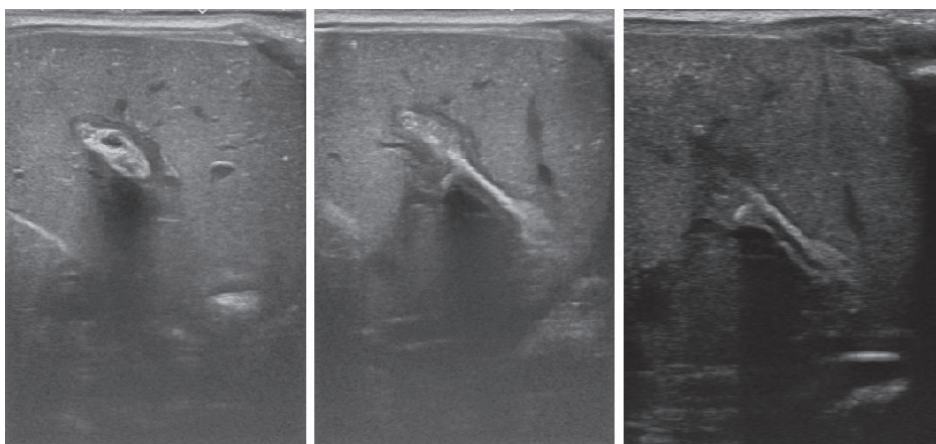


Figure 5. Premature infant with gestational age 31 weeks, 1415 grams. Thrombus in umbilico-portal confluence and ductus venosus. Images performed at day 8 after catheterization, before and after removal of UVC. First two left images with UVC still in situ. Right image: after removal of UVC a linear hole is observed within the thrombus.

Ours is the only study to date that includes a control group of infants without UVCs. Thrombus formation has been suggested as contributing to the physiological process of closure of the ductus venosus.^{87, 88} However, a thrombus was not detected in any of the infants in our control group (**Chapter 8**).

Only a few studies, all with a much smaller study population, compared the risk of thrombosis in the different catheter types used in neonates.^{85, 89-91} In our retrospective study in a cohort of infants born at 34 or more weeks' gestation (**Chapter 9**) we reported a higher incidence of clinical thrombosis in FVCs compared with UVCs and PICCs.⁹² One other study also reports a higher incidence in infants with FVCs compared to UVCs.⁸⁵ In accordance with our study, previous retrospective studies report similar incidences of thrombosis in infants with PICCs and UVCs.^{90, 93}

The clinical significance of thrombi detected by routine screening is debatable and controversial. Current management varies greatly from expectant management to aggressive thrombolytic therapy. However, there is little data concerning the long-term consequences of these thrombi, and current guidelines are mainly based on expert opinion.^{90, 94-96} Most centers do not advise routine screening for thrombi in all infants with UVCs. Currently, a large multi-center prospective observational cohort study is being carried out in the Netherlands to evaluate the efficacy and safety of the national neonatal central venous catheter-thrombosis guidelines and to analyse the risk factors and long-term consequences of central venous catheter-thrombosis (Neoclot study).⁹⁷

Ultrasonography is increasingly used at the NICU by neonatologists for multiple reasons other than screening. As a result, given the high frequency of thrombus formation observed in our population, detection of thrombi will also increase. The optimal man-

agement for catheter thrombosis is controversial and not well known. Some authors advise removing a catheter once a thrombus is detected, unless the catheter is vital for the survival of the infant or for administering thrombolytic therapy,^{5,96} while others opt for a “wait and see” approach. Our study showed that spontaneous resolution of UVC-related thrombi is likely to occur (**Chapter 8**). Until the results of the Neoclot study are published we would advise removing the UVC only in the case of clinical symptoms, such as persistent thrombocytopenia without other explanation. In asymptomatic thrombi detected accidentally or through routine screening the UVC may stay in place with close monitoring, but needs to be removed in case of growth of the thrombus or development of new clinical symptoms related to thrombosis. Importantly, in infants with UVCs, longer catheter dwell time (>6 days) was associated with a higher risk of portal venous thrombosis.⁸⁰ For this and other complications it would be best to use UVCs for the shortest time possible.

Practical recommendations concerning thrombosis

- Do not routinely screen for thrombosis in all infants with UVCs.
- To avoid complications: always remove UVCs as soon as the catheter is no longer needed.
- If thrombosis is found and CVC is still needed: remove catheter only if clinical symptoms are present.

Bloodstream infection

Bloodstream infection is a common complication of all CVCs, including UVCs. In our cohort study the incidence of central line-associated bloodstream infection (CLABSI) was 5.7% in UVCs compared with 4% in PICCs and 8% in FVCs (**Chapter 10**).⁹⁸ Although a trend towards a higher CLABSI incidence in FVCs was observed, there was no statistical difference. Other studies that have compared the risk of CLABSI in different catheter types draw conflicting conclusions.^{85, 91, 99-104} Differences in CLABSI incidences between different CVCs found in some studies may not be caused by the type of catheter but by differences in the selection of infants who receive a specific catheter type. The clinical context, with differences in care during and after insertion, may also play an important role.¹⁰⁵ Emphasizing hand hygiene, using bundles of care, and training a dedicated team to insert CVCs have been proven to reduce the incidence of CLABSI.¹⁰⁶⁻¹⁰⁹

