INFERIOR VENA CAVA DIAMETER MEASUREMENTS FROM ULTRASOUND IN THE NORMAL AND HEALTHY TERM NEONATES WITHIN 1 WEEK OF LIFE IN HOSPITAL USM

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ABBREVIATIONS

IVC	: Inferior Vena Cava
SVC	: Superior Vena Cava
CVP	: Central Venous Pressure
HUSM	: Hospital Universiti Sains Malaysia
PDA	: Patent Ductus Arteriosus
NICU	: Neonatal Intensive Care Unit
SCN	: Special Care Nursery
CPU	: Clinician Performed Ultrasound
SBP	: Systolic Blood Pressure
DBP	: Diastolic Blood Pressure
MAP	: Mean Blood Pressure
HR	: Heart rate
BW	: Birth Weight
PPHN	: Persistent Pulmonary Hypertension of Newborn
IVC_L_B	: The biggest diameter of Inferior Vena Cava in longitudinal view
IVC_L_S	: The smallest diameter of Inferior Vena Cava in longitudinal view
IVC_C_B	: The biggest diameter of Inferior Vena Cava in cross sectional view
IVC_C_S	: The smallest diameter of Inferior Vena Cava in cross sectional view
AGA	: Appropriate to Gestational Age
SGA	: Small for Gestational Age
LGA	: Large for Gestational Age
VSD	: Ventricular Septal Defect
RA	: Right Atrium
CA	: Chronological Age
ELBW	: Extremely low birth weight

ABSTRAK

BAHASA MALAYSIA

PENGENALAN

Pengukuran diameter salur *inferior vena cava* (IVC) menggunakan ultrasound sudah biasa digunakan di dalam perawatan orang dewasa untuk menganggar isipadu darah di dalam badan menerusi konsep "*clinican performed ultrasound"* (CPU). Banyak penyelidikan di kalangan orang dewasa telah menunjukkan kebolehpercayaan dan ketepatan ukuran IVC dalam menentukan isipadu darah dalam badan. Namun demikian, untuk golongan kanak-kanak, terutamamya di kalangan bayi, penyelidikan mengenainya adalah sangat terhad. Justeru, adalah sangat penting untuk menyelidik bagi mengetahui nilai dan julat rujukan normal ukuran IVC bagi kalangan bayi.

OBJEKTIF

Bagi menghasilkan dan menentukan nilai purata diameter IVC melalui ultrasound untuk golongan bayi cukup bulan yang sihat, dan juga membandingkan perbezaan di antara nilai-nilai purata diameter yang diperolehi, bagi kumpulan bayi yang lahir dalam masa 48 jam dan yang berumur lebih daripada 48 jam.

KAEDAH

Seramai 233 orang bayi cukup bulan dan sihat telah di rekrut sepanjang tempoh 6 bulan. Data demografik, kadar denyutan jantung dan tekanan darah telah direkodkan, diikuti dengan pemeriksaan ultrasound oleh penyelidik pada bayi ketika mereka sedang tidur. Diameter IVC telah diukur pada kedua-dua fasa pernafasan inspirasi dan expirasi, dari kedua-dua sudut *longitudinal* dan sudut *cross sectional* bagi setiap bayi.

KEPUTUSAN

Secara keseluruhannya (n= 233), nilai purata diameter terbesar IVC pada sudut *longitudinal* dan *cross sectional* adalah 2.64 mm (SD 0.79) dan 2.58 mm (SD 0.74) masing-masing. Nilai purata IVC dalam 95% *CI* adalah 2.54 – 2.74 mm (sudut *longitudinal)* dan 2.49 – 2.68 mm (*cross sectional)*. Bayi dibahagikan kepada 2 kumpulan berdasarkan umur: kumpulan 1 (umur sehinggga 48 jam selepas lahir) dan kumpulan 2 (selepas 48 jam dari lahir). Pembandingan nilai purata diameter IVC di antara 2 kumpulan ini tidak menunjukkan perbezaan yang signifikan (*p*-value yang berjulat 0.6-0.95).

KESIMPULAN

Kajian ini telah menghasilkan nilai purata diameter IVC, untuk kedua-dua sudut ultrasound iaitu *longitudinal* dan *cross sectional*, bagi golongan bayi baru lahir yang cukup bulan dan sihat, sepertimana yang telah ditunjukkan dalam keputusan di atas. Ukuran diameter IVC bayi dari lahir sehinggaberumur 48 jam (Kumpulan 1) dan selepas berumur 48 jam (kumpulan 2) adalah sama dari segi bandingan dan tiada perbezaan yang signifikan.

ABSTRACT

ENGLISH

INTRODUCTION

Inferior vena cava (IVC) measurement from ultrasound has been used widely in the medical care of adults, based on the clinician performed ultrasound (CPU) concept and numerous research have shown that it is reliable in predicting the intravascular volume accurately. In paediatric age groups, especially the neonatal population, there are only few research and limited reference at present. Hence, the normal reference values of the IVC diameter measurement within the neonates are questions to be answered.

OBJECTIVE

To produce and estimate the mean diameter of the hepatic IVC from ultrasound for the otherwise normal and healthy term newborn infants in HUSM and to compare the difference of these mean diameters, in between those neonates born within 48 hours of life and after 48 hours of life.

