UNIVERSITY OF TWENTE.

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Ultrasound volume sensor for intravascular volume status

Clinical and technological feasibility

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Master thesis
February 7, 2020

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"If we knew what it was we were doing, it would not be called research, would it?"

Albert Einstein

Abstract

Ultrasound volume sensor for intravascular volume status
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by Nynke Wijbenga

Accurate assessment of intravascular volume status remains one of the most challenging task for clinicians. Promising techniques for monitoring intravascular volume status consist of ultrasound assessment of the indexed inferior vena cava, inferior vena cava collapsibility index, and vena jugularis interna (IJV). Ultrasound assessment of the IJV is a promising, non-invasive technique for monitoring the volume status and can be repeated as often as necessary. This technique could be used to monitor a patient's volume status in the intensive care unit, during haemodialysis or major surgery. However, the results of ultrasound assessment are highly user dependent. An ultrasound sensor, such as the SENS-U Bladder Sensor (SENS-U), could offer support in the non-invasive assessment of intravascular volume status. The aim of this study was to explore the clinical and technological feasibility of the ultrasound volume sensor to determine the intravascular volume status by measuring the IJV.

Three proof of principle studies were performed. First a phantom study was conducted to explore the axial resolution of the SENS-U. Second, IJV diameter measurements were conducted on 8 healthy volunteers to further investigate the technological and clinical feasibility. Lastly, a proof of concept study was conducted during surgery to reinforce the choice of using the IJV diameter. The phantom study and the IJV measurements on healthy volunteers showed that the axial resolution needs to be improved for this application by increasing the ultrasound frequency of the SENS-U. Furthermore, the SENS-U needs to be adhered to prevent shifting during the measurements and the size of the device needs to be decreased for correct placement in the neck area. The proof of concept study provided more insights for further research and design requirements for a SENS-U to measure IJV diameters.

Based on the studies, recommendations were made for the development of an ultrasound volume sensor for the assessment of intravascular volume status, including recommendations for the design of a new device, improvement of axial and temporal resolution, and the required amount of piezoelectric crystals for the transducer. Further research could obtain more insight in the change of IJV diameter during fluid shifts.

Preface

Geachte lezer,

Voor u ligt mijn master thesis, het resultaat van mijn werk in het Wilhelmina Kinderziekenhuis. Na een korte stage in de zomer van 2018 op de afdeling kinderurologie was het voor mij vrij snel duidelijk dat ik ook graag op deze afdeling af zou willen studeren. Voor mij was het belangrijk om een uitdagende opdracht te krijgen, maar ook om een prettige werksfeer en een goede band met de begeleiders te hebben. Dit heb ik tijdens mijn afstuderen dan ook mooi mogen ervaren.

Dit project is begonnen als een gedachtenexperiment. Het idee was ontstaan om te kijken of de SENS-U Bladder Sensor voor nog meer dingen dan blaasvolume metingen gebruikt kon worden, zonder eigenlijk zeker te zijn of er iets uit het onderzoek zou komen. Hoewel ik stage heb gelopen op de afdeling kinderurologie, zijn we met dit onderzoek buiten de grenzen van de kinderurologie getreden. Dit past dan ook mooi binnen de strategie van het UMC Utrecht: Connecting U. Connecting U gaat namelijk over verbinding. Verbinding met patiënten, met huisartsen, met onderzoekers, met elkaar. Hoewel de SENS-U Bladder Sensor ontwikkeld is in samenwerking met de kinderurologie, betekend dit natuurlijk niet dat deze niet geschikt zou kunnen zijn voor eventueel andere toepassingen en specialismen. Hiermee worden specialismen aan elkaar verbonden door kennis en nieuwe technologieën met elkaar te delen.

Het afgelopen jaar heb ik zelf ook veel van Connecting U geleerd. In een project sta je namelijk nooit alleen. Verbindingen met elkaar zorgen ervoor dat je elkaar tot een hoger niveau kan helpen, zowel op professioneel als persoonlijk vlak. Daarnaast heb ik ook geleerd om gebruik te maken van de verbindingen die andere mensen hebben met elkaar en heb ik ervaren welke inzichten en richtingen deze kunnen geven.

Tijdens het afstuderen heb ik ontzettend veel kunnen leren en heb ik mijn grenzen verlegd. Hierbij wil ik dan ook Pieter en Paul bedanken voor de mogelijkheden en uitdagingen die zij mij het afgelopen jaar gegeven hebben. Pieter, bedankt voor alle diepe gesprekken die eigenlijk over een tal van verschillende onderwerpen zijn gegaan. Van urologie, tot de grot van Plato, van alles is de revue gepasseerd en heeft mij doen beseffen dat je soms best ietsjes mag afdwalen: “want in zijtunnels zijn vaak een prachtige ontdekking te vinden”. Paul, bedankt dat ik altijd bij je terecht kon waar dat nodig was en voor de rem als mijn hoofd weer eens op hol sloeg met alles wat ik voor mijzelf had bedacht wat ik nog moest doen. Door jullie openheid heb ik veel kunnen groeien het afgelopen jaar en weet ik ook dat ik in onverwachte situaties mijn weg kan vinden. Naast Pieter en Paul wil ik ook graag Bennie en Rian bedanken. Bennie, bedankt voor de gesprekken die we gehad hebben die bij mij telkens weer voor net wat andere inzichten zorgden. Rian, bedankt voor de inzichten die je me gegeven hebt tijdens de intervisie momenten en voor de prettige gesprekken die we gehad hebben. Door jouw begeleiding merk ik dat ik bewuster ben van mijzelf en dat ik daardoor sterker geworden ben.

Ook wil ik graag mijn intervisiegroepje bedanken: Evelien, Jurre en Mirte. De afgelopen 2 jaar heb ik veel aan onze intervisie gesprekken gehad en merkte ik dat ik mede door jullie hulp het steeds makkelijker vond om mijzelf open te stellen tijdens de gesprekken. Jullie goede vragen en opmerkingen hebben mij echt geholpen in mijn persoonlijke ontwikkeling.

En niet te vergeten mijn lieve vrienden en vriendinnen, zowel van de middelbare school (oftewel de "Kluisjestijd" groep) als vanuit Enschede. Door de gezellige etentjes en een weekendje weg naar de kerstmarkt met "Kluisjestijd" kon ik even goed ontstressen de laatste periode. Loes en Sharon, bedankt voor alle lieve woorden en aanmoedigingen, en voor de momenten waarop we gewoon eventjes "helemaal niks" konden doen.

Als laatste wil ik mijn ouders en mijn zusje bedanken voor alles wat ze mij gegeven hebben. Door hun vertrouwen, energie en gegeven adviezen sta ik nu aan het einde van mijn studie, klaar om de volgende uitdaging aan te gaan.

Nynke Wijbenga
Januari 2020

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List of Abbreviations

AP	Anterior-posterior
CCA	Common carotid artery
CI	Collapsibility index
CO	Cardiac output
CSA	Cross-sectional area
CVC	Central venous catheter
CVP	Central venous pressure
ICU	Intensive care unit
IJV	Vena jugularis interna
IVC	Inferior vena cava
IVCCI	Inferior vena cava collapsibility index
IVCDi	Indexed inferior vena cava diameter
JVP	Jugular venous pressure
PAC	Pulmonary artery catheter
PAOP	Pulmonary artery occlusion pressure
PCWP	Pulmonary capillary wedge pressure
PPV	Pulse pressure variation
PVC	Polyvinylchloride
SV	Stroke volume
SVC	Superior vena cava
SVV	Stroke volume variation
TEE	Transesophagal echocardiography
TTE	Trans-thoracic echocardiography

Chapter 1

General Introduction

Accurate assessment of the intravascular volume status remains one of the most challenging tasks for clinicians.[1,2] The intravascular volume status depicts the blood volume in a patient's circulatory system. There are four definitions essential in the assessment of a patient's intravascular volume status:

1. Euvolemia: a state where the vascular volume is adequate for cardiac filling and maintenance of an adequate cardiac output (CO) to generate the appropriate oxygen supply for tissue needs,
2. Fluid responsiveness: a state where an expansion in vascular volume increases stroke volume (SV) and CO,
3. Fluid overload: a state where excessive fluid build-up in the vascular system is caused by excessive parenteral infusion or deficiencies in cardiovascular or renal fluid volume regulation,
4. Hypovolaemia: a state where effective circulatory volume is decreased and there is insufficient oxygen delivery to tissues, possibly resulting in organ dysfunction.

Although there is a clear definition, no gold standard for the diagnosis and treatment of hypovolemia is present.[3] A study by Rivers et al. shows that extensive fluid administration during the first 6 hours of resuscitation of patients with severe sepsis and septic shock is associated with improved outcome.[4] Contrarily, fluid overload has damaging consequences. Fluid overload, and a considerably positive net fluid balance, prolongs mechanical ventilation and increases the mortality of critically ill patients. This occurs more specifically in patients with sepsis, acute respiratory distress syndrome, intra-abdominal hypertension, and acute kidney injury.[2,5] Consequently, the potential benefit from fluid administration must be balanced by the risk of provoking lung and tissue oedema.[6]

In patients subjected to dialysis treatment, volume regulation is also one of the most critical yet challenging aspects. Intradialytic hypotension is a highly frequent complication of haemodialysis and is defined as "a decrease in systolic blood pressure by $\geq$ 20 mmHg associated with symptoms including abdominal discomfort, yawning, sighing, nausea, vomiting, muscle cramps, restlessness, dizziness or fainting, and anxiety".[7,8] An excess volume among dialysis patients manifests regularly as interdialytic hypertension and is associated with increased morbidity and mortality.[1,9]

At the moment, several methods and tests are available to evaluate the patient's intravascular volume status. These methods include both invasive and non-invasive methods. With the conventional clinical tools, the evaluation of a patient's volume status is challenging. Nevertheless, monitoring of the volume status may help to identify a volume deficit or excess and act as a guide for fluid therapy. Hence, it is important to evaluate the volume status and fluid responsiveness in patients in the intensive care unit (ICU) or undergoing haemodialysis.

Promising techniques for monitoring intravascular volume status consist of ultrasound assessment of the indexed inferior vena cava diameter (IVCDi), collapsibility index (IVCCI), and ultrasound assessment of the vena jugularis interna (IJV). These are rapid and non-invasive tools to evaluate the intravascular volume status and can therefore be repeated as often as necessary.[10,11,12]

The results of ultrasound assessment are however highly user dependent. An ultrasound sensor, such as the SENS-U Bladder Sensor, could offer support in the non-invasive assessment of intravascular volume status.

1.1 Aim of the study

The aim of this study was to explore the clinical and technological feasibility of the ultrasound volume sensor to measure intravascular volume status.

To identify the (functional) demands and feasibility for this application, the following research questions were asked:

1. What are the current methods for the assessment of intravascular volume status?
2. Can the SENS-U technology be used to assess the intravascular volume status?
   (a) What is the optimal location to place the SENS-U?
   (b) How accurate does the SENS-U distinguish between (small) structures?
   (c) Can the SENS-U measure a change in vein diameter?
   (d) Are there adjustments to be made to the SENS-U?