Some NICUs advise a maximum UVC dwell time of 7 days to prevent catheter-related infections. However, the evidence suggesting that a dwell time <7 days reduces the risk of infections compared to > 7 days, is weak.^{79, 110, 111} In infants using UVCs for up to 14 or 28 days, reported incidence of bloodstream infection was similar to that of infants with peripheral lines only or a UVC followed by PICC after 7-10 days.^{79, 111} Some authors suggest replacing the UVC with a PICC after the first days of use based on an increas-

ing risk of CLABSI within the first week after insertion.^{105, 112} However, there is little solid evidence to support this advice; applying the same hygiene guidelines during and after catheterization in all catheter types is probably more important than changing a specific catheter after a few days. Moreover, a recent retrospective study comparing CVC-related complications between umbilical and non-umbilical catheters reported a higher incidence of complications (including CLABSI, pericardial effusion and tamponade) in non-umbilical catheters when compared to umbilical catheters.¹¹³

Practical recommendations concerning bloodstream infection

- Implement strict hygiene guidelines and specific care bundles to use during and after UC.
- Use checklists to help physicians apply these guidelines.
- Each NICU should routinely evaluate and benchmark the incidence of catheter-related bloodstream infection to detect fluctuations and strive towards reducing infections.

Balancing risks versus benefits of umbilical catheters

The risks of complications associated with UVCs should always be balanced against their numerous practical benefits. UVCs provide easy and rapid intravenous access and UC can be easily taught to inexperienced caregivers at the NICU. Importantly, in infants with a UVC during the first period of life, less time and money are spent obtaining peripheral line placement and less painful venipunctures are necessary.¹¹¹

Over the past decade an increasing amount of research has led to an improved knowledge on the potential complications of UVCs. Oelberg et al. report no benefit of successful UC in extremely premature infants with respect to reduction of mortality and morbidity when compared to unsuccessful UC,¹¹⁴ and reported a higher survival rate in infants without a UVC. Elborae et al. also report an association between the presence of umbilical catheters and adverse outcome (mortality or major neonatal morbidity).¹¹⁵ However, both studies have a retrospective design and, although adjustment for confounders was performed, the results were most probably limited by selection bias. A causal association between UVC and mortality or morbidity could not therefore be proven.

UVCs share many complications with other CVCs. This raises the question of whether there is one type of CVC with the lowest complication risk. Some physicians and authors are startled if confronted with threatening complications, such as cardiac tamponade, and become hesitant to use UVCs or even discourage their use.¹¹⁶ However, cardiac tamponade and pericardial effusion are described in other types of CVCs as well, apparently with similar incidences.^{117, 118} In our NICU, with infants in need of a CVC, we generally choose between insertion of a UVC or a PICC. FVCs are less likely to be an option, be-

cause a large part of our population has a low birth weight and/or gestational age and neonatologists at our department are not experienced in the insertion of FVCs. Taking into account the results of our studies reported in **Chapters 9 and 10** and the conflicting results of other studies published until now and discussed in this thesis, there seem to be no grounds for discouraging the use of UVCs in infants needing a CVC. Migration of the catheter may increase the risk of serious complications, such as cardiac tamponade, but is reported in PICCs as well.¹¹⁸⁻¹²⁰ This phenomenon therefore cannot support preference for one type of CVC over another.

Although no clear differences exist between complications according to the different CVC types used, physicians should be aware that the use of any CVC, irrespective of its type, may cause severe morbidity. In light of this knowledge, we should always think twice before inserting a CVC in a preterm infant. Guidelines have now been developed to standardize the use of umbilical catheters.¹²¹ These and similar guidelines are implemented at NICUs all over the world to select patients who will benefit and to prevent the overuse of CVCs, including UVCs.

In conclusion, UC is an excellent method for gaining intravenous access in sick infants, especially in extremely premature infants with small and fragile vessels and in infants with haemodynamic instability. The use of UVCs in all infants should therefore not be excluded and the advantages should not be underestimated. However, as in other CVCs, complications cannot always be avoided. This leads to a so-called 'love-hate relationship' between neonatologists and UVCs. Caregivers using UVCs must be able to critically assess the necessity of insertion of a CVC. Then, if the UVC has been inserted, they must remember the essential components of good care: awareness of potential complications, quick evaluation of symptoms that indicate complications, and regular re-evaluation of the position of the catheter and the continued need for its use.

General practical recommendations

- Critically weigh up the necessity of insertion of a UVC with its potential complications before performing UC.
- Be aware of the possible complications related to the use of UVCs and pay attention to potential symptoms of catheter-related complications.
- Regularly re-evaluate the position of the UVC.

FUTURE PERSPECTIVES

Since the first report on UC in 1948 many studies have followed, and the procedure is now common practice at the NICU. However, more knowledge is still needed about the optimal method of inserting catheters in the correct position, how to confirm correct position in daily practice, and the benefits and risks of umbilical and other central catheters.

A) Methods to predict correct insertion length of umbilical catheters

Despite decades of research, the optimal formula or method to predict the correct insertion length of umbilical catheters has not yet been determined. A more accurate formula or method to determine the optimal insertion length is urgently needed, particularly in healthcare situations with no ultrasonography or even radiology available. To develop such a formula, prospective studies using ultrasonography to collect ideal insertion lengths of UVCs in different patient groups must be performed.

B) Methods to confirm the correct position of umbilical catheters

Use of ultrasonography must become more widespread among neonatologists. In analogy to cranial ultrasonography, routine ultrasound examination of the position of central catheters, including umbilical catheters, should be incorporated into daily NICU practice. To reach this goal, neonatologists must be given basic training to carry out targeted neonatal cardiac and abdominal ultrasonography. Moreover, trained clinicians need to be available 24 hours a day and 7 days a week. The feasibility of this implementation in NICUs in the Netherlands therefore needs to be evaluated. Equipment costs and availability of caregivers have to be balanced against the expected benefits of less malposition (and complications) and decreased duration of the procedure in a cost-effectiveness analysis. Furthermore, while UAC tips can easily be detected by ultrasonography, studies to compare ultrasonography with chest X-rays in terms of feasibility and reliability to detect UAC tips are also needed.