METHODS

A sample of 233 normal and otherwise healthy term neonates from the post natal ward and nursery were recruited over period of 6 months. Demographic data, haemodynamic parameters (heart rate and non invasive blood pressure) were collected, followed by portable ultrasound assessment by the author solely, while the neonates sleeping, measuring the IVC diameter in both the inspiratory and expiratory phase, from both the cross sectional and longitudinal views.

RESULTS

As overall (n=233), the mean of the maximal diameter of the IVC among the otherwise healthy and term neonates, in both the longitudinal and cross sectional views were reported as 2.64 mm (SD 0.79) and 2.58 mm (SD 0.74), respectively. The 95 % confidence intervals for the mean maximal IVC diameters were reported as 2.54 – 2.74 mm and 2.49 – 2.68 mm for both longitudinal and cross sectional views, respectively. Samples were divided into 2 subgroups, Group 1 (within 48 hours of life) (n=140) and Group 2 (after 48 hours of life) (n=93) for further analysis. The mean IVC diameters measured in between these 2 groups showed no statistical significant difference, in both the ultrasound views and all the measured diameters, as reflected by *p*-value from 0.6-0.95.

CONCLUSION

This study had produced and estimated the mean diameter of IVC, in both longitudinal and cross sectional views for healthy term neonates in HUSM, as illustrated in the results above. Both the mean diameters of the IVC, regardless of the ultrasound views, between Group 1 and Group 2 were comparable to each other with no statistical significance difference.

CHAPTER 1: INTRODUCTION

1.1 Background

In the era of modern medicine, rapid advances in technology of ultrasound or sonography have made this method to be increasingly used in medical care. At present, the machine is not only smaller and compact but also portable. They include not only 2D images, but also with other complex functions like M-Mode, colour Doppler, pulse or continuous Doppler flow and sometimes tissue Doppler, making it functionally robust. This investigation is also relatively cost-effective. Traditionally, the use of ultrasound was limited to the radiologists in aiding the clinicians in investigating or establishing certain diagnosis or monitoring of pathology. However, due to the wide availability and convenience of portable ultrasound nowadays, the use of ultrasound has been expanded beyond the Radiology department, as more clinicians are willing to learn to acquire the techniques. By incorporating portable ultrasound into their daily routines, clinicians could obtain immediate physiological information at the bedside that can be integrated into their decision making. In most developed countries, intensivists in both the adult and paediatric intensive care units, accident and emergency physicians, as well as the anaesthetists have been utilising portable ultrasound in their work, giving rise to the term **Clinician Performed Ultrasound (CPU**) (Kluckow, 2014).

In this introduction, literature review regarding the practice of CPU in neonatology, as well as the reasoning behind the exploration of Inferior Vena Cava (IVC) diameter measurement via ultrasound in neonates is presented. The importance of accurate fluid assessment within neonates, as well as the relationship of intravascular volume to the IVC dynamics is discussed. The complex physiological transition period in neonates following birth and the postulated hypothesis of associated sequential changes in IVC diameter will also be discussed. Lastly, the comparison of the relevant researches in adult populations, as well as the existing literature review from paediatric population, with regards to the use of IVC measurement as volume and hemodynamic assessment is included.

1.2 The Practice of Clinician Performed Ultrasound (CPU) in Neonatology

In neonatology, CPU assessment of the sick neonate in Neonatal Intensive Care Unit (NICU) has been used in most of the developed countries to address many of the common dilemmas the neonatologists face in their clinical care. Understandably, this increasing use and popularity of CPU among the neonatologists is obvious, as neonate care is delicate and often there are limitations and difficulties in obtaining invasive hemodynamic data from these small and ill infants. With the growing knowledge regarding circulatory transition at birth being a period of rapid change with potential vulnerability, accurate assessment of the hemodynamic of neonates is crucial (Kluckow, 2014).

Among the few examples of CPU that are described in the neonatal care includes the following (Kluckow, 2014; Kluckow *et al.*, 2007):

1. To assess the cardiovascular status

   Sick newborns, especially the vulnerable extremely low birth weight (ELBW) neonates are very prone to low systemic blood flow and its subsequent complications of organ hypoperfusion. Conventional monitoring of systemic blood pressure and capillary refill is inadequate to reflect the adequacy of distant tissue circulation and oxygen delivery. CPU of the heart enables direct visualization of the contractility of ventricular wall movement, as well as semiquantitative assessment of measurements such as ejection/shortening fraction or more precise measurement such as ventricular wall/valve annulus movements by tissue Doppler imaging (Kluckow, 2014; Nestaas *et al.*, 2011) . Besides, cardiac CPU also helps in quantifying the superior vena cava (SVC) flow, which is a shunt independent measure of systemic flow, measuring blood returning to the heart from the brain and upper body. Low ventricular outputs and low SVC flow have been correlated with adverse outcomes in the ELBW infant including intraventricular haemorrhage and long-term neurodevelopmental disability (Hunt *et al.*, 2004; Kluckow and Evans, 2000b).

