NOVEL TECHNOLOGY FOR THE MEASUREMENT OF NEWBORN AND INFANT HEART RATE

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Declaration

To the best of my knowledge and belief, this research work for my thesis toward the Master of Medicine degree does not contain any material which has either been accepted for the award of any other degree in any other university and/or other tertiary institution or been taken from material previously published or written by another person, except where due reference has been made in the acknowledgements and text.

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Abstract

Background

Monitoring heart rate in newborns and infants is crucially important in guiding resuscitation and medical care. Established methods for heart rate assessment of these children have inherent drawbacks. In recent years, novel methods for assessing neonatal and infant heart rate have been developed, with varying levels of evaluation conducted. Digital stethoscopes may provide a better means of heart rate assessment for newborns and infants.

Aim

The aim of this thesis was to comprehensively review existing established and novel technologies used to monitor newborn and infant heart rate, and compare new digital stethoscope technology with the gold standard, electrocardiogram (ECG).

Methods

This thesis (a) outlines the definition and importance of heart rate in medicine, presented in the context of a review of cardiac anatomy and physiology relevant to understanding this vital sign and aspects of its measurement in neonates and infants;

(b) presents a narrative review of established methods for monitoring heart rate;

(c) expands the scope of this review from established to emerging methods for monitoring heart rate with a systematic literature review of novel methods for newborn and infant heart rate assessment;

(d) describes original research using a prototype digital stethoscope attached to a smart device containing software for detecting and displaying heart rate in real-time that was conducted on infants in the neonatal intensive and special care setting, as well in the delivery room setting using an improved version of the device and software.

Results

A review of the literature analysing methods of assessing neonatal and infant heart rate found strengths as well as significant weaknesses in the various methods in clinical use or in development. In the neonatal unit, a prototype digital stethoscope and smartphone device for assessing heart rate had a mean difference (±2 standard deviations) of 7.4 (48.5) beats per minute (bpm) when compared to the gold standard of electrocardiography. The mean (interquartile range) time to first digital stethoscope heart rate display was 4.8 (1 to 7) seconds, and the device failed in 12.3% of use attempts. Repeating the comparison in the delivery room setting using an updated algorithm and new hardware, Bland-Altman analysis revealed a smaller mean difference (±2 standard deviations) between the digital stethoscope and electrocardiography of 0.2 (-18 to +18) bpm including crying periods (Figure 23), and 1.0 (-11 to +12) bpm excluding crying periods. The improved digital stethoscope took a median (interquartile range) of 7 (5 to 11.5) seconds after application to display a heart rate. It failed to detect heart rate in 37% of cases, all of which were in crying infants.

Conclusion

A digital stethoscope and smart device with software can rapidly detect neonatal and infant heart rate. In the delivery room, device failure primarily occurred during infant crying, with improved accuracy during non-crying periods.

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List of Included Third Party Copyright Material

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Abbreviations Used

bpm; beats per minute

CPAP; continuous positive airway pressure

ECG; electrocardiogram

IQR; interquartile range

QUADAS; Quality Assessment of Diagnostic Accuracy Studies

SD; standard deviation

Publications

Note: Publications are included as an appendix item if fully published.

1. Kevat AC, Dawson J, Davis PG, Kamlin CO. Evaluation of a digital stethoscope and smart device technology for assessment of heart rate in the newborn infant.
Archives of Disease in Childhood Fetal and Neonatal Edition: 2015 Nov; 100(6): F562

2. Kevat AC, Bullen DVR, Davis PG, Kamlin CO. A systematic review of novel technology for monitoring infant and newborn heart rate.
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Posters and Presentations

Posters

1. Evaluation of a digital stethoscope and smart device technology for assessment of heart rate in the newborn infant.

Pediatric Academic Societies Annual Meeting, San Diego, 25-28 Apr 2015

2. Evaluation of a digital stethoscope and smart device technology for assessment of heart rate in the newborn infant.

Perinatal Society of Australia and New Zealand Annual Conference, Melbourne, 19-22 Apr 2015

3. Evaluation of a digital stethoscope in transitioning infants in the delivery room.

Pediatric Academic Societies Annual Meeting, San Francisco, 6-9 May 2017

Oral Presentations

1. Evaluation of a digital stethoscope in transitioning infants in the delivery room.

Perinatal Society of Australia and New Zealand Annual Conference, Canberra, 2-5 Apr 2017

Chapter One: Introduction

1.1 Definition and Importance of Heart Rate

Heart rate can be defined as the number of heartbeats, or more specifically, cardiac ventricular contractions, occurring over a period of time, conventionally in one minute. An individual's heart rate is widely-accepted to be one of the 'vital signs' in medical assessment. These vital signs traditionally consist of blood pressure, temperature, heart rate and respiratory rate (1). Heart rate is an important indicator of an individual's overall condition. Derangements suggest varying degrees of stress being placed upon that individual's physiological state.

The value of observable heart rate in clinical decision-making is seen in a multitude of settings and conditions. As a general triage tool, one study found its measurement by experienced emergency department triage nurses to be responsible for over twenty percent of upgrades in a patient's assigned category for those between the ages of three and seventy-four years (2). In acute traumatic injury, tachycardia is an early marker of hypovolaemia, and assessment of heart rate is recommended as one means of identifying patients in hemodynamically significant circulatory shock (3). Dehydration can have similar physiological sequelae, mediated by a decrease in end-diastolic volume affecting left ventricular stroke volume (4). In cases of ischaemia and infarction of the heart itself, the heart rate is often affected. It has been known for over forty years that tachycardia, bradycardia and arrhythmia are relatively common manifestations of the autonomic effects of this pathology and/or the disruption to important conducting pathways due to myocardial damage (5). Tachycardia, bradycardia and arrhythmia from a direct cardiac cause may also arise from structural or conducting pathway abnormalities, congenital or acquired in origin.

Acute pathology impacting other major organs also alters heart rate, mediated by a variety of mechanisms. In acute renal failure, tachycardia may be an examination finding, most often due to a pre-renal cause for the kidney injury (6). In liver failure, multiple mechanisms contribute to heart rate disturbance. These include electrophysiological abnormalities, altered function of beta-adrenergic and muscarinic receptors, attenuation of normal systolic and diastolic responses to stress stimuli and toxin-mediated decreases in myocyte contractility (7). .

Common lung pathologies can cause tachycardia. Pneumonia may do so, with tachycardia often brought on by a fever response in which the body alters its thermostatic set-point in order to improve immune system function, and impair micro-organism replication (8). In fact, any cause of fever may well result in tachycardia as the neuro-hormonal cytokine signalling and activation of the sympathetic nervous system that occurs in the febrile response generates elevation of the heart rate (9). In tension pneumothorax, increasing intra-pleural pressure compresses cardiac structures, negatively impacting stroke volume; in order to maintain cardiac output, progressive tachycardia occurs (10). In acute asthma, dynamic hyperinflation may have similarly adverse effects on the heart and stroke volume. Specifically, the large negative intrathoracic pressure generated during inspiration increases left ventricular afterload and impairs systolic emptying, whilst pulmonary artery pressure may also be increased causing an elevation in right ventricular afterload (11). Tachycardia may occur either in compensatory response to these events, or as a consequence of treatment with beta-agonist therapies such as salbutamol which stimulate cardiac beta-adrenoceptors (12).

Increased intracranial pressure affects the heart rate. Various pathological processes can cause acute rises in intracranial pressure. These include haemorrhage due to trauma or aneurysmal vessel rupture, as well as brain oedema as a consequence of infarction, severe heatstroke or Reye syndrome, a condition which is characterised by an abrupt insult to mitochondria (13). Rapidly-growing neoplasms resulting in obstructive hydrocephalus as well as infections such as meningitis, encephalitis and brain abscesses may also cause raised intracranial pressure (14). It is tonsillar herniation of the brainstem due to increased intracranial pressure which results in the Cushing response of bradycardia and hypertension. This is thought to be mediated through intracranial baroreceptor mechanisms attempting to preserve cerebral blood flow and/or sympathetic over-activity secondary to mechanical distortion of the medulla (15).

Altered heart rate may also be a manifestation of connective tissue diseases, musculoskeletal complaints and dermatological insults. In Toxic Epidermal Necrolysis, heart rate is one of several factors which compose the Severity of Illness Score for Toxic Epidermal Necrolysis (also known as SCORTEN) used to clarify mortality risk in this condition, which exists on the more severe end of a spectrum shared with Stevens-Johnson Syndrome (16). In Ehlers-Danlos Syndrome Type III, joint hypermobility syndromes and chronic musculoskeletal pain, Postural Orthostatic Tachycardia Syndrome can occur; postural heart rate elevation is then a result of excessive sympathetic nervous system activation, impaired circulating volume regulation, body deconditioning and diminished vasoconstriction mediated by the nervous system affecting primarily the lower extremities (17). Auto-inflammatory and autoimmune conditions may induce tachycardia on a chronic or episodic basis also.

Other systemic conditions in which heart rate is highly relevant include septic shock and haematological malignancies. In the development of septic shock, tachycardia often precedes hypotension, but is not necessarily a useful indicator to distinguish it from other conditions as it is a non-specific sign (18). Post-sepsis, in a small number of children with leukaemia, sinus bradycardia has been observed (19), although elevated heart rate is more common in those with leukaemia alone.

It is not only pathology that may alter the cardiac state; drugs may acutely precipitate lowered or increased heart rate, either deliberately or accidentally. Sometimes this may have serious adverse consequences. As just one example, patients who receive dexmedetomidine and develop a greater than thirty percent decrease in heart rate may be at high risk for severe bradycardia leading to pulseless electrical activity (20). Whilst the individual drugs associated with heart rate alterations and the mechanisms by which they manifest are too numerous to list here, an understanding of how prescribed drugs affect the body is vitally important for patients and practitioners to have.

Heart rate is not only relevant assessed over the acute timeframe. It is also relevant when assessed over a longer period. When over four thousand adults were studied for two decades, a higher baseline heart rate was associated with greater cardiovascular and all-cause mortality (21). Whilst it may be that those factors causing an increase in heart rate increase mortality, multiple deleterious effects of heart rate elevation itself, such as chronic increased left ventricular work and consequent hypertrophy may well result in shortened lifespan (22).

1.2 Specific Importance of Heart Rate for Infants and Newborns

The abovementioned pathophysiological challenges affect the heart rate of adults, children and infants alike. However, the importance of heart rate specifically for infants has also been explored.

Physiologically, the neonatal heart is less able to increase stroke volume compared to the heart of older children and adults, due to a greater ratio of non-contractile to contractile elements as well as ionic channel differences (23). Given that cardiac output is a product of this parameter and heart rate, increases in cardiac output are reliant on relative tachycardia. However, with greatly increasing heart rates, ventricular filling time decreases, which can adversely impact the volume of blood ejected with each heartbeat (24). A 1992 study of infants with a median age of 2.5 months found that a heart rate over one hundred and seventy beats per minute (bpm) was a highly sensitive and indeed the most specific sign of severe congestive cardiac failure, compared to other indicators that could be discerned by history or physical assessment; other indicators examined included time and volume of feeds, sweatiness, tachypnoea, respiratory pattern, growth and clinical hepatomegaly (25).

Whilst a threshold heart rate parameter may be of value in the assessment of cardiac failure severity in infants, it is perhaps less valuable when assessing infants with bronchiolitis. An Australian study published in *The Lancet* found that the presence of a pulse rate over one hundred and fifty beats per minute did not predict severity of bronchiolitis in terms of hypoxia defined by pulse oximetry or blood gas analysis (26). It therefore seems that heart rate is of variable importance in different conditions affecting infants. Focussed research on this vulnerable population is clearly important.

Monitoring and responding to heart rate is of special importance in newborns. The process of rapid physiological adaptation to extra-uterine life after leaving the womb involves the establishment of air breathing concurrently with changes in pressures and flows within the infant's cardiovascular system (27). This process occurs without intervention in most cases, but in five to ten percent of infants born in health care facilities, some form of assistance is deemed necessary and approximately half of these neonates receiving aid require assisted ventilation (28).

Heart rate values guide decision-making and action points in the neonatal resuscitation algorithm, as per international guidelines devised on the basis of best available evidence and an up-to-date synthesis of our understanding of neonatal physiology (29). The newborn who is not crying, breathing, and vigorous is initially warmed, dried, stimulated and positioned so as to open the airway. Further management is based on an assessment of heart rate; the heart rate assessment is so important it should be performed prior to one minute of age (29). For infants with a heart rate below one hundred beats per minute at this stage, positive pressure ventilation should be provided, and if the heart rate does not improve, adequate ventilation should be ensured, with consideration given to methods to improve airway patency, including support of the lower jaw, opening the mouth, or in some cases upper airway suction (30). Endotracheal intubation should also be considered, if the heart rate does not improve with these measures. The decision to undertake such a significant management step on the basis of heart rate is testament to the relative importance of this vital sign in newborn care.

For newborns who are bradycardic with a heart rate below sixty beats per minute despite adequate ventilation, chest compressions should be provided and adrenaline administration via endotracheal tube or intravenous infusion considered (29). This is because the likelihood of inadequate cardiac output and compromise of perfusion is considered high with this degree of severe bradycardia.

There are several reasons why heart rate is used as the foremost indicator to guide critical decisions in the resuscitation of neonates. Firstly, it is a marker that can be rapidly assessed using a variety of techniques such as auscultation, umbilical cord palpation, arterial pulse check, ECG monitoring and pulse oximetry. The relative merits and drawbacks of these methods will be discussed later in this thesis.