Chapter 2

Clinical Background

As mentioned in Chapter 1, several methods and tests are available for the assessment of a patient's intravascular volume status. These methods and tests include both invasive and non-invasive procedures and involve physical examination, and monitoring of central pressures and cardiac output. Invasive methods are described as operative procedures in which skin or mucous membranes and connective tissue are incised or an instrument is introduced through a natural body orifice. A summary of the methods for the assessment of intravascular volume status is given in Table 2.1.[2,5]

2.1 Physical examination

The initial assessment of patients includes a patient's history and physical examination. Signs of dehydration are sought during physical examination.[13] An overview of the commonly used clinical and laboratory parameters are given in Table 2.2.

Vital signs are useful indicators supporting clinical judgement, yet dependent on the type and amount of fluid loss. Parameters of physical examination may be useful, though often several confounding factors are found in critically ill patients. The same

Table 2.1: Summary of tools used for the assessment of intravascular volume status

Method	Invasive/non-invasive	Static/dynamic	Fluid responsiveness?
Historical findings	Non-invasive	Static	No
Physical exam	Non-invasive	Static and dynamic	Yes
Chest radiograph	Non-invasive	Static	No
Central venous pressure	Invasive	Static	No
Pulmonary capillary wedge pressure	Invasive	Static	No
Echocardiogram	Non-invasive	Static	No
Stroke volume or pulse pressure variation	Invasive	Dynamic	Yes
Oesophageal doppler	Invasive	Dynamic	Yes
Vena cava diameter	Non-invasive	Dynamic	Yes
Passive leg raising	Non-invasive	Dynamic	Yes

Table 2.2: Commonly used clinical and laboratory parameters.

Vital signs	Blood pressure
	Pulse
	Orthostatic changes in blood pressure and pulse
Physical examination	Mentation
	Capillary refill
	Skin turgor/dryness
	Skin perfusion
	Temperature of the extremities
	Urine output
	Dry weight
Laboratory parameters	Fractional excretion of sodium, urea
	Blood lactate
	Mixed venous oxygen saturation

applies to laboratory parameters, even though they provide useful information, they do not serve as independent markers of volume status.[2,13]

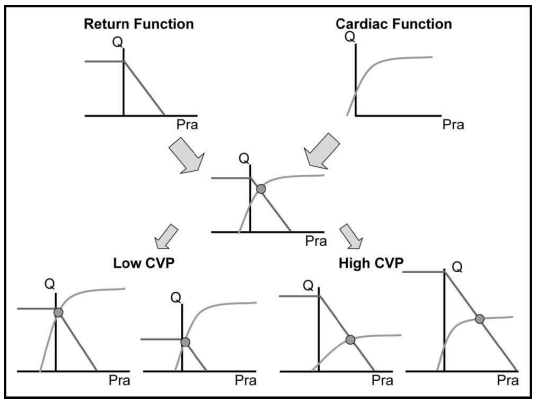
Additionally, daily chest X-rays are used as a diagnostic tool in the ICU. However, typical radiologic signs indicating volume overload are highly insensitive and variable. Both physical examination and chest X-rays present inadequate value for the assessment of a patient's volume status.[2,13]

2.2 Central venous pressure

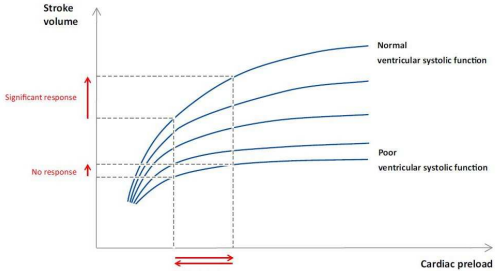
The central venous pressure (CVP) can be used to determine the adequacy of circulating blood volume and cardiac preload. As long as no vena cava obstruction exists, the CVP is equal to the right atrial pressure. In healthy adults the CVP is about 0 – 8 cm H_2O (or 8 – 12 mmHg), varying with spontaneous respiration. During expiration, the CVP is slightly higher due to the increase in intrathoracic pressure.[14,15,16]

Cardiac output and CVP are regulated by the interaction of the cardiac function curve and the venous return curve, which are shown in Figure 2.1a. The return curve shifts to different pressures due to changes in blood volume. A decrease in blood volume shifts the return curve to the left, whereas an increase in blood volume shifts the curve to the right. The cardiac function curve depends on afterload, heart rate, and the heart's contractile state.[17,18] It is presumed that fluid resuscitating patients with a low CVP will increase the stroke volume and cardiac output. However, this depends on the shape of the Frank-Starling curve shown in Figure 2.1b. The Frank-Starling curve varies from one patient to another, and within a patient from time to time. Therefore, a static value of CVP could correlate to fluid unresponsiveness as well as fluid responsiveness.[5] The CVP is particularly unreliable in patients with valvular heart disease, pulmonary vascular disease, tense ascites, isolated left ventricular failure, and right ventricular disease.[2]

The CVP can be evaluated with both invasive as non-invasive methods. A central venous catheter is used for invasive CVP measurements. For non-invasive CVP measurements the jugular vein pressure wave can be used.



(a) Cardiac function and venous return curves.[17]



(b) Frank-Starling curves[5]

Figure 2.1: (a) The cardiac function and venous return curves show the relationship between blood volume and right atrial pressure. (b) The slope of the Frank-Starling curve depends on ventricular systolic function.

2.2.1 Catheterisation

To measure the CVP, a central venous catheter (CVC) can be used. There are three anatomical sites commonly used for the insertion of CVCs. These sites are the subclavian, jugular, or femoral vein.[19,20]

The use of CVCs are associated with complications that are both dangerous for the patient and expensive to treat. These complications occur in more than 15% of patients receiving a CVC. The complications can be subdivided in mechanical (5 – 19% of the patients), infectious (5 – 26% of the patients) and thrombotic (2 – 26% of the patients) complications.[20]

Percutaneous cannulation of the IJV shows a lower incidence of serious complications, including hemothorax and pneumothorax. However, accidental puncture of the common carotid artery is the most common complication during IJV punctures.[21] Complications of iatrogenic trauma to the carotid artery include shock from hemothorax, airway obstruction by cervical hemotoma, pseudoaneurysm, arteriovenous fistula, and stroke from arterial thrombosis or cerebral emboli.[22]

2.2.2 Jugular vein pressure wave

In 1930, Sir John Lewis suggested measuring the patient's venous pressure during physical examination, using the jugular vein pressure wave.[23]

In normal physiological conditions the internal jugular veins have an open connection with the right atrium. Figure 2.2 shows the veins to be continuous with the superior vena cava. Therefore, the jugular veins act as a manometer, reflecting the right atrial pressure. Hence, the vertical height above the right atrium to which they are distended and above which they are in a collapsed state, also known als the jugular venous pressure (JVP) in centimetres, should reflect the right atrial pressure and therefore the CVP.[24,25] To determine the JVP, the highest point of pulsation of the IJV must be identified. This point is then related to the angle of Louis. The vertical distance to the top of the jugular venous wave can be determined as the JVP

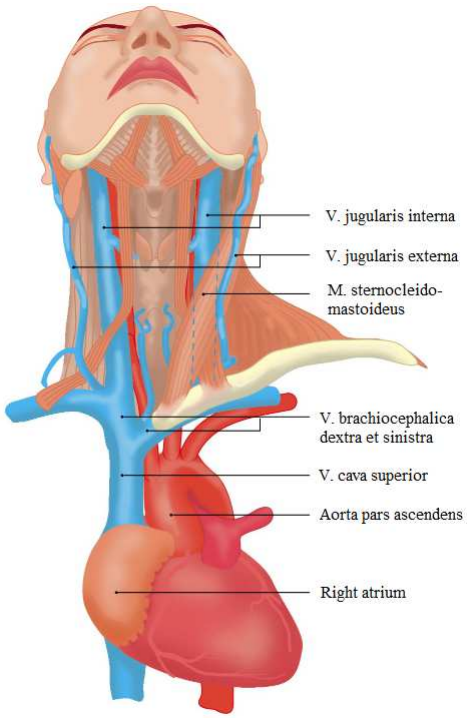


Figure 2.2: The jugular veins are in open connection with the superior vena cava and the right atrium.[24]

in centimetres. The angle of Louis lies 5 cm above the middle of the right atrium. Therefore, the CVP is determined as: $CVP = JVP + 5cm$.[26,27]

To determine the CVP, it is preferred to use the right-sided jugular vein. As shown in Figure 2.2, this vein is in direct line with the superior vena cava (SVC) and the right atrium. Furthermore, the right sided IJV contains no valves.

Visualisation of jugular venous pulsations can, however, be challenging. The JVP may be estimated incorrectly when the jugular vein is tortuous or constricted. In patients with variations in neck morphology (for example shortness and thickness), prior neck surgery, prior catheter placement, and mechanical ventilation the JVP assessment might be difficult.[11,26]

2.3 Pulmonary capillary wedge pressure

Equal to the CVP, the pulmonary capillary wedge pressure (PCWP), or pulmonary artery occlusion pressure (PAOP), is assumed to reflect central blood volume and therefore a reliable guide to volume therapy. Ideally, the PCWP is proportional to left ventricular end-diastolic volume/preload. It would seem to be an ideal parameter for monitoring volume status.[2] However, the PCWP is an indirect volume indicater, like the CVP. Therefore, the PCWP is influenced by lung compliance and intrathoracic pressures.[2] The PCWP experiences many of the same limitations as the CVP.[28]

To measure the PCWP, a pulmonary artery catheter (PAC) is inserted in the vena

subclavia and proceeds through the SVC into the pulmonary artery. During measurement of the PCWP a balloon is inflated.[29] PAC insertion could lead to pneumothorax, hemorrhage, transient arrhythmias, and damage to large thoracic vessels. Other complications of PAC insertion are equivalent to those of CVC insertion. A specific complication for PAC is pulmonary artery rupture with balloon inflation.[30]

2.4 Stroke volume- and pulse pressure variation

Stroke volume variation (SVV) and pulse pressure variation (PPV) are dynamic measures to assess the intravascular volume status and were the first methods developed for dynamic assessment of preload responsiveness.[5,31]

The underlying principles of PPV and SVV are based on simple physiology. Cyclic changes in loading condition of the right and left ventricles are induced by positive-pressure ventilation. Insufflation decreases the preload and increases the afterload of the right ventricle. This leads to a decrease in right ventricular SV. Transmitted to the left side, a decrease in left ventricular preload is induced, which may induce a decrease in left ventricular SV. Cyclic changes in right and left ventricular SV are greater when the ventricles work on the steep rather than the flat portion of the Frank-Starling curve (Figure 2.1b).[5,28]

Limitations of the PPV and the SVV are that they cannot be used during spontaneous breathing, for patients with cardiac arrhytmias, and in patients with low tidal volumes or lung compliance. These conditions are quite common in the ICU.[5]

2.5 Ultrasound assessment

Several two-dimensional and Doppler flow measurements can be obtained from transesophagal or trans-thoracic echocardiography (TEE or TTE). These ultrasound measurements could provide cardiac chamber volume assessment, such as left ventricular dimensions with TEE during mechanical ventilation. These measurements are however hard to interpret and vary from patient to patient. Therefore, static, single echocardiographic measurements are of limited value in the assessment of intravascular volume status.[2]