2. To diagnose and monitor the premature neonates with patent ductus acteriosus (PDA)

   At present, there are 2 different schools of thought and contradicting views regarding the management of PDA, as some may view PDA merely as an innocent physiological bystander (Benitz, 2010), while the others advocate aggressive medical treatment and maintain ductal ligation rates of 25–30% of the ELBW population (Jhaveri *et al.*, 2010). Cardiac CPU allows serial assessment of PDA significance at multiple time points without mobilizing the small and unstable baby to the echocardiographic room and helps in further understanding of physiological effect of PDA, enabling the clinician to identify subgroups of infants who are most likely to benefit from targeted treatment without increasing harm (McNamara and Sehgal, 2007; Sehgal and McNamara, 2012). This could be done by measuring the physical size of PDA, shunt volume, flow pattern, effects on surrounding organ blood flow (diastolic steal from the cerebral or intestinal vascular beds), evidence of increased pulmonary blood flow and evidence of cardiac dilation (increased left atrial: aortic ratio or increased LV end-diastolic diameter) or increased left ventricular output (Su *et al.*, 1997). In those neonates with PDA who have been treated with NSAIDS (ibuprofen/indomethacin), cardiac CPU could help monitoring of the response towards treatment and identify cessation of treatment once ductal closure is achieved and hence reducing the unnecessary exposure to NSAIDS (Carmo *et al.*, 2009).

3. To assess sick asphyxiated neonates

   Cardiovascular dysfunction following hypoxic ischemic insults is associated with decreased tissue perfusion and acidosis. Early CPU enables the assessment of both the contractility and cardiac filling accurately. The needs for inotropes or vasopressors and the effect of improvement could be visualized form ultrasound. With CPU there is better assessment of filling status avoiding excessive use of fluid hence preventing volume overload. Filling is assessed either by observing the residual volume in diastole of the left and right ventricles qualitatively by measuring the end-diastolic diameter or evaluation of the filling of the systemic vein, i.e. the IVC, by direct visualisation within the liver, observing for distensibility compressibility or shape—ellipsoid versus round (Sato *et al.*, 2013).

4. In managing sick neonates with sepsis with rapid deterioration to septic shock

   Neonates with septic shock often have relatively high cardiac output with low systemic vascular resistance. Early CPU showing "empty heart" and collapsed systemic veins helps guide the need for repeated volume replacement, as well as the need for vasopressors support. Early response to fluid boluses as assessed from the ultrasound of the heart and IVC helps to predict the neonatal outcome (De Waal and Evans, 2010).

5. In assessing the central line placements

   Umbilical catheters or peripherally inserted central catheters (PICC) are common invasive lines inserted in sick neonates to assist in multiple blood takings, blood pressure monitoring, infusions of parenteral nutrition or medications. Conventional method of radiograph may expose the neonates to radiation, especially when the central line needs readjustment and repeated images. Ultrasound is also used to aid in insertion of central line, for example in cannulating the internal jugular veins.

Globally, the implementation of CPU, or some name it as Point-of-Care ultrasound in NICU has been looked into recently. Developed countries like Australia, New Zealand, France, Spain, United Kingdom, Canada, as well as the United States have been showing variation in their national implementation of CPU as some are met with resistance. The CPU concept is indeed useful but the barriers to it are owing to the concerns from the consultative specialties that traditionally use ultrasound (paediatric cardiologist), relating to the risk of misdiagnosis but also involving different clinical needs, liability concerns and lack of outcome-based evidence. Hence, safe CPU depends on the close collaboration from the consultative specialties and there is a need to develop more training and accreditation structures for the neonatologists, as well as the medical officers using portable ultrasound. (Evans *et al.*, 2011)

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1.3 The Importance of Hemodynamic Assessment in Neonates

Fluid management in the neonates has always been a great challenge not only for the paediatric medical officers or trainee attending sick neonates but also for the neonatologists. In NICU, apart from ventilatory support, many neonates are sick with certain extent of cardiovascular compromise. Throughout the last few decades, neonatology has been exciting with leap and bound of advances and significant progresses being made, especially in improving the survival of the ELBWs. Most of the increased survivals are attributed to the improvement in particular to the advent of surfactant replacement with better ventilation techniques and strategies, adequate thermal control with incubator care and humidified system, strict infection control and antibiotics policy, early enteral feeding with expressed breast milk and parenteral nutritional support and the improved skills from training of the clinical staff attending to these babies. Another important factor that should not be neglected and needs to be explored, if further improvement of neonatal care service is desired, would be the judicious use of intravenous fluid and accurate assessment of hemodynamic in the neonates, especially relating to the premature babies.

Contrary to the older children or adults, accurate fluid management for neonates is more difficult but yet more important. Physiologically, the proportion of total body water in neonates is higher than the rest of the age group and as much as 70% to 80 % of their body content is contributed by water alone ***(****Gomella 2013****).*** The relatively large in body surface areas to body weight ratios and the increased in the insensible loss due to immature skin barrier results in underestimation of the fluid loss. The fact neonates' body content is primarily comprised of water, suggests that they need an adequate water volume to maintain and facilitate their normal physiological homeostasis and body functions. In other words, neonates, they are at a higher risk of developing complications from hypovolemia or dehydration; whilst the condition of excessive fluid or hypervolemia is also detrimental, especially to the premature ones.

