Heart Rate Assessment Technologies for Neonatal Resuscitation

by

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ABSTRACT

Every year, 13-26 million newborn infants require immediate respiratory support and 1-2 million require extensive resuscitation involving critical interventions, such as chest compressions and epinephrine administration. For these infants, heart rate (HR) is the most sensitive indicator to guide interventions during neonatal resuscitation. An inaccurate or slow HR assessment could lead to inappropriate, prolonged, or delayed interventions, increasing the risk of serious hypoxic injury and death. International neonatal resuscitation guidelines currently recommend umbilical cord palpation, auscultation with a stethoscope, electrocardiography (ECG), and pulse oximetry for HR assessment. However, auscultation and palpation tend to underestimate HR, while ECG and pulse oximetry are suboptimal for initial HR assessment and in special cases. This thesis reviewed novel technologies for HR assessment including digital stethoscope (DS), tap-based mobile apps, Doppler ultrasound, photoplethysmography, camera-based photoplethysmography (cPPG), laser Doppler vibrometry, ECG-based techniques, and sensor-based technologies. While several are promising, limited evidence exists for the use of these technologies during neonatal resuscitation. The objective of this thesis was to evaluate the use of the DS using three auscultation techniques including the recommended 6-sec method (DS+6sec), 10-sec method (DS+10sec), and NeoTapLS app (DS+NeoTapLS), Doppler ultrasound, and cPPG, for neonatal resuscitation.

An animal and clinical study were conducted. In the animal study, piglets (n=20, 1-3 days) were anesthetised, surgically instrumented, mechanically ventilated, and subjected to hypoxia followed by asphyxia. Asphyxia was induced by clamping the

endotracheal tube and disconnecting the ventilator, until asystole was confirmed by zero carotid blood flow (CBF). During asphyxia, HR assessments were performed using DS+6sec, DS+10sec, DS+NeoTapLS, and Doppler ultrasound. These were compared to gold standards, CBF-derived HR and ECG HR. Bland-Altman analysis, intra-class correlation coefficients (ICC), and frequency of errors according to HR decision-making ranges, were used as measures of accuracy. Assessment times for DS+6sec, DS+10sec, and DS+NeoTapLS were also measured. No differences in mean HR were observed when compared to ECG and CBF HR. Bland-Altman analysis revealed mean differences (95% limits of agreement) of -1 (-21 to +19), 0.6 (-23 to +25), 0.7 (-13 to +15), and 0.9 (-13 to +15) bpm, for DS+6sec, DS+10sec, DS+NeoTapLS, and Doppler ultrasound, respectively. An adjusted ICC of 0.935, 0.905, 0.966, and 0.969 was also computed for DS+6sec, DS+10sec, DS+NeoTapLS, and Doppler ultrasound, respectively. The overall proportion of errors was 4% using DS+6sec, DS+10sec, and DS+NeoTapLS, and 9% using Doppler ultrasound. Of the DS auscultation techniques, using NeoTapLS had the shortest assessment time 3(2–4) sec. Surrounding noises could influence the accuracy of DS HR and the use of the 10-sec method placed a greater cognitive workload on the assessor. The accuracy of Doppler ultrasound could also be affected by motion artefacts, ventilation peaks, and low cardiac output.

In the clinical study, early gestational newborn infants (n=40, <37 weeks) requiring respiratory support were recruited from the delivery room. A video camera was installed prior to delivery and used to collect HR recordings for cPPG. ECG was utilized as per local resuscitation procedures and HR was stored for analysis. Bland-Altman analysis and ICC was utilized to measure the accuracy of cPPG HR using ECG HR as the

gold standard. Bland-Altman analysis revealed a mean difference (95% limits of agreements) of +0.4 (- 8.0 to +8.7) bpm between measured mean cPPG HR and ECG HR with an ICC of 0.83. Motion artefacts, ambient light, and low perfusion levels could influence the accuracy of cPPG assessments.

These use of DS+6sec, DS+10sec, DS+NeoTapLS, Doppler ultrasound, and cPPG were all accurate for HR assessment. The use of DS+6sec, DS+NeoTapLS, and Doppler ultrasound, might improve initial HR assessment at birth. DS+6sec, DS+NeoTapLS, Doppler ultrasound, and cPPG have a similar accuracy to ECG and are also promising alternatives for continuous HR assessment. However, further clinical trials and studies are necessary to test if the use of these technologies ultimately enhance neonatal resuscitation and improve outcomes at birth.

PREFACE

This thesis is an original work by Peter Anto Johnson. This thesis consists of multiple research projects, which have received research ethics approval from the University of Alberta Research Ethics Board, including: “Sustained Inflation and Chest Compression”, AUP00002151, April 19, 2017, and “Cerebral regional tissue Oxygen Saturation to Guide Oxygen Delivery in preterm neonates during immediate transition after birth (COSGOD III)”, Pro00065767, June 13, 2016.

Research conducted for this thesis was performed in collaboration with our research team. Chapter 1 includes modified sections from a review published as P.A. Johnson, P.Y. Cheung, T.F. Lee, M. O'Reilly, and G.M. Schmölzer, “Novel technologies for heart rate assessment during neonatal resuscitation at birth - A systematic review” *Resuscitation*, vol. 143, 196-207. I was responsible for conception and design of the review, literature search, composition of the article, and critical revisions. P.Y. Cheung, T.F. Lee, and M. O'Reilly contributed to critical revisions. G.M. Schmölzer was the supervisory author and involved with conception and design of the review, literature search, manuscript composition, and critical revisions.

Chapter 1 also includes modified sections from a review published as P.A. Johnson, G.M. Schmölzer, “Heart rate assessment during neonatal resuscitation” *Healthcare*, vol. 8, article 48. I was responsible for conception and design of the review, literature search, composition of the article, and critical revisions. G.M. Schmölzer was the supervisory author and involved with conception and design of the review, literature search, manuscript composition, and critical revisions.

Chapters 2 and 3 include modified sections from an article published as P.A. Johnson, N. Morina, M. O'Reilly, T.F. Lee, P.Y. Cheung, and G.M. Schmölzer, "Evaluation of a tap-based smartphone app for heart rate assessment during asphyxia in a porcine model of neonatal resuscitation" *Frontiers in Pediatrics*, vol. 7, article 453. I was responsible for conception and design, data collection, data analysis, composition of the manuscript, and critical revisions. N. Morina, M. O'Reilly, T.F. Lee, and P.Y. Cheung, assisted with data collection and critical revisions. G.M. Schmölzer was the supervisory author and involved with conception and design, data collection, data analysis, composition of the manuscript, and critical revisions.

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DEDICATION

Dedicated to my family, friends, mentors, and God.

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I would like to acknowledge all the individuals who have supported and encouraged me through this journey, which has been both exciting and challenging, for making it a rewarding one – this work would never have been possible alone.

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ABBREVIATIONS

bpm	Beats per minute
CBF	Carotid blood flow
CI	Confidence interval
cPPG	Camera-based photoplethysmography
DS	Digital stethoscope
DS+10sec	Digital stethoscope using the 10-second method
DS+6sec	Digital stethoscope using the 6-second method
DS+NeoTapLS	Digital stethoscope paired with NeoTapLifeSupport
ECG	Electrocardiography
ET	Endotracheal
HR	Heart rate
IQR	Interquartile range
PEA	Pulseless electrical activity
PO	Pulse oximetry
PPG	Photoplethysmography
PPV	Positive pressure ventilation
PZT	Piezoelectric transducer
NeoTapLS	NeoTapLifeSupport mobile app
NICU	Neonatal intensive care unit
NRP	Neonatal Resuscitation Program
SD	Standard deviation
SpO_2	Oxygen saturation
STIF	Sensor to infant first
STOF	Sensor to oximeter first

CHAPTER 1. Introduction

This chapter consists of slightly modified sections from two previously published articles and has been reproduced here with the permission of the copyright holders:

1. Johnson PA, Cheung PY, Lee TF, O'Reilly M, Schmölzer GM. Novel technologies for heart rate assessment during neonatal resuscitation at birth - A systematic review. *Resuscitation*. 2019 October 1; 143:196-207. doi: 10.1016/j.resuscitation.2019.07.018.
2. Johnson, P.A.; Schmölzer, G.M. Heart rate assessment during neonatal resuscitation. *Healthcare.* 2020 February 23, 8, 43. doi: 10.3390/healthcare8010043.

1.1. Introduction

When a newborn infant is born, the first minutes of life are extremely critical for transitioning and adapting to the extra-uterine environment. The fetal-to-neonatal transition is a sequence of significant physiological events at birth consisting of clearance of liquid from the lung, lung aeration, establishment of gas exchange, and initiation of spontaneous breathing[1–4]. This results in an increase in oxygen saturation, pulmonary blood flow, and systemic vascular resistance, and occlusion of fetal shunts, which must occur during this time[1,4,5]. Asphyxia at birth is the most common reason that newborn infants fail to make a successful transition, as it can depress myocardial function and act against this sequence, inducing bradycardia and leading to asystole (cardiac arrest)[6].

As a consequence, the Neonatal Resuscitation Program (NRP) recommends the assessment of heart rate (HR) at birth if infants do not breathe or are floppy after the initial steps of newborn care[7,8]. HR is then used to decide what interventions are needed and the changes in HR are used to determine their effectiveness during resuscitation[7,9,10]. As such, if HR is detected too slowly or inaccurately, it will delay critical interventions or lead to inappropriate interventions, which are ineffective to improve the infant's status and/or increase the risk of cardiac arrest leading to infant death or severe hypoxic damage. NRP and other neonatal resuscitation guidelines uses predefined HR targets at 100 beats per minute (bpm) and 60 bpm to initiate mask ventilation and chest compressions, respectively[7,8,10]. It is important to note these cutoffs were chosen arbitrarily, as neither human nor animal data are available to support these cutoffs[11]. Instead, successfulness of resuscitations relies more significantly on how effectively and rapidly the appropriate interventions are delivered based on changes in HR.

Thus, technologies and techniques for HR assessment with longer latency could result in delay or prolongation of these interventions; alternatively, any assessment method that either over- or underestimates HR might result in unnecessary interventions. Therefore, HR assessments at birth must be feasible, safe, and fast, with minimal latency and high accuracy.

1.2. Current recommendations

Until recently, auscultation and palpation along with pulse oximetry (PO) were recommended for HR assessment in the delivery room[12]. In 2015, the updated neonatal resuscitation guidelines added electrocardiography (ECG) as standard monitoring for HR assessment[7,8]. Although these techniques and technologies have been evaluated in literature for accuracy, assessment times, and its limitations (Table 1.1)[13], there is an ongoing debate and uncertainty regarding the optimal recommendations for HR assessment.

1.2.1 Palpation/Auscultation

Palpation involves the assessment of a pulse at the umbilical, femoral, or brachial arteries, whereas auscultation involves using a stethoscope to listen to heart beats, normally from the chest of the infant (Figure 1.1, Table 1.1)[8,14]. The NRP recommends the 6-sec method, which involves counting the heart beats heard over 6 seconds and multiplying by 10 to determine HR in bpm[15]. Accounting for placement, pulse detection, listening window of 6 seconds, and time required for mental computation, this technique allows for quick approximation of HR. While increasing the assessment time (e.g., using

the 10 sec method, which counts beats heard in 10 seconds and multiplies by 6 to calculate HR) using auscultation and palpation has been suggested to improve accuracy[16,17], this can increase the time required for the mental computation of HR. Moreover, both palpation and auscultation are inexpensive and useful in low-resource settings, where access to more advanced HR monitoring technologies are limited. A total HR assessment time ranging from 7-19 sec on average have been previously reported for both palpation and auscultation[18–20].

Owen & Wyllie compared palpation at the femoral and brachial artery and umbilical cord in newborn infants to assess the accuracy of calculating a HR >100 bpm[14]. Auscultation using a stethoscope provided HR>100 bpm in 100% of the cases, whereas palpation did not always result in a palpable HR[14]. Palpation of the umbilical pulse was accurate for 55% of cases, compared to 20% and 25% at femoral and brachial pulse, respectively[14]. Moreover, a concerning 25% and 60% of participants were unable to palpate a pulse, while 15% and 45% incorrectly assessed HR as <100 bpm using the femoral and brachial pulse, respectively[14]. Therefore, auscultation is more accurate than palpating from any of the three locations, but when a stethoscope is not available, palpation of the umbilical cord provides greater accuracy.

Chitkara *et al* and Boon *et al* randomized healthcare providers to either auscultation or palpation, blinding them to high-fidelity simulated neonatal resuscitation scenarios[15,21]. Healthcare providers were randomized to scenarios representing the NRP HR target ranges at >100, 60-100, <60 bpm and required to perform an initial assessment followed by subsequent assessments. Both studies reported the greatest accuracy of HR at <60 bpm, followed by 60-100 bpm, and then >100 bpm[15,21]. Chitkara *et al* additionally

determined no difference between initial and subsequent assessments, with errors occurring an alarming 26-48% and 26-52% of the time, respectively[21]. However, a more recent simulation study by Money *et al* evaluated the accuracy of auscultation according to NRP HR target ranges and identified overestimation of HR <60 bpm and underestimation of HR >100 bpm as a common tendency for participants[22]. The latter observation was similar to a study by Kamlin *et al*, who compared auscultation and umbilical cord palpation with ECG in term newborn infants and reported both auscultation and umbilical cord palpation underestimated HR with a mean HR difference of 14 and 21 bpm, compared to ECG[23]. More recently, Cavallin *et al* confirmed a similar underestimation, with mean differences of 13, 4, 6, and 10 bpm at 60 sec, 90 sec, 120 sec and 5 min using auscultation and mean differences of 20, 25, 23, and 31 bpm at 60 sec, 90 sec, 120 sec and 5 min using palpation, in a randomized clinical trial for newborns requiring resuscitation in a low-resource setting[24]. These studies suggest HR assessments using palpation or auscultation are inaccurate, thereby resulting in a greater number of incorrect assessments for determining HR at birth. This is concerning, as under- or overestimation of HR can result in inappropriate management (i.e., early or delayed interventions) in 28% of cases in a simulated environment alone[18]. During neonatal resuscitation in the delivery room, there is an even greater risk of inappropriate management, as assessment of HR using auscultation has other challenges. Resuscitators need to assess HR while working under high stress levels, high cognitive loads, and varying levels of surrounding noise. Furthermore, due to the wide HR variability, which occurs within the first few minutes after birth, and unpredictable nature of responses in infants, compared to manikins, assessment is much more challenging.

1.2.2. Pulse oximetry

PO can measure both oxygen saturation and HR continuously and is routinely placed on the infant's hand or wrist (Figure 1.1, Table 1.1)[25,26]. Two light diodes emit light at red and infrared frequencies and a photo-detector measure the changes in the transmitted light from the oxygenated and deoxygenated blood and thereby determine oxygen saturation[27]. For HR, the change in intensity of light corresponding to arterial blood volume changes associated with each pulse is detected and used by the oximeter to calculate HR[27]. However, there are several limitations of PO to monitor HR including i) delays in time needed to display first HR values[28,29], ii) potential underestimation of HR compared to ECG outcomes[30], and iii) difficulties in obtaining a good signal quality when HR<100 bpm[28,30]. Other limitations include: low peripheral perfusion, the effect of transitional circulation, low volume state, vernix effects, skin oedema, acrocyanosis, signal dropout, movement artefacts, arrhythmias, and presence of ambient lighting, which might delay or interfere with PO HR measurements[31–35].

The vast majority of studies examining the accuracy and reliability of PO for HR assessment utilize ECG for comparison[36]. Six studies comparing PO to ECG for HR assessment in the delivery room[19,28–30,37,38] and one comparing both of these technologies in the neonatal intensive care unit (NICU)[39] were identified. While accuracy is most commonly described as the level of association with the gold standard (ECG for most cases), reliability is defined by detection and signal quality of a waveform (PO or ECG). Kamlin *et al* analyzed 5877 data pairs of ECG HR and good-quality PO HR (defined by the presence of signal bars and no "low-signal quality" message) in 55 preterm or term

infants reporting a mean (2 SD) difference between ECG HR and PO HR as -2 (26) bpm overall and -0.5 (16) bpm in infants who received either positive pressure ventilation (PPV) and/or cardiac massage[28]. However, at ECG HR<100 bpm, good-quality PO HR <100 bpm could only be detected 89% of the time[28]. While these former results suggest a strong accuracy for PO HR monitoring at birth when compared to ECG HR monitoring, the latter suggests the need to explore specific outcomes during bradycardia. In a study by Iglesias *et al*, both PO and ECG were used to detect bradycardia (HR <100 bpm) during stabilization[37]. PO detects both the start and end of bradycardia episodes a median time of 5 seconds slower than ECG[37], which is concerning as it could lead to delayed initiation of resuscitation interventions or the unnecessary prolongation of interventions.

A study by van Vonderen *et al* examined the accuracy of PO, compared to ECG, for HR assessment in the first minutes after birth[30]. PO underestimated HR, displaying HR <100 bpm and suggesting bradycardia in the first minutes after birth in uncompromised infants[30]. This underestimation was verified by the weaker association of PO HR with left ventricular outflow when compared to ECG HR, which suggests PO missed beats and is unreliable for detecting all pulse waves from the peripheral vasculature in the immediate transition[30]. With the low accuracy and reliability of PO during the first minutes of life, including the Golden Minute, which is the first minute of life when HR assessments are strongly recommended, the latency of signal detection must be a major consideration for HR assessment at birth.

Unfortunately, long latency ranging from 1-2 minutes for sensor attachment and reliable signal display following birth are reported for PO, indicating HR is not detected within the Golden Minute[36,40]. In a study by Mizumoto *et al*, achieving a reliable PO and

ECG signal at birth required a median (IQR) time of 122 (101-146) vs. 38 (34-43) sec, respectively[29]. Furthermore, HR detection was more difficult using PO when compared to ECG, in bradycardic newborn infants with poor perfusion[29]. Therefore, healthcare providers must not rely exclusively on PO, especially during bradycardia, as PO might underestimate HR. Two further studies have examined the fastest approach to detect HR using two different PO application techniques[35,41]. One technique involves attaching the PO sensor to the oximeter first (STOF), whereas the other requires the attachment of the sensor to the infant first (STIF). While the first study determined the STIF method was faster and more reliable providing data within 90 seconds after birth[41], the second showed suggested STOF had a faster signal acquisition time, although both techniques provided a similar time from birth to a reliable signal[35]. In spite of these limitations, PO is valuable for HR assessment in various special cases in the delivery room where ECG may not be effective.

1.2.3. Electrocardiography

ECG is the current "gold standard" to compare HR assessments in newborn infants and it involves the use of electrodes on the infant's chest to measure electrical activity of the heart[30,42,43] (Figure 1.1, Table 1.1). Electrical activity originating from the sinoatrial node of the heart leads to heart muscle depolarization and repolarization for every heartbeat, which is recorded by these electrodes and used to generate a continuous ECG waveform. ECG measures HR by using R-wave detector algorithms utilizing the time between QRS complexes, which represents ventricular electrical activity and can be utilized to confirm the reliability of the signal[44]. With the time delay to achieve HR signal

with PO and lower accuracy associated with auscultation or palpation, current resuscitation guidelines weakly recommend ECG monitoring, which enables "accurate and rapid" HR assessments, for neonatal resuscitation[7,8]. Although Kamlin *et al* has reported similar accuracy between PO and ECG for HR monitoring[28], van Vonderen *et al* reported PO underestimates HR in the first 2 min after birth when compared to ECG[30]. Additionally, three randomized clinical trials by Murphy *et al* and Katheria *et al* demonstrated obtaining HR required a significantly lower median (IQR) time after birth using ECG compared to PO [24 (19–39) sec vs. 48 (36-69) sec and 66 (46-86) sec vs. 114 (75-153) sec][19,38,39]. Similarly, Mizumoto *et al* and Katheria *et al* reported a longer time to obtain HR using PO compared to ECG in both preterm and term infants[29,45]. Furthermore, during bradycardia episodes (HR <100 bpm) during stabilization immediately after birth PO has a longer detection time compared to ECG[37]. A total of 29 episodes of bradycardia were measured using ECG compared to 9/29 (31%) detected with PO having a median time delay of 5 sec to display bradycardia[37]. Progressive bradycardia resulted in significantly lower PO HR measurements compared to ECG, suggesting ECG is more effective, faster, and a higher accuracy at detecting changes in HR[37]. In the context of neonatal resuscitation, this is critical information as bradycardia guide decisions about the need for interventions such as PPV or chest compressions[7,8,46].

Additionally, Murphy *et al* determined auscultation and PO underestimated ECG HR by a mean difference (95% confidence interval (CI)) of −9 (−15 to −2) and −5 (−12 to 2) bpm, respectively[19]. This supports previous studies, which identified the other techniques underestimate ECG HR for infants with HR >100 bpm. In the trial by Katheria *et al*, it was determined PO HR was lower than ECG HR in the first two minutes

of life, yet no significant differences were determined in time to the delivery of the appropriate interventions in both groups[39]. While this is encouraging, this initial underestimation may be more critical in high-risk infants that require advanced interventions such as chest compression. In fact, a recent retrospective study suggests ECG use is associated with increasing administration of chest compressions and fewer endotracheal (ET) intubations in the delivery room[47]. Another benefit of having an early, reliable HR is the improved preparedness of the clinical team for any intervention.