Dynamic measurements using ultrasound assessment include respiratory variation in vena cava and IJV diameter. Both the SVC and the inferior vena cava (IVC) can be used for the assessment of intravascular volume status. Respiratory variations of the SVC show a higher diagnostic accuracy than the respiratory variations of the IVC. However, imaging of the SVC requires performing TEE and is thus a minimally invasive method to assess the intravascular volume status. Imaging of the IVC can be accomplished by performing TTE and is thus a non-invasive method.[5,32]

2.5.1 Vena cava inferior

Ultrasound assessment of the IVCDi and IVCCI is one of the most promising techniques for monitoring intravascular volume. Initially, ultrasound evaluation of the IVC diameter and collapse was investigated by nephrologists for use with dialysis. Afterwards, cardiologists considered it as a surrogate parameter for the right atrial pressure. More recently it has been adopted by intensivists and emergency physicians as a non-invasive and rapid tool to evaluate the intravascular volume status, which can be repeated as often as necessary.[10]

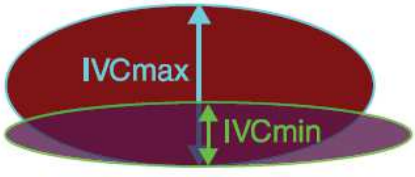
The IVC is a major capacitance vessel of the body, providing a ready supply of blood for the venous return. Its main role is to serve as a reservoir. The vessel itself is rather voluminous with pliable and collapsible vessel walls in a non-volume overload state. The shape and size of the IVC vary with changes in CVP and intravascular volume.[10,33]

Under normal physiological conditions, the venous return increases and IVC diameter decreases during inspiration, due to negative intrathoracic and positive intra-abdominal pressure. A decreasing intravascular volume will result in a decreased IVC diameter and an increase in respiratory variation. An increased intravascular volume will result in an increased IVC diameter and a decrease in respiratory variation. As shown in Figure 2.3, the respiratory variations can be observed with ultrasound. Using these variations, the IVCCI can be calculated:[10,33,34,35]

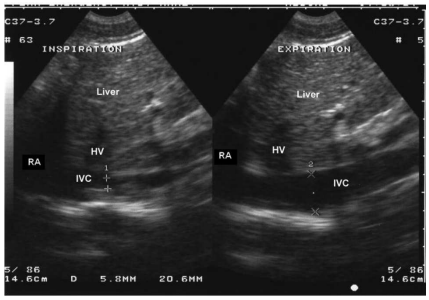
$$IVCCI = \frac{(IVC_{max} - IVC_{min})}{IVC_{max}} \cdot 100 \tag{2.1}$$

In Figure 2.3, for example, the IVCCI can be calculated as $IVCCI = \frac{20.6-5.8}{20.6} \cdot 100\% \approx 72\%$.

Absolute size and collapse index can both be used as quantitative measures of the IVC. No absolute cut-off values for a normal IVCCI exists. However, typically, the IVCCI in healthy subjects is between 25% and 75%. When the collapsibility index (CI) is more closer to 0% or 100%, it is more likely that the patient is volume overloaded



(a) Schematic overview of the IVC diameter



(b) Ultrasound image during inspiration and expiration

Figure 2.3: Respiratory variations in IVC diameter. (a) shows a schematic overview of the change in IVC diameter. (b) shows an ultrasound image of a collapsed IVC during inspiration and the IVC diameter during expiration.[10]

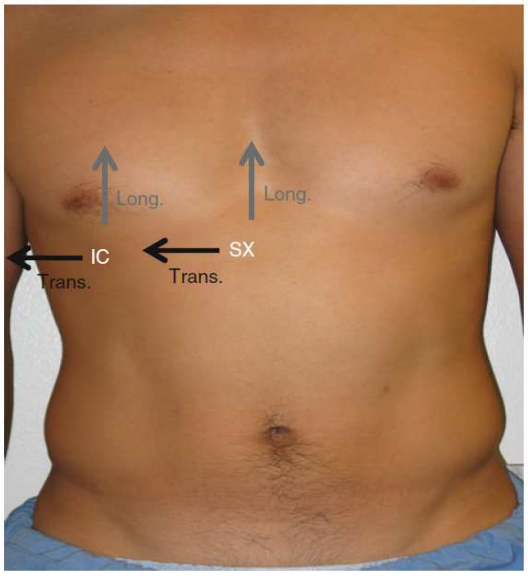


Figure 2.4: The IVC can be imaged using the subxiphoid (SX) or the intercostal (IC) window. Both windows are shown above.[36]

or volume depleted. If the maximum IVC diameter is less than 9 mm, the patient is volume depleted. If the maximum IVC diameter is less than 5 mm, the patient is profoundly hypovolaemic.[10,31,36]

The IVC can be imaged in the subxiphoid window or in the intercostal window, near the junction of the IVC and right atrium.[10,31,36] In Figure 2.4 an overview is shown for the placement of the ultrasound transducer. The intercostal window can be used especially in patients with upper abdominal wounds, interfering bowel gas, or abdominal tenderness.[36]

2.5.2 Vena jugularis interna

Ultrasonography of the IJV can also be used to predict the intravascular volume status. As shown in Figure 2.2, the right IJV is positioned in a continuous line with the SVC an right atrium and has therefore direct communication with the right atrium via the SVC.[24,37]

Several methods are available for ultrasound assessment for predicting the intravascular volume status, for instance the use of ultrasound to localise the internal jugular vein collapse to aid in the traditional visual assessment of jugular venous pulsations for assessment of CVP (Section 2.2.2). Other methods include measurements of the IJV diameter, IJV cross-section area, and IJV collapsibility index.[11,12,38,39,40,41]

For measurements of the IJV diameter, several cut-off values were found. In a study of Donahue et al., the IJV diameter was related to the CVP. They found that the IJV diameter could distinguish whether a patient had a high or low CVP. Cut-off values were found for both: a maximum IJV diameter of 5.7 – 8.3 mm relates to a CVP < 10 mmHg, a maximum IJV diameter of 11.2 – 13.8 mm relates to a CVP > 10 mmHg.[11] A study of Avcil et al. determined the cut-off values for a high CVP 10 mmHg and 6 mmHg for a low CVP. For the maximum IJV diameter they found a cut-off value of

$\leq$10.1 mm for a low CVP. For a high CVP they determined a cut-off value of $\geq$10.4 mm for the maximum IJV diameter.[40]

The IJV collapsibility index (CI) was investigated by, among others, Killu et al. and Jassim et al. The CI can be calculated using maximum and minimum anterior-posterior (AP) diameters or cross-sectional area (CSA):[12,41]

$$IJV_{AP} - CI = \frac{IJV_{AP\ max} - IJV_{AP\ min}}{IJV_{AP\ max}} \cdot 100\% \tag{2.2}$$

$$IJV_{CSA} - CI = \frac{IJV_{CSA\ max} - IJV_{CSA\ min}}{IJV_{CSA\ max}} \cdot 100\% \tag{2.3}$$

All studies found a good correlation of the ultrasound measurements of the IJV with invasive measured CVP. Ultrasound measurements of the IJV can therefore be a feasible, readily accessible, and reproducible method for the assessment of intravascular volume status. Limited technical expertise is required to examine and measure the IJV. As a result, this method to assess the intravascular volume status could be used by any physician with limited ultrasound experience.

Chapter 3

Technical Background

As mentioned earlier, ultrasound assessment of the IVC and/or IJV are promising techniques for the assessment of intravascular volume status.

3.1 Ultrasound

The active component of ultrasound transducers consists of piezoelectric elements. When an electrical current passes through a piezoelectric crystal within the transducer, ultrasound waves are generated.[42,43] The ultrasound waves pass through the body and interacts with different tissues. If a pulse migrates through a patient, it encounters the boundaries between different tissues. Here a part of the pulse's energy will be reflected. The remaining energy will pass on. The reflected waves are detected by the transducers and the time between the generated (pulse) and returned (echo) wave is measured.

Using the pulse-echo principle, the distance of an object from the transducer can be measured. This principle is also used in nautical sonar equipment to measure water depth. An example of the pulse-echo principle is shown in Figure 3.1.

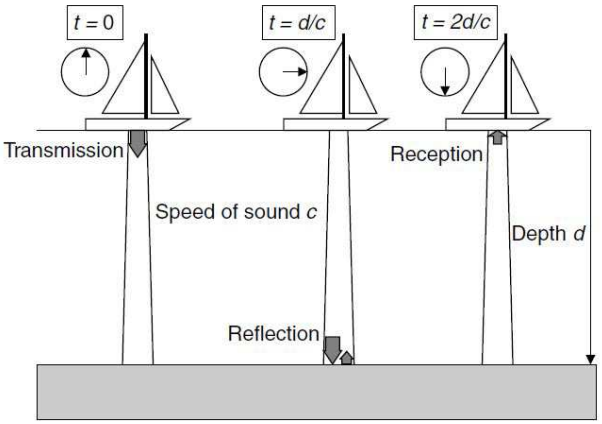


Figure 3.1: Example of the pulse-echo principle. The water depth is calculated by measuring the time from pulse transmission to reception of the pulse.[42]

The distance to the ground can be calculated by using the speed of sound and measuring the time between pulse transmission to reception. This is calculated using the following equation: $d = \frac{c \cdot t}{2}$, with c the speed of sound and t the time. Subsequently, a one-dimensional (A-mode) or a two-dimension (B-mode) image can be created.[42,44,45]

3.1.1 Resolution

The ability of an ultrasound machine to distinguish between structures at a particular depth, also known as spatial resolution, is mainly determined by the transducer. Spatial resolution can be divided into axial and lateral resolution.

Lateral resolution reveals the ability to distinguish between two targets perpendicular to the transducer. Lateral resolution is primarily regulated by the beam width of the ultrasound, meaning that lateral resolution will be high if the ultrasound beam width is narrow. Axial resolution the ability to distinguish between two targets parallel to the transducer. Axial resolution is high when the spatial pulse length is short. The spatial pulse length is determined by the wavelength of the pulse. As the wavelength is inversely proportional to the frequency, the axial resolution depends on the frequency of the ultrasound transducer.[42,46] An overview of lateral and axial resolution is given in Figure 3.2.

The ability to distinguish between rapidly moving structures is called temporal resolution. Temporal resolution is defined by the pulse repetition period. When this period is short, a high temporal resolution can be achieved. A short pulse repetition period can be obtained by a high pulse repetition frequeny and a shallow penetration depth of the ultrasound waves.[46]

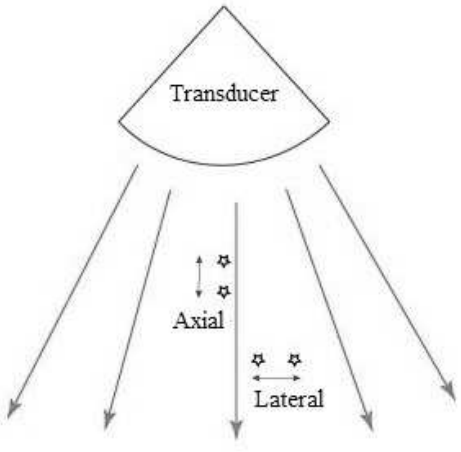


Figure 3.2: A schematic overview of lateral and axial resolution.