From clinical experiences and research, the presence of patent ductus arteriosus (PDA) in the premature babies is highly associated with increased morbidity and mortality (De Buyst *et al.*, 2012;

Jaleel and Rosenfeld, 2013; Schneider, 2012). Physiologically, the ductus arteriosus (DA) usually starts to close as soon as after the birth but it may remain persistently patent; or it could be reopened, mostly as a result of fluid overload. It is known that the event of re-opening or persistence of the ductus arteriosus (DA) results in other deleterious complications such as pulmonary haemorrhage, intraventricular haemorrhage, necrotising enterocolitis, kidney injury, congestive heart failure and bronchopulmonary dysplasia (Evans and Kluckow, 1996; Jaleel and Rosenfeld, 2013; Kluckow and Evans, 2000a; Rakza *et al.*, 2007). The pathophysiology and proposed mechanisms include increased pulmonary blood flow and decreased systemic artery pressure and peripheral organ perfusion. At present, numerous randomized controlled clinical trials had been made to explore more effective ways to manage PDA, as well as prophylactically close it, to prevent any of the complications mentioned above (Benitz, 2010; Lin *et al.*, 2010; Oncel *et al.*, 2014; Sosenko *et al.*, 2012). This global trend has signified the burden of problem of PDA in taking care of the ill neonates, especially the premature ones.

Hence, it is very important to avoid hypervolemia due to inadvertently administered fluids within the neonates to avoid the persistence or re-opening of the functionally closed ductus. Other factors like birth asphyxia, feto-maternal haemorrhage, neonatal sepsis or congenital pneumonia have also been believed to be the culprits leading to symptomatic PDA (Benitz, 2010). To address the issue of fluid overload causing symptomatic PDA, some researchers have even gone to the extent of fluid restriction, in order to prevent symptomatic PDA, quoting a meta-analysis (Bell and Acarregui, 2008), which showed analysis of the five randomized controlled trials taken together indicating restricted water intake significantly increases postnatal weight loss and significantly reduces the risks of patent ductus arteriosus and necrotizing enterocolitis. With restricted water intake, there are trends toward increased risk of dehydration and reduced risks of bronchopulmonary dysplasia, intracranial haemorrhage, and death, but these trends are not statistically significant. Optionally, rather than fluid restriction, it would be better to accurately assess fluid with some other mean, i.e: ultrasound measurements of the IVC diameters.

1.4 The Literature Review on The Use of IVC Measurement From Ultrasound In Assessing The Hemodynamic Status

Hemodynamic assessment reflects the adequacy of systemic circulation and oxygen delivery to the distant tissue, the degree of venous filling into the heart and its contractility. By definition, an adequate cardiac output is determined by the amount of blood returning to the heart (preload), the strength of myocardial contractility and the resistance which the heart must pump against (afterload). Therefore, it is important to determine the preload correctly while choosing the treatment strategies for dealing with cardiovascular compromise in neonates (Sato *et al.*, 2013).

In general, there are a few possible methods of assessing the preload or the intravascular volume status. Clinicians could primarily assess the hemodynamic status from physical examinations findings of shock and tissue hypoperfusion and the changes from vital signs changes, i.e. the heart rate, blood pressure and urine output. Besides, monitoring of the biochemical markers of metabolism i.e. serum lactate, blood gases could also give some ideas regarding the adequacy of circulation at the tissue level. Lastly, by measuring the central venous pressure readings and this have been used in most of the intensive care physicians worldwide. During the older days, and in fact in some of the countries still, particularly in the adult intensive care, central venous pressure (CVP) monitoring is often the most common method of intravascular volume assessment and is presumed as the "gold standard" to assess the preload in ill patients. The placement of a pressure transducer within the right atrium helps to reflect the cardiac filling pressure and the intravascular volume status. This procedure, though accurate is invasive and require good training and skill prior, as failure to appropriately insert a central venous catheter especially in ill patients may itself causes complications like pneumothorax, bleeding and shock.

More recently, researchers have gone extra miles in their effort to find a non invasive way of assessing the hemodynamic status, i.e. utilizing the bioreactance and bioimpedance physics principles. Bioimpedance measurements detect electrical changes occurring with altering fluid levels in the thorax.

Levels change as the left ventricular contracts and blood flows into the thoracic aorta. This causes a corresponding change in resistance within the thorax because the fluid level in the aorta increases. This change in impedance can be measured as a change in voltage passing between electrodes placed on a patient's chest. Bioimpedance measures the amplitude of the voltage change across the thorax. Bioreactance, by contrast, tracks the phase of the electrical currents traversing the chest. The underlying scientific phenomenon is that the higher the cardiac stroke volume, the more significant these phase shifts become. These are non-invasive technologies that measure cardiac output, and other hemodynamic variables such as stroke volume and cardiac index, example is the non-invasive cardiac output monitoring (Cheetah NICOM). The use of this relatively new technology is rather limited and mainly confined to certain centers due to the cost incurred and it is yet to be established in neonates.

Relating back to the topic of research, IVC measurement through portable ultrasound appears to be a rather non invasive, convenient and yet reliable option. The CPU method of direct visualization and measurement of the hepatic part of the IVC has gained popularity in the medical practice recently. Numerous research, especially within the adults had been conducted over years with regards the use of IVC measurement through ultrasound in determining the hemodynamic, particularly in those who are critically ill. The results from all these research thus far have been positive and promising.