However, the routine use of ECG for HR assessment also has some limitations. ECG-electrodes can easily become dislodged, due to wet skin (e.g., blood, mucus, vernix or amniotic fluid). In addition, extremely premature infants have more delicate, fragile skin, where the application of ECG-electrodes can result in skin injury[45]. Moreover, several case reports and animal studies reported pulseless electrical activity (PEA), which results in the display of HR when there is no cardiac output[48–55]. Patel *et al* and Loung *et al* reported PEA is present in 40-50% of asphyxiated newborn piglets, which falsely displayed a HR on the ECG[51,52]. Similarly, case reports and case series reported a total of seven cases of PEA during neonatal resuscitation in the delivery room[49,53–55]. This is concerning as PEA might delay the start of interventions as the clinical team may be misled or reassured by the displayed ECG HR. In addition, a recent case report of a preterm infant with a diagnosis of non-immune hydrops fetalis, with bilateral pleural effusions, ascites, and subcutaneous edema reported ECG is not always sufficiently sensitive[56]. The ECG was unable to display QRS complexes and thus PO HR was used to guide resuscitation[56]. Once circulation and perfusion was improved ECG signal returned[56]. This also suggests circumstances exist wherein healthcare professionals

should not solely rely on ECG for HR monitoring alone and rather use a combination of techniques or novel, more effective techniques or technologies.

1.3. Novel techniques and technologies

While several novel techniques and technology for monitoring heart rate have been identified for HR assessment in newborn infants[36,40,57], the majority of studies were carried out in newborn infants not requiring resuscitation and therefore constitute an indirect form of evidence[36]. As such, there is a need for more evidence for the clinical efficacy of novel techniques and technologies for HR assessment during neonatal resuscitation. Of the identified novel technologies, they can be classified into several groups including continuous contact (e.g., ECG, PO, dry-electrode ECG, electrical velocimetry, reflectance photoplethysmography, electromyography), intermittent contact (e.g., auscultation/palpation, Doppler ultrasound, DS), non-contact (camera-based photoplethysmography, laser Doppler vibrometry), sensor-based (e.g., capacitive sensors, piezoelectric sensors), and assistive technologies (e.g., tap-based mobile apps)[13].

1.3.1. Digital stethoscope

A digital stethoscope (DS) is an intermittent contact technology, which converts acoustic sound into electronic signals and can be used to assess HR (Figure 1.1, Table 1.2). The DS provides an amplified sound output, attenuates ambient noise and filters frequencies outside the range for heartbeats, providing greater accuracy and precision than conventional stethoscopes[58,59]. Recent updates have also enabled automated HR assessments via connected or built-in computer algorithms[58]. Nonetheless, DS' have

many similar limitations as auscultation with a normal stethoscope in a delivery room environment, as it can be stressful, noisy, require greater cognitive demands (for non-automated assessment), and be challenging for HR assessment. Kevat *et al* compared DS with auscultation or palpation in 50 infants admitted to the neonatal intensive care unit to assess the accuracy, latency, and efficacy of HR assessments[60]. The mean difference (SD) in DS HR compared to ECG HR was 7.4(24) bpm, which was lower than previously reported differences between ECG and standard auscultation or palpation[60], suggesting a higher accuracy with a DS. However, Gaertner *et al* compared DS utility in 37 infants and reported DS technology detected HR in only 23/37 infants within 30 sec[61]. The mean difference (95% CI) was of 0.2 (-17.6 to 18) bpm with a higher correlation with the ECG HR[61]. In the remaining 14 infants HR could not be assessed due to crying[61]. Similarly, Treston *et al* compared HR assessment using DS versus handheld ultrasound versus ECG and reported successful HR assessment in 13/20, 20/20, and 20/20, respectively[62]. In addition, DS overestimated HR by a mean difference of 17 bpm compared to ECG and took the longest time from birth to obtain HR (120 sec)[62]. All study infants were vigorous and crying[62], which could have affected the accuracy and time needed for assessments using the DS. While crying during assessment appears to be a limitation of this technology, it is reasonable to assume most crying babies have a HR >120 bpm. Further studies should evaluate the DS during neonatal resuscitation to address accuracy and time needed for assessments.

1.3.2. Tap-based mobile apps

HR assessment using auscultation and palpation has been reported to be inaccurate in 33% to 75% of cases, which might be due to mental computation to convert

counts to HR[8,18,63]. Tap-based mobile apps are assistive technologies that use screen tapping to estimate HR and may reduce these inaccuracies (Table 1.2). NeoTapLifeSupport (NeoTapLS; Tap4Life, Stockholm, Sweden) is a tap-based smartphone app enabling a user to tap the screen of a smartphone or tablet in sync with HR that is auscultated or palpated. Hook *et al* compared NeoTapLS plus auscultation versus NeoTapLS plus palpation to calculate heart rates of <60 bpm, 60-90 bpm, or 100-140 bpm during simulated neonatal resuscitation[20]. Overall, the time (95% CI) to assess HR was similar between both groups with 15 (13 to 16) sec compared to 16 (15 to 18) sec, respectively[20]. However, the time (95% CI) to assess HR <60bpm was significant longer with 19 (17 to 20) sec compared to 15 (13 to 16) sec and 15 (13 to 17) sec for 60-90 bpm, or 100-140 bpm, respectively ($p<0.001$)[20]. Similarily, Binotti *et al* reported good accuracy and quick assessment of HR during simulated neonatal resuscitation using the NeoTapAdvancedSupport (Tap4Life, Stockholm, Sweden), an App designed for iPad devices only[63]. These data suggest tap-based applications might have the potential to improve HR assessment. Combining auscultation with tap-based apps might also enable for faster HR detection at birth or integrated during regular assessments. This may be especially valuable in low-resource settings where apps are more universally accessible than ECGs and more complicated assessment technologies. However, the current available data is derived from simulation studies and studies in the delivery room are lacking. These studies are needed before this technology can be translated into routine clinical care.

1.3.3. Doppler ultrasound

Doppler ultrasound is an intermittent and continuous contact technology, which uses high frequency sound waves to detect blood flow based on differences in the frequency of emitted and reflected sound waves (Figure 1.1, Table 1.2)[64]. During pregnancy and fetal development Doppler ultrasound is used for prenatal screening, diagnosing congenital heart disease among others. However, its use for HR assessments in the delivery room is novel. Studies comparing Doppler ultrasound with auscultation/palpation reported faster and accurate HR acquisition using Doppler ultrasound[43,65]. Dyson *et al* compared ECG with PO, audible Doppler, and Doppler display to assessed HR in a cohort of 51 term and preterm infants[66]. Audible Doppler was as accurate as ECG or PO to obtain a HR[66]. However, when audible Doppler was compared with the Doppler display, the Doppler display overestimated the HR by an average (95% CI) of 5(-12.8 to +2.1) bpm[66]. This data suggest audible Doppler has similar reliability and accuracy compared to ECG[66]. Similar observations were reported by Goenka *et al* who randomized 92 term infants to HR assessment using Doppler ultrasound, PO, or ECG HR[67]. This study also suggested Doppler ultrasound might have a greater usefulness than PO especially during the first minutes after birth, with a mean time of 18 sec for Doppler ultrasound HR assessments compared with 64 sec for PO measurements[67]. However, noise in real-life resuscitations might interfere with audible signals and unlike ECG and PO, Doppler ultrasound requires a dedicated operator.

1.3.4. Photoplethysmography

Photoplethysmography (PPG) is a continuous contact, optical technique that detects blood volume changes in tissues microvasculature (Figure 1.1, Table 1.2)[68]. PPG

is used to detect HR and works by emitting two wavelengths of light and using a photodiode to detect either reflected or transmitted light, which provide information about blood volume changes in the tissue[68]. Furthermore, PPG is used to measure an infant's respiratory rate and HR. While PO is a form of PPG, this paragraph focuses on forehead PPG. In a pilot study of six infants, Johannson *et al* reported the forehead reflectance PPG to have 1.1% false negative heart beats and 0.9% false positive heart beats, when compared with ECG[69], which suggests PPG has good accuracy for HR assessments. This is further supported by two recent studies reporting high degrees of correlation (r=0.99) between PPG and ECG[70,71]. Most recently, Grubb *et al* used a forehead reflectance PPG for HR assessment in 77 newborn infants admitted to the neonatal intensive care unit[72]. The reliability in infants ≥32 weeks gestation was 97.7% with a limit of agreement between +8.39 and -8.39 bpm between ECG and PPG[72]. For infants <32 weeks the reliability was 94.8% with the limits of agreement between +11.53 and −12.01 bpm[72]. These observations indicate PPG may be a useful tool to continuously monitor HR non-invasively.

PPG could also be implemented in resource-limited environments in Fitbit devices or smartphone applications. Lin & Wei recently described the possibility of detecting HR in an extremely preterm infant (24 weeks with a birth weight of 700 g) using a smart watch (Apple Watch 2, Apple Inc., Cupertino, CA) through a plastic bag for heat-loss protection "within a few seconds", which was comparable to detecting the HR with the ECG[73]. As PPG uses similar mechanics to PO for detection, it is limited by the same factors including low peripheral perfusion, signal dropout, movement, arrhythmias, and ambient lighting.

1.3.5. Camera-based photoplethysmography

An alternative non-contact assessment technology using PPG is camera-based PPG (cPPG), which uses an algorithm to calculate HR based on pulsatile changes in color resulting from perfusion at the surface of the skin, which can be detected by video recordings (Figure 1.1, Table 1.2)[74]. Aarts *et al* compared cPPG with PO and ECG to detect HR in a pilot study in 19 newborn infants admitted to the neonatal intensive care unit[75]. A strong association between cPPG and ECG with a bias of 0.3bpm compared with -0.6 bpm for PO vs. ECG was observed[75], suggesting its validity for clinical use. In another study with 30 preterm infants, accuracy between cPPG HR and ECG HR was ±2.4 bpm in 80% of measurements[76]. This is concerning as this would potentially underestimate HR during resuscitation and could result in unnecessary interventions. Major limitations to detect a HR includes i) infants movements, ii) ambient light[75,76], and iii) obstruction by equipment or healthcare providers. These limitations are concerning particularly during resuscitation as movement of the resuscitator or various light sources may influence the displayed HR. Future studies should examine if PPG and cPPG technology can be used during neonatal resuscitation.

1.3.6. Laser Doppler vibrometry

Laser Doppler vibrometry is another non-contact method, which uses a laser beam to detect movements in thoracic walls of infant as a result of cardiac activity (Table 1.2). Marchionni *et al* evaluated this technology in 20 infants in the NICU, reporting a fairly accurate mean difference (SD) of 0(8) bpm when Laser Doppler HR was compared to ECG HR[77]. However, there was a moderate <6% difference between measures, as well as a high cost and complexity associated with the vibrometry system itself[77]. As

conventional methods are simpler, these factors, in addition to variables during resuscitation such as interventions, may be limiting for the implementation of laser Doppler vibrometry in the delivery room.

1.3.7. ECG-based techniques and technologies

In a study by Gulati *et al*, a novel technique has been suggested to overcome the delay in attaching leads by pre-setting ECG electrodes in a triangle formation facing up on the bed for easier and faster attachment to the infants back[78]. Although signal loss appears to be more frequent with this technique compared to the conventional method, the setup allows ease of access for chest compressions[78], and more space for other devices on the chest. However, this technique has yet to be evaluated in infants requiring resuscitation.

The *dry electrode ECG sensor* (Figure 1.2, Table 1.2) is another solution, which could overcome the problem of long assessment times as well as preventing skin injury, by using conductive textiles instead of gel electrodes to allow for loose skin contact and flexibility[79]. Linde *et al* report a median (IQR) time of 3(2-5) sec for application of this dry-electrode system and good-quality HR measurements within 10 sec in 55 term infants[80]. However, further investigation of this technology is required before implementation in the delivery room.

Transcutaneous electromyography is another technique, which uses electrical activity of muscle tissue (i.e., the diaphragm) to isolate the electrical activity of the heart and calculate HR (Table 1.2). Kraiijenga *et al* demonstrated this technique had a high degree of accuracy with a mean difference (95% levels of agreement) of -0.3(-5.3 to 4.7)

bpm, when compared to ECG[81]. However, it was determined likely not to offer an advantage when compared to current practice and ECG for HR assessment, having similar limitations[81].

Electrical velocimetry is a different novel technology, which uses impedance cardiography techniques to determine HR and requires the attachment of four electrodes (Table 1.2). In a cohort study involving 100 term infants, Freidl *et al* evaluated electrical velocimetry and had to exclude 76% (1143/1500) of assessments, as they did not have a signal quality index above 80%[82]. As such, this technology offers little to no advantages over ECG and appears to be still in its developing stages, when considering its utility for HR assessments during resuscitation.

1.3.8. Sensor-based techniques

Piezoelectric transducer sensors (PZT) detect acoustic vibrations or pressure changes produced by the heartbeat or respiratory movements, which are converted into electrical signals, which are then translated into HR or respiratory rate (Figure 1.2, Table 1.2)[83]. Wang *et al* reported a pilot study in preterm infants with a ±8.24% error rate compared to ECG[84]. They concluded the technology was useful as a contactless assessment strategy[85], which may be suitable for delicate and thin skin in premature infants. Similarly, Sato *et al* compared PZT sensors to ECG in 38 infants and reported an average correlation coefficient of 0.92 ±0.12 when compared with ECG[86]. Nukaya *et al* reported PZT can be used for HR monitoring but identified key limitations including i) body movements artefacts, ii) crying, and iii) mechanical ventilation[87]. Underestimation, noise and an overall low accuracy was associated with mechanical ventilation[86,87], and as

such, this technology is currently unfeasible for HR assessment, requiring further development before implementation in neonatal resuscitation.

Capacitive sensors are another form of non-contact method of HR detection, which couples an insulator (typically a garment, towel or mattress) between the infant's skin and a conductive electrode to form a capacitive electrode, which can be used to form an ECG signal by determining electrographic voltage based off capacitance (Figure 1.2, Table 1.2)[88]. Kato *et al* used the described system to compare with ECG for neonatal HR detection and demonstrated comparable accuracy between the two[88]. Atallah *et al* also reported capacitive sensors can reliably detect HR 86% of the time[89]. More recently, a proof-of-concept study established the feasibility of a class of feedback-enhanced, electrometer-based capacitive sensors known as electric potential sensors, which was built in to a neonatal mattress to measure HR accurately within 30 sec[90].

Dynamic light scattering, also a recently developed non-contact sensor-based method, uses laser diodes to detect light scatters from moving hemoglobin to measure HR[91]. However, Gangaram-Panday *et al* described a good agreement between HRs for only 80% of the time using dynamic light scattering compared to ECG in stable infants in the NICU, concluding the sensor was sensitive to movement and less accurate than current recommendations[91]. These studies are promising for neonatal resuscitation in context, but further studies are still needed prior to routine clinical use.

1.4. Purpose statement

The primary purpose of this work was to evaluate whether five identified assessment methods, DS using 6-sec (DS+6sec), DS using 10-sec methods (DS+10sec), DS using NeoTapLS (DS+NeoTapLS), Doppler ultrasound, and cPPG, can be used to assess HR at birth.

1.4.1. Study objectives

The primary objective was to determine if using (i) DS+6sec, (ii) DS+10sec, (iii) DS+NeoTapLS, (iv) Doppler ultrasound, and (v) cPPG are accurate for HR assessment during neonatal resuscitation. The secondary objective was to determine the auscultation method between (i) 6-sec (ii) 10-sec, and (iii) NeoTapLS, requiring the least amount of time for HR assessment.

1.4.2. Hypothesis

It was hypothesized that using the DS+6sec, DS+10sec, DS+NeoTapLS, Doppler ultrasound, and cPPG would have a similar accuracy for HR assessment during neonatal resuscitation.

Table 1.1. Recommended techniques for heart rate assessment, associated outcomes including accuracy, time required for assessment, and reliability of technique, and limitations. Abbreviations: HR: heart rate; PO: pulse oximetry ECG: electrocardiography; PEA: pulseless electrical activity; bpm: beats per minute; sec: seconds. Adapted from Johnson and Schmölzer[13].

HR assessment technique	Palpation	Auscultation	PO	ECG
Accuracy	• Underestimates HR>100 bpm, fairly accurate <100 bpm • Underestimates 21 bpm, compared to ECG	• Underestimates HR>100 bpm, fairly accurate <100 bpm • One study suggests healthcare providers overestimate HR<60 bpm	• Accurate, but underestimates HR in the first minutes of life (~2 min) • Poor signal quality/loss of signal during hypoxia/asphyxia events interfere with accuracy	• "Gold standard"
Time required for assessment	~7–19 sec	~7–19 sec	~60–120 sec	~30–60 sec
Method to confirm reliability	Feeling pulse	Hearing heartbeats	Observing a regular waves on the PO waveform	Observing regular QRS complexes on ECG waveform
Limitations	• Requires great deal of concentration and attention • Factors such as noise, cognitive load, and stress can result in inaccurate HR	• Requires great deal of concentration and attention • Factors such as noise, cognitive load, and stress can result in inaccurate HR	• High latency for reliable HR detection (48 sec from sensor application) • Underestimates HR in first 2 min • Low peripheral perfusion, volume, movement, ambient lighting, etc. can result in loss or unreliable HR signal	• High latency (24 sec from lead application) • Requires time for cleaning of skin from fluids • Increases risk of skin damage, injury, or infection in premature infants • PEA, hydrops & other special cases may result in loss or unreliable HR signal

Table 1.2. Novel technologies for heart rate assessment identified and studied before. Each technology is characterized according to its classification (continuous contact, intermittent contact, non-contact, sensor-based, and assistive), functional description and strengths, and limitations. Abbreviations: HR: heart rate; ECG: electrocardiography; PO: pulse oximetry; PPG: photoplethysmography; EMG: electromyography; cPPG: camera-based photoplethysmography; sec: second. Adapted from Johnson and Schmölzer[13].

Novel technology	Classification	Description	Limitations
Dry-electrode ECG	Continuous contact	Uses dry-electrodes to detect reliable, accurate HR with short latency (within ~10 sec)	Requires drying infant prior to use & movement causes interference.
Electrical velocimetry	Continuous contact	Uses blood conductivity to measure cardiac output, stroke volume, & HR, providing accurate HR compared to ECG.	Only assessed in term infants before with low quality signals for >75% of the time & movement causes interference.
Reflectance PPG/PO	Continuous contact	Uses reflectance instead of transmission to monitor SpO_2 & HR, providing accurate HR.	Similar limitations to PO.
Transcutaneous EMG	Continuous contact	Uses electrical activity of muscle tissue & has a high degree of accuracy compared to ECG	Similar to ECG and have limited advantages over it.
Doppler ultrasound	Continuous contact, intermittent contact	Uses ultrasound frequency sound waves to detect HR accurately & within a short period of time.	Movement can affect skin-gel interface, while noise & ventilation can interfere with audible & visual signal, respectively.
Digital stethoscope	Intermittent contact	Uses electronics to augment sound detected by auscultation with greater clarity to improve HR accuracy.	Influenced by movement & noise & has similar limitations to auscultation.
cPPG	Non-contact	Uses changes in wavelengths over a region of interest to determine HR, offering a high degree of accuracy to ECG.	Signal loss is common about 20% of the time due to ambient light, movement, & obstructions.
Capacitive sensors	Non-contact, sensor-based	Forms a capacitive electrode between the infants' skin & an electrode without directly touching the infant to determine an accurate ECG signal.	Signal loss is common about 15% of the time due to movement, etc.

Novel technology	Classification	Description	Limitations
Piezoelectric sensors	Non-contact, sensor-based	Uses acoustic vibrations from heartbeats to produce electrical signals providing HR, offering accurate data compared to ECG.	Movement from ventilation, infant movement, or resuscitator movement greatly affects signals.
Dynamic light scattering	Non-contact, sensor-based	Uses lasers to detect light scatters from moving hemoglobin to measure its speed and size to produce a pulsatile waveform that calculates HR.	High sensitivity to movement and lower accuracy than current recommendations (ECG and pulse oximetry).
Laser Doppler vibrometry	Non-contact	Uses a laser beam to detect movements in thoracic walls of infant due to cardiac activity, providing a fairly accurate HR compared to ECG.	There is uncertainty as well as a high cost & complexity associated with the system.
Tap-based smartphone apps	Assistive	Uses screen tapping, which is paired with auscultation to detect HR based on timing between heartbeats and provides a fast and accurate HR in simulation scenarios. Also useful and accessible in low-resource settings.	Technical software problems, risk of infection with smartphone use, requires auscultation & therefore has the same limitations

Figure 1.1. Current and novel technologies or techniques for heart rate assessment identified by Johnson *et al*[36]. An illustration of current recommendations, including electrocardiography, pulse oximetry, auscultation with a standard stethoscope, and palpation from brachial, femoral, and umbilical arteries, and novel technologies, including auscultation with a digital stethoscope, Doppler ultrasound, photoplethysmography, camera-based photoplethysmography for heart rate assessment. Reproduced with permission from RETAIN Labs Medical Inc. (https://www.retainlabsmedical.com).