C) Complications associated with umbilical catheterization

To determine the benefits and risks of UVCs in comparison with the alternatives, such as a PICC or no CVC at all, and to evaluate the association with mortality and morbidity in (preterm) neonates, randomized controlled trials (RCTs) are needed. In these trials infants should be randomized to a UVC, a PICC, a UVC followed by a PICC, or no CVC at all. These studies should also evaluate the effect of different timing of insertion (directly after birth versus a few hours or days afterwards, or later placement based on clinical need). Mortality, incidence of complications such as bloodstream infection and thrombosis, infant temperature, impact on the patient, and investment of time by the physi-

cian should all be evaluated. It is essential to develop an improved knowledge of the risks and associations of migration of UVCs as well as PICCs. Finally, more studies (ideally RCTs) are needed to evaluate the benefits and risks of UACs compared to peripheral artery catheters or no artery catheter at all.

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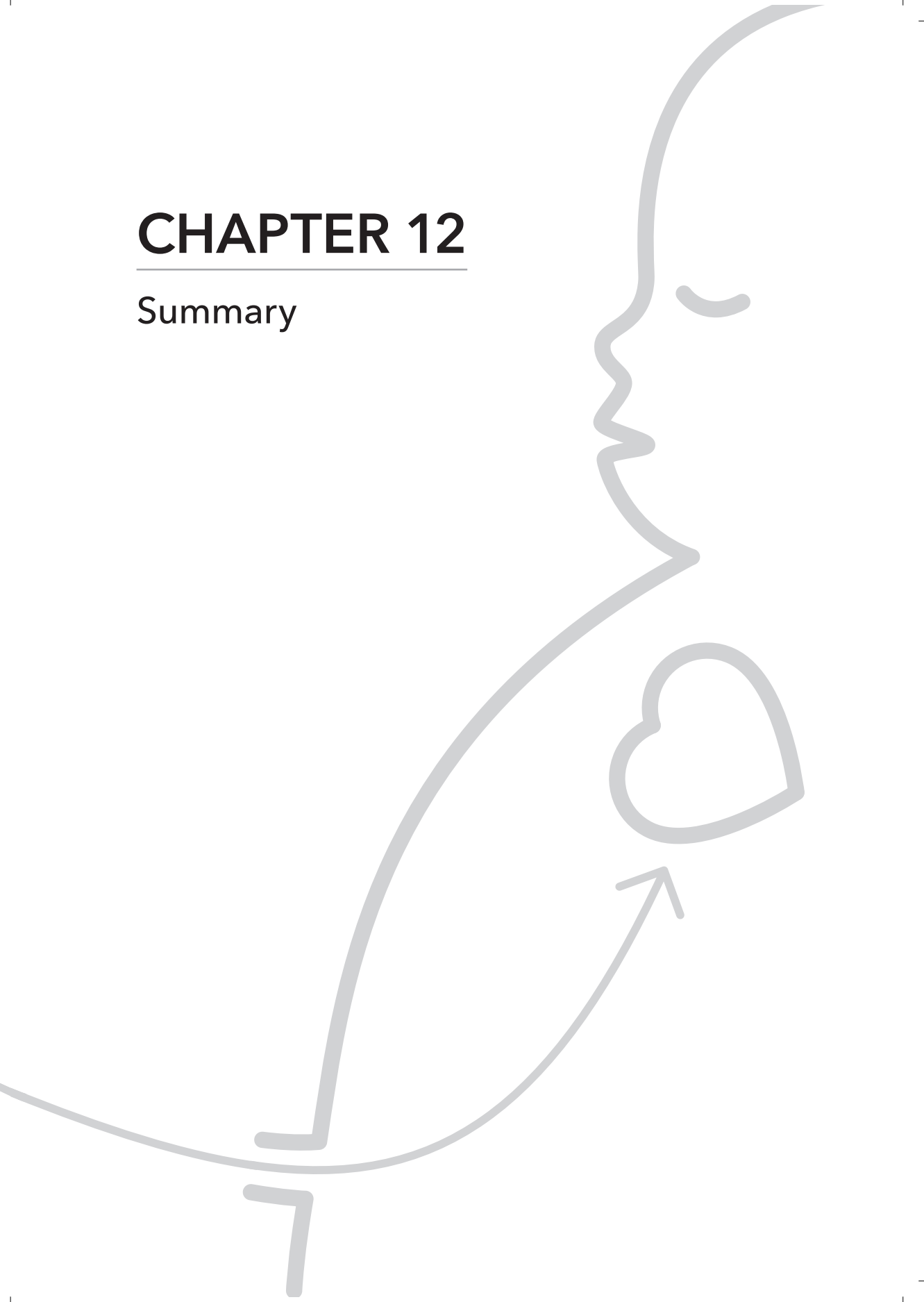
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CHAPTER 12

Summary



Umbilical catheters have been used for decades in neonatal care. There are many advantages to using them, but they also carry risks of complications. In order to reduce catheter-related complications and improve the outcome in preterm and seriously ill infants at the Neonatal Intensive Care Unit (NICU), more research about the positioning and use of catheters – as well as potential complications – is necessary. The general aim of this thesis is to optimize positioning of umbilical catheters and to improve their use, thus limiting complications.