The complex physics of fluid dynamics, in relation to the flow, volume and pressure may be slightly confusing to some minds. However, as a basic concept, the preload of the heart is determined by the filling pressure into right atrium. The immediate vessels before all the venous blood is returned into the right atrium are both the SVC and IVC. The amount of blood that return into the heart, or the preload, is contributed most by IVC , as the venous blood from lower limbs, trunks, extremities and other intra-abdominal organs like kidneys and liver are returned via this route, whereas only circulation from the head and neck area is returned via the SVC route. Hence, IVC being one of the most compliant vessels within the body determines the venous capacitance of the body; the diameter of it correlates with and reflects the intravascular volume to the closest. During the expansion of intravascular volume or

hypervolemia, the diameter of the IVC increases accordingly to accommodate the changes that occur within the system. Vice versa, during the period of hypovolemia or dehydration, the IVC diameter reduces. During the state of dehydration or hypovolemia, physiological neurohormonal mechanism tends to conserve blood flow towards the brain (head and neck) due to cerebral blood flow autoregulation mechanism, meanwhile diverting and reducing the blood flow from the intra abdominal organs via vasoconstriction. Hence, comparatively the blood flow of SVC is more constant, making IVC diameter ideal to monitor intravascular volume change.

Due to the intrinsic compliance of the hepatic part of IVC, it is sensitive to changes of external pressure i.e. the intra-abdominal and intra-thoracic pressure. Physiological variation occurs in relation to changes in respiration, as well as during cardiac cycles. In Inspiration, there is sudden increase in the negative intra-thoracic pressure that promotes the right atrial filling from both SVC and IVC, with the concomitant rise in the intra-abdominal pressure due to the contraction of diaphragm, leading to the reduction of IVC diameter. In expiration, the reverse occurs and the positive intra-thoracic pressure with the concomitant reduction of intra-abdominal pressure as the diaphragm and abdominal rectus muscles relax results in the increase in IVC diameter. The changes that happen in IVC relating to the cardiac cycle are often difficult to detect via ultrasound as the heart rate is often too fast and the changes are not discernible. The IVC collapsibility index reflects the degree or percentage of IVC collapse during respiratory cycle. It is usually defined as mathematic equation of:

$$[\ (\text{Largest diameter} - \text{Smallest diameter}\ ) \div \text{Largest diameter}\ ] \times 100\%.$$

The degree of IVC collapsibility indirectly indicates the volume filling of the cardiovascular system, as well as reflecting the fluid responsiveness in clinical practice. Its use has been explored mainly by adult medicines, particular in critical care. The related literatures, explanation, as well as its significance would be discussed further.

Meta-analysis in adults has shown there is moderate level of evidence that suggests low IVC diameter is consistent with hypovolemic state and the subsequent return to euvolemic status following fluid replacement is followed immediately by the increase in the diameter (Dipti *et al.*, 2012).

Quoting further, the following studies have shown that the IVC diameter, as well as the IVC collapsibility index correlates significantly with the CVP readings and they are reliable in estimating the preload or the intravascular fluid status in the adults (Barbier *et al.*, 2004a; Brennan *et al.*, 2006; Feissel *et al.*, 2004; Kircher *et al.*, 1990; Lee *et al.*, 2014; Lyon *et al.*, 2005; Moreno *et al.*, 1984; Stawicki *et al.*, 2009; Yung and Butt, 1995; Zhang *et al.*, 2014). Most of these were studies were conducted by the anaesthetists, intensivists and the emergency physicians, signifying the importance of its use in managing critically ill patients. For instance, from the Critical Ultrasound Journal, the mean diameter of IVC in normal adults was quoted as 13.8mm with 95% CI 8.41 to 19.2mm with the mean respiratory collapse of 34.8%. (Blehar *et al.*, 2012). However, these reference in adults do vary from studies, as others had reported IVC diameter as 17.5 mm with SD 1.6 (Zhang *et al.*, 2014), and the collapsibility index of > 50% correlate with CVP < 8mmHg in dehydrated patients (Nagdev *et al.*, 2010).

In the paediatric age, relating to older children, the use of ultrasound measurement of IVC is useful in dealing with End Stage Kidney Disease (ESKD) children who require regular haemodialysis. The difficulty to ascertain and estimate accurately the dry weight for these children due to their continuous growth in body mass have resulted them at higher risk of developing both hypovolemia and hypervolemia post dialysis. Apart from body weight, the IVC diameter has been used reliably to assess the intravascular volume pre and post dialysis. It is expressed as the unit of cm/m2. One of the studies in the Nephrology Dialysis Transplant had shown that both IVC diameter and the collapsibility index showed significant differences for these children pre and post dialysis treatment. The mean IVC diameter post dialysis was quoted as 0.75 ± 0.26 cm/m2. (Krause *et al.*, 2001). Meanwhile, in the Emergency Department (ED), ED physicians had also innovated another sonographic parameter, the "IVC/aorta (Ao)

diameter (IVC/Ao) index," that was found to be correlating with the intravascular volume among children (Kosiak *et al.*, 2008). The limitations of using IVC measurements in paediatric patients, however, are the inherent variations with the body surface area (BSA), the dynamic change associated with respiration cycles, as well as the lack of reference, especially in the paediatric population (Krause *et al.*, 2001).

Relating to neonates, there is minimal research about IVC measurement via ultrasound. Up to present, there is only one published study in Japan by (Sato *et al.*, 2013) that had reported that subcostal cross sectional view of the IVC diameter correlates significantly with the measurement of CVP. It had also demonstrated that both the gestational age and the body weight correlate positively and strongly with the IVC diameter measured from ultrasound. The difference of diameter during respiration (smallest diameter/largest diameter ratio) is much less affected by the gestational age and birth weight but it correlates with the CVP strongly in the mechanically ventilated infants (Sato *et al.*, 2013). To explain further, this study had studied a number of 57 infants, recruiting those neonates from as early as 27 weeks up to 38 weeks of gestation age, with a spectrum of birth weight ranging from 1077 gram till 3582 gram. All these measurements of IVC diameter were taken by the author after 5 days of life. Out of the 57 infants selected, there were 14 neonates who were ventilated. Due to the presence of confounding factors like birth weight and gestational age that may affect the IVC diameter measurement, the derivation of normal references for IVC diameter from this study is not possible.