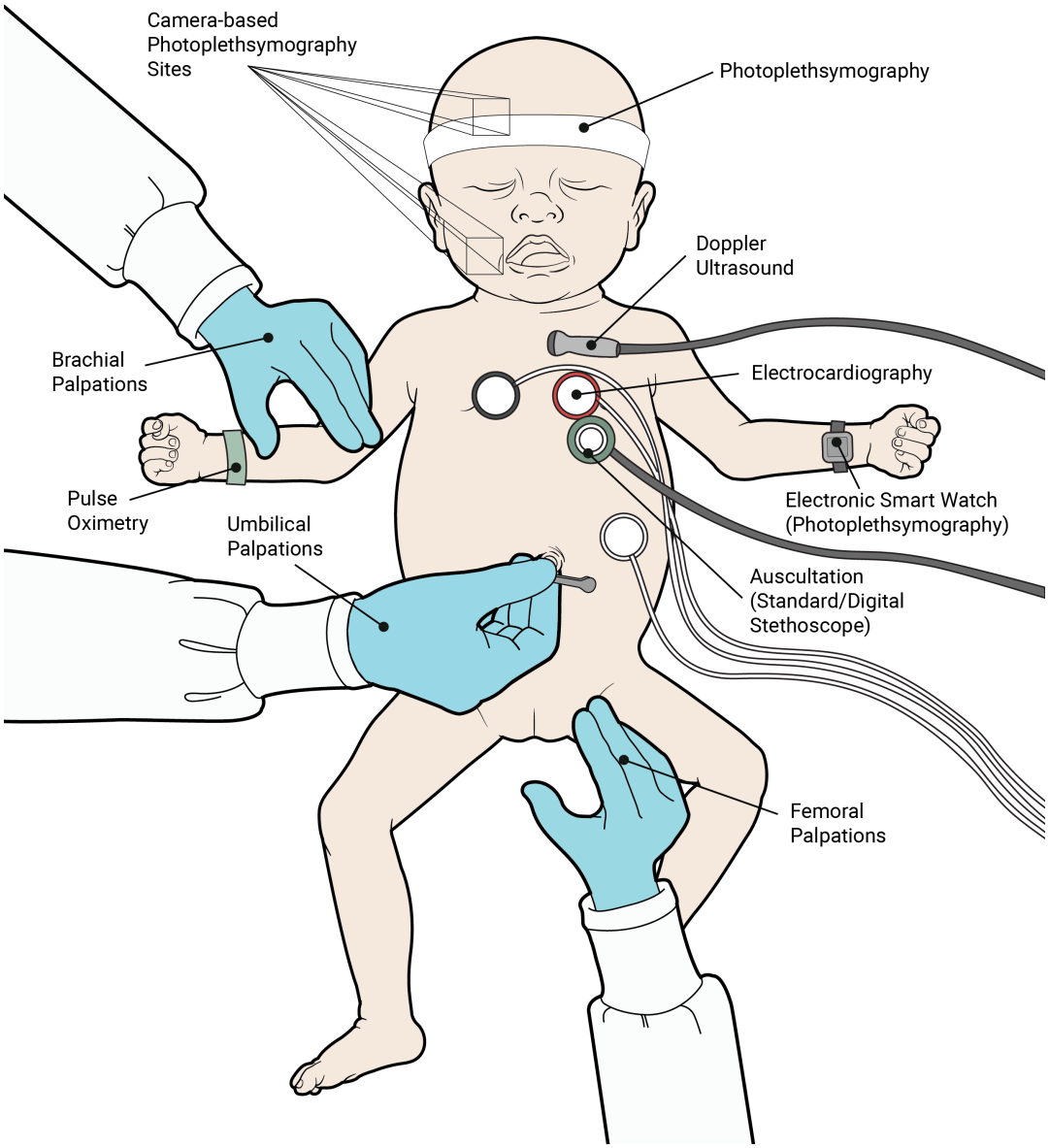
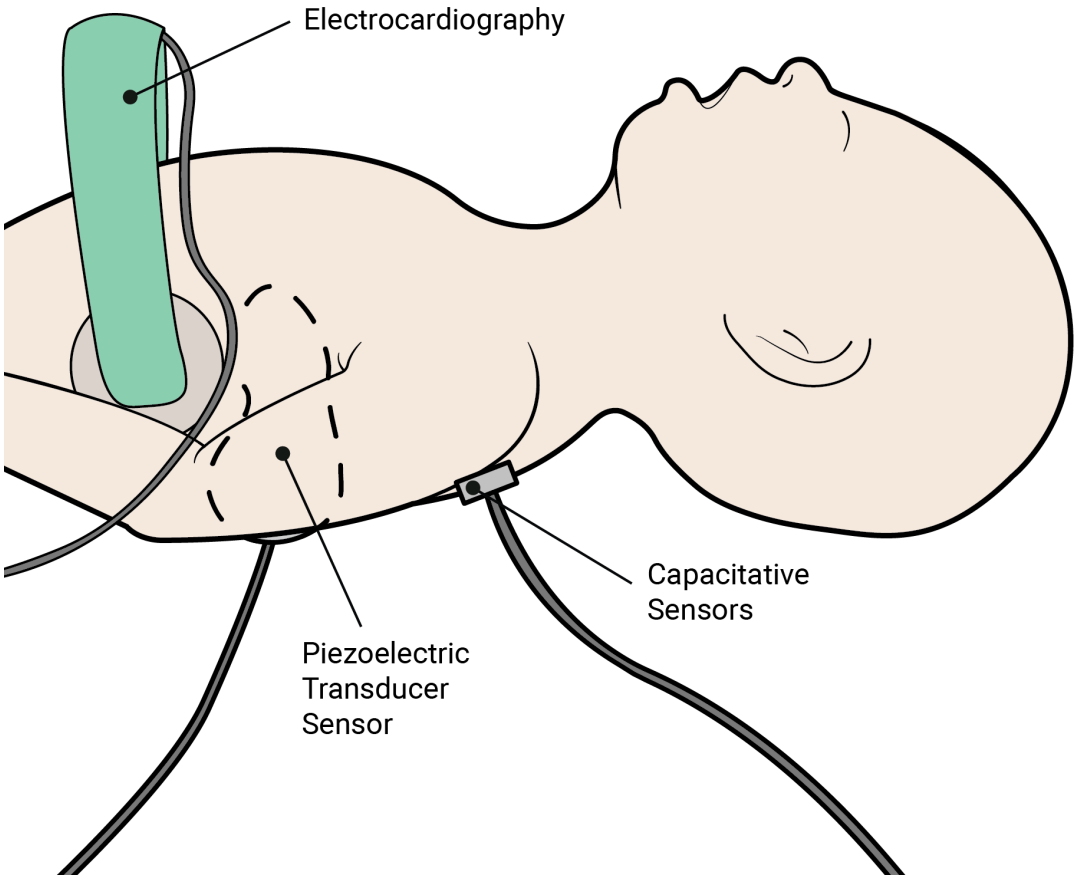


Figure 1.2. Current and novel technologies or techniques for heart rate assessment identified by Johnson *et al*[36]. An illustration of novel technologies including dry-electrode electrocardiography, and two sensor-based methods, piezoelectric and capacitive sensors, for heart rate assessment. Reproduced with permission from RETAIN Labs Medical Inc. (https://www.retainlabsmedical.com).



CHAPTER 2. Methods

This chapter includes slightly modified sections from a previously published article and has been reproduced here with the permission of the copyright holders:

Johnson PA, Morina N, O'Reilly M, Lee TF, Cheung PY, Schmölzer GM. Evaluation of a Tap-Based Smartphone App for Heart Rate Assessment During Asphyxia in a Porcine Model of Neonatal Resuscitation. *Front Pediatr*. 2019;7:453. Published 2019 Nov 5. doi:10.3389/fped.2019.00453

2.1 Part I: Animal study in a porcine model of neonatal asphyxia

2.1.1. Porcine model of neonatal asphyxia

While 10% of infants require respiratory support at birth, less than 1% of cases require extensive cardiovascular support via chest compression and administration of medications at birth[6,92]. This means cases of bradycardia and changes in HR leading to asystole are rarely observed in the delivery room. An animal model can overcome this challenge in studying these HR patterns at birth. In the context of HR assessment in experimental settings, the use of an animal model of asphyxia would also enable invasive HR monitoring as a gold standard measure[13,51,53,56,93]. Although several preclinical models of neonatal asphyxia including rodents, large precocials, non-human primates, rabbits, sheep, and porcine exist, porcine models are the most extensively used in the context of asphyxia-induced neonatal resuscitation[94–96].

We used a well-established porcine model of neonatal asphyxia using a modified experimental protocol first described by Cheung *et al*[97]. Compared to other models, newborn piglets have a similar cardiac and pulmonary anatomy, body systems (especially cardio- and cerebrovascular systems), comparable development to newborn 36-38 week human infants at birth, and similar body size, allowing for instrumentation and monitoring of HR, hemodynamic, and other physiological parameters[95,97,98]. Importantly, asphyxia-induced newborn piglets reproduce biochemical profiles analogous to human newborns requiring resuscitation at birth where an acute mixed respiratory and metabolic acidosis is observed as asystole is approached[95]. Due to its close similarity with newborn infants at birth, this model is translational to clinical settings.

2.1.2. Animal enrollment and ethical approval

Experiments were conducted in the University of Alberta Medical Sciences Building Neonatal Research Laboratory on twenty mixed-breed, term newborn piglets (1-3 days of age, weighing 2.0±0.4 kg) obtained from the University Swine Research Technology Centre. Piglets enrolled in these studies were a convenience sample recruited from a larger randomized trial, which studied the use of different techniques during resuscitation, namely chest compressions with sustained inflation or chest compressions with asynchronous ventilations. For this study, HR assessments were performed during the asphyxia stage of the trial protocol, prior to any intervention (Figure 2.1). This was done in adherence to ethical standards to reduce the number of animals enrolled by refining the study design when possible. All experiments were performed in accordance with guidelines and approval of the Animal Care and Use Committee (Health Sciences), University of Alberta (AUP00002151), presented according to the ARRIVE guidelines (Appendix A)[99], and registered at preclincialtrials.eu (PCTE0000155 and PCTE0000161).

2.1.3. Animal preparation and surgical instrumentation

Piglets were initially placed on 5% isoflurane in 100% oxygen, which was inhaled via a nose cone mask placed over the snout, using an anesthetic machine at a flow rate of 2L/min to induce anesthesia. The appropriate depth of anesthesia was confirmed by absence of the withdrawal reflex when the piglet's toes were pinched. Once confirmed, anesthesia was maintained with 2-3% isoflurane with adjustments depending on the pig's condition. The piglet was secured, connected to a Nellcor N-200 pulse oximeter (Nellcor Puritan Bennett LLC, Pleasanton, CA) for oxygen saturation (SpO_2) and HR monitoring,

and a rectal digital thermometer (RX533, Rexall Pharmacy Group Ltd., Mississauga, ON, Canada) was inserted for temperature monitoring, throughout the experiment. The piglet's body temperature was maintained at 38.5-39.5°C using an overhead warmer and a heating pad.

The major stages of the surgical protocol included catheterization of the femoral artery and vein, tracheostomy, ET intubation, and placement of the common carotid flow probe. Once prepared for surgery, a scalpel was used to make a skin incision along the right groin region. Blunt dissection was used to separate tissues, muscles, and surrounding fascia from the vessels. The catheters were then prepared and flushed to ensure no leaks or occlusions. A 5 French Argyle® double lumen venous catheter (Klein-Baker Medical Inc. San Antonio, TX) was inserted to 15 cm, which corresponds to the entrance of the right atrium, offering an optimal point of access for the delivery of fluid and anesthetic drugs. Following this, the primary port of the catheter was attached to an infusion line for maintenance fluids (10% Dextrose solution) and anesthetic drugs (morphine and propofol), whereas the secondary port was connected to the monitoring system for central venous/right atrial pressure measurements.

To provide an access for blood sampling and blood pressure (systolic, diastolic, and mean arterial pressures) monitoring, the femoral artery was catheterized similarly. A 5 French Argyle® single lumen arterial catheter was inserted to 5 cm, corresponding to a location above the renal artery to avoid interference from renal blood flow.

Once the femoral artery and vein were successfully catheterized, tracheostomy and ET intubation were followed. A horizontal incision was made at the neck to isolate the trachea and the right common carotid artery, which was used for carotid blood flow

(CBF) monitoring (see section 2.1.5.1). Depending on the size of the piglet's trachea, a 3.0 or 3.5 mm ET tube was prepared. Bolus morphine (200 μg/kg) and propofol (2 mg/kg) were administered intravenously before tracheostomy to ensure the sedative state of the animal during transition. A small incision was made between cartilage rings and the ET tube was immediately inserted and attached to the mechanical ventilator (Sechrist IV-100B Infant Ventilator, Sechrist Industries Inc., Anaheim, CA). The ventilator was initially set to at a respiratory rate of 16–20 breaths/min and pressure of 20/5 cmH_2O.

Upon completion of surgical instrumentation, intravenous propofol and morphine were infused at a rate of 10-30 mg/kg/hr and 100-200 μg/kg/hr, respectively. Alongside these medications to maintain anesthesia, 10% dextrose solution was also delivered at 10 mL/kg/hr to maintain hydration and the glucose supply of the animal. If there were signs of tachycardia, elevated blood pressure, tearing and autonomic stress, doses of propofol and morphine were increased accordingly. Bolus fluids and/or medications, which included morphine (100-200 μg/kg), propofol (1-3 mg/kg), and Ringer's lactate (5-10 mL/kg), were also given as needed. After this, an ultrasonic flow probe was applied to the common carotid artery for CBF measurements and skin incisions at the groin and neck were sutured to prevent drying.

2.1.4. Hemodynamic monitoring

Mean systemic arterial pressure, central venous pressure, HR, and percutaneous oxygen saturation were continuously measured and recorded throughout the experiment with a Hewlett Packard 78833B ECG monitor (Hewlett Packard Co., Palo Alto, CA). Transonic flow probes, heart rate and pressure transducer outputs were digitized and

recorded with LabChart® programming software (ADInstruments, Houston, TX). Periodic arterial blood gas measurements were measured using an i-Stat 1 Analyzer (Abbott Laboratories, Lake Bluff, IL), which measured parameters including blood pH, partial arterial CO_2, partial arterial O_2, SpO_2, base excess, hemoglobin, and lactate levels following the surgical protocol. These parameters were used to assess the animal's status, determine any variations from expected values, and guide decisions appropriately (e.g., ventilator rate was adjusted to maintain partial arterial CO_2 of 35-45 torr).

2.1.5. Heart rate assessment

Various techniques and technologies were utilized for HR assessment and monitoring throughout asphyxia. CBF HR and ECG HR were used as comparison standards. Auscultation with a DS using the 6-sec method, 10-sec method, NeoTapLS app, and the Doppler ultrasound were assessed. In addition to the accuracy of HR assessment, time required to assess HR was also compared.

2.1.5.1. Carotid blood flow

A 2 mm transit time ultrasonic flow probe (Transonic Systems Inc., Ithica, NY) was clipped around the common carotid artery to measure CBF. CBF can then be converted to HR and recorded continuously using LabChart® programming software. As a result, CBF HR was selected as the experimental gold standard as it offers a direct measure of HR, remaining accurate in the setting of asphyxia and unaffected in the likely event of PEA[93].

2.1.5.2. Electrocardiography

Following the surgical protocol, a 3-lead ECG using adhesive leads was placed on skin at the right fore limb, left fore limb and left hind limb of the piglet. As previously described, ECG is the clinical gold standard that measures HR using the electrical activity of the heart detected by surface electrodes. ECG HR was recorded by the LabChart® programming software and was also assessed real-time on the monitor.

2.1.5.3. Digital stethoscope

The DS is an electronic stethoscope, which functions by converting the audial heartbeat signal into an electronic signal followed by amplification to provide clearer detection. Several studies report the DS can be utilized for HR assessment in newborn infants requiring respiratory support with better accuracy, compared to a standard stethoscope[36,60,61].

In this study, auscultation was performed using a DS (Thinklabs One, Denver, CO). Assessments using the DS were performed using the (i) 6-sec method (DS+6sec) and ii) 10-sec method (DS+10sec), and NeoTapLS (DS+NeoTapLS). The 6 sec method is currently recommended by the Neonatal Resuscitation Program (NRP)[10], whereby HR is calculated by multiplying the number of heartbeats heard in 6 sec by 10. The 10 sec method has previously been recommended for initial HR assessment at birth[16,17], and calculates HR by multiplying the number of heartbeats heard in 10 sec by 6. The frequency filter of the DS was set between 30 and 500 Hz, which produces low frequency heart sounds and filters out lung sounds, and amplification was set to 6 on the 0–10 Scale.

2.1.5.4. NeoTapLS smartphone app

The NeoTapLifeSupport (NeoTapLS; Tap4Life, Stockholm, Sweden) smartphone app was downloaded from the App Store (Apple, Cupertino, CA) and paired with the DS for HR assessments. The NeoTapLS is a recent development for HR assessment, however has only been tested in high-fidelity resuscitation simulation scenarios[20,36,63,100]. NeoTapLS functions by displaying a HR generated by at least three taps on the smartphone screen, which coincides with what the healthcare provider auscultates. Based on this predefined calculation algorithm, when HR is 30 bpm, a minimum of 6 sec is required to assess HR [3*(60/30) = 6 sec], and at 18 bpm, it will take a minimum of 10 sec [3*(60/18) = 10 sec]. Thus, it was expected to be faster than the 6 and 10 sec method on average.

2.1.5.5. Doppler ultrasound

The Ultrasound Cardiac Output Monitor (USCOM) Doppler ultrasound (USCOM 1A, Uscom Ltd, Sydney, Australia) utilizes ultrasound waves generated by alternate current in a transducer containing piezoelectric crystals, which creates acoustic energy with a specific frequency in response to vibrations. These waves are then converted into an electronic signal, which is displayed on the monitor along with an audible signal. The USCOM 1A device detects HR non-invasively by integrating the velocity-time profile of the cardiac ejection flow by positioning a transducer to detect blood flow using either a pulmonary or aortic valve examination mode[64,101,102]. It automatically measures flow profile data using the FlowTracer feature, which is used to determine the real-time HR. In

this study, the transducer was positioned suprasternal and the aortic valve examination mode was utilized. During the experimental protocol, the Doppler-US audio was disabled to blind the operator from the audible signal.

2.1.6. Experimental protocol

Following at least 1 hour of stabilization after the surgical protocol to allow the animals to reduce the effects of anaesthesia and surgical stress, piglets were subjected to 30 min of hypoxia (FiO_2 10–15%). Hypoxia was induced by introducing nitrogen gas at 20 mL/min and delivered through the ventilator, though this was reduced to allow up to FiO_2 17-19% if the animal could not tolerate it. The respiratory rate was also decreased step-wise by 10 breaths/min every 10 min, but was lightened if the animal could not tolerate. This stage was necessary to create the study model to better represent the physiological stresses and demands of neonatal asphyxia at birth. Hypoxia was then followed by asphyxia until asystole, which was achieved by disconnecting the ventilator and clamping the ET tube. This meant the piglet was provided with no air throughout this period. Asystole was defined as no audible HR during auscultation for at least 10 sec and zero CBF. All HR assessments were performed during the asphyxia time leading to asystole (i.e., between disconnecting the ventilator and clamping the ET tube and confirmation of asystole). HR assessments comprised of auscultation using the DS in three different methods: (i) NeoTapLS, (ii) 6 sec, and (iii) 10 sec (Figure 2.2), which were performed by a single investigator (Georg Schmölzer), who was blinded to HR displayed by ECG and CBF. All NeoTapLS, 6 and 10 sec HR assessments were assessed from the same starting time point. For NeoTapLS, the same investigator simultaneously

tapped the smartphone screen for each auscultated heartbeat, and the displayed HR was recorded by another investigator (Peter Anto Johnson). For 6 and 10 sec, the number of heartbeats auscultated was verbalized by Georg Schmölzer at 6 and 10 sec and recorded by Peter Anto Johnson. Georg Schmölzer was not required to perform arithmetic for determination of HR in bpm; this was determined independently during data analysis. Assessment times for all methods were measured using a timer and recorded by Peter Anto Johnson.

Doppler ultrasound was also evaluated and used for HR assessment during asphyxia (Figure 2.2). The Doppler-US was operated by another personnel (Megan O'Reilly), who was also blinded to CBF and ECG HR display. Megan O'Reilly was responsible for starting the recording, application of ultrasound gel on transducer, and placement of transducer on the animal's chest for a continuous signal throughout asphyxia. FlowTracer Doppler velocity flow profiles were continuously displayed on the screen and could be used to confirm the reliability of signals. All HR assessments were recorded by Peter Anto Johnson. The time required for initial assessment was also recorded by Peter Anto Johnson.

In each piglet, assessments by each of these techniques were performed every 30 sec throughout asphyxia until asystole. This enabled HR assessment to be performed as levels of bradycardia increased and represent different clinical situations (i.e., HR >100, between 60 and 100, or <60 bpm). Markers were placed within the LabChart® program to indicate HR assessment times. Post-experiment, the markers were compared to waveforms from the ECG and CBF to determine HR at the time of assessment using 6 and 10 sec methods, NeoTapLS, and Doppler ultrasound. HR as determined by CBF was

defined as the gold standard. Following interventions, piglets were allowed to recover for 4 hours after achieving recovery of spontaneous circulation with continuous monitoring and drug/fluid delivery. The piglets were then euthanized via the administration of 100 mg/kg Euthanyl.

2.1.7. Statistical analysis

A single assessor was used for auscultation, eliminating any user bias and error caused by variations between assessors and the need for randomization, while concurrently allowing for comparison of the same HR at a given point in time. Another assessor made the HR assessments using Doppler ultrasound. Assessors were blinded from ECG and CBF HR.

Results from HR assessments were presented as mean (SD) and compared to ECG and CBF HR. To determine differences at varying HRs during asphyxia, assessments were additionally clustered into subgroups based on CBF HR for comparison. Subgroups were defined *a priori* as per NRP HR cut-offs: HR <60, 60–100, and >100 bpm[10]. Mean (SD) HR and error frequencies using each technique according to subgroups were determined. Time to assess NeoTapLS, 6 and 10 sec methods were recorded as median (IQR). The data was tested for normality and compared using a one-way ANOVA with Bonferoni post-test. P-values are two-sided and $p<0.05$ was considered statistically significant. Statistical analyses were performed with Stata (StataCorp, College Station, TX).

In order to determine comparability between two sets of measures, it is necessary to evaluate the agreement as opposed to the correlation between them[103]. Bland-Altman

plots allow for the effective quantification of the level of agreement by determining mean difference between variables while establishing the limits of agreements[104]. The mean difference and 95% limits of agreement for the measured HR using the DS+6sec, DS+10sec, DS+NeoTapLS, and Doppler ultrasound intervention groups compared to CBF HR, were assessed using Bland-Altman plots.