Secondly, heart rate reflects the level of physiological compromise experienced by the neonate. Cardiac muscle is adapted for aerobic respiration. It is packed with mitochondria that fill twelve times as much of the cell compared to skeletal muscle fibres, making it resistant to fatigue but highly vulnerable to interruptions in oxygen supply (31). The newborn heart in particular functions relatively close to maximal capability to meet the basic demands for oxygen delivery. With lack of oxygen delivery to the tissues, the neonatal heart rate often falls as the newborn heart itself is affected. This is due to an immature myocardium and underdeveloped regulating autonomic nervous system (32). The lack of adequate blood perfusion and tissue oxygenation interferes with cellular function (33). Lack of oxygen delivery to tissues occurs either in utero when placental supply of oxygenated blood is compromised or after birth if transition to pulmonary ventilation is inadequate (33).

More rarely, transition can be affected by congenital cardiac, pulmonary, or other causes. Cardiac causes include cardiac malformations and heart block which may be related to vertical transmission of Anti-Ro or Anti-La antibodies in cases of maternal systemic lupus erythematosus or Sjögren's syndrome (34). Pulmonary causes include pulmonary hypoplasia (itself produced by a range of conditions such as diaphragmatic hernia, hydrops fetalis, prematurity and airway stenosis/atresia), alveolar capillary dysplasia with misalignment of the pulmonary veins, and surfactant disorders. Haemolytic disease of the newborn may affect the oxygen-carrying capacity of blood, as might the rare condition of perinatal carbon monoxide poisoning afflicting the neonate (35).

Thirdly, neonatal heart rate changes rapidly in response to changes in an infant's condition thus providing clinicians with a real-time indication of the need for and response to resuscitation. Resolution of bradycardia with improvements in the cardiopulmonary state are rapid over seconds to minutes, and can be monitored in the delivery room (33). Conversely, severe deteriorations lead to a worsening of the heart rate over similar timeframes. The absence of a heart rate for a period of ten minutes despite resuscitative efforts is reasonable grounds to consider the futility of continuing resuscitation (28). However, it should be noted that in cases where the heart rate is less than sixty beats per minute at birth and does not improve after a similar length of time the choice is much less clear because there is insufficient evidence about outcome to inform guidelines on whether to withhold or continue resuscitation (29).

For those newborns who survive the transition from intrauterine to extrauterine life but continue to require inpatient medical attention in the neonatal intensive or special care setting, heart rate monitoring continues to be of great importance. As in adults, tachycardia may indicate haemorrhage, inadequate analgesia (36), infection or necrotising enterocolitis, a clinical entity more likely to affect prematurely born neonates (37). Bradycardia may be an indicator of central nervous system depression, or an early sign of a blocked endotracheal tube or raised intracranial pressure (36). Therefore, whether considering long-term survival or acute pathology at birth, heart rate is a vitally important sign to measure and understand for humans of all ages.

Over the last two decades, the parameter of heart rate variability has been studied and found to correlate with a variety of adverse conditions in young infants. Heart rate variability, which can be defined as the variation in the time interval between heartbeats, arises from the interplay of the sympathetic and parasympathetic arms of the autonomic nervous system, which serve respectively to speed and to slow the heart rate in response to normal phasic physiological features such as respiration (38). Early studies identified that heart rate variability was reduced in neonates with sepsis and increased by up to threefold with recovery from circulatory and respiratory compromise; heart rate alone did not change dramatically (38, 39). Heart rate variability was calculated from continuous ECG monitoring in place in the neonatal intensive and special care setting.

In a multicentre cohort of prematurely born infants, an algorithm which derived a dynamic heart rate characteristics score from both heart rate variability and transient decelerations detected by monitoring showed abnormal heart rate characteristics were

detectable prior to the development of necrotising enterocolitis requiring surgery (40). The same algorithmic score has been shown to lead to an overall decrease in mortality in very low birthweight infants when displayed in the intensive care, in a multicentre randomised controlled trial which enrolled over three thousand neonates (41). In this study, clinical responses to changes in the score were not mandated but left up to the treating team, making it difficult to understand exactly how displaying the score helped. Nevertheless it is believed that the disruption of usual autonomic interplay by significant neonatal illness which causes sympathetic nervous system stimulation early on in pathology development is a likely explanation for why decreased heart rate variability precedes more obvious clinical signs of infant deterioration (40, 41). Using this score incorporating heart rate variability compares favourably to other risk scores when used to predict neonatal morbidity and mortality in high-risk infants (42). Despite this, conventional neonatal and infant monitoring of heart rate does not routinely include calculation and display of heart rate variability and clinical use of this is not at all widespread.

1.3 Normal Values

Normal paediatric and neonatal heart rate ranges referred to in clinical practice such as those published by Pediatric Advanced Life Support on their website (43) or written in manuals or textbooks about paediatric critical care (44) are largely established by consensus, with notable variation in given values. Nevertheless, there is a clear pattern regarding heart rate trends over aging in normal infants and children. On the basis of multiple observational studies, it can be seen that normal heart rate peaks at one month of age and then falls (45, 46).

A systematic review incorporated data from 69 studies measuring heart rate and/or respiratory rate in normal children between birth and 18 years of age to form centile charts which were then compared to aforementioned published thresholds (Figure 1). This study found that deviation between these popular published sources and the centile charts derived from the multi-source normative data analysed was significant enough to warrant revision of clinically-utilised cut-offs (47).

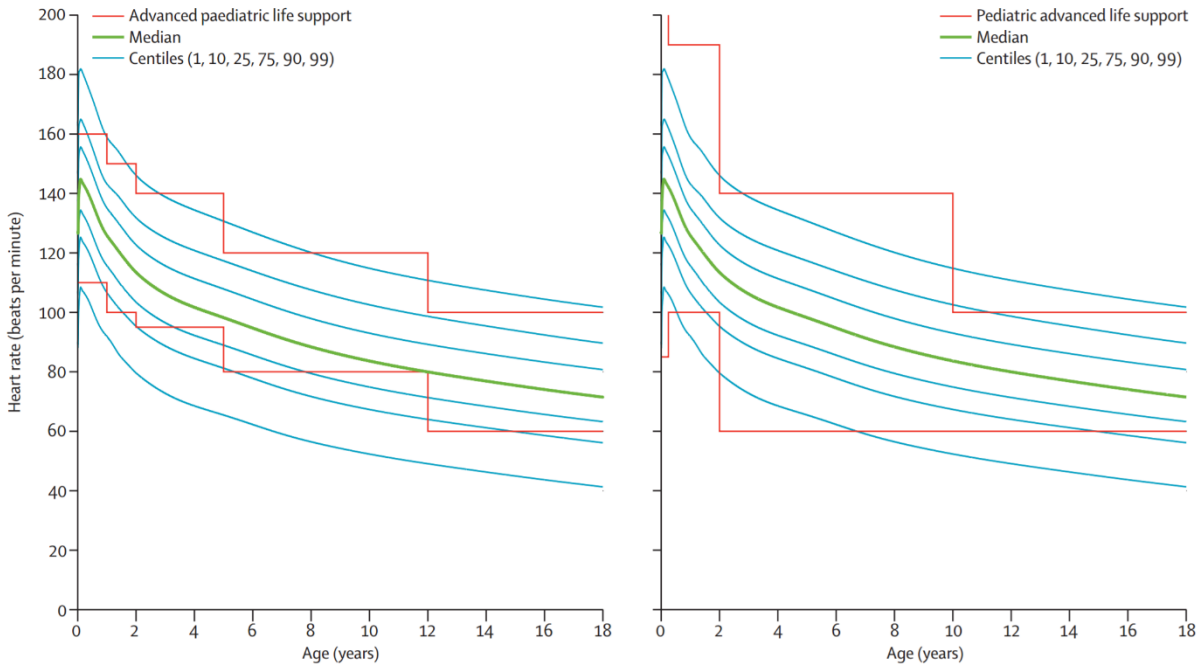


Figure 1. Comparison of heart rate centiles with paediatric reference ranges from the advanced paediatric life support and pediatric advanced life support guidelines. Reproduced here with permission. Fleming et. al. © Elsevier 2016.

Whether based on clinical experience and consensus or more systematic study, normal values proposed for child and newborn heart rates differ, although overall trends such as the falling of heart rate values after the neonatal period with age are more universally represented.

1.4 Cardiac Embryology, Anatomy and Electrophysiology

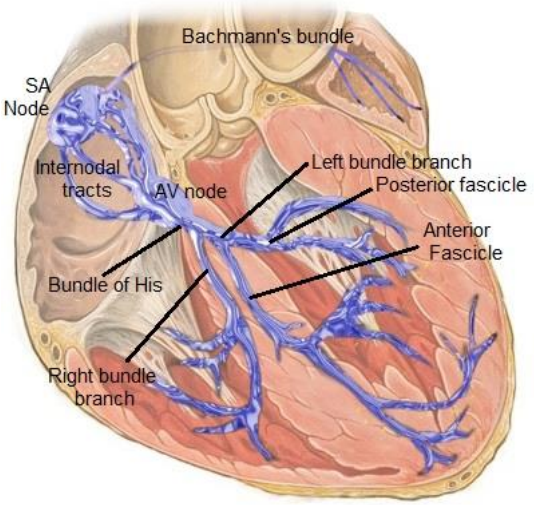


Figure 2. Cardiac conduction system. Reproduced here with permission under the Creative Commons Attribution-Share Alike 4.0 International license, and available from https://commons.wikimedia.org/wiki/File:Cardiac_conduction_system.jpg © Nicholas Patchett 2015, Adapted from an original by Patrick J. Lynch and C. Carl Jaffe MD.

The anatomy of the heart and electrophysiological generation of the heartbeat are inextricably interwoven. A good understanding of these aspects of human anatomy and physiology are needed in order to be able to appreciate the strengths, weaknesses and mechanisms of the various means of heart rate monitoring. A knowledge of cardiac embryology informs anatomical and physiological understanding of this vital structure.

The heart is largely formed from mesodermal tissue, which is originally the middle of three germ layers of tissue forming the embryo; the other two layers are the ectodermal and endodermal layers which are initially continuous with the amnion and yolk sac respectively (48).

In the third week of foetal development, two mesodermally-derived cardiogenic plates grow and fuse in the midline to form a single cardiac tube with a caudal arterial end and an rostral venous end (49). As development progresses, the tube undergoes a series of looping, ballooning and bending events, with further expansion of regions destined to become cardiac chambers (50). Septation of the resultant cardiac structure into chambers is a complex process involving multiple simultaneously-developing septa (51) as well as the incorporation of pulmonary venous structures contributing to the development of the left atrium (49). Additionally, cell types such as previously-mentioned neural crest cells that originate outside the initial cardiac tube are important in the development of the structure (50).

As early as 1973, it was shown the foetal heartbeat could be detected by seven weeks gestation using ultrasonography in 100% of viable pregnancies, and it can often be detected a fortnight earlier (52). At birth, the heart consists of many different cell types such as myocardial cells, specialised conducting cells, endothelial cells, smooth-muscle cells and fibroblasts (50).

The average adult human heart is approximately the size of a closed fist, and weighs around two hundred and fifty to three hundred grams (53). Situated within the mediastinal space in the thoracic cavity of the chest, around one-third of the heart lies to the right of the midline and two-thirds to the left of this imaginary dividing line. The inferior surface of the heart is positioned atop the central tendon of the diaphragm, the anterior surface is behind the sternum, and the posterior aspect of this essential structure lies superficial to the oesophagus and its close relation, the descending aorta (54). On either side of the heart lie the pleural sacs of the left and right lungs (55).

The heart itself is encased in a fibrous sac known as the pericardium; this has a visceral and parietal layer and contains thirty to fifty millilitres of serous pericardial fluid normally, which acts as a lubricant to decrease friction as the heart contracts and relaxes (53). The heart tissue itself has three main layers. From outermost to innermost, these are the epicardium (synonymous with the visceral pericardium), the myocardium and the smooth inner lining known as the endocardium, which the blood is in contact with.

There are four main chambers in an anatomically normal heart. Blood returning from the body and collected via the systemic venous system drains into the right atrium via the superior and inferior vena cavae. This blood then passes through the tricuspid valve and into the right ventricle, which is more anteriorly positioned than the left (54). Ventricles fill during the cardiac phase known as diastole (53). Blood from the right ventricle passes through the pulmonary valve into the pulmonary artery and then through right and left pulmonary artery branches. These undergo many further divisions to eventually form tiny capillaries which surround the alveoli. Gas exchange occurs across the pulmonary gas exchange membrane as red blood cells pass through these capillaries (56). Oxygen-replete blood from these capillaries is then collected by pulmonary veins which drain into the left atrium. After passing through the mitral valve, this blood enters the left ventricle prior to ejection through the aortic valve during ventricular contraction, known as systole. This blood flows on to supply systemic tissues via vascular structures, as well as on to cardiac tissue via the coronary arteries. In healthy children, the aortic valve closes slightly prior to the pulmonary valve due to a normal delay in the cardiac cycle between the left and right heart, causing a physiological splitting of the second heart sound.

In an adult, with each beat of the heart, approximately seventy millilitres of blood is ejected from the left ventricle and through the aortic valve into the aorta and systemic circulation (53). This process supplies vital organs and peripheral tissues with oxygen essential for metabolism. Carbon dioxide, a cellular waste product of aerobic respiration, is collected from tissues and travels via the circulation to the lungs, where it crosses the gas exchange membrane and is expelled by exhalation (56).