1.5 The Reasoning Behind The Use of Ultrasound Measurement of IVC As An Adjunct in Hemodynamic Assessment in The Neonates

In neonatal medicine, the continuous monitoring of CVP via a catheter is rarely practiced, except at the most specialized neonatal cardiac centres, due to its invasiveness, and the needs of specialized and delicate equipments, as well as the associated technical difficulties and risks. Conventionally, most neonatologists have relied upon clinical indicators of cardiovascular function such as heart rate, capillary refill time, blood pressure, skin turgor, mucous membrane, urinary output, the presence of acidosis, and the body weight to assess the adequacy of systemic blood volume and distant tissue oxygen delivery in sick neonates. However, these clinical parameters have their inherent shortcomings, for instance, the heart rate could be tachycardia in a newborn with pain or discomfort, hyperthermia, and due to medication such as aminophylline toxicity; urine output and the body weight could also be erroneous due to the difficulty in monitoring among the small and premature infants.

With recent introduction and recognition of CPU concept in NICU, ultrasound has become an important adjunct in the management of sick neonates, especially in assessing the intravascular volume status or hemodynamic of the neonates. Advantages of ultrasound are obvious as it is non invasive and devoid of exposure to radiation, applicable for serial assessment and monitoring in the neonates safely without causing much concern to the healthcare providers and to the parents. Due to smaller physical size of the neonates and the relatively more superficial organs and vessels, it provides better echo window in neonates. Rather than doing complicated measurement of end diastolic volume of right ventricle to determine the cardiac filling or intravascular volume in neonates, another easier way for clinicians is to by looking at the IVC diameter that lies just behind the liver (hepatic part of the IVC). It is easily visualized, after enhanced by overlying liver which serves as a good echo window. Even for critically ill nenonates who are ventilated with hyperinflation, the hepatic IVC still visible via ultrasound as it is assessed form the subxiphoid region, i.e. at the epigastric region.

1.6 The Physiological Transition from Foetal Circulation to Adult Circulation

Neonates, being a unique group of physical beings, have to undergo a series of complex yet important transitional processes soon after their birth, in order to successfully adapt to their postnatal life. This physiological transition involves all their body systems and in particular, the cardiovascular system, where the most apparent changes.

During foetal life, the cardiovascular system is distinctly different from the adult circulation. In-utero, the placenta functions as the main organ in gas exchanges, transportation of nutrients and excretion of waste products. Venous blood circulated through the placenta is enriched with oxygen and nutrients, and is returned to the right heart. From the right atrium, it crosses the patent foramen ovale to the left atrium and is then ejected into the systemic circulation, supplying distant organs. In foetal life, the systemic pressure is low due to the presence of the low-vascular resistance placenta. Blood flows with ease through placenta vascular beds where both maternal and foetal blood interfaces through thin layers of specialized cells. The pulmonary circulation, on the other hands has high pulmonary vascular flow resistance as the arterioles are mainly vasoconstricted. Through PDA, the oxygenated blood from pulmonary artery is shunted into the systemic circulation, bypassing the lungs that are quiescent in foetal life, making the right heart functionally the dominant ventricle in-utero. Presence of patent ductus venosum makes the liver quiescent at foetal life as most of the body metabolism is being handled by the mother's liver.

Post-natal circulation changes start as soon as placenta separation and the initiation of baby's first breath. The sudden loss of placental circulation, as low pressure reservoir, leads to an immediate increase within the systemic circulation. The normal process of vaginal delivery process, which involves the compression of the rib's cage as the baby moves along the birth canal, squeezes out most of the alveolar sac fluids. Following birth and the baby's first cry, the high negative intra-pleural pressure abruptly opens most of the initially collapsed alveoli, bringing in more oxygenated gases into the alveolar tissue and

promoting further vasodilation of the pulmonary arterioles. These occur within seconds and the drop of pulmonary pressure is the greatest immediately after birth. It continues gradually for approximately 2-3 months to complete. Post-natally, the lungs become the main organ that exchange gases, removing carbon dioxide from the venous blood and replenishing oxygen from the alveoli into the arterial blood. The increase of pulmonary venous return into the left atrium makes the left heart pressure rises and flips the foramen ovale towards the right side and closes the shunt in between the both atria.

Functional closure of the ductus arteriosus starts within 8-12 hours of birth, facilitated by the sudden increase in blood oxygen and acute reduction of local prostaglandin production. This is followed by the anatomical closure that involves fibrosis of the duct that usually starts after 7 to 10 days of life, which would eventually resulting ligamentum arteriosus. With the closure of PDA, there is no direct communication between both the systemic and venous circulation, and thus no unrestricted shunting of blood from the systemic to venous circulation.

1.7 The Postulation of Changes in The IVC Diameter In Relation To Circulatory Transition

With the understanding that the transition of foetal circulation to adult circulation occurs immediately following birth, by the first 48 hours of life, most neonates should have their foetal shunt or the PDA functionally closed. The persistence of DA, however, would theoretically causes continuous diastolic shunting or stealing of the systemic blood into the pulmonary circulation, causing the presumptive increase in pulmonary blood flow, which would affect the right heart and alter the IVC diameter. At the same time, the closure of ductus venosum that happens after birth causes an increase of the portal blood flow perfusing the liver and exiting to the hepatic vein confluence before draining into the IVC. This process by itself, may also affect the IVC diameter.