Chapter 2 shows the results of a questionnaire study investigating the variations that occur in measurements of the shoulder-umbilicus length (S-U length) performed by paediatric professionals in the Netherlands. This length is used by Dunn to predict the correct insertion length of umbilical catheters. Dunn defined the S-U length as ‘the distance between the top of the shoulder over the lateral end of the clavicle and a point vertically beneath it that was level with the centre of the umbilicus’. Only 14% of 101 respondents in our study measure the S-U length according to Dunn’s definition, however. Other methods of measuring this length may lead to positioning the umbilical venous catheter (UVC) too deep, which is potentially dangerous. Professionals using the Dunn method should adhere more strictly to the original description of the measurement of the S-U length.

Chapter 3 presents a comparison of the accuracy of the Dunn method and the Shukla method, two of the most common methods used to estimate the insertion length of umbilical catheters. An anteroposterior thoraco-abdominal radiograph is performed to check the position of the catheter tip after insertion. We observe that with the use of the Dunn method 41% (28/69) of UVCs are placed in the correct position immediately, compared with 24% (20/84) with use of the Shukla method. Umbilical artery catheters (UACs) in the Dunn group are placed in the correct position in 63% of cases (24/38) compared with 87% (39/45) in the Shukla group. We conclude that the accuracy of both methods is poor and their use often leads to too high positioning, especially for UVCs. For UVCs the Dunn method is more accurate than the Shukla method in predicting the insertion length, whereas for UACs the Shukla method is more accurate. However, combining two different methods for inserting umbilical catheters is not practical and may lead to confusion and mistakes.

In **Chapter 4** we present a revision of the Shukla formula for predicting the correct insertion length for UVCs, that is $(3 \times \text{birth weight in kg} + 9)/2$ cm. We compare this revised formula with the Shukla formula $((3 \times \text{birth weight in kg} + 9)/2 + 1)$ cm. With use of the new formula 43% (40/92) of UVCs are placed directly in the correct position versus 26% (24/93) with use of the Shukla formula. UVCs are also over-inserted less frequently (54%

versus 73%). The rate of inadequate lower positioning is not increased. We therefore advise use of the revised formula to predict the insertion length of UVCs.

In our NICU, migration of UVCs is regularly observed in chest X-rays in the first few days after placement. In **Chapter 5** we therefore investigate UVC migration using serial ultrasonography. Migration of UVCs is detected in 63% (25/40) of infants on 32 occasions, leading to malposition in 68% (17/25) of infants. Most UVCs migrate inwards (56%) and most migrations occur before day 3 after placement (66%). In this study we also compared ultrasonography with chest X-rays – when performed as part of standard care – as methods of determining UVC position. When malposition is detected by ultrasonography, it is also detected in routinely performed chest X-rays on 11% of occasions. It is important to increase awareness of the possibility of migration. We recommend re-evaluation of the position of UVCs at least once, within 24 hours after placement and preferably by ultrasonography.

In **Chapter 6** we describe the effect of umbilical catheterization (UC) on skin temperature and cardiorespiratory status in preterm infants. Hypothermia, defined as a temperature below 36.5°C, already exists in 69% (38/55) of the infants before start of UC, and increases to 89% (49/55) during UC. During the procedure mean skin temperature decreases 0.6°C and is followed by a rise of 0.4°C after reaching minimal temperature. The duration of the procedure is not associated with the development of hypothermia. We observe a 10 beats/min increase in heart rate, but this change is only temporary. We conclude that hypothermia is frequent in preterm infants before the start of UC and increases during UC. Postponing the procedure until the infant has a normal temperature should be considered.

Chapter 7 focuses on two patients with cardiac arrhythmias due to umbilical venous catheterization. One neonate had a supraventricular tachycardia requiring treatment with adenosine. The other neonate had an atrial flutter that was managed successfully with synchronized cardioversion. In this chapter we also review the literature about cardiac arrhythmias associated with UC. The primary cause of cardiac arrhythmias after UC is inappropriate positioning of the UVC within the heart. The first step to treat them should be to pull back or even remove the catheter.

In **Chapter 8** the incidence of thrombosis in the UVC route from the umbilico-portal confluence to the heart is determined prospectively by serial ultrasonography. Thrombi are detected in 75% (30/40) of infants with UVCs. In a control group of infants without UVCs no thrombi are detected. Thrombi in the UVC-group are located in different parts of the UVC route, including the right atrium, ductus venosus and umbilico-portal confluence.

Most thrombi are asymptomatic and disappear spontaneously with expectant management. Routine screening for thrombi in infants with UVCs is therefore not advised.

Chapter 9 presents a comparison of the incidence of thrombosis in infants born at or after 34 weeks of gestation with UVCs, femoral venous catheters (FVCs) and peripherally-inserted central catheters (PICCs) placed after birth. The occurrence of thrombosis in infants with FVCs (7.8%) is higher than in infants with UVCs (1.7%) or PICCs (1.1%). Thrombi in infants with FVCs are more likely to totally occlude the blood vessel compared with thrombi in infants with other types of central venous catheters. Caregivers using FVCs should be aware of the increased risk of thrombosis associated with this catheter type.