A two-way mixed absolute agreement intraclass correlation coefficient (ICC) was also calculated and used as a quantitative measure for the strength of the agreement between the four assessment methods when compared to CBF HR as well. Both a raw and adjusted ICC was calculated. To adjust for repeated measures taken consequently from the same subject, linear mixed models with random effects (SAS procedure MIXED) were fitted with HR as an outcome and a method (i.e., DS+6sec, DS+10sec, DS+NeoTapLS, Doppler ultrasound, or CBF) as a fixed independent variable[105]. To adjust for consequent repeated measures taken from the same subject, effect of a subject, time of the measurement, and method were also included as random effects in the model[105]. ICC (95% CI) between measurements taken from two different methods (intervention method and CBF) was computed using the formula ρ=(variability between methods)/(total variability)[106].

2.2 Part II: Clinical study in newborn infants in the delivery room

2.2.1. Patient recruitment and ethical approval

This observational cohort study was performed between June 2016 to September 2016 in preterm infants born in the delivery rooms at the Royal Alexandra Hospital, Edmonton, which is a tertiary center admitting over 350 infants with birth weight <1500

g annually. The Royal Alexandra Hospital Research Committee and Health Ethics Research Board, University of Alberta (Pro00065767) approved the study, which was conducted and reported according to the STROBE guidelines (Appendix B)[107]. Parental written consent was obtained prior to delivery. We also used convenience sampling in the recruitment of infants. All preterm infants <37 weeks gestational age admitted to the neonatal nursery and requiring HR monitoring at birth, over the study period were included. Infants were excluded if they had congenital conditions or their gestational age was uncertain. The use of video cameras in the delivery room was non-invasive and not anticipated to impact the recommended care provided to the infant at birth. Additionally, the research team did not participate in the clinical care of infants.

2.2.2. Local resuscitation protocol

The steps of resuscitation were performed according to current neonatal resuscitation guidelines[7,8] (Figure 2.3). As per local hospital policy, delayed cord clamping was routinely performed 60 sec after delivery unless contraindications such as, bradycardia, apnea, or antepartum hemorrhage, were noted by the obstetrics team, in which case the cord was clamped earlier. Infants were placed under a radiant warmer to prevent heat loss. As respiratory support was anticipated in all cases due to early gestation, ECG was used for monitoring the infants' HR. Infants received continuous positive airway pressure and PPV via an appropriately sized round silicone face mask (Fisher & Paykel Healthcare, Auckland, New Zealand). Respiratory support was provided with a T-piece resuscitator (Giraffe Warmer, GE Health Care, Burnaby, Canada), which is a continuous flow, pressure-limited device with a built-in manometer

and a positive end expiratory pressure (PEEP) valve. The default settings used a gas flow of 8 L/min, peak inflation pressure (PIP) of 24 cm H_2O and PEEP of 6 cm H_2O. According to the local protocol, predefined intubation criteria were used if chest compressions were required (i.e., if HR <100 bpm after 60 sec of PPV or prolonged PPV of >10 min). All members of the clinical team involved in the deliveries were trained in the Neonatal Resuscitation Program resuscitation protocol and use of equipment.

2.2.3. Heart rate assessment and data collection

ECG: Three Micro-Premie Leads (Vermed, Bellows Falls, VT) placed on the infants' chest, together with an IntelliVue MP50 monitor (Philips Healthcare, Markham, ON, Canada), were used to continuously measure ECG HR. The start and end time points of ECG monitoring were recorded and all measured ECG HR data was stored in the monitor's memory.

cPPG: A high definition surveillance video camera (Axis Communications, Lund, Sweden) installed above the resuscitation table recorded the resuscitation at 24 frames per second with a resolution of 1280×960 pixels and stored using "alpha-trace digital MM" (B.E.S.T. Medical Systems, Austria). After birth, the infant was placed on the fixed resuscitation table, the skin was dried as needed, adequate lighting was maintained in the delivery room, and the camera was focused on the infant's forehead. Recordings started upon delivery and stopped after the infant was stabilized. These time points were recorded to allow comparison with ECG HR. For each infant, videos were divided into 10 sec frames, which were randomly sampled for analysis, and imported into MATLAB (MathWorks, Natick, MA). A region of interest on the infant's forehead was selected

from the recording. A multichannel filter was used to obtain three HR values corresponding to reflection wavelengths: Red, Green, and Blue, from this region of interest (Figure 2.4). These values were then averaged to determine cPPG HR for each infant and then compared to corresponding ECG HR, which was defined as the gold standard.

2.2.4. Statistical analysis

Assessments for HR were performed by a member of the research team not involved with the clinical care of the newborn.

The demographics of included infants were collected and results from cPPG HR assessments were presented as mean (SD) and compared to ECG HR. The data was tested for normality and compared using one-way ANOVA with Bonferoni post-test. P-values are two-sided and $p<0.05$ was considered statistically significant. Statistical analyses were performed with Stata (StataCorp, College Station, TX).

A Bland-Altman plot was used to determine mean difference and 95% limits of agreement between mean cPPG and ECG HR. A two-way mixed absolute agreement ICC (95% CI) was computed to quantify the strength of agreement between ECG and average cPPG system measures for HR.

Figure 2.1. Experimental protocol for animal study. HR: heart rate, CBF: carotid blood flow, ECG: electrocardiography, DS+6sec: digital stethoscope using 6-sec method, DS+10sec: digital stethoscope using 10-sec method, DS+NeoTapLS: digital stethoscope using the NeoTapLS app, Doppler: Doppler ultrasound.

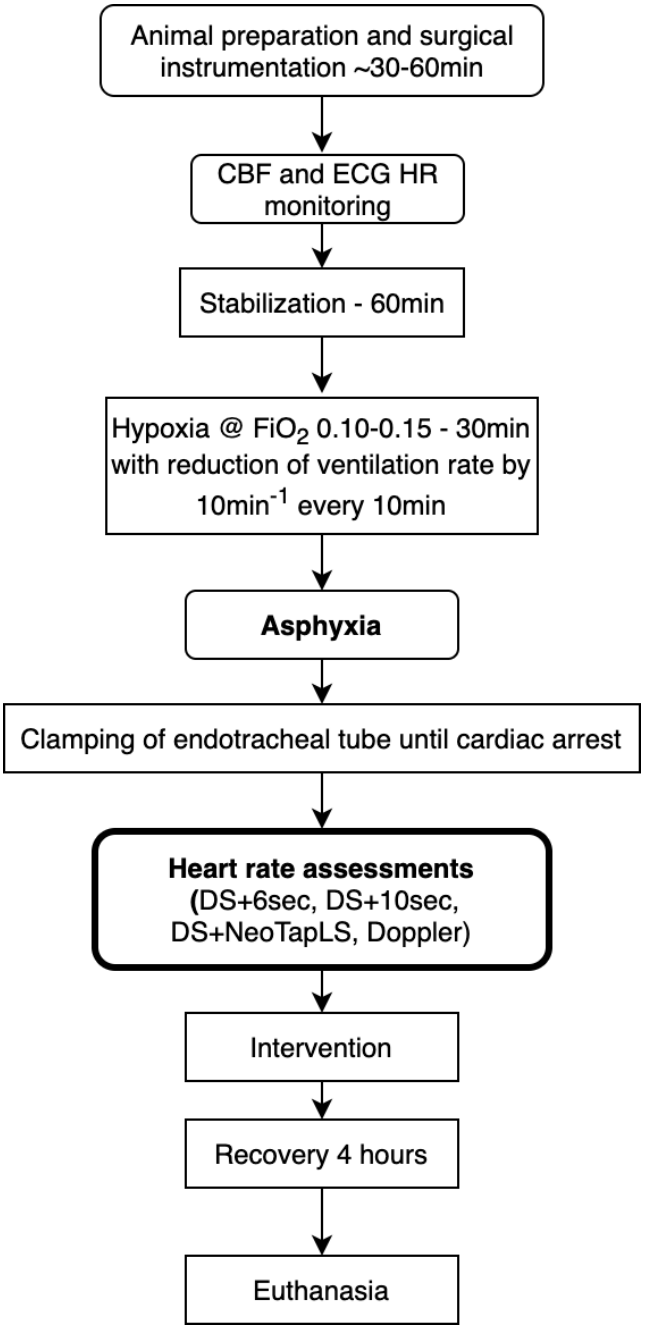


Figure 2.2. Experimental setup for animal study. The animal was instrumented, intubated, catheterized, and induced with asphyxia. Heart rate throughout asphyxia was continuously monitored using carotid blood flow and ECG gold standards. Heart rate assessments were performed every 30 sec using DS+6sec, DS+10sec, DS+NeoTapLS, and Doppler ultrasound. ECG: electrocardiography, DS+6sec: digital stethoscope using 6-sec method, DS+10sec: digital stethoscope using 10-sec method, DS+NeoTapLS: digital stethoscope using the NeoTapLS app. Reproduced with permission from RETAIN Labs Medical Inc. (https://www.retainlabsmedical.com).

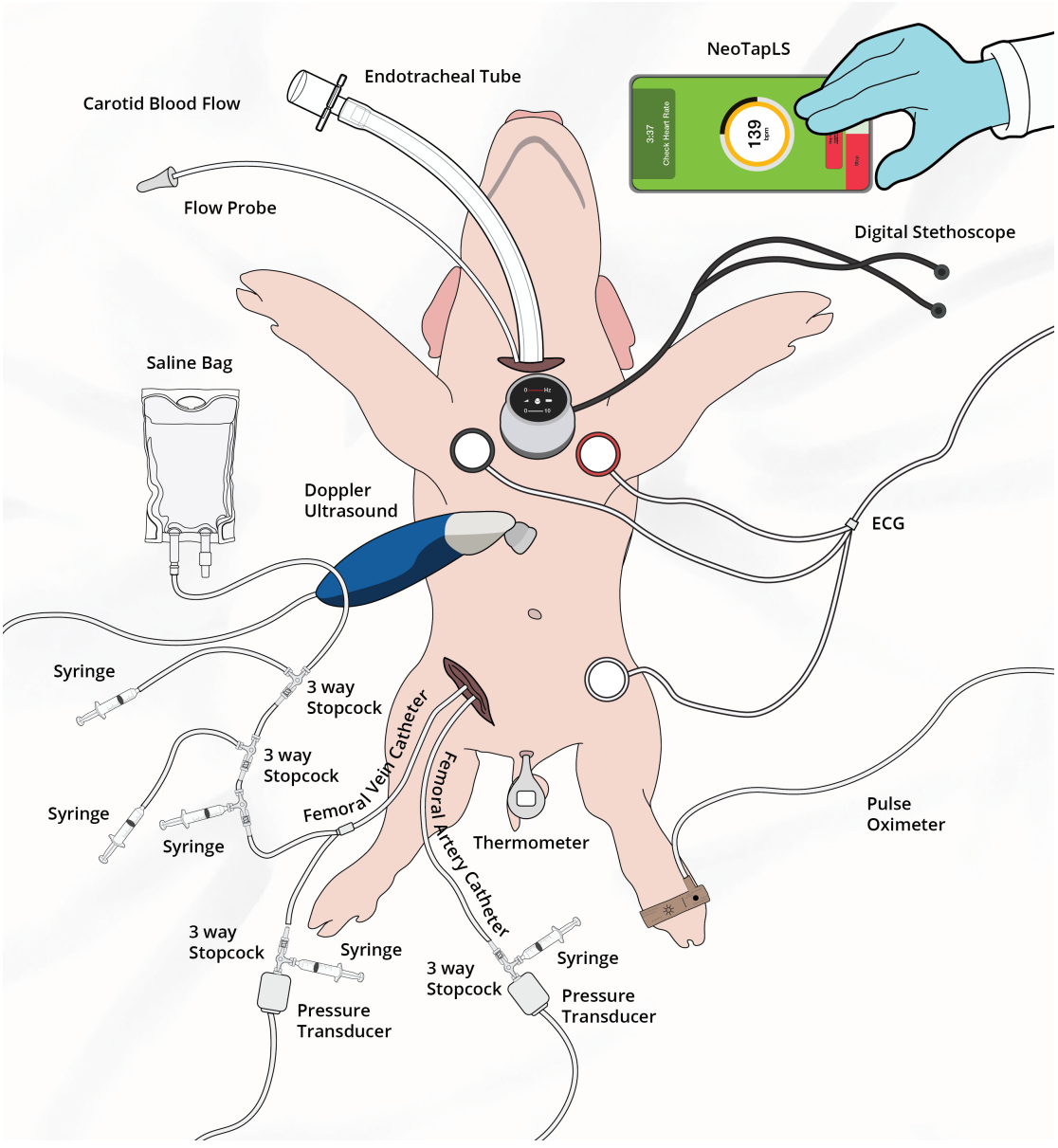


Figure 2.3. Experimental protocol for cPPG clinical study. HR: heart rate, ECG: electrocardiography, cPPG: camera-based photoplethysmography, NRP: Neonatal Resuscitation Program.

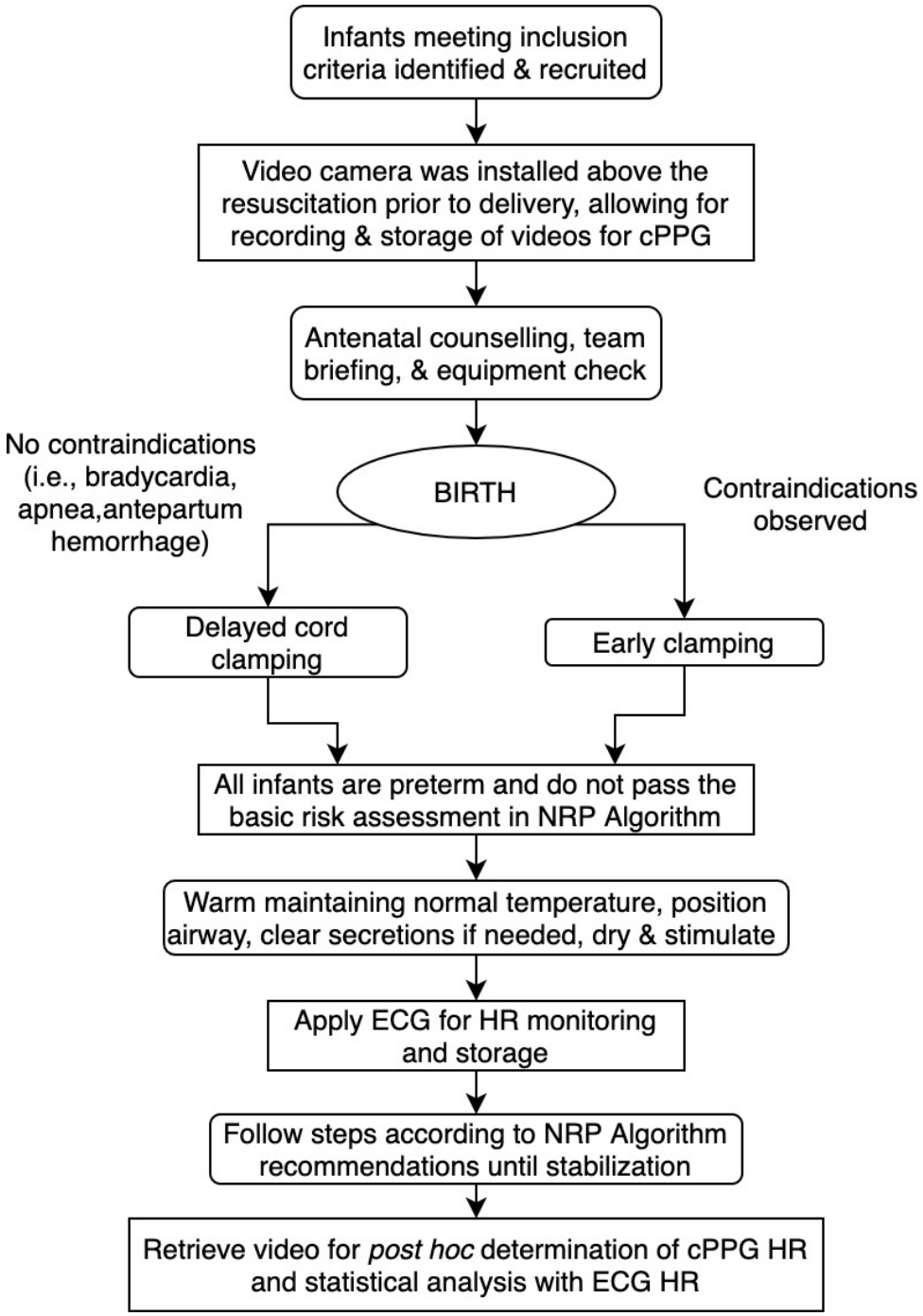
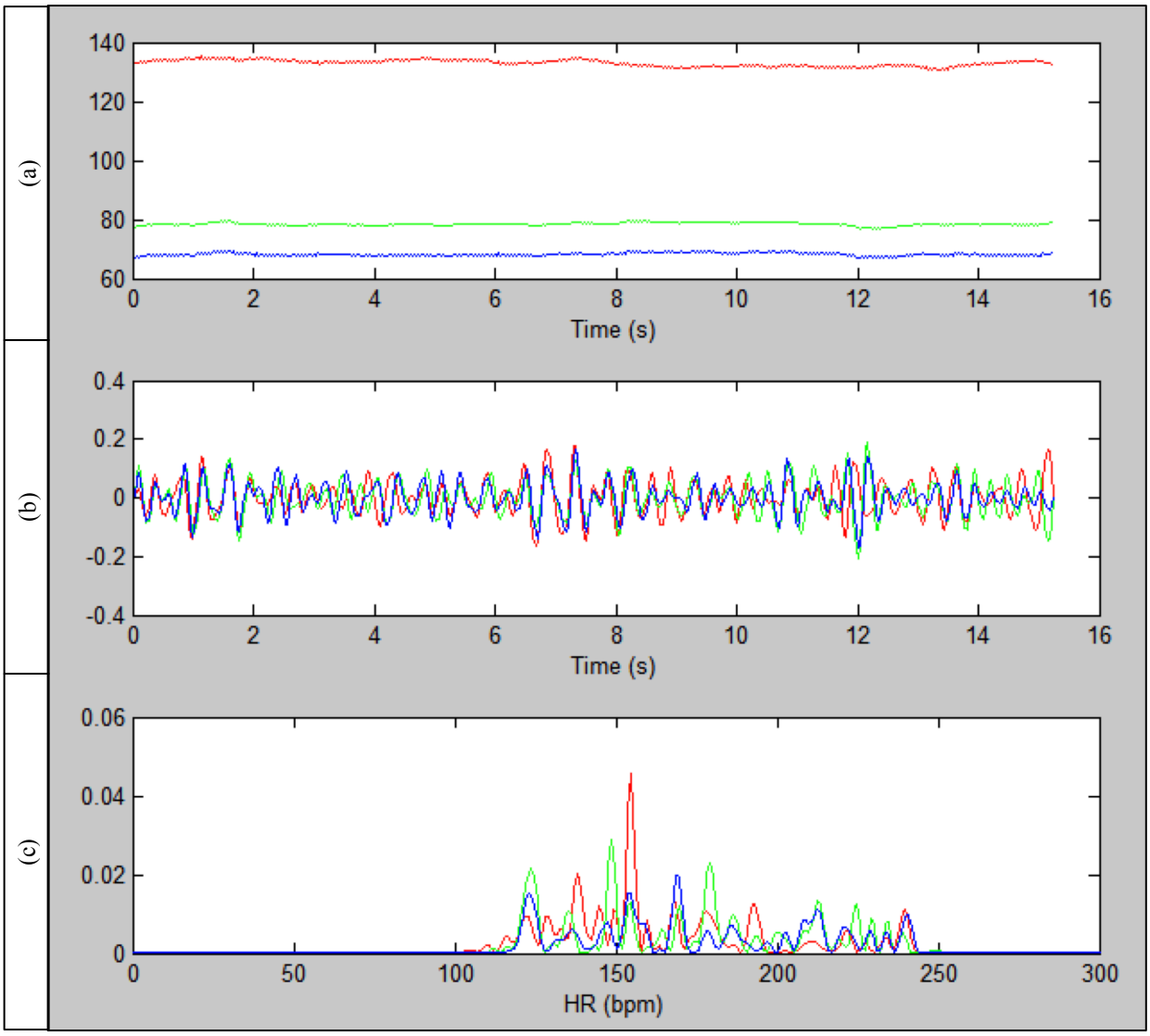


Figure 2.4. Extraction, processing, and averaging of the camera-based photoplethysmography (cPPG) signal. (a) Raw across-pixel averages of unit-free non-calibrated values for red, green and blue (RGB) wavelength channels for the selected region of interest on the infant. (b) Processed and combined cPPG signal from RGB channels. (c) Amplitude of cPPG signals as a function of heart rate. From this plot, the averaged RGB peak signal is used to calculate heart rate.



CHAPTER 3. Results

This chapter includes slightly modified sections from a previously published article and has been reproduced here with the permission of the copyright holders:

Johnson PA, Morina N, O'Reilly M, Lee TF, Cheung PY, Schmölzer GM. Evaluation of a Tap-Based Smartphone App for Heart Rate Assessment During Asphyxia in a Porcine Model of Neonatal Resuscitation. *Front Pediatr*. 2019;7:453. Published 2019 Nov 5. doi:10.3389/fped.2019.00453.

3.1. Part I: Results of animal study examining DS methods and Doppler ultrasound

Twenty newborn mixed breed piglets were obtained on the day of the experiment; baseline data are presented below (Table 3.1). All piglets were assessed using auscultation with the DS+6sec, DS+10sec and DS+NeoTapLS, whereas only 16 of these piglets were assessed using Doppler ultrasound due to resource availability constraints and convenience. The baseline data for these piglets are presented in Table 3.2.