The heart muscle itself differs significantly from skeletal and smooth muscles. Cardiac myocytes are short, and branched whereas skeletal and smooth muscles cells are generally longer (31). Unlike smooth muscle cells, cardiomyocytes are striated and have a very limited ability to regenerate although they can do so to some extent, for example post-infarction (57). Unlike somatically-innervated skeletal myocytes, heart muscle cells are innervated by the autonomic nervous system, do not require innervation for action potential generation and generally have only one nucleus which tends to be centrally located (31).

Unlike other muscle cells where sodium influx is the trigger for contraction, cardiomyocytes undergo excitation-contraction coupling as a consequence of a phenomenon labelled calcium-induced calcium release. The transmitted action potential triggers influx of calcium ions through L-type calcium channels in the sarcolemma which then act on ryanodine receptors, causing the sarcoplasmic reticulum to release further calcium stores (58).

This causes intracellular calcium levels to rise to the level where calcium binding to the myofilament protein troponin C switches on the contractile machinery; muscle contraction occurs until intracellular calcium levels fall as the ions are transported out of the cytoplasm by a variety of means to a level where dissociation of calcium molecules from the troponin filament eventuates (59). Cardiomyocytes are tightly bound together, joined by intercalated discs (31) and held together by strong proteins. Within these connections, low electrical resistance pathways called gap junctions are formed, so that electrostatic attraction can cause a local current flow (ion movement) between the depolarised membrane of an active cell and the polarised membrane of an adjacent resting cell (58). Importantly, a failure of oxygen supply for aerobic metabolism processes that make adenosine triphosphate (ATP) may compromise movement of calcium out of the cytosol as some of the key mechanisms facilitating this are ATP-dependent (58). This results in a delay to cellular repolarisation, limiting the cell's ability to respond to or propagate arriving action potentials.

The myocardium derives its arterial supply of oxygenated blood from the right and left coronary arteries which are the earliest branches from the aorta. These coronary arteries emerge from sinuses just above aortic valve leaflets (55). An important difference between systemic and coronary blood flow is that the former is facilitated by systole, whereas the latter is impeded by it. This is because it is during diastole that cardiac muscle is relaxed and vascular resistance to coronary perfusion is low (54). This may be the mechanism by which tachycardia, which proportionally decreases the amount of time spent in diastole compared to systole, contributes to impaired myocardial supply and subsequent compromised myocardial function (21).

Coronary arteries supply not only heart muscle but also the specialised cardiac cells responsible for conveying electrophysiological impulses that govern co-ordinated myocyte activity resulting in the synchronised heartbeat contractions which drive effective circulation. Whilst most myocardial cells are designed for contraction, some are specifically designed for the purpose of more quickly and regularly depolarising to generate action potentials which travel down conducting pathways to standard cardiomyocytes which in turn not only contract but propagate them to their neighbours via gap junctions (58). This impulse creating function of myocardial cells is known as auto-rhythmicity (31).

The cells with the highest intrinsic impulse-generating rate act as the physiological pacemaker for the heart. Under normal conditions, this function resides in the collection of cells called the sinoatrial node (55), just under the epicardium (31). In adults, the sinoatrial node is almost always found in the anterior wall of the right atrium near the upper end of the sulcus terminalis with potential extension over the front of the superior vena cava (60). In infants however, a study found the sinoatrial node was in a slightly different position, located inferior to the crest of the right atrial appendage in twenty-two out of twenty-five hearts of individuals and it extended into the interatrial groove in the other three examined specimens (61). It is believed that age-related cardiac changes cause this difference (60). When heart contractions are caused by signalling generated from the sinoatrial node, the heart rhythm is called sinus rhythm.

The rate of firing of the sinoatrial node has a natural set-point which is modifiable, facilitating increases and decreases of heart rate whilst in sinus rhythm. The autonomic nervous system is a key modifier.

At rest, parasympathetic influences dominate and cause the heart rate to be lower, mediated by vagal nerve release of acetylcholine which increases potassium and decreases slow inward calcium influxes in sinoatrial node cells suppressing their intrinsic rate (62). Interrupting this vagal nerve influence can cause the resting heart rate to increase, for example through the administration of atropine which has a vagolytic effect that combats bradycardia. In preterm infants this drug is used to counteract bradycardic effects of other agents administered to facilitate airway intubation (63). Sympathetic influences brought about by stress response activation, for example in response to noxious stimuli or bodily insults, also cause relative tachycardia. Sympathetic activation results in increased noradrenaline and adrenaline which act to decrease potassium and increase slow inward calcium and sodium cellular influxes, causing the pacemaker potential to more rapidly reach the threshold for action potential generation (62).

Impulses generated from the specialised cardiomyocytes of the sinoatrial node travel to another group of similarly specialised conducting cells known as the atrioventricular node. In general it is situated in the triangle of Koch which is bordered by the tricuspid valve attachment, tendon of Tadaro and coronary sinus ostium (60). Impulses reach the node by travelling through the atrial myocardium. The existence of specialised internodal tracts has been questioned given that it is impossible to recognise such tracts on the basis of gross histological appearance (60). Nevertheless, electrophysiological studies demonstrate multiple pathways through small bands of atrial fibres where conduction is more rapid than in surrounding atrial tissue (64).

These have been labelled as the anterior internodal tract of Bachmann, the middle internodal tract of Wencheback and the posterior internodal tract of Thorel (53). The middle tract is often the most poorly developed (65). An important function of the atrioventricular node is to delay conduction of the arriving impulse to the ventricular conducting system, in order to permit atrial contraction to occur first (62). This fills the ventricles further (known as the 'atrial kick') prior to their own contraction, facilitating increased cardiac output. Indeed, this effect also controls the number of impulses transmitted to the ventricles, ensuring time for ventricular filling in between contractions (53). This helps to prevent atrial arrhythmias, such as atrial fibrillation, being conducted into the ventricles at dangerously high rates (66).

In cases where the opposite is true and signals from the sinoatrial node are infrequent or absent, for example following infarction to that area of the heart, the atrioventricular node can assume the role of physiological cardiac pacemaker (66). When the atrioventricular node acts as the primary pacemaker of the heart, the rhythm is called 'atrioventricular escape'. This is possible because the atrioventricular node has auto-rhythmicity. In adults it tends to have an intrinsic rate of around forty to sixty beats per minute, and like the rate generated by the sinoatrial node this can be modified by the autonomic nervous system (62).

It is worth noting that other factors besides those mediated by the autonomic nerves can influence nodal rate and transmission. Thyroid hormone can increase the heart rate, and even in individuals afflicted by subclinical hyperthyroidism, heart rates are elevated compared to normal (67).

Ectopic foci (abnormal pacemaker sites) can cause additional beats or supraventricular tachyarrhythmia (62). However, they are only responsible for around ten percent of supraventricular tachyarrhythmia; the majority are in fact caused by re-entrant pathways that facilitate increased atrioventricular nodal signal transmissions (68). These may occur in the grossly structurally normal heart triggered by factors such as caffeine, alcohol or recreational drug intake (68), but also may arise due to damage to conducting tissues as a consequence of infarction or coronary ischaemia (62), or in cases of congenital cardiac disease including hypertrophic cardiomyopathy and Ebstein's anomaly (68).

After an electrical depolarisation causing atrial myocardial contraction propagates through the atrial conduction pathways and then more slowly traverses the atrioventricular node, it passes to the Bundle of His. This structure is a continuation of the distal portion of the atrioventricular node where the cells lose their network arrangement and form parallel strands (69). The Bundle of His divides into two separate bundles, termed the left and right bundle branches, which travel through the left and right ventricular myocardium respectively (70). Unlike atrial pathways, these bundles are histologically identifiable by the presence of encapsulating connective tissue, although this may be partially disrupted in cases of ventricular septal defect (60). After bifurcating at the crest of the muscular ventricular septum immediately distal to the membranous septum, fibres of the left bundle forming a cascade down the left ventricular septal surface whereas fibres from the right course to the apex of the right ventricle (69). They are largely composed of Purkinje cells, which are specialised for rapid propagation of depolarising current in the heart (71).

Terminal Purkinje fibres connect with the ends of the bundle branches, and form a plexus or network which penetrate and spread excitation through the ventricular walls in a fashion that causes the inferior aspects of the ventricles to contract first (54). This promotes co-ordinated emptying of blood from ventricular chambers.

Cells composing bundle branch and Purkinje fibres have end-to-end cell intercalated disc connections for rapid current conduction, as well as side-to-side connections to distribute depolarisation to adjacent cells in order to spread myocardial cell contraction widely (69). Whilst Purkinje fibre abnormalities have been implicated in ventricular arrhythmia (71), in most individuals the cardiac electrophysiological system as a whole leads to harmonised myocardial contraction for each and every heartbeat, propelling blood to the lungs and body efficiently and successfully.

1.5 Summary of Physiological Considerations

To summarise, the structurally normal heart is composed of four chambers and four valves. The cardiac muscle contracts to circulate blood to the lungs and body in order to collect and deliver oxygen to tissues and cells to enable cellular metabolism as well as to remove toxins and by-products such as carbon dioxide via respiration. Contraction of the cardiac muscle is co-ordinated by the conducting system of the heart which is formed by specialised, adapted cardiac cells. Whilst this system may be adversely affected by drugs, toxins, hypoxia and congenital abnormalities, generally the propagation of electrical impulses to cardiac myocytes to stimulate their contraction is carried out without aberration. This generates a heartbeat.

Heart rate is most often quantified as the number of heartbeats occurring in one minute for a particular individual, with heartbeats perhaps being best defined as occurring with ventricular contraction. In order to understand the mechanisms by which heartbeats are generated, a basic appreciation of cardiac anatomy and physiology, especially electrophysiology, is needed. When it comes to monitoring heart rate, this understanding becomes particularly important. This is because various devices monitor different aspects or arms of the physiological process of heartbeat generation; for example, ECG interrogates the electrical signals which cause the ventricles to contract, whereas auscultation detects sound waves created by muscular contraction of the cardiac tissues pumping the blood inside of them.

Heart rate is a vital physiological parameter to measure in humans. In acute traumatic injury, raised intracranial pressure, organ failure, systemic or local infection, autoimmune and malignant processes, heart rate can be deranged through a variety of mechanisms. Additionally, drugs and toxins may deliberately or accidentally modify heart rate as well (68).

In newborns in particular, because of comparatively less myocardial contractility and a relatively fixed stroke volume, heart rate provides crucial information that reflects the extent of physiological compromise experienced by that infant. This is used to guide resuscitation efforts in the delivery room, as well as to monitor unwell neonates and young infants in hospital.

Chapter 2: Established Methods for Heart Rate Monitoring

2.1 Overview of Heart Rate Monitoring

Methods for monitoring heart rate take various forms. These vary in expense, and, depending on their nature and the device, may be more often applied on an intermittent basis for a brief period of time on each occasion, or applied continuously. In addition, different heart rate monitoring techniques assess different aspects of the heartbeat generation process, thereby resulting in particular strengths and weaknesses, especially when applied to the vulnerable and challenging group of neonates and infants.

Several forms of heart rate monitoring have become widely accepted in clinical medical practice, with important research conducted to illuminate the benefits and weaknesses of these different methods. The most well-established means of heart rate assessment include auscultation, palpation of pulse, ECG, transmission pulse oximetry and Doppler techniques. These are discussed here in greater detail, with specific reference to advantages and drawbacks when applied to newborn and infant monitoring scenarios.

2.2 Pulse Examination

2.2.1 Pulse Detection

Pulse examination is the oldest form of heart rate assessment. The pulse can be measured at areas where an artery passes close to the skin, such as the back of the knees (popliteal pulse), anterior upper arm (brachial pulse), groin (femoral pulse), neck (carotid pulse), temple (temporal pulse), dorsum of the foot (dorsalis pedis pulse), inner ankle (tibialis posterior pulse) and at the wrist where it is known as the radial pulse (72).

The anatomy of the newborn makes some of these palpations more difficult than others; during emergencies palpation of a central pulse is recommended, but short neck and close proximity to the trachea make the carotid inappropriate unlike in adults. In these situations, brachial and femoral pulses are recommended and in newly-born infants, the umbilical cord pulse can also be used (73).

Using the pulse to detect heart rate is reliant on accurate counting of the number of pulsations felt within the given timeframe, as well as sufficient cardiac output from each left ventricular contraction to generate a palpable pulse at the chosen examination site. Therefore, in situations where counting is inaccurate or when pulsatile systemic circulatory output is compromised, heart rate assessed by pulse palpation will be unreliable.

Consistent detection of pulse even without the added component of counting it to establish a pulse rate is not always dependable. In a study of carotid pulse palpation for detection of cardiac arrest by 206 lay-persons and ambulance officers who did not know if the patient was on or off cardiopulmonary bypass conducted on sixteen adult patients in the operating theatre undergoing coronary artery graft surgery, it was found that the sensitivity of pulse examination for detecting a pulseless adult was 90% (74). This means that 10% of pulseless patients were thought to have a pulse. Subsequently, the pulse check was removed from adult resuscitation guidelines for basic life support (75).

A similar study of health professionals entering a paediatric intensive care unit asking them to assess the pulse of patients supported by extracorporeal membrane oxygenation circuits who may or may not have had a pulsatile component to blood flow dependent on their own cardiac recovery found a similar sensitivity for pulse examination (site chosen by preference of examiner) of 86% (76). The study authors concluded that this implied that in 14% of circumstances paediatric rescuers might withhold cardiac compressions when the patient had no true pulse (76).