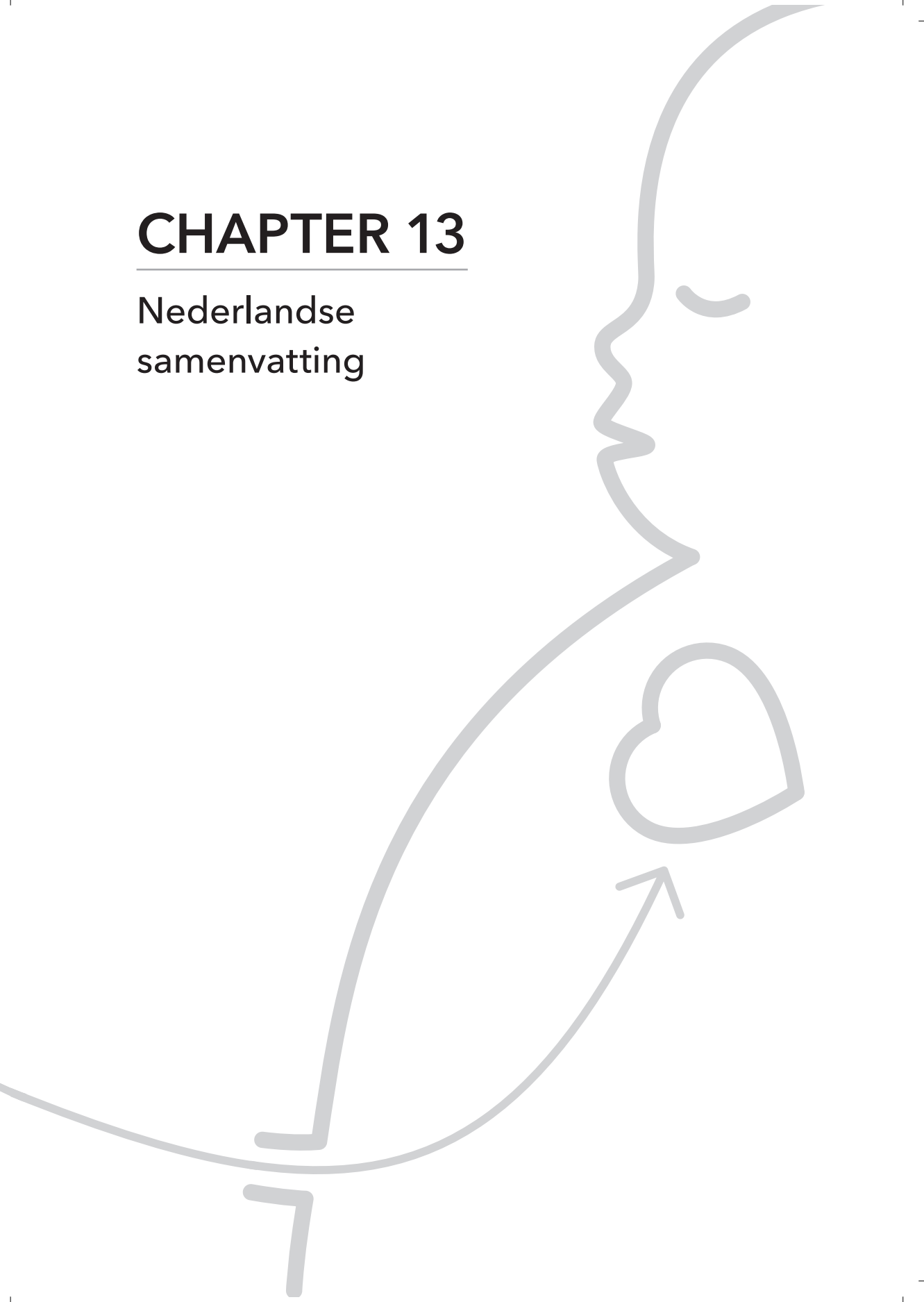
In **Chapter 10** the incidence of bloodstream infection in UVCs is compared with the incidence in FVCs and PICCs. The incidence rate of central line-associated bloodstream infection varies from 12.3 per 1,000 catheter days in FVCs to 10.6 per 1,000 catheter days in UVCs and 5.3 per 1,000 catheter days in PICCs. We do not find a statistical difference between the catheter types ($p=0.29$). In this retrospective study occurrence of bloodstream infection is associated with parenteral nutrition, male gender and higher birth weight, whereas antibiotic treatment within 24 h post-partum is associated with a decreased risk.

Finally, in **chapter 11** we discuss the results of our studies and review the recent literature on umbilical catheters. Based on the conclusions of this thesis, practical recommendations are provided and future perspectives discussed. To predict the correct insertion length of umbilical catheters we recommend the use of a simple method without complex body measurements or combined calculations. However, no method or formula has been proven to reliably predict the correct insertion length. Moreover, UVCs tend to migrate even after correct positioning. Regular evaluation of the position of UVCs - preferably by ultrasonography, and starting during or directly after placement - is therefore advised to prevent complications caused by malpositioning. Physicians using UVCs should be aware of the possible complications. However, despite the risk of complications UC is an excellent method for gaining intravenous access in sick infants, especially in cases of extremely premature birth or haemodynamic instability.



CHAPTER 13

Nederlandse
samenvatting



Navellijnen worden al decennia gebruikt in de neonatale zorg. Het gebruik van deze lijnen heeft veel voordelen, maar brengt ook risico's op complicaties met zich mee. Meer kennis over positionering, gebruik en mogelijke complicaties van navellijnen is nodig om lijn-gerelateerde complicaties te verminderen en de uitkomst van premature en ernstig zieke pasgeborenen op de neonatale intensive care unit (NICU) te verbeteren. Het algehele doel van dit proefschrift is om de positionering van navellijnen te optimaliseren en het gebruik van deze lijnen te verbeteren, zodat complicaties beperkt kunnen worden.