3.2 SENS-U Bladder Sensor

Recently, the SENS-U Bladder Sensor (SENS-U) (Novioscan B.V., Nijmegen, The Netherlands) became available. An example is shown in Figure 3.3. The SENS-U is a new, wearable ultrasonic bladder sensor (95 x 55 x 16 mm) designed to aid in the training of children with day-time urine incontinence by estimating the anterior–posterior (AP) bladder dimension. A study by van Leuteren et al. in 2018, clinically evaluated the SENS-U in 30 children during (video) urodynamic testing. During this study, a positive correlation (median r_s = 0.94) between infused volume in the bladder and estimated bladder dimensions were found.[47] In 2019 a pilot study was conducted by van Leuteren et al. to evaluate the performance of the SENS-U during daily life activities. This pilot demonstrated an equally accurate performance during daily life activities as during (video) urodynamic testing.[48]

The SENS-U is based on a combination of four piezoelectric crystals, placed within a field of view of 30°. The crystals are placed at an angle of respectively 5°, −5°, −15°, and −25°. The SENS-U relays an ultrasound wave with a frequency of 3.5 MHz, with a pulse repetition frequency ranging from 0.033 Hz (2/minute) to 1 Hz (1/s), and has a receive sample frequency of 1.14 MHz.

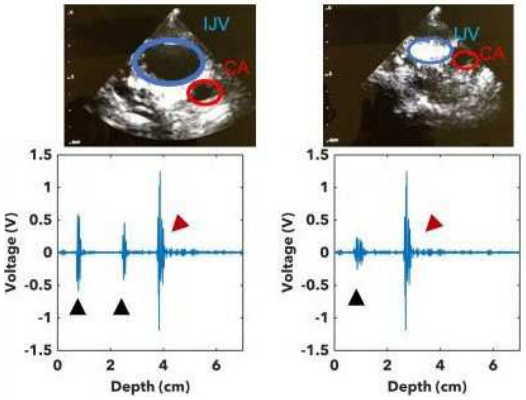
With the SENS-U, an A-Mode ultrasound image is created. The vertical peaks of the A-Mode image correspond to the depth of structures the ultrasonic wave encounters in different tissues. The SENS-U automatically processes the reflections of the bladder walls within these vertical peaks. As a result, the AP bladder dimension can be calculated.

The technology of the SENS-U could offer support in the non-invasive assessment of the volume status. As mentioned in Chapter 2.5, ultrasound assessment of the IVC and the IJV are promising techniques for monitoring intravascular volume status. However, with the current methods for ultrasound assessment the results are highly user dependent and it is not possible to continuously measure the changes in IVC and/or IJV diameter. The technology of the SENS-U could aid in the non-invasive assessment of intravascular volume status.

Figure 3.3: An example of the SENS-U Bladder Sensor

In comparison, Singh et al. investigated in 2017 the use of a force-coupled single crystal ultrasound transducer for non-invasive assessment of the jugular venous pressure. In Figure 3.4, the used transducer and the obtained A-mode images are shown. In this research, they concluded that a single crystal ultrasound transducer was sufficient to create acoustic profiles corresponding to sonographic images of the internal jugular vein in basal and collapsed states.[49] This study used a technology comparable with the SENS-U, which reinforces the idea to use SENS-U technology for the assessment of intravascular volume status.

(a) Force-coupled single crystal ultrasound transducer as used by Singh et al.



(b) B-mode ultrasound images of the IJV in basal and collapsed states, and the corresponding single crystal A-mode images. The black arrowheads show the IJV, the red arrowheads the carotid artery (CA)

Figure 3.4: The used ultrasound transducer and the obtained A-mode images from the study by Singh et al.[49]

Chapter 4

Proof of principle

As mentioned in Chapter 2, several methods and tools are available to assess the intravascular volume status of a patient. These include both invasive as non-invasive methods. Ultrasound assessment of the IVC or the IJV are methods that could be used to assess the volume status. Both are non-invasive, rapidly performed and can be repeated as often as necessary. SENS-U technology could be applied to support both methods.

To measure the diameter of the IVC, a probe must be positioned in the subxiphoid or intercostal window. To use the subxiphoid window, pressure needs to be applied to the probe to obtain the right angle and reduce ultrasound artifacts caused by air in the stomach. The intercostal window does not require pressure, but for this window an experienced sonographer is required.[10] For IVC imaging, a 3 – 5 MHz phased-array or curvelinear probe is preferred. The IVC depth can be superficial ($\leq$ 8.5 cm), moderate (8.5 – 12.5 cm) or profound ($\geq$ 12.5 cm).[50]

The IJV lies superficially ($\pm$ 1.5 cm) in the neck. The IJV can be measured 2 cm above the clavicle, without applying any pressure to the probe. Linear, high frequency (7.5 – 10 MHz) probes are preferred to visualise the IJV.[51] Little sonographic experience is needed to locate the IJV.

An overview of both methods is shown in Table 4.1. Using the SENS-U technology for the assessment of the IVC, difficulties in distinguishing between tissues (e.g. the liver, hepatic veins and arteries) are expected, especially using the intercostal window. Furthermore, due to the needed pressure on the probe, the SENS-U cannot be used for continuous measurements with the subxiphoid window.

It is expected that the frequency of the SENS-U is currently not adequate enough to properly assess the IJV. Nonetheless, since the IJV lies superficially and little sonographic experience is required, SENS-U technology could be suitable to aid in the assessment of IJV diameter for intravascular volume status.

Table 4.1: Inferior vena cava vs. internal jugular vein ultrasound to assess the intravascular volume status.

	Inferior vena cava (IVC)	Internal jugular vein (IJV)
Ultrasound frequency (MHz)	3 – 5	≥ 7
Probe position	Subxiphoid or Intercostal window	On the right side of the neck, 2 cm above the level of the clavicle
Vein depth (cm)	≤ 8.5 (superficial) 8.5 – 12.5 (moderate) ≥ 12.55 (profound)	± 1.5
Volume status assessment	Vena cava diameter Collapsibility index	Cross section area IJV collapsibility index IJV collapse pressure AP diameter IJV
Limitations	Difficult to distinguish between tissues with the SENS-U	Hard/impossible to measure in patients with neck morphology

Therefore, proof of principle studies were performed to explore the feasibility of the ultrasound volume sensor to measure intravascular volume status using the IJV. The first step of the proof of principle consisted of a phantom study with the SENS-U Bladder Sensor. Subsequently, IJV diameter measurements with the SENS-U Bladder Sensor were conducted on healthy volunteers. Lastly, a case study during surgery was performed.

4.1 Phantom study

To investigate the technological feasibility of the use of SENS-U technology to measure intravascular volume status, a phantom study was conducted. During this study, the axial resolution of the SENS-U Bladder Sensor was explored. Additionally, the smallest distinguishable AP diameter was examined.

4.1.1 Methods

A phantom was designed and developed to analyse the accuracy of the current ultrasound volume sensor to measure small diameters. This phantom consisted of tissue-like ultrasound phantom material and three tubes, declining in diameter. A mold for the phantom was created using a polyvinylchloride (PVC) pipe of 250 mm, with a diameter of 100 mm. Within the PVC, the three tubes were lined up and secured. The inner/outer diameters of the tubes were, respectively, 12/16 mm, 9/11 mm, and 4/6 mm. A 3D model of the mold is shown in Figure 4.1 and the finished phantom is shown in Figure 4.2.

Subsequently, tissue-like ultrasound phantom material was created using the method of Bude et al.: 140 g gelatin was dissolved in 1.7 L boiling water. Wallpaper glue with cellulose was added to the gelatin suspension to mimic the acoustic properties of tissue.[52]

Thereafter, the mixture was poured into the mold and chilled until firm. After the phantom was removed from the mold, the three tubes were closed with a plug on one side. Thereafter, the tubes were filled with water using a 10 cc syringe and closed off completely. Subsequently, measurements were conducted on the phantom.

First the propagation speed in the phantom was calculated. As ultrasound machines assume a propagation speed of 1540 m/s, the propagation speed through the phantom can be determined using a depth measurement with the ultrasound machine and a manual depth measurement with a ruler. This is shown in Figure 4.3. Subsequently, the propagation speed can be calculated using: $V_{sound} = \frac{\Delta x}{\Delta t}$.

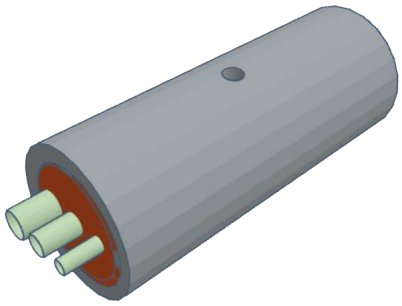
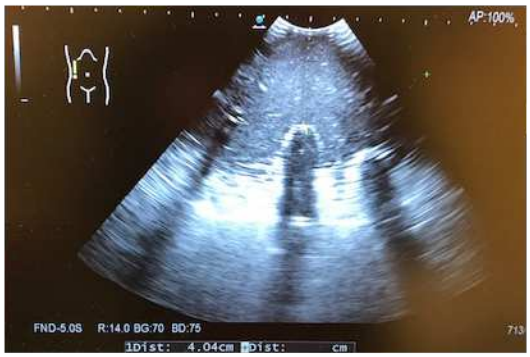
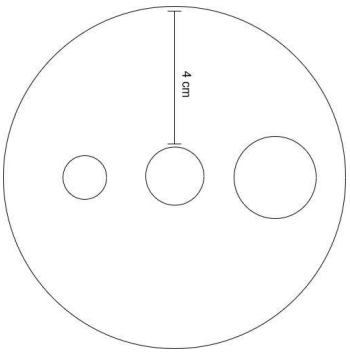


Figure 4.1: A 3D model of the mold used to create the phantom.

Figure 4.2: The finished phantom.



(a) Ultrasound image of the phantom (end)



(b) Schematic drawing of the phantom

Figure 4.3: The propagation speed through the phantom was calculated using the ultrasound machine. The 9/11 tube was found with the ultrasound machine at a depth of 4.04 cm. Manually measured depth was approximately 4 cm.

For the measurements, the SENS-U was placed on top of the phantom as shown in Figure 4.2. The AP diameter of the tubes were measured with the SENS-U in a longitudinal plane. The measured data from the SENS-U was saved in .csv files. The .csv files were analysed using Matlab R2018a (Matlab, The Mathworks Inc., Massachusetts, USA). For all tubes, the AP-diameter was calculated using a peak-detection algorithm, shown in Appendix **??**. Additionally, the AP-diameters were corrected for the angle of the piezo-electric crystals.