In a single-centre 2006 study, a cohort of hypotensive infants undergoing surgery, resuscitation-trained doctors and nurses were only able to obtain a heart rate using fifteen-second palpation of brachial, femoral and carotid pulses 41%, 65% and 52% of the time respectively (77). In comparison to the reference standard of ECG monitoring to which the examiners were blinded, clinically determined heart rates deviated by between 9.3 and 15.3 beats per minute, dependent on the pulse examination site, with the femoral site being most closely correlated (77).

2.2.2 Clinical Assessment of Pulse Rate in the Delivery Room

The degree of unreliability revealed by the abovementioned study is mirrored in findings of another delivery room based study performed in 2004. Femoral, brachial and umbilical cord pulse detection rates taken five minutes after birth by junior doctors or midwives from term newborns not undergoing resuscitation were 40%, 65% and 75% respectively, when thirty seconds was allotted to obtain the pulse (73). Concordance of the pulse rate counted over fifteen seconds with the heart rate obtained by standard auscultation at the same time was highly variable.

When obtained, the femoral, brachial and umbilical cord pulse rates were below one hundred beats per minute 38%, 69% and 27% of the time respectively, even though by auscultation all sixty newborns had a heart rate above 100 beats per minute (73). This finding is particularly important when it comes to resuscitation, given that the internationally-agreed management algorithm for newborn infants with a heart rate below one hundred beats per minute calls for application of positive pressure ventilation (29). Providing positive pressure ventilation is a significant intervention which carries the risk of pneumothorax (78) and airway obstruction (79), and therefore inaccurate heart rate measurement could lead to iatrogenic adverse events.

Given the inaccuracy of standard auscultation as a means of assessing newborn heart rate in the delivery room (discussed below), perhaps a more suitable reference standard for the accuracy of pulse examination is ECG. In a 2006 single-centre study of 26 well, term-born infants in the delivery room umbilical cord palpation performed by medical staff with neonatal experience was compared to 3-lead ECG application in determining heart rate (80). In this investigation, Kamlin and colleagues found that umbilical cord palpation underestimated the heart rate by an average exceeding twenty beats per minute, and was a technique that did not successfully obtain heart rate nineteen percent of the time (80).

Pulse examination in critically unwell patients has been shown to have a level of unreliability for detecting the presence or absence of a pulse that is unacceptable, given the high-stakes nature of resuscitation (76). Even when the pulse can be detected in neonates and infants, it correlates poorly with other, more accurate means of heart rate assessment.

The key advantages pulse examination has over other means of heart rate measurement is its rapidity and the fact that no specialised equipment is required. This makes it a technique that is more likely to be relied upon in low-resource neonatal care health settings, for example in Nepal where a 2008 survey found that not all centres had a stethoscope for newborn auscultation available (81).

2.3 Auscultation

Auscultation using a standard acoustic stethoscope is a commonly-used method for heart rate assessment in all age groups. Whilst some experts maintain that it remains the best method for assessing heart rate in newborns immediately at the time of birth (82), others argue that a tendency to inaccurately estimate the true heart rate renders this method to be inferior to others (80). Concerningly, a simulation study assessing both the accuracy and time taken to assess an electronically pre-set heart rate in a baby manikin using stethoscopes found that although mean time to assess heart rate was rapid and less than ten seconds, at least 28% of assessments led to incorrect management decisions due to imprecision (83). This finding is in keeping with results from another neonatal manikin simulation study which found that in 38% of cases, errors of omission such as failure/delay in providing positive pressure ventilation or chest compressions occurred due to inaccuracy of auscultatory heart rate assessment, and errors of commission such as providing/continuing positive pressure ventilation or chest compressions or proceeding to inappropriate intubation occurred in more than half of cases (84).

Ausculation may overestimate or underestimate the true heart rate. The abovementioned simulation study found that overestimation by this method occurred around three quarters of the time (83). In contrast, a delivery room study in term newborns found that the mean difference between ECG and auscultation was fourteen beats per minute, with auscultation underestimating heart rate compared to the espoused gold standard of ECG (80). However, this 2006 study has been criticised due to using a relatively short six-second sampling time for auscultation (82) with the heart rate derived by multiplying the obtained figure by ten. Additionally, the authors themselves note that all studied infants had a heart rate greater than one hundred beats per minute, so they could not determine if the same degree of inaccuracy between auscultation and 3-lead ECG would occur in bradycardic infants requiring resuscitation or not (80).

Whilst some acoustic stethoscopes are expensive, many are produced and made available cheaply and differences in sound transmission between brands are small (85). This makes the equipment both affordable and widespread in hospitals – for example even in post-conflict rural northern Liberia, a 2008 survey found that more than three quarters of the 1405 health facilities assessed had more than one stethoscope available (86). Like palpation, auscultation for heart rate assessment can be performed rapidly, and head to head comparison of the two methods in a clinical setting has shown that auscultation with an acoustic stethoscope was more accurate in determining newborn heart rate (80). Whether the value of rapidity and widespread availability of binaural acoustic auscultation devices outweighs drawbacks such as underestimation of derived heart rate in neonatal clinical studies is something that continues to be debated (82).

2.4 Transmission Pulse Oximetry

The central tenet upon which the operation of a pulse oximeter is based is the Beer-Lambert law, which states that the concentration of an absorbing substance in solution can be determined from the intensity of light transmitted through that solution, given the intensity and wavelength of incident light, the transmission path length, and the characteristic absorbance of that substance at a specific wavelength (87). Currently available conventional pulse oximeters use two light-emitting diodes each producing a narrow, specific bandwidth of light of different wavelengths, combined with a single semiconductor photodetector (88) which measures the intensity of light transmitted through the cutaneous vascular bed of the patient to which the oximetry device is attached (87). Light-emitting diode wavelengths are typically red and infrared or near-infrared (89).

The light-absorbing qualities of haemoglobin at varying levels of oxygenation (from fully deoxygenated to fully oxygenated) are known for each of the two wavelengths of light emitted (88). Therefore, by comparing emitted and calculated absorbed light values from each wavelength, the relative concentrations of saturated and desaturated haemoglobin can be determined. In order to calculate this purely for the arterial component of blood separate from that of venous blood, connective tissue, and other absorbers located between the light-emitting diodes and photodetector, the transmitted light values are calculated several hundred times per second and the variable, pulsatile component of arterial blood is distinguished from the unchanging, static component of the signal representing absorption by these other anatomic components (87).

Most oximeters display the arterial oxygen saturation as a percentage, as well as a plethysmograph trace and the pulse rate (88), calculated by detecting the number of previously-mentioned variable component peaks occurring per minute.

Successful acquisition of heart rate using pulse oximetry is subject to a number of limitations. These may be expected because of the way the device functions and the conditions which it may be subjected to in the delivery room. The most important interfering factors include extraneous light picked up by the photodetector, limb movement, venous pulsations and poor perfusion. All these factors may impede pulse oximetry performance in detecting newborn heart rate.

Ambient light is potentially a major source of interference, even though manufacturers have taken some steps to compensate for this. Fluorescent lighting, lamps in the operating room, fibre-optic instruments and sunlight can all affect oximeter function, although covering the probe with an opaque shield is a simple, easily-implemented solution (87).

Pulsatile veins may cause false readings since the oximeter cannot differentiate between venous and arterial pulsations (89). Whilst rarely considered, this may be relevant in patients with tricuspid regurgitation and in neonates with a hyper-dynamic circulation (90).

As the change in absorbed light energy due to the cardiac cycle is only one to two percent of the total absorption, even small movements will have a significant effect on the signal quality (88). Newborns often exhibit spontaneous movement when they are born. Even obtunded infants requiring resuscitation may move spontaneously, or be subject to movement in the course of medical intervention. Newer-generation pulse oximeters utilise advanced signal-processing mechanisms to mitigate the effect of movement (91). Trials in both healthy adult volunteers and neonates have shown that they significantly outperform older-generation pulse oximeters, but do not completely eliminate motion induced signal disturbance (92, 93). Such movement artefact is detected on the plethysmographic trace, and many oximeters display a warning when noise-to-signal ratio is deemed inappropriately high (88).

Not only can signal quality be affected by movement, but it is also pulse-dependent, meaning an adequate pulse volume is required for an accurate reading to be generated (90). Perfusion to extremities in newborns undergoing the process of transition from foetal to neonatal circulation is variable, and is often poor in neonates requiring resuscitation. In infants with poor perfusion due to severe persistent pulmonary hypertension of the newborn being transported in order to receive nitric oxide or extracorporeal membrane oxygenation therapy, newer-generation pulse oximeters significantly outperformed older-generation versions, but still failed five percent of the time, with failure defined as an absent oxygen saturation reading or a heart rate value more than five beats per minute different to the ECG value (94).

Importantly, in the delivery room setting, pulse oximetry takes some time to successfully apply. Time from birth to first data display usually exceeds 65 seconds, regardless of whether the sensor is applied to the infant before or after connection to the oximeter unit (95). In one study of twenty delivered infants, the median time from birth to heart rate display using pulse oximetry exceeded two minutes (96).

Evaluation of heart rate forms a key component of assessment in the 'golden minute' of neonatal resuscitation. This approach is taught in a global strategy called 'Helping Babies Breathe' which aims to improve neonatal outcomes by promoting effective newborn resuscitation by birth attendants and which has been shown to reduce perinatal mortality (97). Some experts suggest that a method of pulse rate measurement that takes longer than a minute is suboptimal as the sole means of determining heart rate in newly-born infants (82, 96).

Pulse oximetry is often slower than other methods for determining neonatal heart rate. Multiple studies have shown that ECG can more rapidly determine newborn heart rate in the delivery room (96, 98). In evaluation against auscultation, the above-mentioned average times taken to determine heart rate using pulse oximetry compare poorly to time taken for auscultation which has been shown to take on average less than twenty seconds in simulation (83). Similarly, palpation methods took less than thirty seconds in approximately two-thirds (femoral pulse palpation) to three-quarters (umbilical cord palpation) of attempts in the clinical setting (73).

Accuracy with pulse oximetry is also of some concern. Whilst it is more accurate than auscultation or palpation, more than ten percent of the time it failed to detect heart rate less than one hundred beats per minute compared to ECG (99). Although on average, heart rate was only two beats less per minute using pulse oximetry, the 95% limits of agreement were wider than expected and were more than twenty-five beats per minute in one study (100).

To summarise, whilst transmission pulse oximetry is a potentially very useful tool and has the unique advantage of being able to provide information about oxygen saturations in pulse-delivered blood, when used to measure heart rate of neonates in the delivery room, significant drawbacks exist. These include limitations such as interference from movement, ambient light and venous pulsations, as well as a small but potentially relevant degree of deviation from ECG-detected heart rate values and a significant delay in successful acquisition of data from the time of birth that exceeds globally-accepted practice standards and ideals.

2.5 Electrocardiography

The invention of the ECG is largely credited to Dutch physiologist William Einthoven who made the first recordings of a clinically applicable nature in 1902, seven years after the discovery of X-rays (101). The device records the variation in potential differences over time between the sites on the body surface to which leads are attached. These variations reflect differences in transmembrane voltages between myocardial cells that occur during the cardiac depolarisation and repolarisation process (102).

ECG has been used extensively in neonates and infants for several decades. Studies of newborns found that some rhythm disturbances such as sinus bradycardia, sinus arrhythmia, sinus pauses, premature beats and superior axis previously thought to be pathological were more likely to be normal variants (103, 104). Studies such as these, which also described heart rate trends, helped establish the role of electrocardiographic techniques as tools for monitoring heart rate in this population group.

In current neonatal medical practice, monitoring is an integral part of the care process, with the aim being to ensure that appropriate therapy can be given prior to the onset of complications (105). Not only can two or three skin-surface electrodes be used for continuous ECG monitoring of heart rate, but they can also be used to monitor respiratory rate by measuring transthoracic impedance, with a salient caveat being that lead positioning on the chest wall in order to obtain reliable signals is of great importance (106).

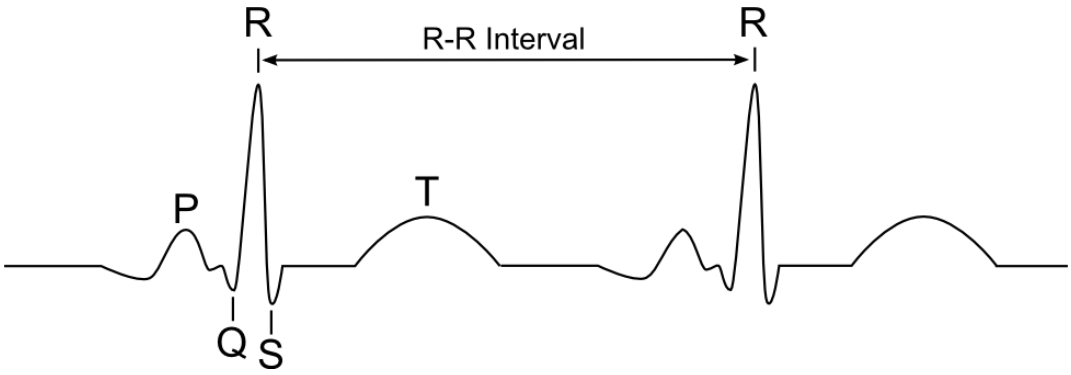


Figure 3. ECG waveform. Reproduced here with permission under the Creative Commons Attribution-Share Alike 4.0 International license, and available from https://commons. wikimedia.org/wiki/File:Ecg.png © Ted Burke 2007.