In **Hoofdstuk 2** worden de resultaten van een vragenlijstonderzoek beschreven waarin de variatie in het meten van de schouder-navel afstand (S-N afstand) door kindergeneeskundige professionals in Nederland wordt onderzocht. Deze afstand wordt gebruikt door Dunn om de juiste inbrengdiepte van navellijnen te voorspellen. Dunn definieerde de S-N afstand als 'de afstand tussen de bovenzijde van de schouder ter plaatse van het laterale uiteinde van de clavicula en een punt verticaal daaronder op het niveau van het midden van de navel'. Slechts 14% van de 101 respondenten in het onderzoek meet de S-N afstand volgens de door Dunn beschreven definitie. Andere methoden om deze afstand te meten, kunnen leiden tot een te diepe positie van de navelvenelijn (NVL), welke mogelijk gevaarlijk is. Professionals die de Dunn-methode gebruiken, zouden zich strikter moeten houden aan de originele beschrijving van de meting van de S-N afstand.

Hoofdstuk 3 presenteert een vergelijking van de nauwkeurigheid van de Dunn-methode en de Shukla-methode, twee van de meest gebruikte methoden om de inbrengdiepte van navellijnen te schatten. Na het inbrengen van de lijn(en) wordt een voor-achterwaartse thoraco-abdominale röntgenfoto gemaakt om de positie van de lijntip te controleren. Bij gebruik van de Dunn-methode blijkt 41% (28/69) van de navelvenelijnen direct in de juiste positie geplaatst vergeleken met 24% (20/84) bij gebruik van de Shukla-methode. Navelarterielijnen in de Dunn-groep worden in juiste positie geplaatst in 63% (24/38) vergeleken met 87% (39/45) in de Shukla-groep. We concluderen dat de nauwkeurigheid van beide methoden slecht is en dat het gebruik van deze methoden vaak leidt tot te hoge posities, met name van navelvenelijnen. Voor navelvenelijnen is de Dunn-methode nauwkeuriger dan de Shukla-methode in het voorspellen van de inbrengdiepte, terwijl voor navelarterielijnen de Shukla-methode nauwkeuriger is. Het combineren van twee verschillende methoden bij het inbrengen van navellijnen is echter niet praktisch en kan leiden tot verwarring en fouten.

In **Hoofdstuk 4** wordt een revisie van de Shukla-formule voor het voorspellen van de juiste inbrengdiepte voor navelvenelijnen gepresenteerd, namelijk $(3 \times \text{geboortegewicht in kg} + 9)/2 \text{ cm}$. We vergelijken deze gereviseerde formule met de Shukla-formule

$((3 \times \text{geboortegewicht in kg} + 9)/2 + 1 \text{ cm})$. Door de nieuwe formule te gebruiken, wordt 43% (40/92) van de navelvenelijnen direct in de juiste positie geplaatst versus 26% (24/93) met gebruik van de Shukla-formule. Navelvenelijnen worden minder vaak te diep ingebracht (54% versus 73%). Het aantal lijnen met inadequate lage posities neemt niet toe. Daarom adviseren wij gebruik van de gereviseerde formule om de inbrengdiepte van navelvenelijnen te voorspellen.

Migratie van navelvenelijnen wordt regelmatig op thoraxfoto's gezien op onze NICU gedurende de eerste dagen na plaatsing. In **Hoofdstuk 5** wordt daarom met behulp van seriële echografie de migratie van navelvenelijnen onderzocht. Migratie van navelvenelijnen wordt gedetecteerd in 65% (25/40) van de pasgeborenen in 32 gevallen, leidend tot malpositie in 68% (17/25) van de pasgeborenen. De meeste navelvenelijnen migreren naar binnen toe (56%) en de meeste migraties vinden plaats vóór dag 3 na plaatsing (66%). In dit onderzoek wordt ook de positie van de NVL bepaald door echografie vergeleken met de positie op thoraxfoto's als deze gemaakt worden tijdens standaard zorg. Wanneer malpositie gedetecteerd wordt door middel van echografie, wordt dit in 11% van de gevallen ook gedetecteerd op routinematig gemaakte thoraxfoto's. Bewustwording van migratie is nodig. Wij bevelen herevaluatie van de positie van navelvenelijnen aan, in ieder geval eenmalig en binnen 24 uur na plaatsing, bij voorkeur middels echografie.

In **Hoofdstuk 6** beschrijven we het effect van katheterisatie van de navelstreng op de huidtemperatuur en cardiorespiratoire toestand van premature pasgeborenen. Hypothermie, gedefinieerd als een temperatuur lager dan 36.5°C, is al aanwezig in 69% (38/55) van de pasgeborenen voor start van de procedure en neemt toe tot 89% (49/55) tijdens katheterisatie. Tijdens de procedure daalt de gemiddelde huidtemperatuur met 0.6°C gevolgd door een stijging van 0.4°C na het bereiken van de minimale temperatuur. De duur van de procedure is niet geassocieerd met de ontwikkeling van hypothermie. Een toename in hartfrequentie van 10 slagen/min wordt waargenomen, maar deze verandering is slechts tijdelijk. We concluderen dat hypothermie frequent aanwezig is bij premature pasgeborenen vóór starten van katheterisatie van de navelstreng en toeneemt tijdens de procedure. Het uitstellen van de procedure tot de pasgeborene een normale temperatuur heeft, moet overwogen worden.

Hoofdstuk 7 doet verslag van twee patiënten met hartritmestoornissen door katheterisatie van de navelvene. Eén neonat had een supraventriculaire tachycardie waarvoor behandeling met adenosine nodig was. De andere neonat had een atrium flutter die succesvol behandeld werd met gesynchroniseerde cardioversie. In dit hoofdstuk geven we ook een overzicht van de literatuur over hartritmestoornissen die geassocieerd zijn

met navelvenelijnen. De primaire oorzaak van hartritmestoornissen na katheterisatie van de navel is onjuiste positie van de NVL in het hart. De eerste stap om ze te behandelen moet terugtrekken of zelfs verwijderen van de lijn zijn.