4.1.2 Results

Propagation speed

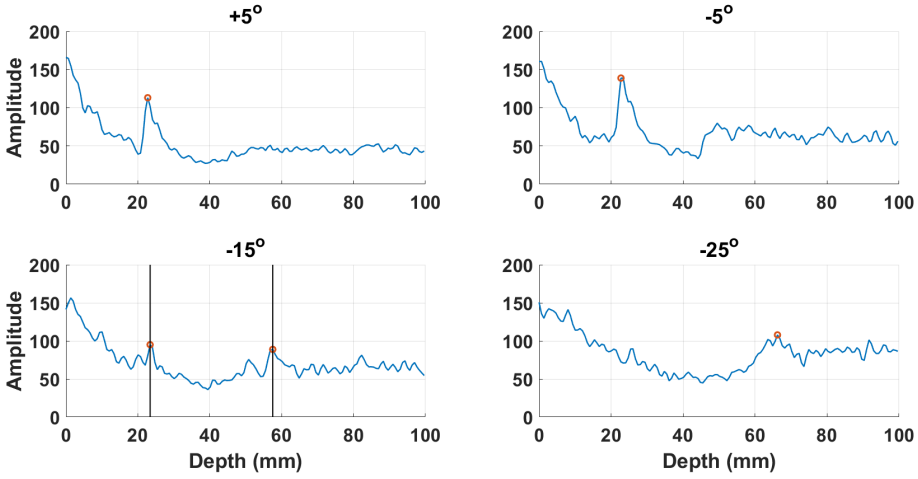
With the ultrasound machine, Δt (in seconds) was determined to be 1540 $m/s = \frac{0.0404\ m}{\Delta t}$, $\Delta t = \frac{0.0404}{1540} = 2.62 \cdot 10^{-5}\ s$. Using this Δt, the propagation speed through the phantom was determined to be: $V_{sound} = \frac{0.04\ m}{2.62 \cdot 10^{-5}\ s} = 1525\ m/s$.

Phantom

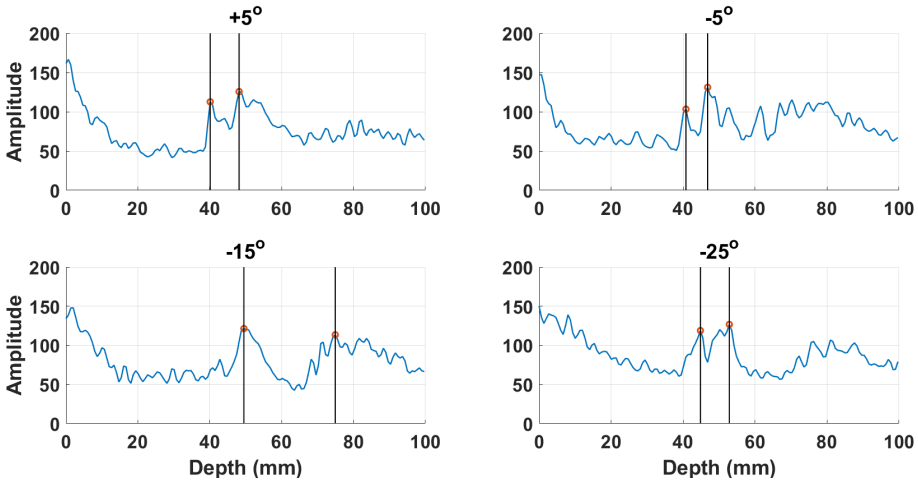
The AP diameter of the tubes was calculated using a peak detection algorithm. The results of the peak detection are shown in Figure 4.4. The calculated AP diameters can be found in Table 4.2.

Table 4.2: Measured AP diameters of the tubes for every angle with the SENS-U.

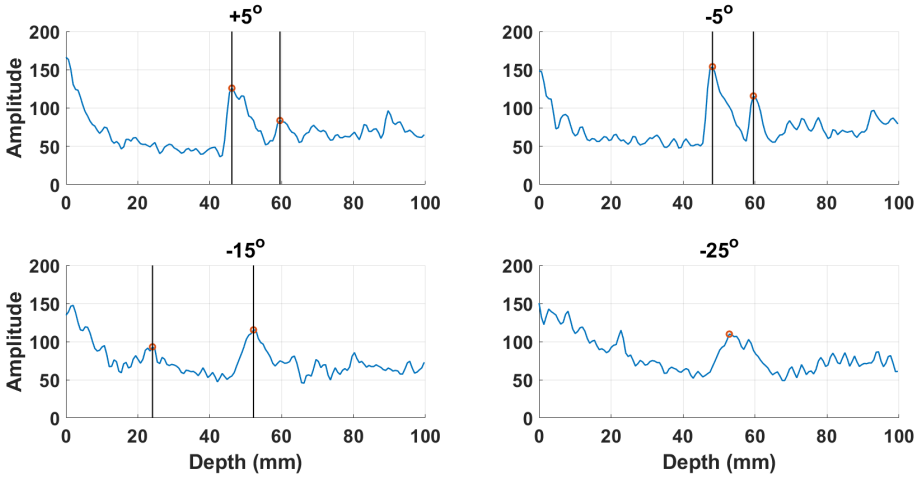
Tube diameter inner/outer [mm]	AP-diameter per angle [mm]			
	+5°	-5°	-15°	-25°
4/6	-	-	32.9	-
9/11	8.0	6.0	24.6	7.3
12/16	13.3	11.3	27.1	-



(a) Phantom 4mm



(b) Phantom 9mm



(c) Phantom 12mm

Figure 4.4: Peak detection of the tubes in the phantom for all angles of the SENS-U. The black lines depict the measured AP diameter of the tubes.

The AP diameters of the 4/6 tube could not be detected correctly and were therefore not correctly calculated or absent. Figure 4.4a shows no correct detection of the anterior and posterior wall of the tube.
For the 9/11 tube, acceptable similar diameters were found for the 5°, −5°, and −25° angles. The −15° did not correctly calculate the AP diameter. Looking at Figure 4.4b, it can be noticed that at the depth of the tube (at approximately 4 cm) no anterior wall was detected for this angle.
The 12/16 tube shows acceptable similarities in AP diameters for the 5° and −5° angles. For the −15° angle, the AP diameter was not correctly calculated. In Figure 4.4c an inadequate peak detection and an absent peak for the anterior wall of the tube can be observed. For the −25° angle, the calculated AP diameter is missing. Figure 4.4c reveals an inadequate peak detection for this angle, leading to the absent diameter.

4.1.3 Discussion

Looking at the results, the SENS-U could not measure the 4/6 mm tube of the phantom. Figure 4.5 shows a close-up of the measurements of the 4/6 mm tube of the phantom. It can be seen that the anterior wall of the tube was detected by the SENS-U. The posterior wall of the tube however coincides with the peak of the anterior wall. This is shown with the black arrows in Figure 4.5. The black arrows point at the small peak where the posterior wall of the tube should be detected. However with the current ultrasound frequency of the SENS-U, the axial resolution is too low to measure such small diameters. Therefore, a higher ultrasound frequency of the SENS-U is needed to measure diameters smaller than 9 mm, based on the phantom.

Looking at Table 4.2, an inaccuracy between the 9/11 and 12/16 mm tube diameters and the measured AP diameters can be found. This inaccuracy could be explained by the ultrasound resolution of the SENS-U. However, looking at Figure 4.2, a curve in the tubes inside the phantom can also be observed. Due to this curve, there is a possibility that the SENS-U was not positioned exactly above the tubes, leading to incorrect measurements of the AP diameters. This curve could also explain the detected AP diameters for the -15° angle.

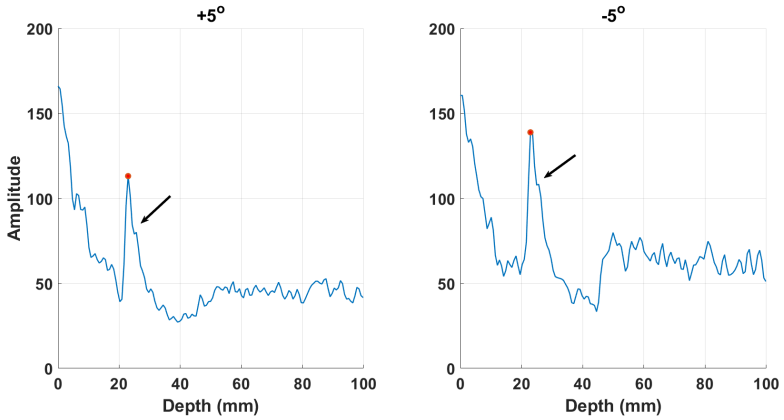


Figure 4.5: A close up at the 5° and −5° angles of the AP detection for the 4/6 tube. The black arrows show a small bulge where the anterior wall was supposed to be detected.

4.1.4 Conclusion

A phantom study was conducted to investigate the technological feasibility of the use of the SENS-U to measure intravascular volume status. A phantom was designed to explore the axial resolution of the current SENS-U and the smallest distinguishable AP diameter.
Based on this phantom, the SENS-U struggles with the correct detection of diameters smaller than 9 mm. For the correct detection, the axial resolution needs to be improved by increasing the ultrasound frequency of the SENS-U.

4.2 Healthy volunteers

After the phantom study, measurements of the IJV diameter with the SENS-U were conducted on healthy volunteers to further investigate the technological feasibility, and to examine the clinical feasibility.

4.2.1 Methods

Selection of participants

In total, the IJV diameter of 8 healthy adults was examined. Inclusion criteria included age greater than 18 years, voluntary participation and informed consent. Exclusion criteria included vascular disease (current or past), use of vasoactive drugs and neck morphology.

Methods of measurements

The subjects were positioned on an exam table, with the head at 0° supine. Initially, the head lay in a neutral position and was rotated toward the left. This is shown in Figure 4.6. The ultrasound machine and transducer (Acuson S1000 Ultrasound System and Acuson 14L5 Linear Array Probe 5 – 14 MHz; Siemens Medical Solutions) allowed to precisely measure the IJV diameter.

The IJV was visualised both transversal as longitudinal. Figure 4.7 shows the ultrasound image of one subject. The IJV diameter was measured end-expiration. Subsequently, the SENS-U was used to measure the IJV diameter longitudinally. Thereafter the measurements were repeated with the head slightly tilted downwards, to imitate a "fluid challenge". Other recorded data included age, sex, length, weight, BMI, and neck circumference. The measuring protocol can be found in Appendix A.