In using ECG to detect heart rate, algorithms utilise detection of R-wave peaks and calculate rate based on the R-R interval (107). This algorithmic approach is also used in low resource ECG monitoring systems (108). ECG leads positioned in line with (ie. proximal and distal to) the overall direction of depolarising current will capture the greatest R-wave deflection; there is a great degree of variability of this axis in normal newborns although in most cases this axis is between ninety and one-hundred and eighty degrees (109).

Each ECG complex is representative of cardiac electrical signalling. In rare instances the ECG may fail to correspond with effective mechanical contraction of the heart chambers, even when R-R intervals can be measured. In cases of electromechanical dissociation, cardiac electrical activity is pulseless (110). In children, pulseless electrical activity usually develops as a consequence of cardiac arrest. Epidemiological studies have found that between seven and fourteen percent of paediatric out-of-hospital cardiac arrests present with an initial rhythm of pulseless electrical activity (111, 112). Specific risk factors in newborns for the development of electromechanical dissociation include severe hypoxia, shock and pulmonary vascular compromise. The phenomenon has been noted to occur as an extreme manifestation of cardiac stun syndrome associated with extracorporeal membrane oxygenation use in this age group as well (113). However, serious arrhythmia in newborns is rare (114), and even in young children it is much less common than in adults (115). Nevertheless, arrhythmia-related uncoupling of the normal association between ECG complexes and true pulse should be kept in mind; in such cases, ECG-derived heart rate will no longer reflect the true heart rate. In all others, however, an ECG complex will be associated with ventricular contraction.

Although the pulse transit time measured from the ECG R-wave to detectable arterial pulsation will vary between and within individuals depending on their cardiovascular physiological state (116), this is of little consequence to heart rate monitoring and the ECG can be thought of as the gold standard method of assessing this vital sign in newborns (82, 117, 118) as well as being a similarly valuable tool for heart rate assessment in young children (119).

In comparison to auscultation and palpation methods, ECG is more accurate at determining newborn heart rate, especially in the delivery room (80). In comparison to oximetry, the accuracy improvement by using ECG is much less, although there is some discrepancy between heart rates obtained by the two different devices (99). Whilst auscultation and palpation are quicker than ECG in obtaining a newborn's heart rate in the delivery room, results conflict when the latter is compared to oximetry application. One study of 55 infants found that in a direct comparison of the two devices, the median time taken to acquire heart rate using pulse oximetry was 68 seconds whereas for 3-lead ECG it was 80 seconds (100). In this study twenty ECG malfunctions versus only twelve pulse oximetry failings resulted in failure to acquire heart rate (100). Another study with less participants found that ECG (median time of 38 seconds following birth) was quicker to measure heart rate than oximetry (median time of 122 seconds post-delivery) in the same setting (96). A third head-to-head comparison study of ECG and pulse oximetry in forty-six infants in the delivery room (thirty with extremely low birthweight of less than 1500 grams) found no significant difference in the time to place ECG leads versus the oximetry probe (98).

Given these conflicting findings, there was debate about the use of ECG to determine delivery room heart rate in newborns when the task force convened to update international guidelines for neonatal resuscitation published in 2015 (29), and it remains a controversial area of practice. Certainly, the time taken to obtain accurate heart rate using ECG in some studies would not facilitate meeting recommendations to determine heart rate by one minute post-birth. Furthermore, the expense of having ECG monitors in low resource settings is prohibitive. Importantly, the ECG cannot deliver information regarding oxygen saturations (29), and it is therefore unlikely that ECG will replace the pulse oximeter in the delivery rooms of developed nations, although it may be used as an adjunct.

2.6 Doppler Techniques

Doppler technology has been used to detect foetal heart rate for over half a century (120), although the existence of a detectable foetal heartbeat stretches centuries prior to Lannaec's 1816 invention of the stethoscope (121).

The earliest preliminary report of continuous foetal heart rate monitoring came in the form of phonocardiography; in 1931, microphones recorded S1 and S2 components of the foetal heartbeat when attached to a pregnant woman's abdomen using tight-fitting belts, but the signal was noisy (121). ECG-based foetal heart rate monitoring preceded Doppler use. In 1958 Dr Edward Hon used an ECG monitor placed on the maternal abdomen to detect foetal electrical cardiac signals (122). However, maternal cardiac signals as well as those from uterine contractions frequently overrode the weaker signals emanating from the foetus, making this technique less suitable for clinical purposes compared to Doppler ultrasonography (121).

This technique was brought to the fore by Callaghan and colleagues, who described in the early 1960s their compact, reliable and relatively inexpensive Doppler instrument for detecting foetal heart rate (123). Since then, use of foetal Doppler monitoring has become routine for high-risk pregnancies in many countries. In mothers with higher-risk presentations such as post-term pregnancies, previous pregnancy loss, women with hypertension, diabetes, intrauterine growth restriction or other maternal pathology, foetal Doppler monitoring has been shown to reduce the risk of perinatal deaths and result in less obstetric interventions (124). Meta-analysis for its use in low-risk pregnancies however did not find strong evidence that it benefited mother or baby (125).

Doppler sonography is based on the principle of the Doppler effect which relates the frequency of sound waves generated or reflected by a moving source with the frequency measured by an observer or sensor. The frequency is higher with the source or object moving closer to the measuring device, and lower when moving away (126). Doppler ultrasound devices emit sonic waves in a targeted fashion and capture the frequency and intensity of signals reflected back by moving components such as blood inside vessels or cardiac chambers, or even moving heart tissue itself. Since the detected frequency shift is proportionate to the flow velocity, by comparing the transmission and reception frequency, the velocity of the moving component can be determined (127). With each heartbeat, cardiac structures move, as does blood around the body; in particular, blood in arteries moves with a sudden increased then tapering velocity with each heartbeat. Therefore, a Doppler ultrasound device situated over the heart or an artery will be able to detect a cycle of velocity change with each heartbeat, and this information can be relayed to the user in a way that permits derivation of a heart rate in beats per minute, by automated counting and/or audible feedback.

In an Australian study of fifty-one stable young infants, a handheld Doppler ultrasound probe was used to measure heart rate when positioned over the child's praecordium at the angle of Louis and/or left and right sternal edges (128). Audible Doppler-derived heart rate correlated closely with ECG-derived heart rate (mean difference <1 bpm, 95% limits of agreement -14.4 to +15.8 bpm) but device-displayed heart rate as counted by its automatic process was less accurate (mean difference 5.4 bpm, 95% limits of agreement −50.2 to +39.4 bpm). Interestingly, using either method, correlation was better in those infants weighing less than 1.5 kilograms which was thought to be due to the focal depth of the probe used, set at approximately one centimetre (128). Heart rate acquisition was generally rapid (median of three seconds) and successful in most cases using the audible, manually counted method, although pulse oximetry still had slightly fewer missing data points compared to this technique. Failure to detect a heart rate using ultrasound may be due to the fact that ultrasound capture of flows is to a large degree dependent on the angle between the ultrasound beam and the flow axis, and can sometimes fail if this is not optimised (127).

A separate study in the delivery room setting did not compare precordial newborn Doppler against ECG but rather compared it to auscultation, pulse oximetry and umbilical cord palpation in 33 non-emergent deliveries. Whilst values were comparable between pulse oximetry and Doppler-derived heart rate, the pulse oximeter often took greater than one minute from time of delivery to establish a reading, whereas the Doppler method was the fastest of all four techniques (129).

Doppler sonography has long been used to assess foetal heart rate, but use in neonates is much more recent. Whilst documented trials in this age group are few, it is a rapid method for acquiring newborn heart rate and in non-emergent situations appears to be accurate when compared to ECG and/or pulse oximeter devices. In the delivery room, it can be faster than auscultation and cord palpation methods in determining heart rate, but it has not been tested in emergency, premature or low birthweight deliveries. One strength is that the presence of an audible Doppler feedback sound implies that there is cardiac output/blood flow, while the presence of an ECG heart rate does not always imply cardiac output; nevertheless, Doppler device performance is limited by unreliable automatically-counted heart rate displays, user skill and available probe choices (128).

2.7 Summary of Established Heart Rate Monitoring Methods

Multiple methods for assessing heart rate exist, each assessing different aspects of the vital cardiovascular function of pulsatile blood flow generation co-ordinated by cardiac electrical activity, and each with their own individual strengths and weaknesses.

Palpation is the oldest means of assessing heart rate, and is still relevant to newborns today. Feeling the pulse can be done rapidly (73), requires no equipment, and provides some level of qualitative feedback regarding the cardiac output state as well (130). However, successful detection of pulse regardless of the chosen assessment site is by no means guaranteed even if the pulse is present. In clinical studies, rates of failure to detect a pulse in newborns in the delivery room right through to adults with compromised cardiac function are likely unacceptably high for this to be considered the ideal means of heart rate assessment (73, 74, 80).

Furthermore, the manual counting of pulse to determine a heart rate is inaccurate, to a degree which makes it unsuitable to guide neonatal resuscitation decision-making according to internationally-formulated guidelines (29, 77, 80).

Auscultation of the heart using acoustic stethoscopes has been performed for centuries. Modern day analogue stethoscopes are very similar to the binaural stethoscope created by Dr George Cammann in 1855, who's device was an adaptation of the monoaural device made by Lannaec (131). Using a modern-day binaural acoustic stethoscope to assess newborn or infant heart rate is relatively easy, although accuracy both in the delivery room and in simulation studies has been shown to be lacking (80, 83, 84). Proponents supporting this method of heart rate detection point out that accuracy is generally better than pulse palpation, and that auscultation is much more rapid to establish in the delivery room than heart rate detection using monitoring equipment such as pulse oximetry (82, 95). Furthermore, stethoscopes are widely available, inexpensive and listed on the World Health Organization Generic Emergency Equipment List (132) means that in developing nations it is often the method of choice for newborn heart rate evaluation in the delivery room and hospital care setting. Even in developed nations, their use is supported (82).

The use of pulse oximetry to monitor patients of all ages is widespread in healthcare. Whilst some have raised concerns with level of correlation to ECG in neonates (133), pulse oximetry has been shown by others to have a clinically acceptable level of accuracy in detecting heart rate (118).

Furthermore, pulse oximetry provides information about arterial oxygen saturation levels, facilitating titration of oxygen therapy which may be required in newborn resuscitation (29). The drawbacks of pulse oximetry, especially in delivery-room care, are however quite significant. In multiple delivery room studies, it has been shown to take greater than one minute on average to display a heart rate (95, 96, 129), and given its reliance on pulse pressure delivery to the monitored extremity, may be less reliable in low cardiac output states (90). Interference due to movement and ambient light can also contribute to difficulties acquiring reliable heart rate data (92). Although pulse oximetry is the standard of care in many delivery rooms, expense may prohibit its use in resource limited settings (134).

Doppler sonography has been used to assess heart rate for several decades, and has become most-well developed in obstetric care in order to detect foetal cardiac contraction (120). In high-risk pregnancies, its use has been shown to improve maternal and neonatal outcomes, but its use in detecting the newborn heart rate directly is more recent and less well-established (124). Two neonatal intensive/special care-based studies have shown it to be both accurate and rapid in detecting heart rate when compared to ECG (128, 129). However, delivery-room experience is limited to a small experimental trial of non-emergent deliveries (129), and probe factors such as set focal depth and angling may also limit the success of rapid neonatal and infant heart rate detection using this technology (127, 128).

ECG detects electrical impulses generated by specialised cardiac cells that cause depolarisation and contraction of cardiomyocytes (69, 135). Unlike other methods of heart rate detection, the assumption that this implies blood flow through the heart or delivery of blood to peripheral tissues does not always hold true, for example in instances of pulseless electrical activity (110). Nevertheless, it is a highly accurate means of heart rate assessment, and is considered to be the gold standard method of assessing this vital parameter in newborns and young infants (117, 135). Substantial support for its use in monitoring newborns in delivery-room settings is both a recent and controversial development (29). ECG tends to be slower than both auscultation and palpation methods. Additionally, a 2008 delivery room study found it to be significantly slower to successfully apply than pulse oximetry and more likely to malfunction (100), although a more recent clinical evaluation suggests otherwise (98). The capacity to deliver neonatal ECG technology to delivery rooms around the world is limited (82), confining this approach to well-resourced healthcare facilities.

No one means of establishing newborn heart rate in the delivery room is clearly superior to all others. For each method, significant limitations exist. The ideal of accurate newborn heart rate determination within the 'golden minute' of initial resuscitation (97) is likely not being met using currently available techniques (136). The need to develop improved methods for rapid, accurate heart rate assessment of infants and newborns is apparent. Despite limitations, the potential future direction for heart rate assessment at birth, with new technologies on the horizon, is exciting (82). Certainly, these new technological approaches should be rigorously studied (99).

Chapter Three: Systematic Review of Novel Methods for Assessment of Newborn and Infant Heart Rate

3.1 Introduction

3.1.1 Background

Measuring and monitoring neonatal and infant heart rate accurately is important to clinicians around the world. It is a vital sign with an important role in assessing the need for resuscitation and emergency medical intervention (137, 138) and may serve as a marker to identify critically unwell children requiring escalation of medical attention (139).