In **Hoofdstuk 8** wordt de incidentie van trombose in het NVL-traject van het verzamelsysteem in de lever tot het hart prospectief bepaald middels seriële echografie. In 75% (30/40) van de pasgeborenen met navelvenelijnen worden stolsels gedetecteerd. In een controlegroep van pasgeborenen zonder navelvenelijnen worden geen stolsels gedetecteerd. Stolsels in de NVL-groep zijn in verschillende delen van het NVL-traject gelokaliseerd, inclusief het rechter atrium, ductus venosus en het verzamelsysteem in de lever. De meeste stolsels zijn asymptomatisch en verdwijnen spontaan onder een expectatief beleid. Routinematige screening voor stolsels in pasgeborenen met navelvenelijnen wordt daarom niet geadviseerd.

Hoofdstuk 9 presenteert een vergelijking van de incidentie van trombose in pasgeborenen geboren op of na een amenorroeduur van 34 weken met navelvenelijnen, veneuze lieslijnen en diepe veneuze lijnen (de zogenaamde perifeer geplaatste centrale of 'PICC'-lijnen) geplaatst na geboorte. Trombose komt vaker voor bij pasgeborenen met lieslijnen (7.8%) dan bij pasgeborenen met navelvenelijnen (1.7%) of PICC-lijnen (1.1%). Stolsels bij pasgeborenen met lieslijnen zorgen vaker voor volledige occlusie van het bloedvat in vergelijking met stolsels bij pasgeborenen met andere typen centraal veneuze lijnen. Zorgverleners die veneuze lieslijnen gebruiken, moeten zich bewust zijn van het verhoogde risico op trombose dat geassocieerd is met dit lijntype.

In **Hoofdstuk 10** wordt de incidentie van bloedbaaninfectie in navelvenelijnen vergeleken met de incidentie in veneuze lieslijnen en PICC-lijnen. De incidentie van centrale lijn-geassocieerde bloedbaaninfectie varieert van 12.3 per 1000 lijndagen in veneuze lieslijnen tot 10.6 per 1000 lijndagen in navelvenelijnen en 5.3 per 1000 lijndagen in PICC-lijnen. Er wordt geen statistisch verschil gevonden tussen de lijntypes ($p=0.29$). In dit retrospectieve onderzoek is het voorkomen van bloedbaaninfectie geassocieerd met parenterale voeding, mannelijk geslacht en hoger geboortegewicht, terwijl antibiotische behandeling binnen 24 u na geboorte geassocieerd is met een verlaagd risico.

Tenslotte bediscussiëren we in **Hoofdstuk 11** de resultaten van onze onderzoeken en geven een overzicht van de recente literatuur over navellijnen. Gebaseerd op de conclusies van dit proefschrift worden praktische aanbevelingen gedaan en worden de perspectieven voor toekomstig onderzoek besproken. Om de juiste inbrengdiepte van navellijnen te voorspellen bevelen we het gebruik van een eenvoudige methode aan, zonder ingewikkelde lichaamsmetingen of gecombineerde berekeningen. Echter, geen

enkele methode of formule heeft bewezen de juiste inbrengdiepte betrouwbaar te kunnen voorspellen. Bovendien hebben navelvenelijnen de neiging te migreren na juiste positionering. Daarom is regelmatige evaluatie van de positie van navelvenelijnen, bij voorkeur middels echografie en beginnend tijdens of direct na plaatsing, te adviseren om complicaties van malpositie te voorkomen. Artsen die navelvenelijnen gebruiken, dienen zich bewust te zijn van de mogelijke complicaties. Echter, ondanks het risico op complicaties is katheterisatie van de navelstreng een uitstekende methode om intraveneuze toegang te verkrijgen bij zieke pasgeborenen, met name bij extreem premature geboorte of hemodynamische instabiliteit.