The author had postulated that there is possible difference in between the IVC diameter and its collapsibility index, in those newborns within 48 hours of life, compared to after 48 hours of life. The reason of comparing these 2 groups at the threshold of 48 hours is due to the postulation that functional closure of PDA occurs usually by 48 hours of life after birth. The IVC diameter within 48 hours of life is postulated to be relatively smaller, as compared to those after 48 hours of life, on the basis that neonates within 48 hours of life have more of their systemic blood volume is shunted through the PDA into the pulmonary circulation, leading to increment in pulmonary blood flow and reduction of systemic perfusion.

1.8 The Rationale of The Study

The rationale of this study is to explore a less invasive and the same time, more convenient way of assessing the intravascular volume/ "the preload" in neonates accurately other than central venous pressure (CVP) measuring, using portable ultrasound with the measurements of the hepatic inferior vena cava (IVC) as well as the collapsibility, by a non-radiologist/cardiologist person, via the Clinician Performed Ultrasound (CPU) concept. Apart from deriving the mean reference values for IVC diameter among the normal and healthy term neonates, this study also intends to compare both mean values of IVC diameter within 48 hours and after 48 hours of life.

There have been lots of studies using IVC measurement from ultrasound and its collapsibility to determine intravascular volume status in the adult population. However, so far, there is only one study published with regards of IVC diameter in the neonates that shows the significant correlation of IVC diameter with CVP readings (Sato *et al.*, 2013). There is no published data relating to the normal reference values for IVC measurement from ultrasound for the neonatal age group. Extrapolating the reference values from adults or older children population is not accurate and potentially hazardous. The presence of normal reference values is important for clinical use in identifying the critically ill or volume depleted neonates.

Presently, the mean IVC diameter and its associated parameter like the collapsibility index have remained unknown for the neonatal population, due to the limiting research despite the increasing use and development of CPU concepts in the NICU worldwide.

CHAPTER 2: OBJECTIVES

2.1 GENERAL OBJECTIVE

To produce reference values for the mean diameter of inferior vena cava (IVC) among the normal and healthy term newborns in HUSM.

2.2 SPECIFIC OBJECTIVES

1. To estimate the mean values of the hepatic inferior vena cava (IVC) diameter measurement for normal and healthy term newborn infants in HUSM, within 48 hours of life

2. To estimate the mean values of the hepatic inferior vena cava (IVC) diameter measurement for normal and healthy term newborn infants in HUSM, after 48 hours of life

3. To compare the difference of the mean diameter of IVC of normal and healthy term newborns between those within 48 hours with another group that is after 48 hours of life

2.3 RESEARCH HYPOTHESIS

There is statistical significant difference between the means of IVC diameter of those within 48 hours and after 48 hours of life

CHAPTER 3: METHODS

3.1. Study Design

- Study type: Observational
- Study design: Cross Sectional

3.2. Study Settings

- Hospital Universiti Sains Malaysia (HUSM) in Kubang Kerian, Kelantan.
- Duration: 6 months for samples collection from December 2014 till May 2015
- Location: Post-natal ward (***2 Topaz***) and Special Care Nursery (***1 Timur Belakang***)

This was an observational study with cross sectional design. It was conducted in a university hospital in Kubang Kerian, Kelantan, namely Hospital Universiti Sains Malaysia (HUSM). HUSM is one of the tertiary hospitals in the Kelantan with high number of deliveries and is equipped with both the specialty of Obstetrics and Gynaecology and Paediatrics, with the subspeciality of neonatology as well.

3.3. Study Population

- Reference Population :
  - Healthy term newborns in Malaysia
- Source Population :
  - Healthy term newborns in Kelantan state
- Sampling Frame:
  - All hospitals in Kelantan state:
  - Tertiary Hospital: Hospital USM, Hospital Raja Perempuan Zainab II (HRPZ II), Kota Bahru, etc
  - District Hospital : Hospital Tanah Merah, Hospital Pasir Puteh, etc
- Study Samples:
  - All newborns who are born in Hospital USM, Kubang Kerian
- Study Subjects:
  - Healthy term newborns in HUSM consented by the parents/ guardians

This study involved the author as the main researcher who had collected the data for analysis. The data was collected for a period of 6 months, recruiting samples from the healthy and term babies who were born or admitted in HUSM, of whom their parents had consented for participation. These babies were selected from either the postnatal ward or the special care nursery.