Although it did not interfere with HR assessment, it was noted that certain noises, conversations, and alarms could still be heard when assessments were being performed with the DS.

Table 3.1. Baseline parameters for all enrolled piglets. Reproduced with permission from Johnson *et al*[108].

n	20
Sex	
Female	7
Male	13
Weight (kg)[†]	2.08 (1.8-2.2)
Age (days)[††]	1.85 (1-3)
SpO_2 (%)	98.8 (97-99)
Heart rate (bpm)	175 (160-204)
MAP (mm Hg)	59.2 (55-71)
CVP (mm Hg)	3.9 (2-5)
pH	7.52 (7.4-7.6)
$PaCO_2$ (torr)	36.1 (32.8-40.6)
PaO_2 (torr)	102.5 (81-130)
BEcf (mmol/L)	4.6 (0-6)
HCO_3 (mmol/L)	30.1 (24.2-32.8)
Asphyxia time (sec)[††]	404 (72-600)

Data are presented as median (IQR) unless indicated [†]mean (SD) or [††]mean (range)

Table 3.2. Baseline parameters for all enrolled piglets assessed by Doppler ultrasound. Adapted with permission from Morina *et al*[109].

n	16
Sex	
Female	6
Male	10
Weight (kg)†	2.08 (1.8-2.2)
Age (days)††	1.79 (1-3)
SpO_2 (%)	97.8 (97-99)
Heart rate (bpm)	173 (160-206)
MAP (mm Hg)	59.5 (55-72)
CVP (mm Hg)	4.0 (2-5)
pH	7.51 (7.4-7.6)
$PaCO_2$ (torr)	35.2 (31.7-40.8)
PaO_2 (torr)	101.9 (81-129)
BEcf (mmol/L)	4.4 (0-7)
HCO_3 (mmol/L)	30.3 (24.2-32.8)
Asphyxia time (sec)††	414 (72-600)

Data are presented as median (IQR) unless indicated †mean (SD) or ††mean (range)

3.1.1. Heart rate assessments using DS auscultation methods

For the auscultation methods using DS, the median (range) number of assessments per animal was 11 (2–20) observations with a total of 138 HR assessments, which were performed during asphyxia. Of these, 16 observations were made when CBF HR was >100 bpm, 68 observations were made when CBF HR was between 60 and 100 bpm, and 54 observations when CBF HR <60 bpm using all auscultation techniques.

The mean (range) time for asphyxia was 404(72–600) sec. The median (IQR) time needed to assess HR during asphyxia using DS+NeoTapLS, DS+6sec and DS+10sec methods were 3 (2–4), 6 (6–7), and 10 (10–11) sec ($p<0.05$).

During asphyxia, the mean (SD) CBF and ECG HR were 68(27) and 68(27) bpm, respectively. The HR using DS+NeoTapLS, DS+6sec and DS+10sec methods were, 66 (26), 68 (26), and 68 (27) bpm, respectively (Figure 3.1). There were no significant differences in the mean (SD) HR measured using CBF, ECG, DS+NeoTapLS, DS+6sec and DS+10sec method. The Bland-Altman comparisons for CBF HR vs. DS+NeoTapLS or DS+6sec or DS+10sec are displayed in Figures 3.2-3.4, respectively. These revealed a mean difference (95% levels of agreement) of 0.7 (-13 to 15) bpm, -1 (-21 to 19) bpm, 0.6 (-23 to 25) bpm was observed for NeoTapLS, 6, and 10 sec methods when compared to CBF HR, respectively.

Two-way mixed absolute agreement was used to compute an ICC (95% CI), unadjusted for repeated measures taken from the same subject, of 0.965 (0.951 to 0.976), 0.926 (0.897 to 0.947), and 0.895 (0.854 to 0.925) for NeoTapLS, 6-sec, and 10-sec method, respectively. When adjusted for consequent repeated measures taken from the same subject, effect of a subject, time of the measurement, and method using random

effects in the model, the adjusted ICC (95% CI) was computed to be 0.966 (0.955 to 0.977), 0.935 (0.906 to 0.956), and 0.905 (0.864 to 0.915) for NeoTapLS, 6-sec, and 10-sec method, respectively.

Analyses by HR cutoff ranges: <60, 60–100, and >100 bpm are presented in Figure 3.5. At HR <60 bpm, assessment using CBF, ECG, DS+6sec, DS+10sec, and DS+NeoTapLS revealed a mean (SD) HR of 41 (10), 41 (10), 44 (13), 44 (12), and 42 (13) bpm, respectively. At HRs between 60-100 bpm, assessment using CBF, ECG, DS+6sec, DS+10sec, and DS+NeoTapLS revealed a mean (SD) HR of 77 (11), 77 (12), 77 (14), 74 (12), and 76 (12) bpm, respectively. At HR >100 bpm, assessment using CBF, ECG, DS+6sec, DS+10sec, and DS+NeoTapLS revealed a mean (SD) HR of 119 (12), 120 (10), 120 (12), 121 (22), and 119 (11), respectively.

Additionally, the frequencies of errors using each method categorized according to the NRP cutoff ranges and in total are summarized in Table 3.3. Using the DS+6sec method, all errors in determining the correct range occurred when HR was between 60-100 bpm, resulting in correct identification of 93% of measurements in this range. Using the DS+10sec method, errors in determining the correct range occurred in all ranges when HR was <60, 60-100, and >100 bpm, resulting in correct identification 98, 94, 91% of measurements in each range, respectively. Using the DS+NeoTapLS method, errors in determining the correct range occurred when HR was <60 and 60-100 bpm, resulting in correct identification of 98 and 93% of measurements in each range, respectively. In general, the total frequency of errors using each technique was 4% and similar between all methods. DS+6sec, DS+10sec, and DS+NeoTapLS underestimated 1%, 2%, and 3% of all assessments and overestimated 2%, 2%, and 1% of all assessments, respectively.

Figure 3.1. Mean (SD) heart rate during asphyxia assessed using the DS+6sec, DS+10sec, DS+NeoTapLS interventions and standards (ECG and CBF). DS+NeoTapLS, Assessment group using the NeoTapLS smartphone app paired with the digital stethoscope; DS+6sec, Assessment group using the 6 sec method using a digital stethoscope; DS+10sec, Assessment group using the 10 sec method using a digital stethoscope; ECG, electrocardiogram; CBF, carotid blood flow. Reproduced with permission from Johnson *et al*[108].

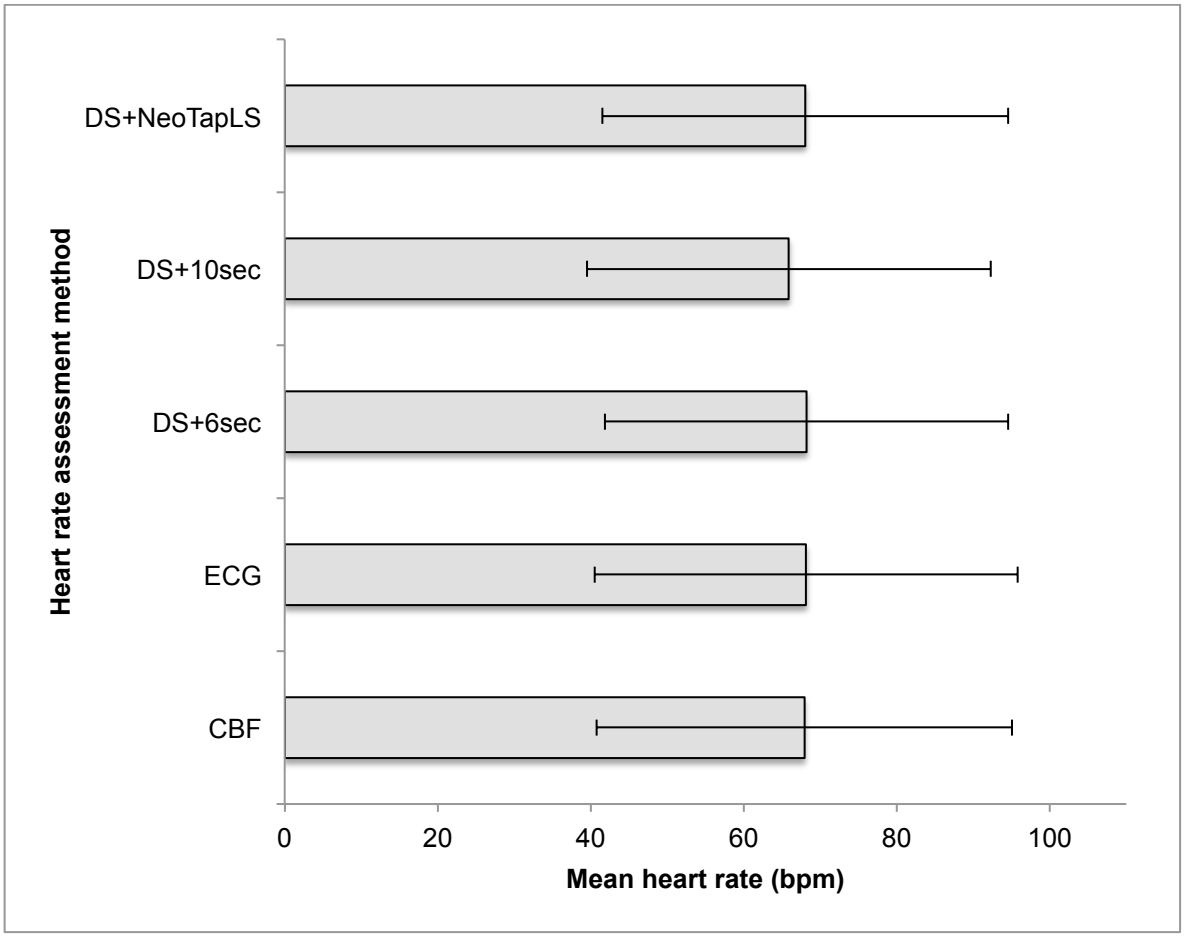


Figure 3.2. Bland-Altman plot for DS+NeoTapLS vs. CBF heart rate assessments during asphyxia. CBF, carotid blood flow; DS+NeoTapLS, digital stethoscope paired with NeoTapLS app. Reproduced with permission from Johnson *et al*[108].

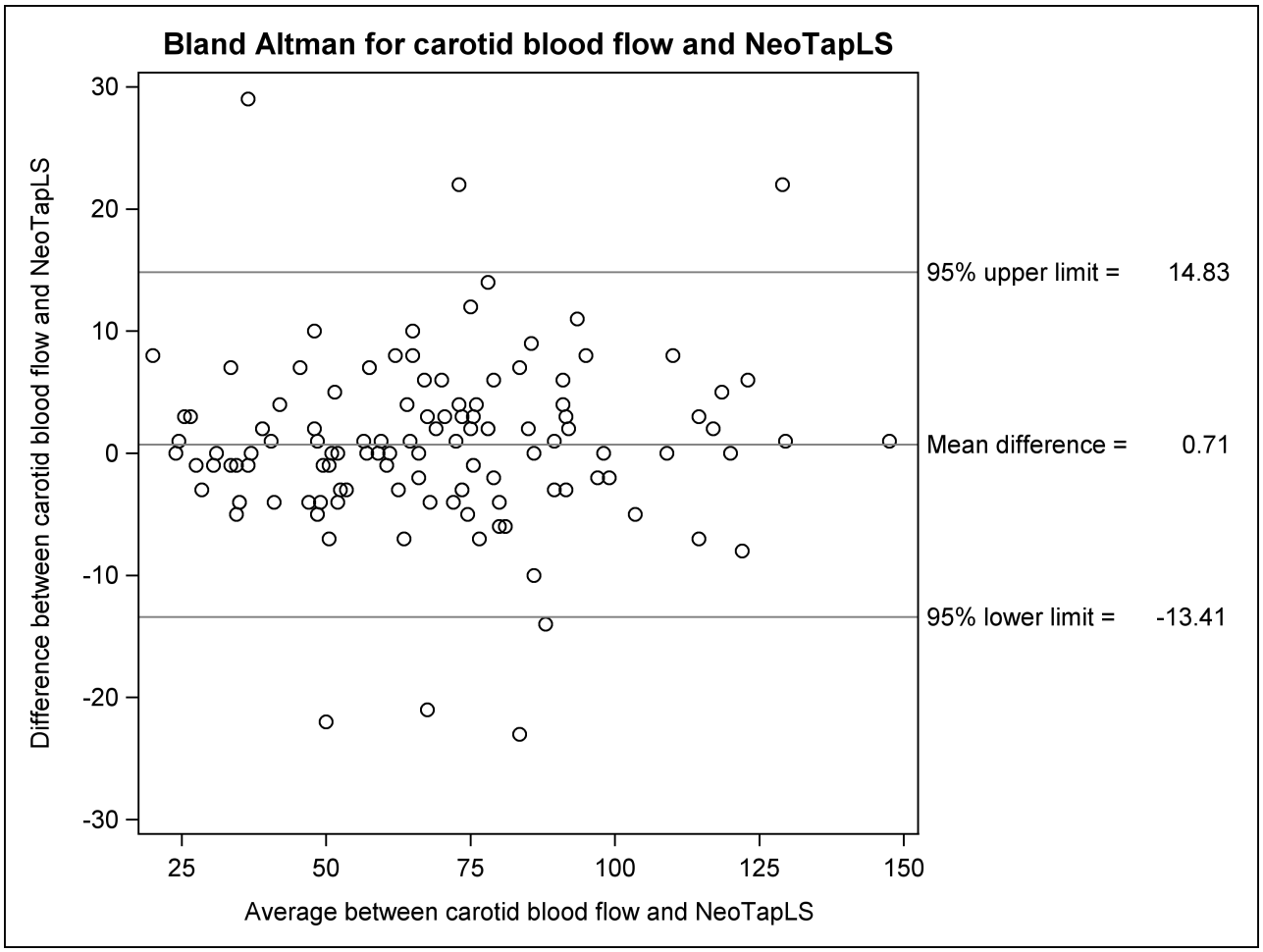


Figure 3.3. Bland-Altman plot for DS+6sec vs. CBF heart rate assessments during asphyxia. CBF, carotid blood flow; DS+6sec, digital stethoscope using 6-sec method. Reproduced with permission from Johnson *et al*[108].

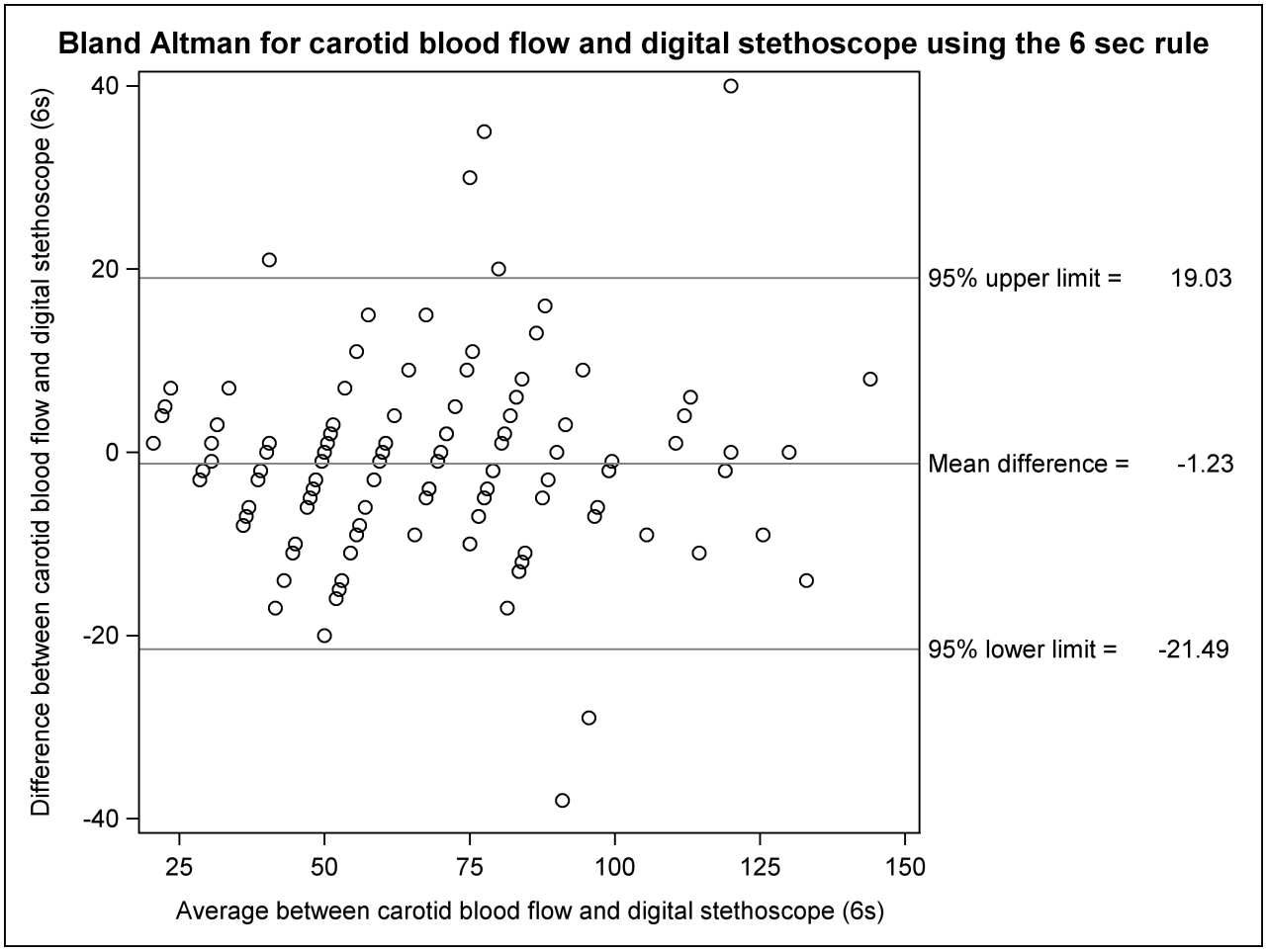


Figure 3.4. Bland-Altman plot for DS+10sec vs. CBF heart rate assessments during asphyxia. CBF, carotid blood flow; DS+10sec, digital stethoscope. Reproduced with permission from Johnson *et al*[108].

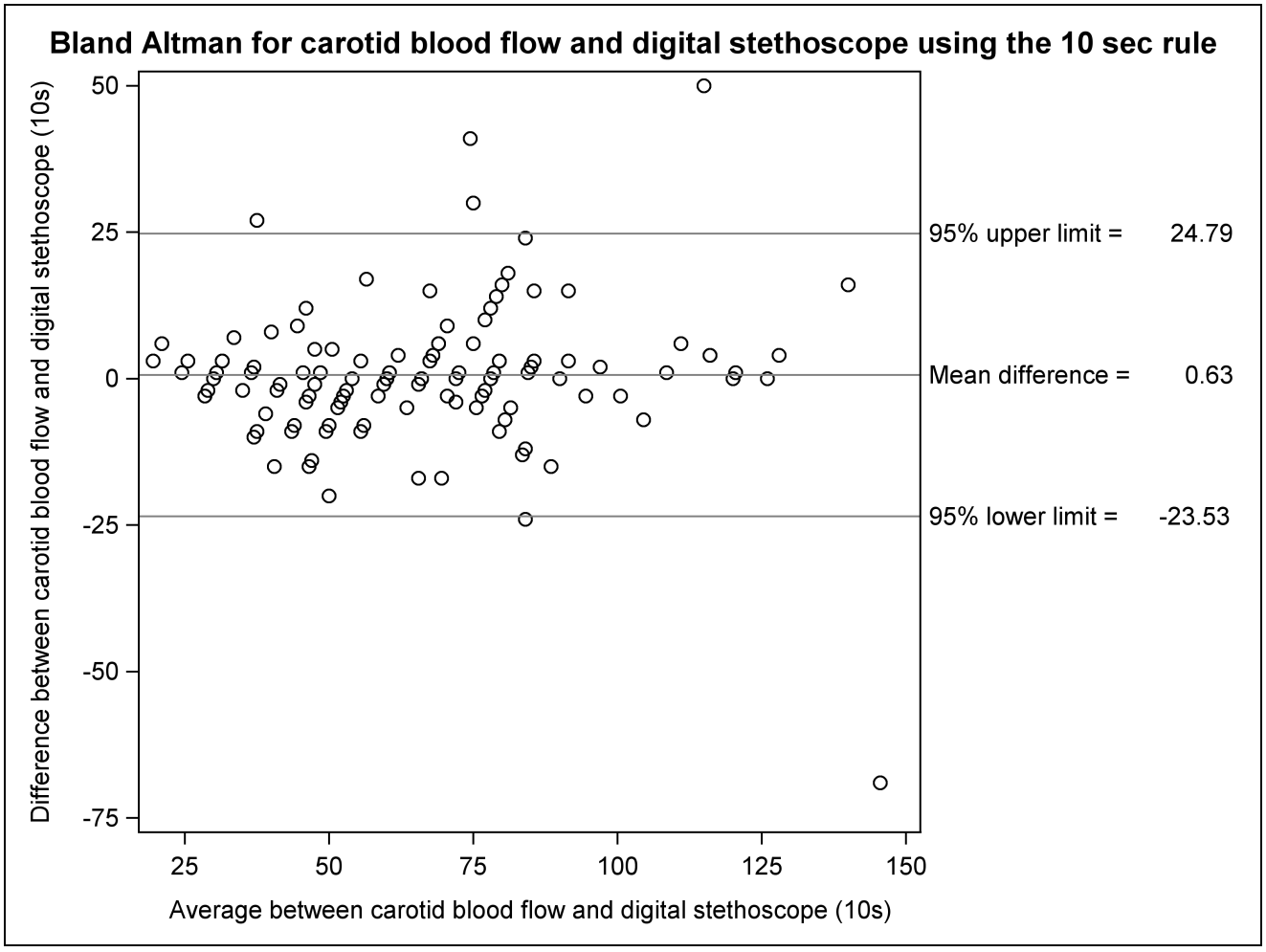


Figure 3.5. Mean (SD) heart rate during asphyxia assessed by CBF, ECG, DS+6sec, DS+10sec and DS+NeoTapLS, according to subgroups: CBF HR<60 bpm, 60<CBF HR<100 bpm, and CBF HR>100 bpm. HR: heart rate; DS+6sec: 6-sec method using a digital stethoscope; DS+10sec: 10-sec method using a digital stethoscope; NeoTapLS: NeoTapLS app paired with the digital stethoscope; ECG: electrocardiography; CBF: carotid blood flow. Reproduced with permission from Johnson *et al*[108].