3.1.2 Index tests

ECG is the established gold standard for assessment of neonatal heart rate (117) and is an indispensable tool for assessment of heart rate in children (119). For newborns requiring resuscitation in the delivery room, ECG may be the fastest way of accurately determining heart rate (96, 140). For infants, there are a variety of situations in which ECG monitoring is indicated, including episodes of apnoea and bradycardia, critically unwell children, perioperative assessment, evaluation of temporary pacing, and drug overdose (141).

Transmission pulse oximetry has become commonly used in the delivery room to measure oxygen saturations, as well as heart rate (100, 142). In this setting, it is used to guide resuscitation (29). For unwell young children, pulse oximetry is an essential element of patient monitoring, for both oxygen saturations and for assessment of heart rate in similar situations to those described above for ECG monitoring (141, 143).

3.1.3 Rationale

Both pulse oximetry and ECG in their current clinical forms have drawbacks. Both modalities can become inaccurate with movement artefact (142, 144). Pathophysiological states such as pulseless electrical activity and poor peripheral perfusion can render ECG and pulse oximetry respectively highly misleading (110, 143). Application of current monitoring sensors may be time-consuming in critical situations such as in neonatal resuscitation (136).

The application of monitoring leads with adhesives to sensitive skin, especially in preterm infants, may cause severe skin damage through burns and pressure ulcers (145-147). An underlying predilection for this is the lack of subcutaneous tissue that especially affects preterm infants (145). Skin damage can in turn contribute to susceptibility to infection (148), a life-threatening risk in this vulnerable group of patients. Electronic monitoring leads can pose a safety risk to non-neonatal infants as well, in other clinical situations such as during radiological imaging acquisition (149).

In addition, there may be a significant impact of ECG and pulse oximetry monitoring on parents and parent-child bonding. The potential for making physical contact with, and disturbing, monitoring wires has been shown to heighten mothers' anxiety and to discourage breastfeeding and healthy physical contact with their newborns in the neonatal intensive and special care setting (150). Furthermore, parents with young children who developed post-traumatic psychopathology following their child's paediatric intensive care admission have specifically commented on the emotional shock and burden of visible monitoring wires (151).

The effects on the mother-child dyad may have long term negative consequences for children, as can the young infant's sensory experience; exposure to high sound levels from frequent monitoring alarms and noxious stimuli, such as monitoring lead application, may exert deleterious effects on the immature brain and alter its subsequent development (152).

These challenges, combined with increasingly sophisticated scientific advancements, have driven the development of novel technologies to assess newborn and infant heart rate in ways that seek to overcome limitations and weaknesses inherent in current practice. However, establishing optimal performance and accuracy of novel devices is vital given that critical clinical decisions may be made on the basis of detected heart rate.

3.1.4 Critical Appraisal

Critical appraisal of scientific articles is essential to the provision of evidence-based care (153). Like other studies, those evaluating accuracy are at risk of bias. Major sources of bias originate in methodological deficiencies across diverse areas including participant recruitment, data collection, executing or interpreting the test, or in data analysis (154). In order to systematically assess for risk of bias, there are many checklists for the assessment and critical appraisal of tools used in medicine. However, few are validated (155). The Quality Assessment of Diagnostic Accuracy Studies (QUADAS) developed in 2003 is validated, and was improved and revised in 2011 (156). The revised version was used to guide critical appraisal of the scientific publications included in this systematic review.

3.2 Objectives

3.2.1 Primary Objectives

The primary objectives of this systematic review were

To identify and describe novel technologies for monitoring neonatal and infant heart rate, and

To provide an overall summary of the accuracy and performance of these technologies, including an analysis of their applicability to neonates and infants

3.2.2 Secondary Objectives

Where studies of novel technologies presented comparable statistical expressions of their diagnostic accuracy in the assessment of neonatal and infant heart rate, their diagnostic performance was comparatively evaluated.

3.3 Methods

3.3.1 Criteria for Study Consideration

Types of Studies:

We included studies of original research describing novel technology for assessing heart rate if they

- Were published in the last ten years
- Evaluated the technology in a relevant clinical population, defined as neonates and/or infants less than two years of age
- Performed a comparison against an established high-quality means of heart rate assessment, defined as transmission pulse oximetry or electrocardiography

Although review articles and articles published by the author of this thesis were not eligible for the version of the systematic review presented here, several reviews identified through the search process were read originating from sources bridging diverse disciplines, such as engineering, biotechnology, and medicine, in order to inform discussion and provide informative comments (99, 157, 158).

Participants

Participants were human subjects less than two years of age.

Index Test(s)

Index tests were novel technologies for heart rate assessment.

Target Condition

The target condition of this review was defined as newborn and/or infant heart rate.

Reference Standard(s)

Reference standards were designated as heart rate obtained by electrocardiography or transmission pulse oximetry.

3.3.2 Search Methods for Identification of Studies

Electronic Searches

We searched the following electronic databases to identify reports of relevant studies:

- MEDLINE, through OVID (15/04/2016)
- EMBASE, through OVID (18/04/2016)
- Science Citations Index (Expanded), through Web of Science (21/04/2016)
- Conference Proceedings Citation Index – Science, through Web of Science (21/04/2016)

The keyword search terms [with MeSH terms additionally used whenever available] used were: Neonat* OR infant OR newborn [neonatology] [infant] [newborn]; Heart rate OR heartbeat [heart rate]; Monitoring [monitoring,physiologic]. Full details of each search are listed in Appendix 1.

Other Considerations and Searches

Given the focus on newly developing technologies, the search was limited to articles published in the last ten years. The reference lists of publications eligible for inclusion were also reviewed, as well as lists of articles citing eligible publications (as found on Google Scholar), to identify additional relevant works.

3.3.3 Data Collection and Analysis

Selection of Studies

The initial searches were undertaken independently by two reviewers and studies assessing heart rate monitoring were identified based on the title of the articles. Review articles and articles assessing only well-established methodologies for heart rate assessment, such as ECG, auscultation and transmission pulse oximetry, were excluded from analysis. The two reviewers then independently assessed the abstract of each reference identified by this search against the remaining inclusion criteria. Additional relevant works identified by reviewing the reference lists of publications eligible for inclusion, and list of articles citing those eligible studies, underwent the same process. Any disagreements that arose between authors were resolved through discussion.

Data Extraction and Management

We extracted the following data from each included study:

- Study design
- Study population
- Reference standard and information relating to performance of the reference standard
- Index test and data relating to the performance of the index test
- Technical details of the index test method(s) used; the diagnostic modalities of studies' index testing methods were classified in order to group similar technologies
- QUADAS-2 items

Two review authors extracted the data. Disagreements were resolved by discussion, including discussion with a third author where necessary.

Assessment of Methodological Quality

As quality assessment of diagnostic accuracy studies is strongly recommended by STARD (Standards for Reporting of Diagnostic Accuracy) (159), all included studies were independently assessed by two reviewers using the QUADAS-2 tool (156). The QUADAS-2 assessment tool lists four key domains: patient selection; index test; reference standard; flow and timing.

Each study was evaluated for risk of bias under each of these four domains (156) and each study was also evaluated for applicability under each of the first three of these domains. This evaluation was undertaken following recommendations of the QUADAS-2 framework by use of appropriate signalling questions, which are listed in Table 1, to form judgements.

Domain:	1. Patient Selection
Subsection:	*A. Risk of bias*
Questions:	1. Was a consecutive or random sample of patients enrolled? 2. Did the study avoid inappropriate exclusions? Overall: Could the selection of patients have introduced bias?
Subsection:	*B. Concerns regarding applicability*
Question(s):	Is there concern that the included patients do not match the review question?

Domain:	2. Index Test(s)
Subsection:	*A. Risk of bias*
Question(s):	3. Were the index test results interpreted without knowledge of the results

	of the reference standard? 4. If a threshold was used, was it pre-specified? Overall: Could the conduct or interpretation of the index test have introduced bias?
Subsection:	*B. Concerns regarding applicability*
Question(s):	Is there concern that the index test, its conduct, or interpretation differ from the review question?
Domain:	3. Reference Standard
Subsection:	*A. Risk of bias*
Question(s):	5. Were all relevant data relating to the index test included and analysed appropriately?
Subsection:	*B. Concerns regarding applicability*
Question(s):	Is there concern that the target condition as defined by the reference standard does not match the review question?
Domain:	4. Flow and Timing
Subsection:	*A. Risk of bias*
Question(s):	6. Was there an appropriate interval between index test(s) & reference standard? 7. Did patients receive the same reference standard? 8. Were all patients included in the analysis? Overall: Could the patient flow have introduced bias?

Table 1: Signalling questions

The outcomes were discussed and consensus between the reviewers was reached. Where consensus could not be reached, a third reviewer (PD) was consulted.

Statistical Analysis and Data Synthesis

The data from each study were collated and presented in tabular and graphical format. For each study, data relating to the number of patients and/or recordings included and, if possible, the number of minutes of recording(s) analysed is presented. Where studies presented the mean difference and standard deviation (SD) and/or 95% confidence intervals in bpm between the novel technology index test and the reference standard, these data are displayed across differing index tests in order to facilitate comparison of the novel technologies. Where studies did not present this data, listed corresponding authors were contacted by electronic mail to request this data and in instances where this was made available, it has been included. Information relating to data exclusions disclosed by each eligible publication is also presented.

3.4 Results

3.4.1 Results of the Search

The initial search strategy identified 1672 references (Figure 4). After screening titles and abstracts and authors, 24 articles were selected for full-text review. Of these, thirteen studies were excluded for various reasons: did not include new original research data relating to the study question (160, 161), no comparison of novel technology with an appropriate reference standard (162-166), no actual testing on newborns or infants reported (167-172). After inclusion of five additional studies identified through references and citation of eligible studies (173-177), sixteen articles were identified for analysis in this review (173-189).

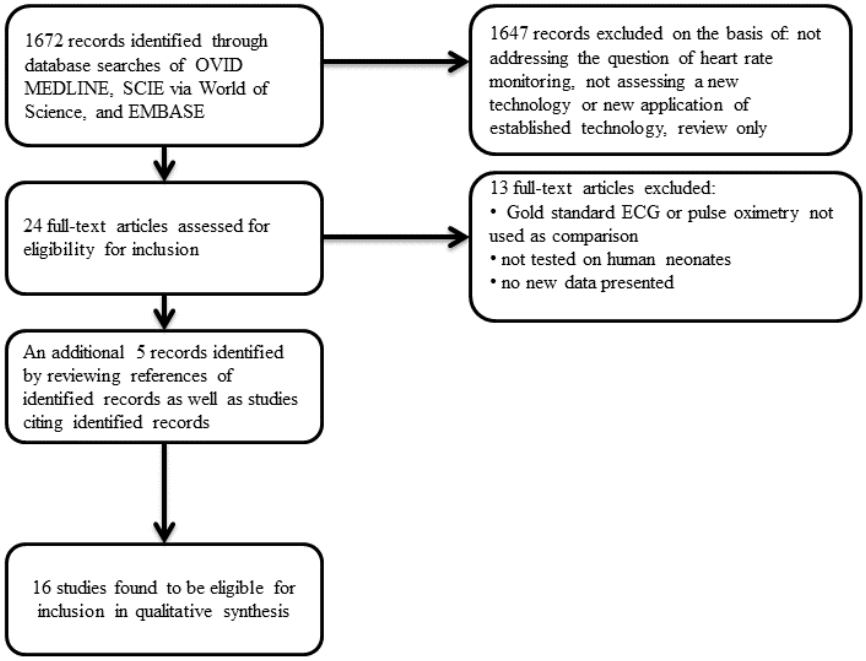


Figure 4. Initial search strategy.

The technologies assessed by these studies were camera-based photoplethysmography (175, 177, 178, 181, 185, 186), reflectance pulse oximetry (180, 182), laser Doppler methods (188), capacitive and load-cell sensors (174, 176, 179), piezoelectric sensors (173, 187, 189), and transcutaneous electromyography (184).

3.4.2 Results from Included Studies

In all included studies (individually summarised in Appendix 2), data on novel methods of heart rate detection compared to an appropriate reference standard device were collected from a total of 270 neonates and infants less than two years of age. Fifty-nine underwent camera-based heart rate detection, 102 were tested with reflectance pulse oximetry and twenty were assessed by laser Doppler vibrometry.

Nineteen, four, and 35 children less than two years of age had heart rate detection performed by capacitive, load-cell, and piezoelectric sensors, respectively. Kraaijenga and colleagues assessed 31 neonates using transcutaneous electromyography (184).

Brief descriptions of novel technologies

As a key objective of the review was to identify and describe novel technologies used, a brief description of each technological method is presented here.

- Camera-based photoplethysmography is a simple and low-cost optical technique that can be used to detect blood volume changes in the microvascular bed of tissue. It is often used non-invasively to make measurements at the skin surface. It works by amplifying subtle colour and/or light changes detected by a video camera, such as the slight skin colour change occurring with each heartbeat due to pulsation and perfusion. These changes are filtered and analysed to detect changes corresponding to heart rate, either in real-time during video capture or after recording is complete (post-hoc).

- Reflectance pulse oximetry uses light-emitting diodes and a detector which are both located on the same probe surface and hence are placed on the same body part surface. Some of the red and near-infrared light transmitted via the light emitting diode is absorbed by the body tissue, whereas some is reflected back to the sensor. As arterial blood changes the nature of light reflected back to the sensor with each pulse, the heart rate can be determined.