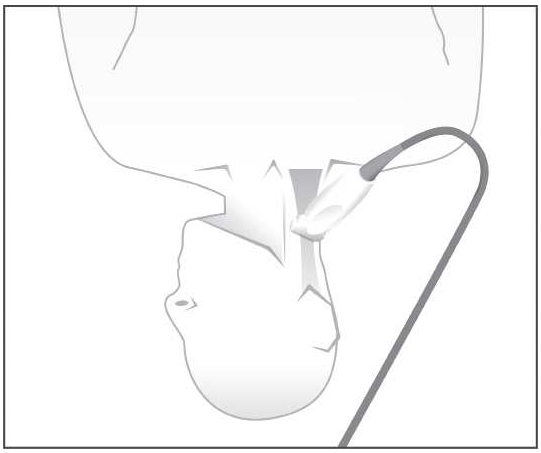
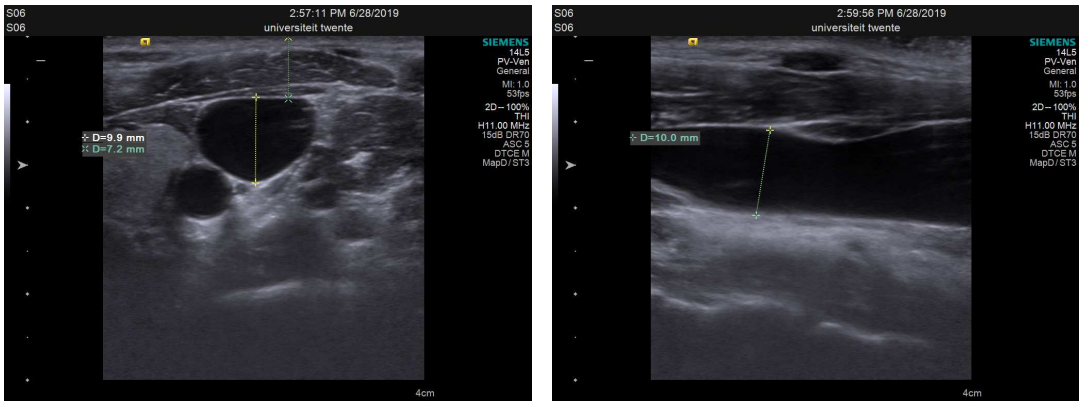


Figure 4.6: Positioning of the healthy volunteers for examination. The head was rotated to the opposite side to obtain a clearer view of the IJV.



(a) Transversal view **(b)** Longitudinal view

Figure 4.7: Ultrasound images of the right IJV of 1 healthy subject.

Data analysis

The measured data from the SENS-U was saved in .csv files. The diameters from the ultrasound measurements were documented and the images were saved anonymously on a flash drive. The .csv files from the SENS-U were analysed using Matlab R2018a (Matlab, The Mathworks Inc., Massachusetts, USA). The AP diameter of the IJV was determined using the peak-detection algorithm in Appendix **??** and compared to the obtained diameters from the ultrasound measurements. For the calculation of the AP diameter a propagation speed of 1540 m/s (the propagation speed in soft tissue) was used. Additionally, the AP-diameters were corrected for the angle of the piezo-electric crystals.

4.2.2 Results

In total, 8 healthy volunteers participated in the study. The characteristics of the participants are summarized in Table 4.3. Further subject information is included in Appendix B. Measurements with a "fluid challenge" were available for subject 4 till 8. For subject 2, two sets of measurements were acquired with the head at 0° supine. This led to, in total, 14 measurements of the AP diameter.

An overview of the measured AP diameters with the SENS-U is given in Appendix C, Table C.1. The fluid challenge implemented by subjects 4 till 8 caused the IJV to expand for four subjects. For one subject the IJV diameter became smaller after the fluid challenge.

Table 4.3: Demographic variables for the healthy volunteers.

Variables		Participants (n=8)	
Age	*(years [SD])*	21.75	[1.98]
Gender	*Male*	1	(12.5%)
	Female	7	(87.5%)
BMI	*(kg/m^2 [SD])*	20.88	[0.89]
Neck circumference	*(cm [SD])*	34.25	[1.93]

The 5° angle of the SENS-U could measure an AP diameter for 8 measurements. These 8 measurements had a relative margin of error of -9.5%. For the −5° angle of the SENS-U, only one AP diameter could not be determined. The relative error for this angle was 12.9%. The −15° angle determined for 11 measurements the AP diameter, with a relative error of 33.2%. Lastly, the −25° angle determined the AP diameter for 9 measurements. The relative error for this angle was 34.6%.

The Bland Altman plot in Figure 4.8 shows the agreement between the AP diameters measured with the ultrasound and the AP diameters measured with the SENS-U. It is notable that the agreement between both methods becomes smaller as the angle of the SENS-U becomes larger.

To visualize the agreement between the AP diameters measured with the ultrasound and the AP diameters measured with the SENS-U, the data of the SENS-U was plotted over the obtained image from the ultrasound machine. This is shown in Figure 4.9 for one subject.

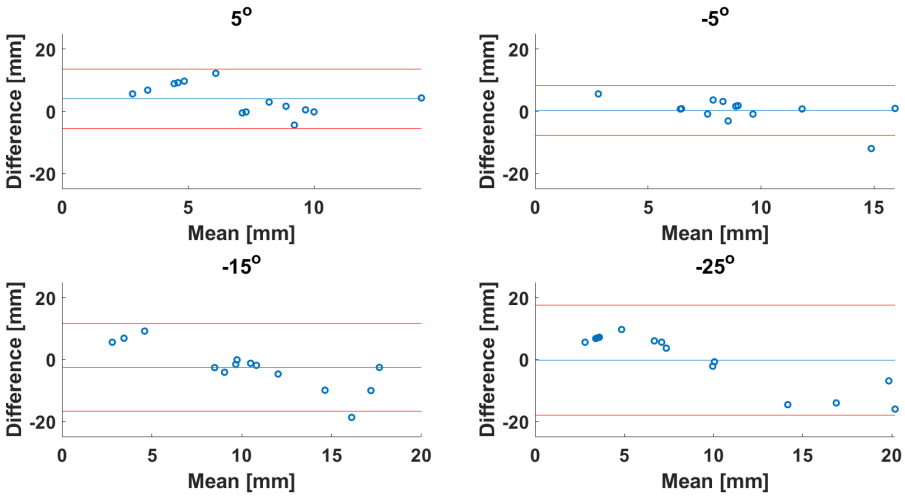


Figure 4.8: Bland Altman plot of agreement between both methods.

4.2.3 Discussion

During the IJV measurements, the protocol changed slightly. In the beginning (subject 1 – 3), only the supine 0° measurements were performed. However, during the measurement of subject 1, the head of the exam table was not positioned at 0° supine position, resulting in a fluid challenge. This eventually led to the change in protocol from subject 4 onwards, to include a measurement with the head slightly tilted downwards. Therefore, not all subjects have double measurements.

Looking at the measured diameters with the SENS-U, it can be noted that the −25° angle of the crystals incorrectly detects the diameter at almost all the subjects. This is also shown in the Bland Altman plot in Figure 4.8, as the −25° crystal shows the least agreement between the methods. The largest agreement can be found at the 5° and the −5° angles of the SENS-U. These are the smallest viewing angles of SENS-U and have a more direct view on the vein than the −15° and −25° angles. For the larger angles, more interference with surrounding structures could occur.

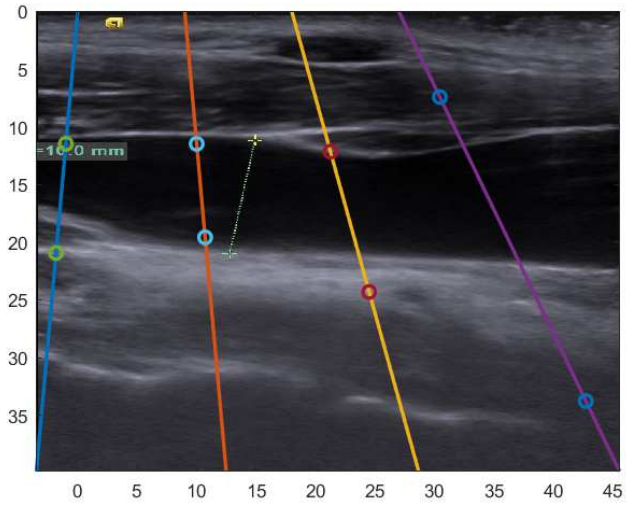


Figure 4.9: Transversal ultrasound image of the IJV of subject 6 (head 0° supine). The data from the SENS-U is plotted over the image.

It can be noticed that the smaller diameters are again absent or wrongly detected by the SENS-U. As noticed in the Phantom study, the ultrasound frequency of the SENS-U needs to be increased to measure smaller vein diameters.

During the measurements, difficulties were encountered considering the placement of the SENS-U. It was noticed that, during the measurements, the SENS-U easily shifted to another position on the neck. This could have led to incorrect readings of the SENS-U, and thus inadequate measured AP diameters. Therefore, the data was corrected by analysing the mean of all the collected data for one measurement. Additionally, the current SENS-U is quite large (95 x 55 x 16 mm) for placement in the neck area. This also led to difficulties with the placement of the SENS-U as it was harder to check the position of the transducers above the IJV. Therefore, it is possible that, for some measurements, surrounding structures were measured instead of the IJV.

Lastly, anatomic variations of the IJV exist. These variations include the shape, location, and relationship of the IJV to the common carotid artery (CCA).[21] As can be seen in Figure 4.10, the CCA and the IJV could have diverse configurations with respect to one another. These configurations also have an affect on the shape of the IJV. This could lead to incorrect measurements of the IJV with the SENS-U if the IJV is not priorly localised with an ultrasound machine. Therefore, the configuration of the IJV and the CCA must be examined before placing the SENS-U.

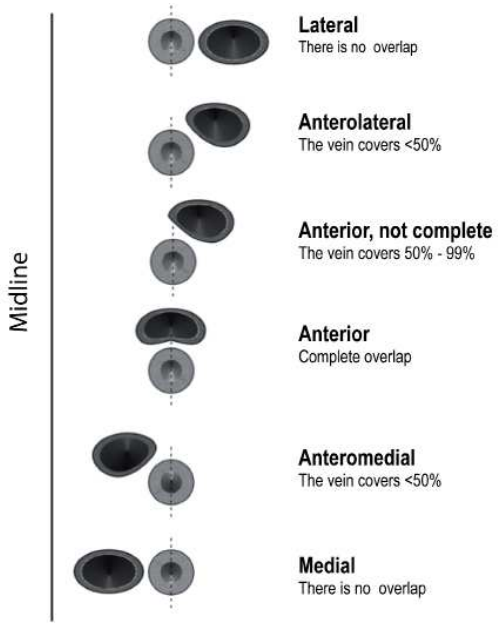


Figure 4.10: Anatomical relationship between the IJV and the CCA. The IJV and the CCA can have various configurations.[53]

4.2.4 Conclusion

Measurements of the IJV diameter with the SENS-U were conducted on healthy volunteers. In total 8 subjects were included, leading to 14 measurements. This study reinforces the idea of increasing the ultrasound frequency for the SENS-U. Additionally, the IJV must first be examined with an ultrasound transducer before placing the SENS-U on the IJV. Furthermore the SENS-U needs to be adhered to prevent shifting during the measurements. Additionally, the SENS-U should become smaller for correct placement in the neck area.

4.3 Proof of concept

A proof of concept study was conducted on one patient to reinforce the choice of using the internal jugular vein diameter. This study took place with help of an anaesthesiologist during surgery.