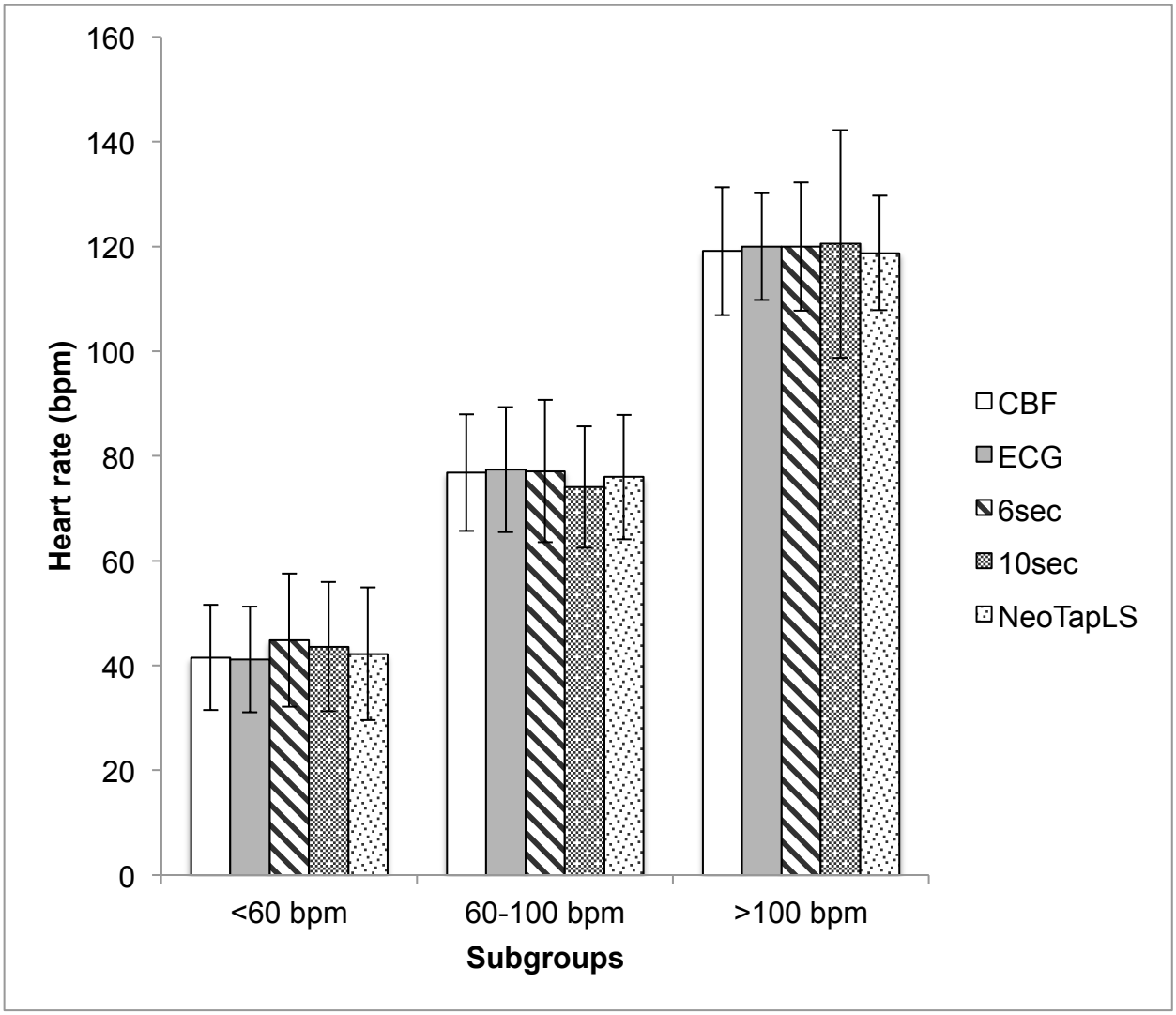


Table 3.3. Frequency of errors using (A) DS+6sec, (B) DS+10sec, and (C) DS+NeoTapLS according to Neonatal Resuscitation Program cutoff ranges (<60, 60-100, >100 bpm). Shaded cells represent the proportion of correct assessments and boxed cells represent total proportion of resulting error. Values in each cell are represented as the proportional percentage and ratio of the error frequencies or correct assessments to the total assessments in its cutoff range. DS+6sec: 6-sec method using a digital stethoscope; DS+10sec: 10-sec method using a digital stethoscope; NeoTapLS: NeoTapLS using the digital stethoscope; CBF: carotid blood flow.

	CBF HR			**Total errors**
	<60 bpm	60-100 bpm	>100 bpm	
(A) DS+6sec HR				
<60 bpm	100% (54/54)	3% (2/68)	0% (0/11)	1% (2/138)
60-100 bpm	0% (0/54)	93% (63/68)	0% (0/11)	0% (0/138)
>100 bpm	0% (0/54)	4% (3/68)	100% (11/11)	2% (3/138)
Total errors	0% (0/54)	7% (5/68)	0% (0/11)	4% (5/138)
(B) DS+10sec HR				
<60 bpm	98% (53/54)	3% (2/68)	0% (0/11)	1% (2/138)
60-100 bpm	2% (1/54)	94% (64/68)	9% (1/11)	1% (2/138)
>100 bpm	0% (0/54)	3% (2/68)	91% (10/11)	1% (2/138)
Total errors	2% (1/54)	6% (4/68)	9% (1/11)	4% (6/138)
(C) DS+NeoTapLS HR				
<60 bpm	98% (53/54)	6% (4/68)	0% (0/11)	3% (4/138)
60-100 bpm	2% (1/54)	93% (63/68)	0% (0/11)	1% (1/138)
>100 bpm	0% (0/54)	1% (1/68)	100% (11/11)	1% (1/138)
Total errors	2% (1/54	7% (5/68)	0% (0/11)	4% (6/138)

3.1.2 Heart rate assessments using Doppler ultrasound

A total of 109 assessments were made using Doppler ultrasound with a median (range) of 8 (2–20) assessments per animal. Of these, 12 observations were made when CBF HR was >100 bpm, 58 observations were made when CBF HR was between 60 and 100 bpm, and 39 observations when CBF HR <60 bpm with the Doppler ultrasound.

The mean (range) time for asphyxia was 414 (72–600) sec and assessments were obtained within 10 to 15 sec. During asphyxia, the mean (SD) CBF, ECG, and Doppler ultrasound HR were 69 (27), 70 (28), and 69 (27) bpm, respectively (Figure 3.6). There were no significant differences in the mean (SD) HR measured using CBF, ECG, and Doppler ultrasound.

The adjusted Bland-Altman analysis revealed a mean difference (95% limits of agreement) of 0.9 (−13 to +15) bpm between Doppler ultrasound and CBF HR (Figure 3.7).

Two-way mixed absolute agreement was utilized to compute an ICC (95% CI), unadjusted for repeated measures taken from the same subject, of 0.968 (0.954, 0.978) when using Doppler ultrasound. When adjusted for consequent repeated measures taken from the same subject, effect of a subject, time of the measurement, and method using random effects in the model, the adjusted ICC for Doppler ultrasound was computed to be 0.969.

Analyses by HR cutoff ranges: <60, 60–100, and >100 bpm are presented in Figure 3.8. At HRs <60 bpm, assessment using CBF, ECG, and Doppler ultrasound revealed a mean (SD) HR of 40(11), 41(11), and 41(9) bpm, respectively. At HRs between 60-100 bpm, assessment using CBF, ECG, and Doppler ultrasound revealed a

mean (SD) HR of 79 (12), 80 (12), and 77 (15) bpm, respectively. At HRs >100 bpm, assessment using CBF, ECG, and Doppler ultrasound revealed a mean (SD) HR of 118 (14), 119 (11), and 117 (14) bpm, respectively.

Additionally, the frequencies of errors using each method categorized according to the NRP cutoff ranges and in total are summarized in Table 3.4. Using the Doppler ultrasound, errors in determining the correct range occurred when HR was 60-100 bpm, resulting in correct identification for 83% of measurements. Compared to the auscultation techniques, using Doppler ultrasound resulted in a greater frequency of errors (9% versus 4%). All errors occurred when CBF HR was 60-100 bpm and most errors (8%) were underestimations while the remaining 1% was due to overestimation.

During asphyxia, peak signal size decreased as bradycardia progressed (Figure 3.9). In addition, the visualized signals from continuous HR assessment using the Doppler ultrasound were observed to be interfered by mechanical ventilation artifacts (Figure 3.10.A). This was later confirmed by the false positive peaks observed in the euthanized pig post-experiment (Figure 3.10.B).

Figure 3.6. Mean (SD) heart rate during asphyxia assessed using Doppler ultrasound and standards (ECG and CBF). Doppler, assessment using Doppler ultrasound; ECG, electrocardiogram; CBF, carotid blood flow.

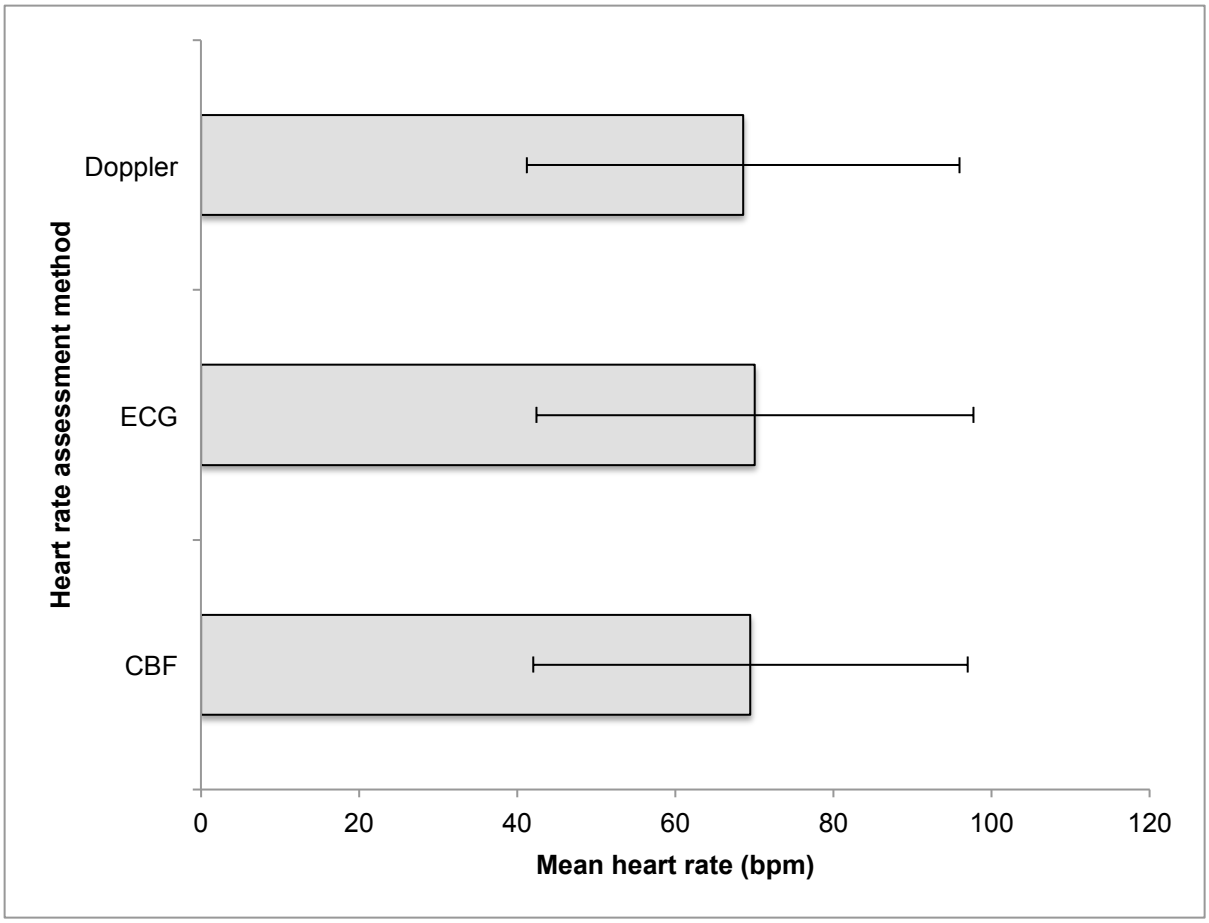


Figure 3.7. Bland-Altman plot for Doppler ultrasound heart rate versus carotid blood flow heart rate during asphyxia. Abbreviation: Doppler: Doppler ultrasound.

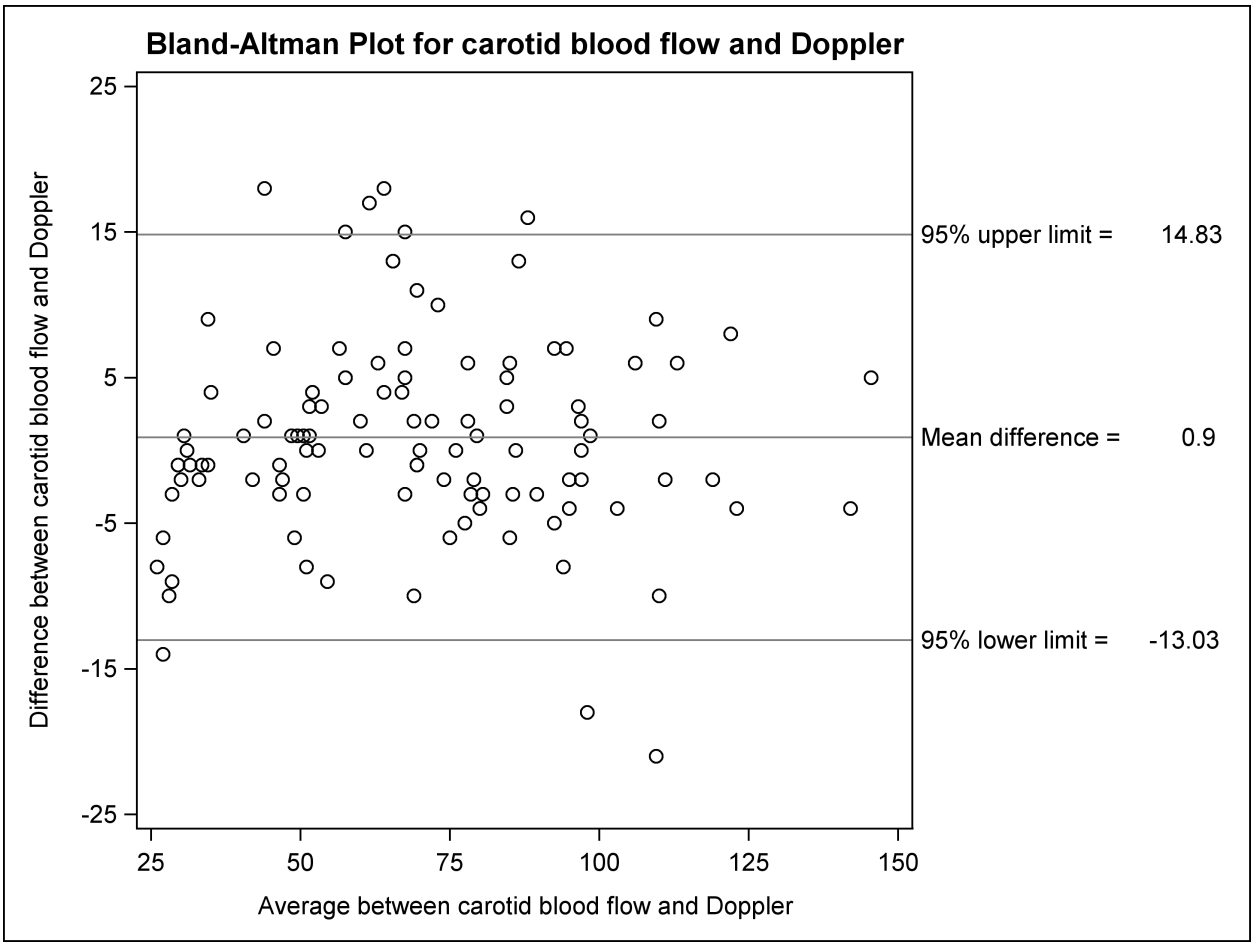


Figure 3.8. Mean (SD) heart rate during asphyxia assessed by CBF, ECG, and Doppler ultrasound, according to subgroups: CBF HR<60 bpm, 60<CBF HR<100 bpm, and CBF HR>100 bpm. Abbreviations: ECG: electrocardiography; CBF: carotid blood flow; Doppler: Doppler ultrasound.

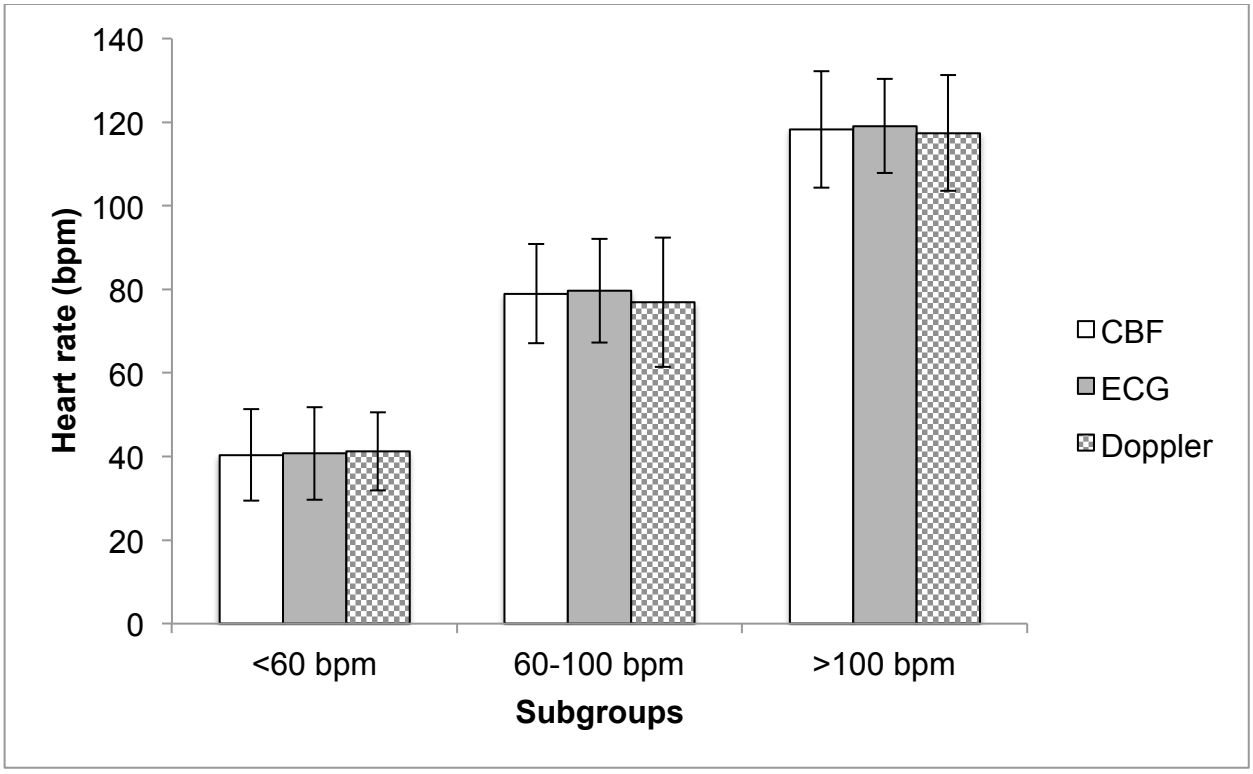


Table 3.4. Frequency of errors using Doppler ultrasound according to Neonatal Resuscitation Program cutoff ranges (<60, 60-100, >100 bpm). Shaded cells represent the proportion of correct assessments and boxed cells represent total proportion of resulting error. Values in each cell are represented as the proportional percentage and ratio of the error frequencies or correct assessments to the total assessments in its cutoff range. Doppler: Doppler ultrasound; CBF: carotid blood flow.

	CBF HR			**Total errors**
	<60 bpm	60-100 bpm	>100 bpm	
Doppler HR				
<60 bpm	100% (39/39)	16% (9/58)	0% (0/12)	8% (9/109)
60-100 bpm	0% (0/39)	83% (48/58)	0% (0/12)	0% (0/109)
>100 bpm	0% 0/39	2% (1/58)	100% (12/12)	1% (1/109)
Total errors	0% (0/39)	17% (10/58)	0% (0/12)	9% (10/109)

Figure 3.9. Visualization of Doppler flow profiles during bradycardia. As heart rate decreases, signals decreasing in peak size and quantity over the course of asphyxia. Visualized heart rates are **(a)** 63 bpm, **(b)** 42 bpm, and **(c)** 23 bpm. Reproduced with permission from Morina *et al*[109].