- Laser Doppler technology uses a laser beam directed at a target, and sensor, which detects light reflected back after hitting the target (e.g. newborn chest). Small movements of the target (e.g. chest wall movement with each cardiac contraction) can be detected and counted.

- Load-cell sensors convert the load acting on them into electrical signals. They are used in several types of measuring instruments such as laboratory balances and industrial scales. Variations in the load acting on them change the electrical signal transmitted, which can be measured and counted.

- Piezoelectric sensors are used in a variety of industries and applications, including in pressure sensors on mobile phone touchpads. They rely upon the mechanical stress exerted upon them to generate a small charge within the contained element. Changes in the mechanical stress placed upon the sensor, e.g. movement created by heartbeat, generates changes in the polarisation charge of the element, which can be detected and counted. Piezoelectric sensors can be very similar to (or considered a subtype of) load-cell sensors; a key property is that they contain within them a piezoelectric element which undergoes a charge-generating change itself in response to a stimulus.

- Capacitive sensors are used in a variety of commonly-encountered technologies such as interactive kiosk screens and other touchscreens. Capacitive sensors work by detecting a change in capacitance, the electric charge between sensor nodes, due to the influence of an external force, such as that which may be generated by the mechanical movement of the chest wall with a heartbeat or breath. This change in capacitive coupling between nodes can be counted.

- Transcutaneous electromyography refers to the recording of the electrical activity of muscle tissue (or its representation as a visual display or audible signal) using electrodes attached to the skin.

Camera-based photoplethysmography studies

Non-contact photoplethysmography was the method that was described by the greatest number of studies. This technology derives a heart rate by detecting and amplifying small changes in the colour of skin occurring with each heartbeat. All of these trials were small (<20 patients) initial studies and based in intensive care departments. Movement artefact was a key factor in all of these studies compromising accuracy; other factors affecting accuracy were described including illumination (175, 177, 178), infant positioning (185) and anaemia (181). Interestingly, the presence of staphylococcal scalded skin syndrome and phototherapy seemed to be associated with increased signal clarity and improvements in non-contact technology precision (178), although one study specifically excluded those undergoing phototherapy (186). The recruited patient populations, recording lengths, and statistical reporting approaches of the six studies varied.

Aarts and colleagues studied nineteen neonates and found that for thirteen, more than ninety percent of the time a heart rate within five bpm of the ECG standard could be derived using post-hoc analysis (178). The nineteen infants were recruited from two different neonatal intensive care units, located in the Children's Hospital of Orange County, California, USA and in the Máxima Medical Center, Netherlands. This study can be commended for recruiting a diverse set of neonates, and recording them in variety of states. Recruited neonates were between 25 and 42 weeks gestation, and three days to four weeks old. Weight ranged from 470 to 3810 grams. Infants receiving high frequency oscillation ventilation, being rocked by a parent, undergoing phototherapy and with skin disease were all included.

Video recordings were one to five minutes in length. They were made in ambient light using a standard 300 pixel, 8 bit camera placed on a tripod at approximately one-metre distance. A MATLAB-based graphical interface for non real-time heart rate extraction using an algorithmic approach which included motion detection was applied to the video recordings. Interestingly for an infant with Staphylococcal Scalded Skin Syndrome, the extractable photoplethysmographic heart rate signal was even stronger in affected skin than in adjacent healthy skin, probably due to the increased perfusion of affected tissue. Encouragingly, both a newborn being rocked in their mother’s arms, as well as one receiving high frequency oscillation ventilation, could be successfully monitored. However for nearly a third of patients, camera-derived heart rate was more inaccurate than the study cutoff for more than 10% of the time. Much of this was likely due to interfering movement artefact combined with the impact of poor lighting.

Dedicated illumination was felt likely to improve device performance, but the authors commented that it would be elegant, however, to use ambient light instead of dedicated illumination in line with their original approach. While the authors concluded that better hardware and algorithms were needed to improve robustness, this is a broad conclusion, and the details of envisaged required development was not specified.

Villaroel and colleagues found non-contact heart rate values were >4 bpm different compared to ECG for approximately twenty percent of the recording time, even after excluding video segments in which their two reported infants interacted with health professionals or parents (177). This was a single centre study, with patients recruited from the neonatal intensive care of the John Radcliffe Hospital in Oxford, United Kingdom. Video recordings were made in ambient and artificial (mostly fluorescent) lighting over four days for each preterm infant using a video camera (JAI AT-200CL, Figure 5). This had three separate sensors to measure red, green and blue light intensity independently so that these components could be best captured for independent analysis, known as Independent Component Analysis (Figure 6).

Figure 5. Monitoring equipment showing a mannequin inside the incubator. Villarroel et. al. Reproduced here with permission under the Creative Commons Attribution 3.0 license, and available from http://digital-library.theiet.org/content/journals/10.1049/htl.2014.0077 © IET 2014

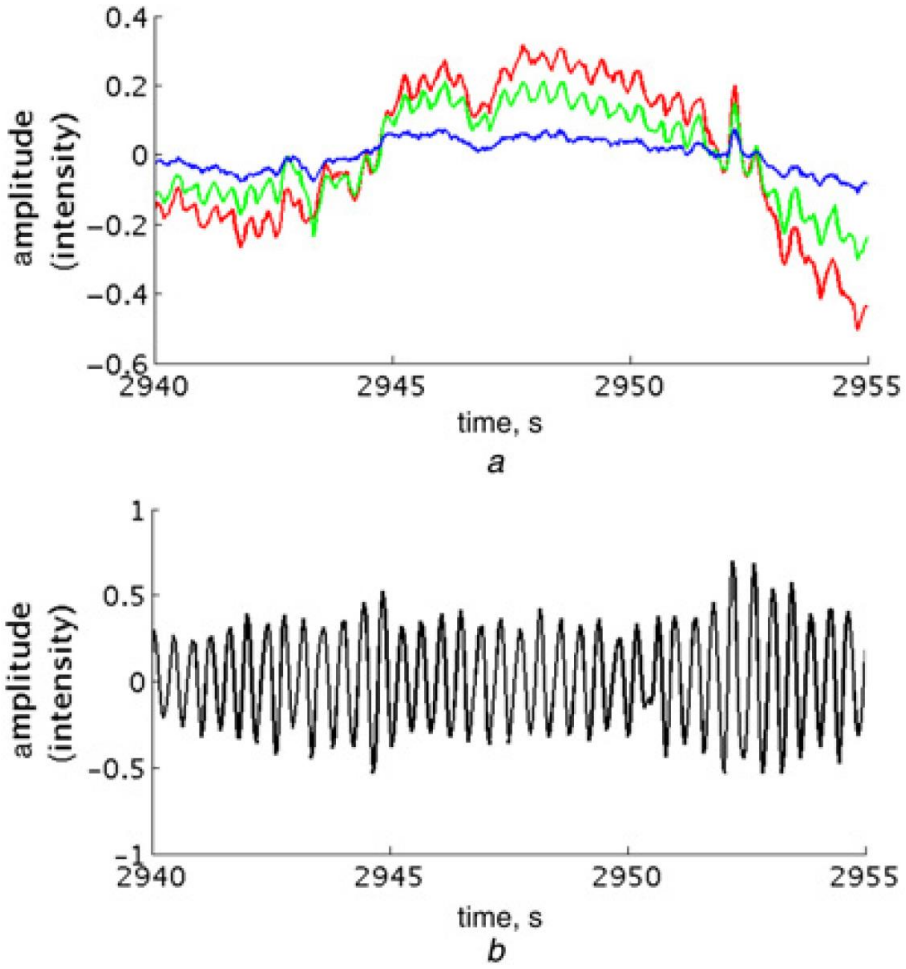


Figure 6. Independent Component Analysis with extraction of heart rate signal. Villarroel et. al. Reproduced here with permission under the Creative Commons Attribution 3.0 License, and available from http://digital-library.theiet.org/content/journals/10.1049/ htl.2014.0077 © IET 2014

Over forty hours of footage in segments of varying lengths, from 53 minutes to 7.32 hours, were taken. Heart rate was extracted from the recordings using customised software on a workstation running the Fedora Linux Operating System and using a Xilinx Spartan Field Programmable Gate Array (FPGA) board.

The authors concluded that the main barriers preventing increased accuracy of the novel device were threefold: Major changes in lighting conditions, lack of visible skin area, and variation in the baby's activity patterns as small pre-term infants made irregular movements throughout the day which made it difficult to compute the frequency components of the heart rate and respiratory rate in the pulsatile reflectance waveform (177).

In two of the non-contact photoplethysmography studies (181, 185), the mean difference and 95% limits of agreement between camera-derived and ECG heart rate were <±5 bpm. However, Klaessens and colleagues chose only to report results from selected segments of their eight recordings during which the patient was still (185), and Bal studied only three infants of an age eligible for this review who were all intubated (181). The study by Klaessens and colleagues recruited seven infants of 24-39 weeks gestation from a single Amsterdam-based neonatal intensive care, who were 11-87 days old (2 patients actual age unspecified) and weighed between 1670 and 3000 grams. No exclusion criteria were specified. Seven recordings were made in standard room lighting or daylight, one from each of the seven infants. A MATLAB-based software analysis program for non real-time heart rate extraction used an algorithmic approach. Novel device heart rate values were then compared to simultaneously-captured ECG heart rate values. Recording time was unspecified, and only video segments in which the infant was not moving were used for analysis. The authors concluded that more work was required to develop reliable real-time analysis of infant heart rate using camera photoplethysmography (185).

Bal studied three infants between two and twelve months of age in a Turkish intensive care setting, at the Tepecik Training and Research Hospital. All were intubated and sedated, thereby minimising movement. Reason for admission to the paediatric intensive care included meningococcal sepsis, cardiomyopathy and acute disseminating encephalomyelitis. Recruitment and exclusion criteria as well as recording time length were unspecified. A Lenovo Thinkpad T430 Laptop built-in webcam was used in these experiments.

All videos were recorded in 24-bit colour, and either indirect sunlight or fluorescent light was used as the illumination source. A non real-time heart rate extraction algorithm was used to derive photoplethysmographic heart rate, which was compared to ECG. In this highly controlled scenario with a small number of non-moving participants, camera photoplethysmography heart rate values were within five bpm of ECG values >95% of the time.

In two other non-contact photoplethysmography studies (175, 186), the mean difference and 95% limits of agreement between camera-derived and ECG heart rate were between ±5-10 bpm. Scalise and colleagues studied seven infants in a single neonatal intensive care unit, in their case located in Ancona, Italy. They were 30-37 weeks gestation, and weighed 1030-3120 grams. There were no specified exclusion criteria. A standard digital webcamera (Microsoft LifeCam VX-3000) was used, which contained a sensor with a maximum video resolution of 640 x 480 pixels and a maximum frame rate of thirty frames per second, although for the study a fifteen frame-per-second, 320 x 240 pixel setting was chosen.

Unlike the aforementioned studies, a large band light source was used to illuminate the skin surface at which the web camera was directed, rather than relying on ambient or room lighting. Recording were thirty seconds in length. Each subject was measured 8 times (for a total monitoring time per recruited infant of 240 seconds) whilst at rest in a supine position. All the video and physiological recordings were analysed offline using custom software written in MATLAB that facilitated Independent Component Analysis for the extraction of heart rate from a manually-selected region of interest (areas of skin selected on the video of the patient) in the video. The photoplethysmographically-detected heart rate was then compared to heart rate using Lead II ECG as the reference. Although the reported mean difference was less than one beat per minute, and >95% of novel device heart rate values were within ten bpm of the ECG value, Scalise and colleagues discarded more than 40% of the expected data points likely due to webcam or ECG inaccuracy; only data from 33 recordings were reported and analysed (175).

Rather than excluding and minimising movement, Mestha and colleagues utilised an approach with a strong focus on motion compensation (186). They studied eight neonates of term gestation, between three days and four weeks old, weighing 2400 - 3620 grams. Preterm infants, neonates requiring ventilator support, and neonates on phototherapy for management of neonatal hyperbilirubinemia were excluded from the single centre study conducted in the Neonatal Intensive Care Unit of Manipal University Hospital in Manipal, India. A commercially-available High Definition webcamera, with image resolution of 640x480 was used to make recordings in normal unit lighting without any additional modifications. Eight thirty-minute recordings were made, one from each recruited infant.

Heart rate was extracted from the videos post-hoc (non real-time extraction), and compared to that shown on an IntelliVue MP 20 Philips Neonatal monitor (although it was not specified whether ECG or pulse oximetry was used as the reference device).

A salient additional feature of this group's approach was the use of decision algorithms which influenced the determined photoplethysmographic heart rate value. Given that multiple regions of interest on the subject's skin were tracked, a pulse rate could be estimated from each; if that pulse rate was in agreement with other regions of interest and/or was close to the immediately previously detected heart rate, it was considered more likely to be accurate rather than adversely affected by movement. This approach presupposes that changes in heart rate changes over a short time period (for example, one second) are small, but does address the problem of movement artefact in an ingenious fashion. Despite this, large motions resulting in loss of accurate monitoring occurred approximately 10% of the time for their half-hour recordings of eight term-born infants. During the remaining time, camera-derived heart rate had a mean difference in comparison to reference heart rate of three bpm, and values were within ten bpm of the reference standard for >95% of the time.