3.4. Sample Size Estimation and Calculation

- Specific Objective 1
  - To estimate the mean values of the hepatic inferior vena cava (IVC) diameter for the normal and healthy term newborn in HUSM, within 48 hours of life

    Sample Size calculation (For Single Mean)
  - $N = (Z\ \sigma/\ \Delta)2$

    σ = population standard deviation

    Δ = the estimated difference from population mean
  - **$N = = (1.96\ X\ 1\ /0.2)^2 = 96$ babies**
  - Applying the concept of effect size, to choose the smallest difference that would be of clinical or biological significance, $\Delta = 0.2$
  - $\sigma = 1$ (derived via expert opinion, no references before)

- Specific Objective 2
  - To estimate mean values of the hepatic inferior vena cava (IVC) diameter for normal and healthy term newborns in HUSM, after 48 hours of life

    Sample Size calculation (For Single Mean)
  - $N = (Z\ \sigma/\ \Delta)^2$

    σ = population standard deviation

    Δ = the estimated difference / precision from population mean
  - **$N = (1.96\ X\ 1\ /0.2)^2 = 96$ babies**
  - Applying the concept of effect size, to choose the smallest difference that would be of clinical or biological significance, $\Delta = 0.2$
  - $\sigma = 1$ (derived via expert opinion, no references before)

- Total Sample Sizes = Sample Sizes for Specific Objective 1 + Specific Objectives 2

  Total Sample Sizes = 96 + 96 = 192 (≈200 samples)

- Specific Objectives 3
  - To compare the means difference between IVC diameters of newborns within 48 hours and after 48 hours of life
  - <u>Sample Calculation (For Comparing 2 means)</u>
  - $N = 2\sigma^2 / \Delta^2 (Z_\alpha + Z_\beta)^2$

    Δ= standard deviation of either group

    σ= expected detectable difference between two groups
  - $Z_\alpha = 1.96$ for $\alpha = 0.05$ (two-tailed)
  - $Z_\beta = 0.84$ for 80% power
  - **$N = 2 \times 1^2 / 1^2 \ (1.96 + 0.84)^2$ = 16 babies per group (Total 32 babies)**
  - Again, applying the concept of effect size, Δ represent the smallest difference that would be of clinical or biological significance, thus $\Delta = 1$

3.5. Sampling Method

All the samples were selected based on non- probability sampling method**.** In other words, convenience and availability sampling was applied in recruiting babies for this study. This was due to the limitation of time and duration of the study and hence, each person in the population had a slightly greater, but unknown chance of being included.

3.6. Study Subjects

The samples comprised of only the term healthy newborns, fulfilling both the inclusion and exclusion criteria. Babies who were detected to have incidental findings of congenital abnormalities from the bedside ultrasound assessment were dropped from the samples. These babies were then referred to the appropriate specialties for further investigation and management. Their parents were informed and explained regarding the incidental findings briefly.

3.6.1. Inclusion criteria

i. Term newborns

ii. Healthy and well babies

iii. Appropriate for gestational age (AGA)

3.6.2. Exclusion criteria

i. Gestational age less than 37 completed weeks or more than 42 weeks.

ii. Birth Weight is less than 2.5kg or more than 4kg

iii. Neonates with significant weight loss, more than 10 % of body weight

iv. Neonates who are unwell (Please see definitions)

v. Neonates with congenital anomalies (Please see definitions)

vi. Small for gestational age (SGA) or Large for gestational age (LGA) (Please see definitions)

3.6.3.Definitions

- Neonates that are unwell

  i. Who have poor APGAR score (APGAR < 6 in one minute and < 7 in 5 minutes)

  ii. Require neonatal resuscitation at birth (ie: oxygen/positive pressure ventilation)

  iii. Require intravenous fluid boluses or fluid maintenance

  iv. Require dextrose boluses for hypoglycemia

  v. Require oxygen supplementation,

  vi. Require intubation or ventilation

  vii. Who are unable to feed orally and require ryle's tube feeding

  viii. Who appear to be cyanose (SpO2 < 96% on room air)

  ix. Who appear to be in respiratory distress

  x. Who appear to be syndromic/dysmophic baby

  xi. Whose Blood Pressure falls outside the normotensive range *

  xii. Whose Heart rate falls outside the normal range *

- Neonatal references for normal range of resting heart rate & blood pressure

  - Resting heart rate : 90-160/min
  - Systolic blood pressure (SBP) : 65-90 mmHg
  - Diastolic blood pressure (DBP) : 26-55 mmHg

  Adapted from Robert M. Kliegman, et al, editors, Nelson Textbook of Paediatric, 19th edition (Philadephia: Saunders Elsevier, 2011), Page 1532-1534

- Neonates with congenital anomalies

- Cardiovascular System: Any form of congenital heart defects, cyanotic and acyanotic, i.e. ventricular septal defect, tetrallogy of Fallot etc

- Neurological System: Neural tube defects, brain malformations, congenital hydrocephalus, craniosynotosis, congenital brain infection, spinal muscular atrophy, etc.

- Gastrointestinal System: Omphalocoele, gastrochisis, oesophageal atresia, duodenal atresia, ileal atresia, hirschprung disease, imperforate anus, etc

- Genitourinary systems and kidneys: Caudal regression syndrome, Prune Belly Syndrome, hydronephrosis/ hydroureter, multicystic dysplastic kidney, single kidney, etc

- Respiratory System: Congenital cystic adenomatoid malformation (CCAM), congenital emphysema, congenital diaphragmatic hernia, etc

- Orthopaedic problems: Arthrogryposis multiplex congenita, fixed congenital talipes equinovarus, development dysplasia of the hip (DDH), skeletal dysplasia,

- Congenital infections , Teratogenic malformation, maternal substance abuse, TORCHES infection, foetal alcohol syndrome, etc

- Chromosomal aneuploidy or genetic disorders : Any recognized or unrecognized dysmorphism , i.e. Down Syndrome, Patau Syndrome, Edward Syndrome, Single gene or polygenic defects, ie: Cri-du chat, Di George syndrome, Prader Willi Syndrome etc