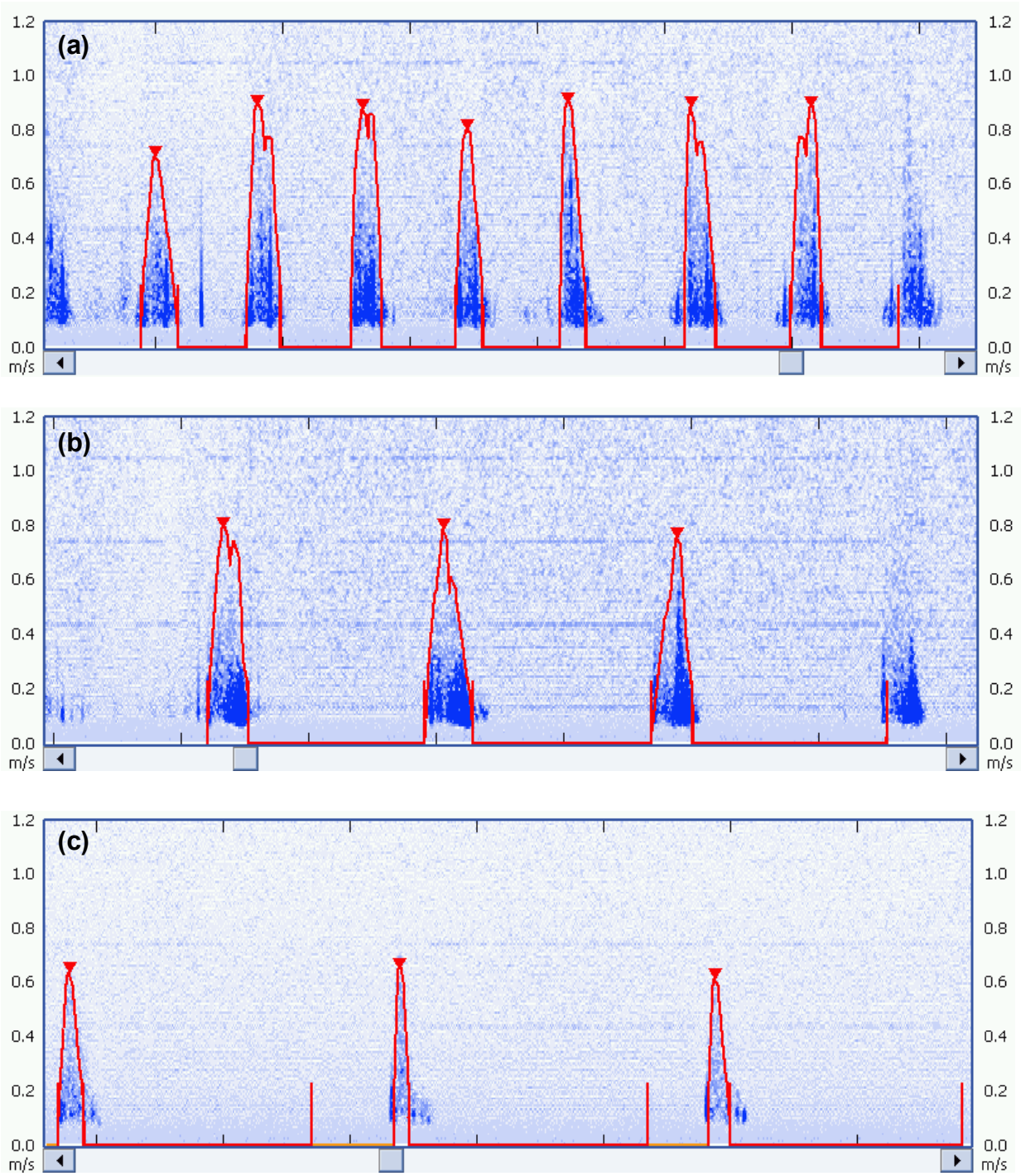
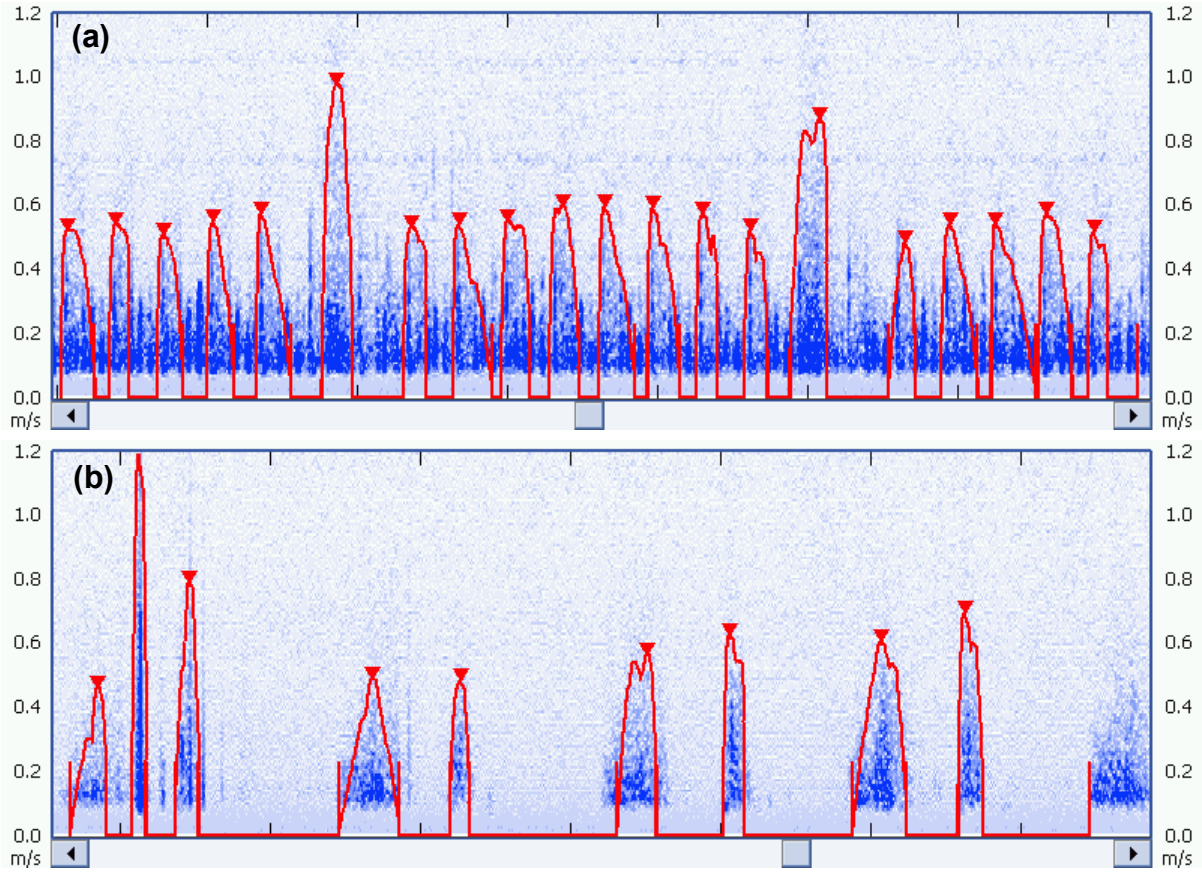


Figure 3.10. (a) Influence of mechanical ventilation on heart rate (HR) signal detection by USCOM. Two distinct higher peaks caused by piglet's emphasized chest movement due to ventilation are observable in the monitor image. The automatic flowtrace function of USCOM calculates the average HR in real-time, but ventilation "peaks" can impair this measurement. In the shown image, the calculated average HR is 174 bpm, but after manual removal of the two ventilation-produced signals, this mean increases to 182 bpm. **(b)** False positive signals caused by mechanical ventilation and subsequent chest movement in a euthanized piglet. Reproduced with permission from Morina *et al*[109].



3.2. Part II: Results from clinical study in the delivery room examining cPPG

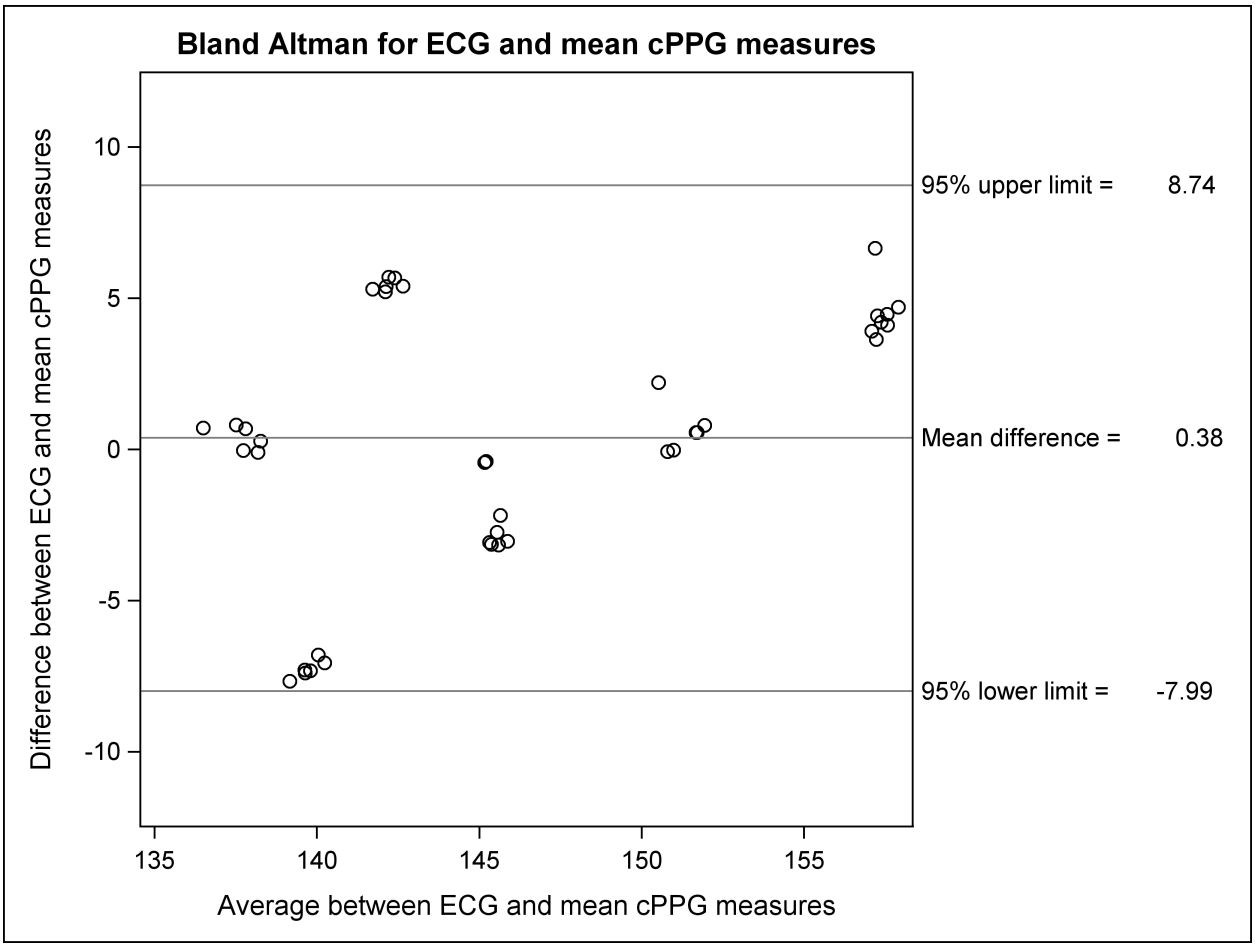
Forty preterm infants were recruited from the delivery room at the Royal Alexandra Hospital in Edmonton, Alberta, Canada. The demographics of the included infants are presented in Table 3.4. Mean (SD) HR for cPPG and ECG HR for all sampled data during resuscitation were 146(6) and 146(8) beats/min, respectively. The Bland Altman analysis revealed several points of the same value, and therefore, a uniform random jitter was performed to better represent data points (Figure 3.11). The analysis revealed a mean difference (95% limits of agreements) of +0.4 (-8.0 to +8.7) beats/min between cPPG and ECG HR. Two-way mixed absolute agreement ICC (95% CI) between ECG and average cPPG HR was computed to be 0.83 (0.70 to 0.91).

Table 3.5. Demographics of enrolled study infants.

*n**	40
Birth weight (g)	1225 (475.2)
Gestational age (weeks)	28.6 (2.6)
Male (%)†	40
Antenatal steroids (%)†	93
Apgar 1 minute#	4.8 (2.3)
Apgar 5 minutes#	6.8 (1.6)

Data are presented as mean (SD) unless indicated #median (IQR), *n, †percent

Figure 3.11. Bland-Altman plot for ECG HR versus mean cPPG HR measures for preterm infants in the delivery room. Abbreviations: ECG: electrocardiography; cPPG: camera-based photoplethysmography.



CHAPTER 4. Discussion

These are the first studies to evaluate these novel approaches for HR assessment during neonatal resuscitation. The animal study examined the use of the various DS auscultation methods, the NeoTapLS smartphone app, and Doppler ultrasound technologies in a model of neonatal asphyxia. Moreover, the clinical study represents the first study to examine the use of cPPG for infants requiring resuscitation in the delivery room.

4.1. Heart rate assessment using DS auscultation methods

Currently, there are conflicting results about the accuracy of using the DS to assess a newborn's HR. In the neonatal intensive care unit and the delivery room, HR assessment using DS compared to ECG have previously demonstrated low and high accuracy for DS with a mean difference (SD) of 7.4 (24) bpm and mean difference (95% limits of agreement) of 0.2 (-18 to +18) bpm, respectively[60,62]. In comparison, all HR assessed by DS auscultation methods in this study had a mean difference within 1 bpm compared to the gold standard CBF HR, suggesting a good accuracy for these methods during resuscitation. Although the mean differences and ICC computed for DS+6sec, DS+10sec, and DS+NeoTapLS suggest a high level of agreement to CBF HR, a wider difference in 95% upper and lower limits of agreement was observed (Figures 3.2-3.5). Currently however, a mean difference (95% limits of agreement) of -13 (-63 to +37) bpm is reported for auscultation with a standard stethoscope compared to ECG in the first minute after birth, with upper and lower limits ranging 50 bpm from the mean difference[24]. In this study, upper and lower limits ranging 20 bpm from the mean difference was observed for DS+6sec, suggesting a higher level of precision and lower range of error compared to the recommended 6-sec auscultation method using a standard

stethoscope. Similar results were seen in a study by Gaertner *et al* that reported upper and lower limits ranging 18 bpm from the mean difference when using the DS, compared to ECG, in transitioning, term infants after birth[61]. In these infants, DS only detected HR in 62% (23/37) of newborn infants within 30 sec, while in the remaining 38% (14/37) of infants, HR could not be assessed due to crying[61]. When these infants were removed, a mean difference (95% limits of agreement) of 1 (-11 to 13) bpm, with upper and lower limits ranging 12 bpm from the mean difference was observed[61]. In this study, all piglets were intubated and sedated/anesthetised and therefore no crying or vocalization was not possible, resulting in a HR assessment detection rate of 100%. Additionally, in a real-life resuscitation scenario, the infant crying or vocalizing is a sign of improved status, which would make further HR assessment and resuscitative interventions unnecessary at that point.

In 33–75% of cases[8,18,63], assessment of HR using auscultation with a standard stethoscope was reported to be inaccurate. However, this was not the case in this study using the DS. This inaccuracy might be due to lack of audibility and clarity of heart sounds, which might have been improved using the DS, and the mental computation required to convert heartbeat counts to HR in a stressful resuscitation situation, which might have been reduced by tap-based mobile applications such as NeoTapLS[36]. The results of this study showed the use of DS+NeoTapLS required a median assessment time of 3 sec during asphyxia, compared to the DS+6sec and DS+10sec, which required an anticipated and minimum median assessment time of 6 and 10 sec to obtain heartbeat counts, respectively. Despite a higher assessment duration (i.e., 10 as opposed to 6 sec) being suggested to increase the accuracy of assessments[16], my results demonstrated the

accuracy remained similar for DS+6sec and DS+10sec, which both had correct classification assessment frequencies of 96%. It was also speculated that time required to assess HR would take longer in a clinical resuscitation scenario with the 10-sec method in the DS+10sec group due to the greater cognitive load required for multiplying numbers by 6, in contrast to the recommended 6-sec method in the DS+6sec group, where numbers can easily be multiplied by 10. Thus, as both methods have similar accuracy, of the two approaches, it was determined DS+6sec method should be favoured due to a faster HR assessment time and convenience.

Three studies reported that the tap-based mobile applications have good accuracy and can be used to quickly assess HR in combination with auscultation during simulated neonatal resuscitation[20,63,100], suggesting it might also have the potential to improve HR assessment in the delivery room. However, studies in the delivery room are lacking. In addition to determining a similar accuracy in assessing HR to DS+6sec, DS+10sec, ECG, and CBF, the DS+NeoTapLS median assessment time was shorter in comparison to the DS+6sec and DS+10sec methods ($p<0.05$). The median (IQR) time required to assess HR using auscultation using the NRP's 6-sec rule in low-risk infants in the delivery room was 14 (10-18) sec[19], while the mean (95% CI) time was 15 (13 to 16) sec and similar using NeoTapLS in simulation[20]. However, in another simulation study, it was determined that the use of the mobile app improved mean time to first communication of HR by 13 sec, mean time to initiation of chest compressions by 68 sec, and mean time to administer epinephrine by 76 sec, when compared to mental computation using the NRP 6-sec method[100]. This was consistent with these findings and suggest that the NeoTapLS application is faster on average during neonatal asphyxia to assess HR. Nonetheless, this

has yet to be examined in the delivery room and may be similar or different in practice. Despite this, the results of this study suggest DS+6sec, DS+10sec, and DS+NeoTapLS are more accurate alternatives to existing recommendations, while both the NRP-recommended 6-sec method and NeoTapLS assessment method are both effective, enabling an equal or shorter assessment time.

While promising, each of these technologies has inherent limitations. First, although it is possible to adjust frequency ranges with the DS, it is extremely sensitive making it possible for noise in the environment to interfere with the audible signal. This may be problematic in a noisy delivery room where there are alarms and conversation between the clinical team members is essential. The DS itself is an expensive tool and can therefore be limited or inaccessible in low-resource areas. For NeoTapLS, assessments require the use of both hands (one for auscultation and one for tapping), which means a clinical team member must be designated for the role when HR is assessed. Additionally, although NeoTapLS is commercially available on mobile phones, this means they must be thoroughly disinfected before and after use during resuscitation and that other functionalities do not interfere with care.

4.2. Heart rate assessment using Doppler ultrasound

Although only a limited number of studies have examined infants requiring resuscitation, the majority of previous studies evaluating Doppler ultrasound for HR assessment suggest it is feasible, accurate, and fast at obtaining HR[65–67,110–113]. The results of this study demonstrated HR assessment using Doppler ultrasound generated a similar HR to that recorded by ECG and CBF, as well as a low mean difference, relatively low

limits of agreement compared to DS and standard auscultation methods, and high ICC suggest a high level of agreement compared to CBF and therefore, a high level of accuracy for Doppler ultrasound (Figures 3.6-3.8). This is consistent with the observations in three studies reporting mean difference (+/- 2 SD) of -3 (-42 to +36) bpm and mean differences (95% CI) of -0.1 (−0.6 to +0.3) and +5 (−13 to +2.1) bpm compared to ECG in primarily stabilized, term, or low-risk infants[66,110,111]. Additionally, these studies report a short assessment time <10 sec and faster assessment when compared to ECG HR acquisition immediately after birth[110,111], which is consistent with the observation that intermittent assessments using the Doppler ultrasound were made within 5-20 sec. However, most of these studies do not represent high-risk infants requiring resuscitation. More recently, Kayama *et al* conducted the first observational study describing the use of fetal Doppler ultrasound for 21 newborn infants requiring resuscitation[112]. In this study, only measurements for 86% (18/21) of infants were possible, as infants that were moving or crying required >10 sec for assessment and were excluded to prevent interference with resuscitation[112]. As these are signs the infant is vigorous, it was thus anticipated that these cases would not require critical interventions. Of these infants, nine had neonatal asphyxia (indicated by a 1-min Apgar score ≤6) and were shown to have their HR assessed by Doppler ultrasound with a good accuracy and short assessment time[112]. Despite this however, none of these infants had HR<60 bpm[112], suggesting data is still limited for infants with bradycardia and those requiring more advanced levels of resuscitation and respiratory support at birth. Nonetheless, the results obtained in this study are comparable, showing a good level of accuracy and short

assessment time using Doppler ultrasound, and suggest its reliability for use for initial HR assessment at birth.

However, when the frequencies of error were classified according to NRP cutoff ranges, it was observed that a higher proportion of total errors for Doppler ultrasound compared to DS auscultation techniques (9% versus 4%; p=0.07; Tables 3.3 and 3.4). In particular, for HR between 60-100 bpm, there was a higher tendency for Doppler ultrasound to misclassify HR as <60 bpm. Although all of these errors were within 5-10 bpm, various factors were identified that could have influenced these assessments. One of these factors was the gasping/ventilation of the piglet, which resulted in interference with the Doppler flow signal used to calculate HR (Figure 3.10). This was confirmed by providing PPV in piglet cadaver and observing a Doppler signal matching the same respiratory rate set on the ventilator. It is therefore significant for the clinical team to recognize PPV may result in interference with the resulting HR and its signal could be mistaken for a heartbeat. Movement from the animal, movement of the operator's hands, and displacement of the transducer was also observed to influence the accuracy of the assessed HR by displaying an incorrect or no signal. Kayama *et al* also describes the limitation of Doppler ultrasound to assess HR in 14% (3/21) of infants due to crying and movement[112], which can critically delay assessment during resuscitation. Additionally, prolonged asphyxia and decreasing cardiac output was observed to result in weaker signals with smaller peak sizes (Figure 3.9), which could also lead to misinterpretation of HR in the delivery room.