APPENDICES

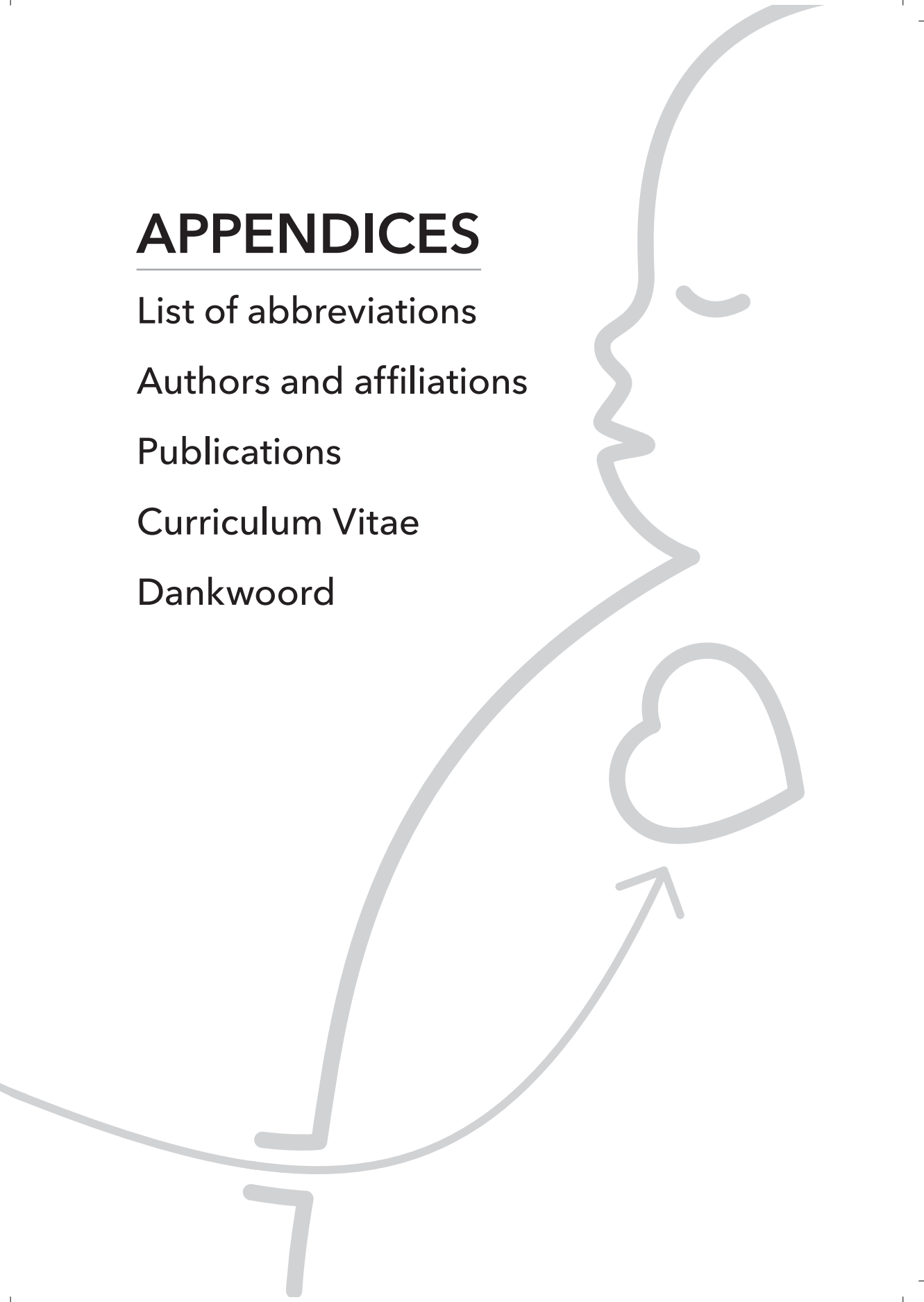
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LIST OF ABBREVIATIONS

CDC	Center of Disease Control
CHD	Congenital heart disease
CI	Confidence interval
CLABSI	Central line-associated bloodstream infection
CoNS	Coagulase-negative Staphylococci
CVC	Central venous catheter
CXR	Chest X-ray
ECG	Electrocardiogram
FVC	Femoral venous catheter
HR	Hazard ratio
IQR	Interquartile range
IVC	Inferior vena cava
IVC/RA junction	Junction between inferior vena cava and right atrium
IVH	Intraventricular hemorrhage
LMWH	Low-molecular-weight heparin
LUMC	Leiden University Medical Center
NEC	Necrotizing enterocolitis
NHSN	National Healthcare Safety Network
NICU	Neonatal intensive care unit
OR	Odds ratio
PDA	Persistent ductus arteriosus
PICC	Peripherally inserted central catheter
RA	Right atrium
RCT	Randomized controlled trial
RDS	Respiratory distress syndrome
SD	Standard deviation
SGA	Small for gestational age
S-U	Shoulder-umbilical
SVT	Supraventricular tachycardia
UAC	Umbilical artery catheter
UC	Umbilical catheterization
US	Ultrasonography
UVC	Umbilical venous catheter

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CURRICULUM VITAE

Gerdina Hermina (Gerdien) Verheij werd op 1 januari 1981 geboren te Scheveningen. In 1999 behaalde zij haar diploma voor het Voortgezet Wetenschappelijk Onderwijs op Christelijke scholengemeenschap De Driestar te Gouda. Vervolgens begon zij aan de studie geneeskunde aan de Universiteit Leiden, waarbij het propedeutisch en doctoraal examen beide cum laude werden behaald. Zowel wetenschapsstage, semiartsstage als keuzecoschap vonden plaats op de afdeling Neonatologie van het Leids Universitair Medisch Centrum (LUMC). Het artsdiploma werd in 2005 behaald, waarna zij als arts-assistent Kindergeneeskunde werkte in 't Lange Landziekenhuis in Zoetermeer en op de Neonatologie van het LUMC. Van 2008 tot 2012 specialiseerde zij zich tot kinderarts in het LUMC te Leiden (opleiders dr. R.N. Sukhai, prof.dr. H.A. Delemarre-van de Waal, prof. dr. F.J. Walther) en in het Groene Hartziekenhuis te Gouda (opleider dr. J.S. Starreveld). Aan het eind van deze periode deed zij een profileringsstage op de afdeling Neonatologie van het LUMC, waarna zij van 2012 tot 2014 achtereenvolgens in het IJsselland ziekenhuis te Capelle a/d IJssel en het Gelderse Valleiziekenhuis te Ede als waarnemend kinderarts werkte. In 2014 keerde zij terug naar het LUMC voor een fellowship Neonatologie (opleider prof.dr. E. Lopriore). Na afronding van het fellowship bleef Gerdien tot en met augustus 2018 als kinderarts-neonatoloog verbonden aan het LUMC, waarna zij in september 2018 in dezelfde functie aan de slag ging in het Haaglanden Medisch Centrum te Den Haag. Vanaf januari 2020 zal zij als kinderarts-neonatoloog in het Groene Hartziekenhuis te Gouda gaan werken.

De onderzoeken die geleid hebben tot dit proefschrift werden opgezet en uitgevoerd in de periode van 2007 tot 2019, met name in de perioden dat Gerdien werkzaam was in het LUMC.

Gerdien is in 2009 getrouwd met Hans Dubbink. Zij wonen in Gouda en hebben drie kinderen: Mart (2011), Nynke (2013) en Linde (2017).

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