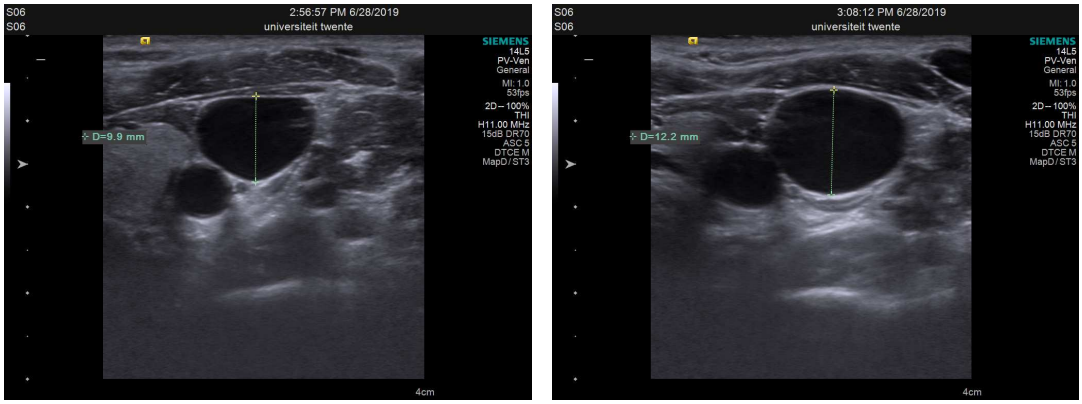
4.3.1 Case report

A 72 year old man arrived at the hospital for planned surgery. This surgery consisted of a right upper lobectomy for suspected malignancy and a coronary artery bypass graft for two- or three-branch disease.

The surgery consisted of two stages. In the first stage the lobectomy took place. Therefore, the patient was mechanically ventilated over the left lung only. The mechanical ventilation was set to pressure control, with a inspiratory pressure of 20 cmH_2O, a positive end-expiratory pressure of 5 cmH_2O, a respiratory rate of 14 breaths per minute and a inspiration time of 1.4 seconds.

The second stage of the surgery consisted of the coronary artery bypass graft. For this part, the patient was ventilated over both lungs during the preparation of the veins. The mechanical ventilation was set to volume control with a tidal volume of 500 mL, a maximum pressure of 30 cmH_2O, a positive end-expiratory pressure of 3 cmH_2O, and a respiratory rate of 14 breaths per minute. For the bypass surgery, the patient was put on the cardiopulmonary bypass. Afterwards the mechanical ventilation was set back to volume control with the same parameters as before the cardiopulmonary bypass.

During the surgery, the IJV diameter was measured in the transversal plane. The ultrasound machine and transducer (GE Vivid S70 Ultrasound Machine and GE 9L-D Linear Probe 2.4 - 10 MHz; GE Healthcare) ensured adequate measurements of the IJV diameter. Unfortunately, the images of the IJV measurements during the surgery cannot be traced. An example of similar IJV measurements is shown in Figure 4.11.



(a) Transversal view, supine **(b)** Transversal view, trendelenburg

Figure 4.11: An example of the IJV diameter measurements is shown.

Table 4.4: IJV diameters measured during the surgery. The right IJV was measured during the first set. The left IJV was measured during the second set.

	IJV diameter [mm]	
	Right IJV	Left IJV
Before fluid shift	17.6	11.0
After fluid shift	12.9	10.3
Difference	*-4.7 [-27%]*	*-0.7 [-6%]*

The measurements could only be performed at two occasions. This led to the two measurements after anaesthesia, but prior to surgery, and two measurements when the patient was ready to come of the cardiopulmonary bypass. During the rest of the surgery, not enough space could be obtained to measure the IJV diameter. During both occasions, 2 measurements were conducted: one measurement before a provoked fluid shift and one measurement after a provoked fluid shift.

For the first set of measurements, a fluid shift was provoked by changing the patient's position from trendelenburg to anti-trendelenburg. These measurements were performed on the right IJV. After this measurement set, a CVC was placed in the right IJV.

For the second set of measurements, a fluid shift was provoked by administering a fluid bolus of 500 cc to the patient. As this measurement took place during the surgery, the fluid shift could not be provoked by changing the patient's position. As the CVC was placed in the right IJV, these measurements were performed on the left IJV. Both measurement sets are found in Table 4.4.

4.3.2 Discussion

For the first set of measurements, a change of 27% in right IJV diameter due to the fluid shift can be observed. As expected, the IJV became smaller in diameter as a result of the provoked fluid shift (a position change from trendelenburg to anti-trendelenburg). The second set of measurements, however, showed no significant change in diameter (6%) before and after the provoked fluid shift (a fluid bolus of 500 cc). This could have several explanations. First, the patient could have been a non responder for fluid responsiveness during the second measurement set. Secondly, there could have been too much interference of other veins for the left IJV. As previous studies mostly focussed on the right IJV (Donahue et al., Jassim et al., for example[11,12]), additional research could focus on the differences between the left and the right IJV diameter.

Unfortunately, only 2 measurement sets could be obtained. During the surgery the lack of space in the neck area prevented the possibility for additional measurement sets. This led to further insights for the design of an ultrasound volume sensor to measure the intravascular volume status. As observed during the measurements with healthy volunteers, the SENS-U is quite large to place in the neck area. During the operation, the available space around the head and neck area was limited. Therefore, it would also be more practical to use a smaller sensor.

4.3.3 Conclusion

A proof of concept study was conducted on one patient during surgery. The IJV diameters were measured with an ultrasound transducer on two occasions.

The measurements on this patient provided more insights on how to continue with the study. The differences between the left and right IJV need further investigation. Additionally, more insights were obtained for the design requirements for a SENS-U to measure the IJV diameters.

Chapter 5

Recommendations

The proof of principle studies in Chapter 4 showed that the SENS-U technology can be used to measure the IJV diameter and could therefore aid in the assessment of intravascular volume status. However, some changes are needed to optimize the SENS-U technology for the measurements of IJV diameter. Additionally, further research must be conducted to obtain more insight in the change of IJV diameter during fluid shifts.

5.1 SENS-U

As mentioned in Chapter 3, the SENS-U was originally designed to aid in the training of children with urine incontinence. To use SENS-U technology for the assessment of intravascular volume status with the IJV, a few adjustments are needed. Therefore, recommendations are made for the ultrasound resolution, real-time measurements, and the design of the SENS-U.

5.1.1 Design

During the measurements with healthy volunteers and the case report, it was noticed that the available space around the head and the neck area was limited. The current SENS-U is quite large, with dimensions of 95 x 55 x 16 mm. A smaller sensor would be more practical to measure the IJV diameter.

The SENS-U Bladder Sensor is a wearable device. For the training of children with urine incontinence it is highly convenient to carry a wearable device, as it is more suitable for activities during daily living. However, this does not apply for patients in need of assessment of the intravascular volume status. Patients that could benefit from this application of the ultrasound sensor are primarily patients admitted to the ICU, or patients undergoing a major surgery and/or haemodialysis. A wearable device will not be primarily necessary for these patient groups.

When it is not required to retain a wearable device, the size of the device can be reduced. Ideally, this would lead to a small patch which contains only the ultrasound transducer module and an external electronics board and battery pack.

When the device is reduced in size to a small patch, positioning of the SENS-U would also become easier. As mentioned in Chapter 4, difficulties were encountered during the positioning of the SENS-U in the neck. These difficulties are largely solved by using a smaller device. Another difficulty was the shifting of the SENS-U in the neck. This could be resolved by using a adhesive patch to secure the SENS-U in the neck. Lastly, as the neck does not posses a completely flat surface, it would be preferred to let the device follow the shape of the neck, and most ideally to use a flexible device. In Figure 5.1, an example of a possible new device in a clinical setting is shown. In this setting, continuous measurements of the IJV diameter for the assessment of intravascular volume status could be achieved.

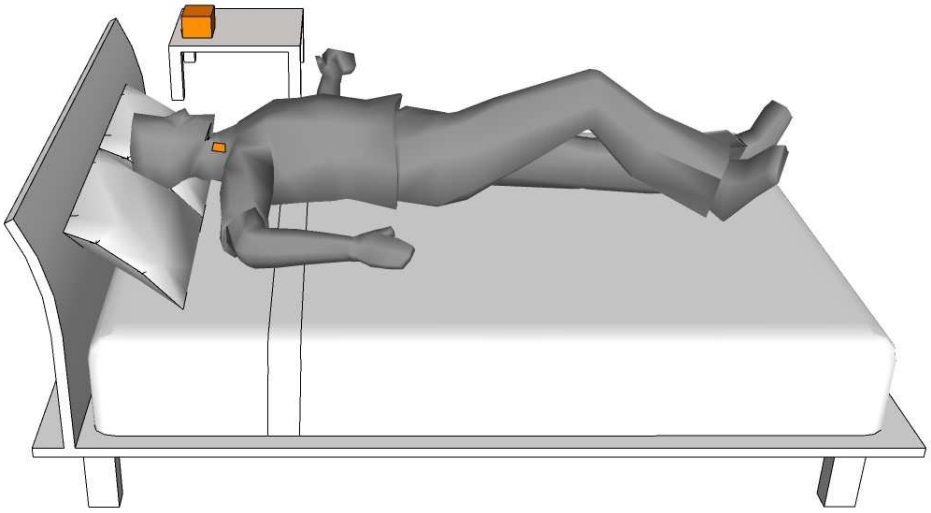


Figure 5.1: An example for a possible new device in a clinical setting. For the assessment of intravascular volume status, the SENS-U is ideally reduced in size to a small, adhesive patch (depicted in orange). This patch is connected through a small wire with an external electronics board and battery pack, simplified shown on the table next to the bed.

5.1.2 Ultrasound resolution

Looking at the results of the phantom study and the study with healthy volunteers, it became clear that the SENS-U has a difficulty with calculating the smaller vein diameters needed for the distinction between a high and low CVP. Therefore, the axial resolution of the SENS-U needs to be improved for this application. As mentioned in Chapter 3, the axial resolution depends on the ultrasound frequency. The SENS-U operates at a frequency of 3.5 MHz. By increasing the frequency of the SENS-U to at least 7 MHz, as used for vascular ultrasound imaging, it is expected to obtain a much better resolution.[51]

5.1.3 Real-time measurements

The IJV diameter changes with the respiratory cycle. Assessment of intravascular volume status using the IJV requires end expiratory measurements of the IJV diameter. To obtain end expiratory IJV diameter with SENS-U technology, real-time measurements of the IJV are required.

Real-time measurements can be obtained by using a high the temporal resolution. This can be achieved by using a short pulse repetition period. As mentioned in Chapter 3, this can be achieved by using a high pulse repetition frequency and a shallow penetration depth.

As the IJV lies at a depth of $\pm$ 1.5 cm, it is possible to use a shallow penetration depth. As the IJV diameter changes with the respiratory cycle, the pulse repetition frequency needs to be high enough to detect the maximum end expiratory diameter.