As a result, the ongoing visualization and evaluation of pulse signals using the Doppler velocity flow profile could be used to enable a good measure of the reliability of

the signal. This feature can also be used to detect the presence of interference from variables including ventilation, gasping, or artifacts from movement of the infant or transducer position, in a clinical setting. Before implementing Doppler ultrasound in the delivery room, it is essential that at least one member on the clinical team is trained and has the skill to detect the type of signal from its shape and peak size and recognize when peaks are not being detected. Moreover, in addition to the Doppler display, the use of Doppler ultrasound's audible signal may also be used to confirm the reliability of the pulse signals. Dyson *et al* has described the innovative use of the audible Doppler signal using the 6-sec method to estimate HR as more accurate than the Doppler display of HR, with mean differences (95% limits of agreement) of 0.7 (-14 to +16) and 5 (-50 to +39) bpm[66]. Although the animal study focused on accuracy of HR assessed on the Doppler display, which required the audible signal to be disabled for blinding purposes, the use of the audible signal for initial HR assessment is also conceivable and promising.

4.3. Limitations of a porcine model of neonatal asphyxia

The use of a piglet asphyxia model is a great strength of this translational study, as this model closely simulates the onset of severe asphyxia leading to bradycardia observed during birth asphyxia in the delivery room[97,98]. Despite these strengths however, it is necessary to recognize there are inherent limitations in the use of this model for this study. First, the fetal-to-neonatal transition and clearance of lung fluids is already completed in this model, which means physiological features such as the transitional shunts, high pulmonary pressures, and other transitional events observed in human infants would be absent[95,98]. Additionally, this model requires the use of anesthesia,

surgical instrumentation, ET intubation involving tracheostomy for mechanical ventilation, and the artificial induction of asphyxia[97]. As human infants typically neither receive anesthesia nor surgical interventions at birth, there is a higher risk of depression from anesthesia and/or surgical stress in newborn piglets. Newborn infants are additionally ventilated using facemasks, where airway obstruction and mask leaks are common, and/or or laryngeal ET intubations, where failed attempts and leaks are recurrent as well. Finally, this model requires artificial induction of asphyxia by alveolar hypoxia followed by airway obstruction, which is different in comparison to natural causes of asphyxia at birth in humans. Furthermore, although this model provides strong internal validity, its dependence on protocoled interventions requiring the same tools, procedures, and assessors could make it difficult to generalize to delivery room settings. Given this protocol, assessors also have a foresight of how the model will respond and lower levels of cognitive load (no arithmetic was performed), compared to infants at birth that are more unpredictable and demand greater cognitive loads.

4.4. Heart rate assessment using cPPG

The clinical study examining cPPG to measure HR during neonatal resuscitation suggests its use is accurate, when compared to ECG HR. As opposed to initial assessment of HR at birth, cPPG was evaluated for its use and accuracy in continuously monitor HR during resuscitation. This was the first study to evaluate cPPG in the delivery room for HR monitoring in preterm infants requiring resuscitation. The results of the Bland-Altman analysis revealed a high degree of agreement between cPPG and ECG HR with a mean difference (95% limits of agreement) of 0.4 (-8.0 to +8.7) bpm. This is better than

pulse oximetry, one of the current recommendations for continuous HR monitoring, which had a mean difference (95% limits of agreement) of 2 (-28 to +24) bpm[28]. This is largely consistent with the results of previous NICU studies, which report good accuracy of cPPG compared to ECG[69,72,75,76,114–117]. Grubb *et al* used the largest cohort of infants, reporting similar mean differences (95% limits of agreements) of 0.0 (-8.4 to +8.4) bpm in 53 infants that were ≥32 weeks' gestation and -0.2 (-12.0 to +11.5) bpm in 24 infants <32 weeks' gestation[72]. As the use of cPPG has yet to be examined during neonatal resuscitation, this study offers a proof-of-concept for its feasibility for HR assessment. The results of this study revealed a 100% (40/40) detection rate for assessments performed using cPPG in all infants. This is promising as an important consideration in the delivery room, where high-risk infants who are more vulnerable and having an increased risk of hypoxia and asphyxia.

Nonetheless, several limitations affecting the accuracy of HR monitored by cPPG were identified during resuscitation including: i) movement, ii) ambient light, and iii) perfusion levels. It was noted that interventions or procedures such as intubations during resuscitation could result in the movement of the infant and/or the environment. Motion artifacts can result in a low signal quality and interfere with an accurate assessment of HR. The effect of movement or motion artifacts was consistently identified in previous NICU studies as well[69,72,75,76,114–117]. Of these studies, three have described the use of more advanced algorithms such as motion-tracking or motion-compensation using a band-pass filter to reduce this effect[75,115,116]. Continuous HR monitoring using cPPG in delivery rooms might benefit from the use of these filters. During procedures such as intubations, where the infant's head might become shifted, it would also be possible to

use a region of interest from other high perfusion skin surfaces such as the infant's hand. Another common issue that identified with the use of cPPG was the influence of ambient fluorescent lighting and/or scattering of light from reflective surfaces in the delivery room, which can interfere with HR assessment. Of the several NICU studies where this issue has been identified[75,76,114,115], Blanik *et al* described the use of an optical infrared filter with a specified band-pass placed in front of the camera's objective lens to minimize these interferences in ambient light[115]. This might be beneficial in overcoming challenges related to lighting in the delivery room. The signal quality of the measured cPPG HR can also be affected by low blood perfusion. Ensuring the selected region of interest is an area of high blood perfusion (e.g., forehead, face, hand, foot, etc.) will minimize this effect[118]. This study suggested the feasibility of cPPG HR assessments using the forehead region in infants with asphyxia and reduced perfusion. While this study provides a proof-of-concept, it is integral for clinical studies using real-time cPPG and ECG HR monitoring at birth to be conducted. The use of cPPG is also promising, as it requires no skin contact with infant, eliminating negative effects, such as skin damage for preterm infants, associated with currently recommended contact techniques.

Nevertheless, further studies and considerations are necessary prior to the implementation of cPPG in the delivery room. These studies are required to show that cPPG can be used real-time and continue to display a high level of agreement over a longer duration of time. Moreover, establishing visualization of cPPG waveforms during resuscitation would be crucial as it would enable the clinical team to confirm the reliability of HR and signal quality. It would also be necessary to measure the time required for cPPG to display a reliable HR immediately after birth and time to process

changes in HR. Another consideration is factors such as skin conditions and ethnicity (different pigmentations) of the infant population, which may influence the displayed cPPG measurements, must be taken into account. In the context of resuscitation in the delivery room, the body of evidence regarding the reliability of cPPG for HR monitoring remains limited and more studies including randomized clinical trials are warranted.

4.5. Considerations for heart rate assessment during neonatal resuscitation

Overall, the DS+NeoTapLS, DS+6sec, DS+10sec, Doppler ultrasound, and cPPG had similar accuracy for HR assessment when compared to ECG and/or CBF. The current recommendations for assessment of HR immediately at birth are auscultation using a standard stethoscope and palpation of the umbilical cord, which has most recently been reported to show a mean difference (95% limits of agreement) of -13 (-63 to +37) bpm and -20 (-80 to 40) bpm, compared to ECG in the first minute after birth[24]. Compared to these reported mean differences and limits of agreements, the results for the use of DS+NeoTapLS, DS+6sec, DS+10sec, and Doppler ultrasound indicate smaller mean differences within 1 bpm and smaller limits of agreement with upper and lower limits, which within 14, 20, 24, and 14 bpm compared to CBF respectively, suggesting the use of DS+NeoTapLS, DS+6sec, DS+10sec, and Doppler ultrasound may all be effective alternatives for immediate assessment of HR at birth. Although cPPG also demonstrated a high level of accuracy in this clinical study, it was not evaluated for its use in immediate assessment of HR at birth.

However, it is important to note that existing clinical studies examining the current recommendations differ from the asphyxia-induced animal model, as HR<100

bpm make up a small number of assessments or are not observed at all in newborn infants for these studies[14,19,23,24], making it difficult to make inferences about the accuracy of using auscultation with a standard stethoscope and umbilical cord palpation in lower HR ranges. The results of the subgroup analysis by NRP cut-off values considers the accuracy and likelihood of errors within these ranges when using DS+NeoTapLS, DS+6sec, DS+10sec, and Doppler ultrasound to guide interventions at birth (Figures 3.5 and 3.8; Tables 3.3 and 3.4). While having limited data for HR<100 bpm, the only clinical studies to determine the frequency of accurate subgroup classification for HR<100 bpm report a 20% (1/5) error rate using auscultation with a stethoscope and a combined error rate of 32% (10/31) (based on error rates from two studies reporting 9% (1/11) and 45% (9/20)) for umbilical cord palpation[14,24]. When compared to these results, current recommendations show a much higher rate of error for HR<100 bpm, compared to 4% (5/122), 4% (5/122), 5% (6/122), and 10% (10/97) rates of error observed when using DS+NeoTapLS, DS+6sec, DS+10sec, and Doppler ultrasound, respectively. The rate of correct classification using each of these techniques were over 90% in all subgroups, with the exception of Doppler ultrasound, which tended to underestimate values in the 60-100 bpm range. Nevertheless, it had a correct classification rate of 83%, which is still above the rate observed for existing recommendations.

Novel approaches for continuous monitoring HR in newborn infants requiring resuscitation were also examined. The use of cPPG in preterm infants admitted to the delivery room was evaluated and the results of this study revealed a high level of accuracy compared to ECG. The results of this study were the first of its kind and as a result, a proof-of-concept for the feasibility of this technology in the delivery room.

Through this study, several limitations and considerations were also identified for the real-time measurement of HR using cPPG in the delivery room. Another possibility is the use of DS+NeoTapLS and Doppler ultrasound methods for continuous assessments. In contrast, the DS+6sec and DS+10sec can only be utilized for intermittent assessment of HR during resuscitation.

While these results are highly promising suggesting a high level of accuracy for all techniques, there are other factors that must be considered prior to the translation and clinical implementation of these approaches. It is significant that the assessment approach has the ability not only to provide an accurate HR but also rapidly detect any changes to HR. The latency of these techniques were determined to either depend on a set interval (i.e., DS+6sec and DS+10sec) or a beat-to-beat interval (i.e., DS+NeoTapLS, Doppler ultrasound, cPPG, ECG, and CBF). While set interval methods always required a consistent, and on average, longer amount of time to detect changes in HR, the beat-to-beat interval methods could detect changes in HR as soon as the consequent heartbeat or pulse was detected. When considering the time required for assessment, the ease of assessment, time required for effective communication, and readiness and anticipatory action taken by members of the clinical team are also significant. Of the approaches evaluated, DS+6sec and DS+10sec allow a single member of the clinical team to make an auditory assessment, perform a mental computation, and communicate HR to the team; DS+NeoTapLS allows a single member to make an auditory assessment and share a visual display to communicate HR to the team; Doppler ultrasound allows a shared auditory signal and visual display of HR to the team; and cPPG allows a continuous visual display of HR to the team. When considering these techniques, the reliability of

different sensory modalities (hearing vs. sight) and objectivity of assessments (i.e., whether the HR is computed by the machine or an individual) are additional factors to be considered. For technologies such as DS, Doppler ultrasound, and cPPG, it is critical for regional or national healthcare programs in both low-resource and high-resource settings to conduct a cost-benefit analysis, including resource availability, economic costs, and estimated benefit of the technology, prior to implementation.

CHAPTER 5. Conclusions and Future Directions

5.1. Conclusions

Although there is a growing body of evidence on novel technologies for HR assessment in newborn infants, the majority of evidence derives from healthy/low risk infant cohorts with limited investigations in delivery room settings for high-risk infants for its effective use during neonatal resuscitation. In this work, an animal study determined that the use of DS+6sec, DS+10sec, DS+NeoTapLS, Doppler ultrasound have a similar accuracy for HR assessment when compared to the gold standards, CBF and ECG. The use of DS+6sec, DS+10sec, DS+NeoTapLS, and Doppler ultrasound were additionally determined to be more accurate than the current recommendations for immediate assessment of HR at birth, which are auscultation with a standard stethoscope and umbilical cord palpation using the 6-sec method. However, the DS can be less accessible in resource-limited facilities and the assessed HR could be influenced by surrounding noises, the assessor's hearing ability, and auscultation technique being used. Between, DS+6sec and DS+10sec, it was determined that DS+10sec was ineffective as it placed a greater cognitive load on the assessor to calculate HR. It was also identified that DS+NeoTapLS required the least amount of time on average to assess HR out of the evaluated auscultation methods. However, the use of this app requires the use of a mobile phone in the delivery room, which might become a distraction or pose the risk of infection through contamination of the healthcare environment, providers, or infant. There were also limitations to using Doppler ultrasound during resuscitation that were identified, such as the influence of ventilation, movement, and a low cardiac output on HR assessed. In addition, the clinical study conducted determined cPPG had a similar accuracy for HR monitoring during resuscitation when compared to the gold standard,

ECG. The results of this study suggested that movement, ambient light, and perfusion levels could influence the accuracy of these assessments. These findings, as a whole, should be used to direct future research concerning the use of these techniques during neonatal resuscitation.

5.2. Future directions

Clinical trials are therefore warranted and forthcoming to evaluate the how effective these novel techniques are in the delivery room, when compared to existing recommendations. These clinical trials should not only evaluate accuracy and time required for assessments, but also how effective these technologies are for improving acute and long-term infant resuscitation outcomes including survival, duration of stay in the hospital, any adverse cardiovascular/respiratory outcomes, need for resuscitation, time to intervention, frequency and type of interventions, etc. Further observational studies are also required in the delivery room using the DS, NeoTapLS, and Doppler ultrasound to gain insight into how the use of these technologies might interfere with the resuscitation approach. In addition to evaluating the individual use of each of these identified technologies, the combined use of these technologies should be investigated as well. Namely, technologies that rely on audial modality for heartbeat detection (i.e., auscultation with a standard stethoscope, auscultation with a DS, and Doppler ultrasound audio) could provide the fastest assessments when combined with NeoTapLS. For monitoring throughout resuscitation, ECG may be combined with cPPG, which is non-contact and poses no additional risks, to confirm reliability and as contingency in rare cases (e.g., PEA, hydrops fetalis, etc.). Future studies should focus on the ease of use for

these novel technologies. More specifically, there may be differences in the accuracy of assessments between users of the technology based on varying clinical expertise, workload, reaction times, differences in sensory abilities (e.g., touch for palpation, hearing for auscultation), and other human factors. Simulation studies are best suited for evaluating these factors. It would also be significant for these studies to determine how effective a certain technology is, in terms of readiness and actions of the entire team (e.g., one that allows for shared assessment of HR by the entire clinical team versus one requiring assessments to be reported by a single assessor).

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ARRIVE

APPENDIX A

The ARRIVE Guidelines Checklist

Animal Research: Reporting In Vivo Experiments

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	ITEM	RECOMMENDATION	Pages/ Section
Title	1	Provide as accurate and concise a description of the content of the article as possible.	First page, not numbered
Abstract	2	Provide an accurate summary of the background, research objectives, including details of the species or strain of animal used, key methods, principal findings and conclusions of the study.	ii-iv
INTRODUCTION			
Background	3	a. Include sufficient scientific background (including relevant references to previous work) to understand the motivation and context for the study, and explain the experimental approach and rationale. b. Explain how and why the animal species and model being used can address the scientific objectives and, where appropriate, the study's relevance to human biology.	2-25, 27
Objectives	4	Clearly describe the primary and any secondary objectives of the study, or specific hypotheses being tested.	20
METHODS			
Ethical statement	5	Indicate the nature of the ethical review permissions, relevant licences (e.g. Animal [Scientific Procedures] Act 1986), and national or institutional guidelines for the care and use of animals, that cover the research.	v, 28
Study design	6	For each experiment, give brief details of the study design including: a. The number of experimental and control groups. b. Any steps taken to minimise the effects of subjective bias when allocating animals to treatment (e.g. randomisation procedure) and when assessing results (e.g. if done, describe who was blinded and when). c. The experimental unit (e.g. a single animal, group or cage of animals). A time-line diagram or flow chart can be useful to illustrate how complex study designs were carried out.	27-37, Fig 2.1, Fig 2.2
Experimental procedures	7	For each experiment and each experimental group, including controls, provide precise details of all procedures carried out. For example: a. How (e.g. drug formulation and dose, site and route of administration, anaesthesia and analgesia used [including monitoring], surgical procedure, method of euthanasia). Provide details of any specialist equipment used, including supplier(s). b. When (e.g. time of day). c. Where (e.g. home cage, laboratory, water maze). d. Why (e.g. rationale for choice of specific anaesthetic, route of administration, drug dose used).	27-37, Fig 2.1, Fig 2.2
Experimental animals	8	a. Provide details of the animals used, including species, strain, sex, developmental stage (e.g. mean or median age plus age range) and weight (e.g. mean or median weight plus weight range). b. Provide further relevant information such as the source of animals, international strain nomenclature, genetic modification status (e.g. knock-out or transgenic), genotype, health/immune status, drug or test naïve, previous procedures, etc.	28, Tables 3.1 and 3.2

Housing and husbandry	9	Provide details of: a. Housing (type of facility e.g. specific pathogen free [SPF]; type of cage or housing; bedding material; number of cage companions; tank shape and material etc. for fish). b. Husbandry conditions (e.g. breeding programme, light/dark cycle, temperature, quality of water etc for fish, type of food, access to food and water, environmental enrichment). c. Welfare-related assessments and interventions that were carried out prior to, during, or after the experiment.	28, 34-36
Sample size	10	a. Specify the total number of animals used in each experiment, and the number of animals in each experimental group. b. Explain how the number of animals was arrived at. Provide details of any sample size calculation used. c. Indicate the number of independent replications of each experiment, if relevant.	28, Tables 3.1 and 3.2
Allocating animals to experimental groups	11	a. Give full details of how animals were allocated to experimental groups, including randomisation or matching if done. b. Describe the order in which the animals in the different experimental groups were treated and assessed.	28
Experimental outcomes	12	Clearly define the primary and secondary experimental outcomes assessed (e.g. cell death, molecular markers, behavioural changes).	20, 34-37
Statistical methods	13	a. Provide details of the statistical methods used for each analysis. b. Specify the unit of analysis for each dataset (e.g. single animal, group of animals, single neuron). c. Describe any methods used to assess whether the data met the assumptions of the statistical approach.	36-37
RESULTS			
Baseline data	14	For each experimental group, report relevant characteristics and health status of animals (e.g. weight, microbiological status, and drug or test naïve) prior to treatment or testing. (This information can often be tabulated).	46-48, Tables 3.1 and 3.2
Numbers analysed	15	a. Report the number of animals in each group included in each analysis. Report absolute numbers (e.g. 10/20, not 50%[2]). b. If any animals or data were not included in the analysis, explain why.	46
Outcomes and estimation	16	Report the results for each analysis carried out, with a measure of precision (e.g. standard error or confidence interval).	49-62
Adverse events	17	a. Give details of all important adverse events in each experimental group. b. Describe any modifications to the experimental protocols made to reduce adverse events.	46, 63-64
DISCUSSION			
Interpretation/ scientific implications	18	a. Interpret the results, taking into account the study objectives and hypotheses, current theory and other relevant studies in the literature. b. Comment on the study limitations including any potential sources of bias, any limitations of the animal model, and the imprecision associated with the results[2]. c. Describe any implications of your experimental methods or findings for the replacement, refinement or reduction (the 3Rs) of the use of animals in research.	69-76, 79-82
Generalisability/ translation	19	Comment on whether, and how, the findings of this study are likely to translate to other species or systems, including any relevance to human biology.	69-76, 79-82
Funding	20	List all funding sources (including grant number) and the role of the funder(s) in the study.	vi

References:
1. Kilkenny C, Browne WJ, Cuthill IC, Emerson M, Altman DG (2010) Improving Bioscience Research Reporting: The ARRIVE Guidelines for Reporting Animal Research. *PLoS Biol* 8(6): e1000412. doi:10.1371/journal.pbio.1000412
2. Schulz KF, Altman DG, Moher D, the CONSORT Group (2010) CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 340:c332.

APPENDIX B

STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title page, ii-iv
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	ii-iv
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2-25
Objectives	3	State specific objectives, including any prespecified hypotheses	20
Methods			
Study design	4	Present key elements of study design early in the paper	37-38
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	37-39, Fig.2.3, Fig.2.4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	37-38, Fig.2.3
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	37-40
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	38-40, Fig 2.3
Bias	9	Describe any efforts to address potential sources of bias	37-40
Study size	10	Explain how the study size was arrived at	37-38
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	39-40, Fig.2.3, Fig.2.4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	40
		(*b*) Describe any methods used to examine subgroups and interactions	40
		(*c*) Explain how missing data were addressed	40
		(*d*) If applicable, explain how loss to follow-up was addressed	40
		(*e*) Describe any sensitivity analyses	40
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	65, Table 3.4
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	Fig.2.3
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	65, Table 3.4
		(b) Indicate number of participants with missing data for each variable of interest	65, Table 3.4
		(c) Summarise follow-up time (eg, average and total amount)	65, Fig.2.3
Outcome data	15*	Report numbers of outcome events or summary measures over time	65-67

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	65-67
		(*b*) Report category boundaries when continuous variables were categorized	65-67
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	65-67
Discussion			
Key results	18	Summarise key results with reference to study objectives	76-78
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	76-82
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	76-82
Generalisability	21	Discuss the generalisability (external validity) of the study results	76-82, 84-86
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	vii

*****Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.