Normal respiratory rate for healthy adults lies between 15 – 20 breaths per minute.[54] If, for example, a patient is breathing with a respiratory rate of 20/min, one respiratory cycle lasts about 3 seconds. During this time, the IJV diameter reaches its minimal diameter at the end of the inspiration and its maximum diameter at the end of the expiration. If we take an exemplary inspiration time of 0.5 seconds, the expiration time will take 2.5 seconds (inspiration:expiration ratio is 1:2). Hence, a pulse repetition frequency of at least 2 Hz (2/second) is required to measure the minimum or maximum diameter of the IJV. With this pulse repetition frequency, it could also be possible to evaluate the trend of the change in IJV diameter and to calculate the IJV collapsibility index. When a patient has tachypneu (respiratiory rate > 20/minute), a higher pulse repetition frequency is needed.

However, increasing the pulse repetition frequency of the SENS-U will lead to a shorter period of operation when powered by a small battery pack. This issue can be resolved by using a larger battery pack, or by plugging the SENS-U into a power outlet. This is only possible as, for this application, it is not primarily necessary for the SENS-U to be a wearable device, which enables the possibility to use an external power source.

5.1.4 Piezoelectric crystals

The SENS-U Bladder Sensor is based on a combination of four piezoelectric crystals, placed at an angle of respectively 5°, $-5°$, $-15°$, and $-25°$, making it able for the SENS-U to estimate the (AP) bladder dimensions. During the filling of the bladder, the bladder dimensions will increase over a three-dimensional plane, leading to the demand of multiple measurement angles. However, the change in IJV AP diameter, when measured longitudinally, occurs solely over a two-dimensional plane. Therefore, less data points are needed for the calculation of IJV AP diameter. As a result, measurements on IJV diameter require fewer piezoelectric crystals.

Reflecting on the results from the study with healthy volunteers, the 5° and $-5°$ gave the smallest relative errors (-9.5% and -12.9% respectively), while the $-15°$ and $-25°$ angles gave rather large relative errors (33.2% and 34.6% respectively). This indicates

that the $-15°$ and $-25°$ give no substantial added value to the measurements of the IJV diameter.

Ideally, one would prefer to place a piezoelectric crystal at an angle of $0°$, to obtain a direct view on the IJV. This is, however, not achievable for the SENS-U. For this reason, it is recommended to solely use two piezoelectric crystals, placed at an angle of respectively $5°$ and $-5°$. By maintaining these angles a position check could be performed, as it is expected that these angles will lead to the same result in measured AP diameter.

5.2 Further research

After adjustments are made for the SENS-U, a new phantom study must be conducted. For the new phantom study, a similar phantom as in this study can be created. With a new phantom study, the axial resolution of the SENS-U can be re-examined.

After the phantom study, new measurements on healthy volunteers can be conducted. For the measurements on healthy volunteers, a new measuring protocol is recommended. During the case study, the measurements on the left IJV did not show a significant change in diameter after the provoked fluid shift. As mentioned in Chapter 4, this could be due to fluid unresponsiveness, or interference of surrounding structures. In a new measuring protocol, the differences between the right en left IJV can be explored. Additionally, the difference between "hypovolaemic" and "fluid overloaded" can be taken into account. A proposal for a new measuring protocol can be found in Appendix D.

Additionally, further research can be conducted on the change of IJV diameter during haemodialysis for example. This could exists in the form of a pilot study. During this pilot study, more insight can be obtained on how the IJV diameter changes exactly during a known fluid shift. For this pilot study, approval from an Ethical Committee is required.

Chapter 6

General conclusion

Accurate assessment of the intravascular volume status remains a challenging task for clinicians. Several methods and tests are available to evaluate a patient's volume status, both invasive and non-invasive. Ultrasound assessment of the IJV is a promising, non-invasive, technique for monitoring the volume status and can be repeated as often as necessary.

Ultrasonographic measurements of the IJV for the assessment of intravascular volume status has many clinical and practical implications. Limited technical expertise is required to examine and measure the IJV. For example, using ultrasound assessment of the IJV could aid in emergency situations where CVC placement will be too time-consuming, to avoid the placement of a CVC for solely measuring the CVP in the ICU, to reduce volume status related complications of haemodialysis, or to monitor a patient during major surgery.

As the results of ultrasound assessment are highly user dependent, an ultrasound volume sensor such as the SENS-U Bladder Sensor could offer support in the non-invasive assessment of intravascular volume status. This study explored the clinical and technological feasibility of an ultrasound volume sensor to measure the intravascular volume status.

Proof of principle studies were performed to explore the feasibility. These studies consisted of a phantom study, IJV diameter measurements on healthy volunteers with the SENS-U, and a case study. Based on these studies, recommendations were made for the development of an ultrasound volume sensor for the assessment of intravascular volume status. These recommendations included the design of a new sensor, improvement of axial and temporal resolution, and the amount of piezoelectric crystals required for the measurements. If a new sensor will be developed, this sensor could determine the AP diameter and the collapsibility index of the IJV. Additionally, a trend of the change in IJV diameter can be evaluated.

Further research could obtain more insight in the change of IJV diameter during (known) fluid shifts and differences between the left and the right IJV.

Appendix A

Measuring protocol healthy volunteers

Measurements with healthy volunteers were conducted according to the following protocol:

1. For each subject the following will be noted:
   (a) Age
   (b) Sex
   (c) Length
   (d) Weight
   (e) BMI (calculated)
   (f) Neck circumference
2. The subject is positioned on the exam table with the head at 0° supine.
3. The subject will be asked to turn the head to the opposite of the measuring site for optimal visualisation of the IJV.
4. The IJV will be localised with an ultrasound transducer and the AP diameter will be measured.
5. Subsequently the SENS-U will be positioned on the neck and the AP diameter will be measured using the SENS-U.
6. The subject is repositioned on the exam table, with the head in trendelenburg.
7. Steps 3 – 5 are repeated for the new position.
8. Images obtained with the ultrasound transducer are saved on a flash drive.

Appendix B

Subject information

Subject	Sex [M/F]	Age	Length [cm]	Weight [kg]	BMI [kg/m^2]	Neck circumference [cm]
1	F	23	180	71	21.9	37
2	F	24	170	62	21.5	34
3	F	25	168	60	21.3	33
4	F	20	172	60	20.3	34
5	F	20	173	59	19.7	35
6	F	21	165	60	22	31
7	F	20	179	65	20.3	33.5
8	M	21	184	68	20.1	36.5

Appendix C

Measurements healthy volunteers

The following page contains the measured IJV diameters for the healthy volunteers.

Table C.1: Measured IJV diameters on the healthy volunteers.

Subject	AP diameter echo [mm]	AP diameter SENS-U [mm]												
		5°			−5°			−15°			−25°			
		Mean	Difference	%	Mean	Difference	%	Mean	Difference	%	Mean	Difference	%	
1	16.4	12.11	-4.29	-26.2	15.47	-0.93	-5.67	18.92	2.52	15.37	23.26	6.86	41.83	n = 9
2	9.7	6.73	-2.97	-30.6	8.07	-1.63	-16.8	19.57	9.87	101.8	–	-9.7	-100	n = 9
	9.7	8.07	-1.63	-16.8	6.06	-3.64	-37.5	9.78	0.08	0.8	10.41	0.71	7.3	n = 9
3	8.9	–	-8.9	-100	20.86	11.96	134.4	10.44	1.54	17.3	11.02	2.12	23.8	n = 11
4 $_{0°}$	6.8	–	6.8	-100	6.06	-0.74	-10.9	25.44	18.64	274.1	–	-6.8	-100	n = 7
4 $_{downwards}$	7	11.43	4.43	63.3	10.09	3.09	44.1	11.09	4.09	58.4	–	-7	-100	n = 8
5 $_{0°}$	7.2	7.4	0.2	2.8	8.07	0.87	12.1	9.79	2.59	36.0	–	-7.2	-100	n = 9
5 $_{downwards}$	9.9	10.09	0.19	1.9	6.73	-3.17	-32.0	11.09	1.19	12.0	4.29	-5.61	-56.7	n = 11
6 $_{0°}$	9.9	9.42	-0.48	-4.8	8.07	1.83	-18.5	11.74	1.84	18.6	23.87	13.97	141.1	n = 9
6 $_{downwards}$	12.2	-	-12.2	-100	11.44	-0.76	-6.2	22.18	9.98	81.8	28.16	15.96	130.8	n = 10
7 $_{0°}$	5.6	–	-5.6	-100	–	-5.6	-100	–	-5.6	-100	–	-5.6	-100	n = 7
7 $_{downwards}$	6.9	7.4	0.5	7.2	6.06	-0.84	-12.2	–	-6.9	-100	21.43	14.53	210.6	n = 10
8 $_{0°}$	9.7	–	-9.7	-100	8.07	-1.63	-16.8	14.35	4.65	47.9	3.67	-6.03	62.2	n = 9
8 $_{downwards}$	9.2	–	-9.2	-100	10.09	0.89	9.7	–	-9.2	-100	5.51	-3.69	-40.1	n = 11

Appendix D

Proposal new measuring protocol healthy volunteers

A proposal for a new measuring protocol for the measurements on healthy volunteers. For these measurements, two groups will be created. One group will have consumed at least 1 L of water prior to the measurements in order to mimic a "fluid overload". The other group will not have consumed any liquid prior to the measurements in order to mimic a "hypovolaemic" state. The following measurement protocol is otherwise the same for both groups.

1. For each subject the following will be noted:
   (a) Age
   (b) Sex
   (c) Length
   (d) Weight
   (e) BMI (calculated)
   (f) Neck circumference
2. The subject is positioned in a supine position on the exam table.
3. The subject will be asked to turn the head to the opposite of the measuring site for optimal visualisation of the IJV.
4. The IJV will be localised with an ultrasound transducer and the AP diameter will be measured.
5. Subsequently the SENS-U will be positioned on the neck and the AP diameter will be measured using the SENS-U.
6. Steps 3 – 5 are repeated for the other IJV.
7. The subject is repositioned in trendelenburg on the exam table.
8. Steps 3 – 6 are repeated for the new position.
9. The subject is again repositioned on the exam table, but now in anti-trendelenburg.
10. Steps 3 – 6 are repeated again for the new position.
11. Images obtained with the ultrasound transducer are saved on a flash drive, data obtained with the SENS-U are saved in .csv files.

Appendix E

Proposal measuring protocol pilot study

A proposal for a measuring protocol for the measurements on patients on for example haemodialysis. Measurements of the IJV diameter during haemodialysis could obtain insights in the trend in the change of IJV diameter.

Inclusion criteria

- > 18 years old
- Voluntary participation
- Informed consent
- Haemodynamic and respiratory stable

Exclusion criteria

- Deep venous thrombosis in the upper extremities (in the patients history, or current)
- Bilateral central venous catheters
- Cardiac arrhythmias
- Clinically significant tricuspid or mitral regurgitation
- Neck morphology
- Neck or chest radiation in the patients history

Measuring protocol

A linear vascular probe will be used to create a two-dimensional ultrasound image of the right IJV. The IJV diameter will be measured both transversal and longitudinal. The ultrasound images will be saved anomalously on a flash drive.

The measurements will take place at predetermined times. For example, during haemodialysis the measurements will take place:

1. A baseline measurement right before the start of the haemodialysis;
2. $\pm$ every 15 minutes during the haemodialysis;
3. and a measurement right after the haemodialysis.

As far as possible, the measurements will be carried out in a 0° supine position.

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