Reflectance pulse oximetry studies

Two studies, by Adu-Amankwa & Rais-Bahrami and Grubb and colleagues (180, 182) used reflectance pulse oximetry. These demonstrated a comparatively high degree of accuracy with novel heart rate within three bpm of ECG more than 90% of the time. However this proportion was reached from analysis of time when data acquisition was stable only, and not from the total time of device use.

The study of a wireless abdominal belt with this technology (180) included data from 25 neonates admitted to the neonatal intensive care unit of Children's National Medical Center in Washington DC, United States of America; their ages and weights were unspecified. Patients were excluded if they had recently undergoing chest or abdominal surgery. The heart rate sensor utilised reflectance pulse oximetry techniques, infrared light, electronic filtering and mechanical stabilisation developed by PGS Medical Research and Electronic Design. Heart rate waveform data were recorded into a file from the wireless research monitor and from the existing NICU equipment (reference pulse oximeter monitor) for a total of ninety minutes per subject. Each file was then reviewed and five selections of at least three minutes duration wherein both monitors were displaying stable waveforms were compared. There was excellent beat-to-beat correlation in these segments; however they represented less than 20% of the total recording time. Furthermore, it is unclear whether data from all subjects were included or not. Whilst the authors concluded that the abdominal monitor described was an accurate, easier method of collecting cardiorespiratory data in the neonatal intensive care unit when compared to standard techniques, it seems that further testing and disclosure of results is necessary before such a view could be supported.

A study of forehead reflectance pulse oximetry was conducted in the neonatal intensive and special care setting, with a view to potential deployment in the delivery room (182). Grubb and colleagues recruited two groups of participants in a neonatal intensive care unit in the United Kingdom. The first comprised 53 neonates of $\geq$ 32 weeks gestation with a mean corrected gestational age of approximately 33 weeks and mean postnatal age of six days.

The second group of 24 premature neonates were <32 weeks gestation, with a mean corrected gestational age of approximately 31 weeks and mean postnatal age of twelve days. The mean birth weight was 1.66 kg for the ≥ 32 weeks gestation group, and 1.26 kg for <32 weeks group. 26.9 weeks was the youngest gestation, with the oldest gestation being 42 weeks. Weight ranged from 750 grams to 4.9 kilograms. Newborns were excluded if they were receiving phototherapy or palliative care, had extensive skin disease, or if there were language or social barriers to obtaining consent. Patients that the attending physicians felt were too clinically unstable were also not recruited into the study. A key strength of this study is the comparably large number of participants recruited. The authors also provide an admirably detailed level of information about their device and study setup (Figure 7) in their article.

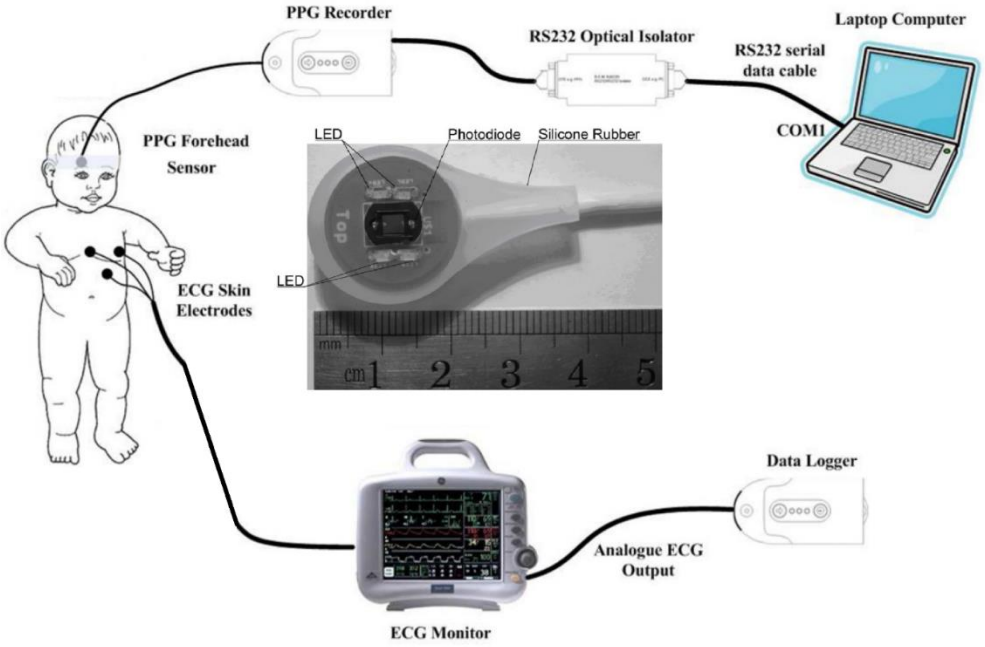


Figure 7. Experimental equipment for simultaneous forehead reflectance pulse oximeter and ECG heart rate recording with photograph of forehead sensor. Grubb et. al. Reproduced here with permission under the Creative Commons Attribution 3.0 license, and available from http://iopscience.iop.org/article/10.1088/0967-3334/35/5/881/pdf © IET 2014

The forehead sensor light source consisted of four 525 nanometer light emitting diodes (Marl, E1S02-3G0A7-02) arranged in pairs either side of a photodetector (Vartec, VTB8440B) to provide even illumination of the tissue beneath the sensor. A green light spectrum was utilised instead of the red and near-infrared spectrum more commonly utilised in transmission pulse oximeters, based on findings from previous research (190). Data-logging was provided by a modified electrophysiological recorder (Monica Healthcare Ltd, AN24), and signal processing was implemented in MATLAB (version 7.12, MathWorks). The reflectance pulse oximetry waveform was displayed in real-time, although selection of data for analysis occurred after recording.

Recordings were evenly truncated to a length of twenty minutes in order to ensure a balance in contribution from each participant, a simple step which was nevertheless not necessarily performed in other studies (of camera photoplethysmography for example). Heart rates in bpm refreshed at one second intervals were compared. In terms of accuracy, the reflectance pulse oximeter heart rate was within ±10 bpm for neonates >32 weeks gestation, and within ±12 bpm for neonates <32 weeks gestation, for >95% of the time in which paired values could be obtained. However, much of the data was excluded prior to this analysis. Data from more than 20% of infants were not included in the analysis due to a failure to log ECG data. This failure disproportionately affected recruited infants <32 weeks gestation. Furthermore, only data obtained when the ECG trace was stable were reported upon, and the proportion of time during which values were not obtained is unreported. Therefore, the proportion of total recording time during which reflectance pulse oximetry was adversely affected and unable to extract a reliable heart rate is unclear.

The authors conclude that the greatest impact on accuracy arose from motion artefact, although heart rate extraction algorithm modifications could also improve device performance. They provide clear direction for future improvements and research including a delivery room study and improved probe fixation to minimise motion artefact (182).

Studies of sensor-based methods

Capacitive and load cell sensors in various forms have been used to assess newborn and infant heart rate. Atallah and colleagues embedded eight 25mm-diameter circular capacitive sensors into a neonatal cot mattress surrounded by a reference electrode made of conductive textile, all covered by a thin polyurethane protective cover (179). Fifteen premature infants from the neonatal unit Maxima Medical Centre in Veldhoven in the Netherlands were monitored for a total time of 75 hours with concurrent ECG. Their ages were not reported but weight range was approximately 750 grams to 2.5 kilograms. Data from each sensor was pre-processed using filtering techniques, before having R-wave peak amplification attempted with automated counting to determine R-R interval, a figure easily transformed into a heart rate in bpm. The final novel device heart rate was determined by an amalgamation of the rates from the two highest-quality processed sensor signal inputs, with quality determined by a complex algorithm. It was found that an accurate heart rate could be determined less than half of the total recording time.

Authors identified subject movement, external detected movements (e.g. of someone walking nearby) and poor coupling with the sensors as key deficits to be overcome. They suggested decreasing the number and thickness of layers of material between the measured subject and the sensors, and realignment of sensors to body shape, in order to enhance coupling, which they speculated would also decrease the relative influence of external movements detected by the capacitive sensors.

Kato and colleagues provide a brief, qualitative description of their study of capacitive monitoring. In an effort to maximise coupling between the subject and sensor, they used thin cotton underwear as the only insulator between the infants and the sensor surface, which was itself made from a deformable fabric. This was conductive fabric made of nickel on copper plated polyester that covered the mattress surface (176). A key strength of the study was pressure mapping, which facilitated dividing the conducting fabric into three separate sensor areas that corresponded to predicted areas of better subject contact. Four infants weighing between 3.5kg and 8kg with an age from ten to 133 days were studied. Length of recordings was not provided. No summary or statistical data was provided. Only one recording was described as successful and an overall comment was made that the system was unstable if the infant was “flopping or crying” (176). The authors concluded that the detected waveform was distorted and that there was room for improvement in terms of their system’s practical use.

Lee and colleagues took multiple heart rate measurement recordings from three infants <2yrs of age and one young child of approximately four years, using small, anodised aluminium load-cell sensors (CBCL-6L, Curiosity Technology, Paju-si, Gyeonggi-do, Korea) placed under each of the four legs of a cot (174). The study was conducted in Seoul, Korea. Rather than record patients in an intensive care setting, home visits were organised for this. Thirteen recordings were taken from the participants on different dates, and were several minutes to hours in length. Reference heart rate was obtained by conventional ECG. Amplification and filtering techniques optimised the electrical signal output from the load-cell sensors, reducing noise and accentuating relevant main peak components.

Signal quality check was based on detection of regularity of main peak components in the expected frequency range. The sensor with the strongest and clearest heart rate signal was selected as the most suitable sensor for measuring the cardiac activity, with rapid periodic re-evaluation of the sensor selected. Analysis revealed that accurate load-cell heartbeats (defined as having an R peak location -0.15s to +0.35s) were obtainable 73.8% of the time, with the remainder of the time being affected largely by movement artefact. The authors inferred that their findings demonstrate a positive feasibility for future studies of this technology for infant monitoring.

Piezoelectric sensors rely upon the mechanical stress exerted upon them to generate a polarization charge within the contained element which generates a proportional output signal (191). Their placement in a variety of locations has been used to detect the heart rate of preterm and term newborns.

Nukaya and colleagues monitored a single infant for sixty minutes using piezoelectric sensors affixed to 80mm polypropylene resin coasters placed underneath the four legs of a neonatal cot, recording movements including those due to heartbeat (173). The infant weighed 2840 grams, was 52 days old and was located in a neonatal intensive care unit in Tokyo, Japan. Movements were detected by the piezoelectric sensors and converted to detectable electrical charge within the piezoelectric element contained within the sensor. Ten millisecond sampling with analog-to-digital conversion and bandpass filtering (3-13 hertz) of the acquired signal was undertaken. Body movement was detected by high voltage signal, which spanned the frequency of the heart rate signal as well as other frequencies; it was confirmed to be due to subject body movement rather than external factors with video monitoring. During these periods, heart rate could not be detected by any of the piezoelectric sensors. However, vibration caused by staff moving along the bedside did not cause significant interference with piezoelectric heart rate signal acquisition. By examining acquired paired values, a Pearson's correlation coefficient of 0.91 between ECG and piezoelectric-derived heart rate was reported by Nukaya and colleagues (173).

Sato and colleagues used a piezoelectric sensor (Figure 8) embedded within a towel-covered neonatal mattress (187).

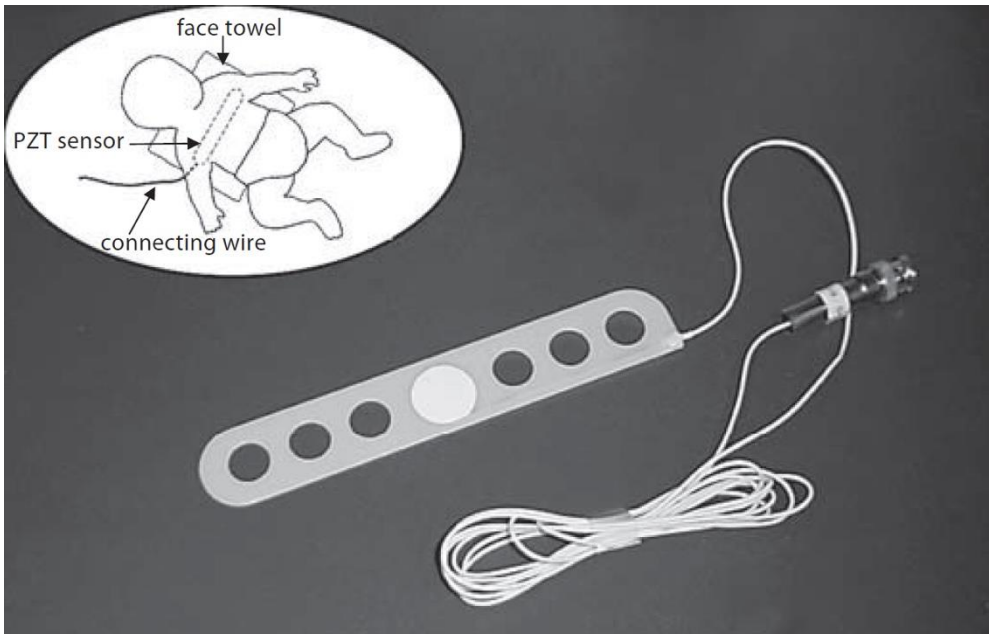


Figure 8. Piezoelectric sensor. Sato et. al. Reproduced here with permission. © Karger Publishers 2010

After excluding two recordings due to data quality issues, Sato and colleagues evaluated segments from 27 remaining patient recordings. These 27 neonates had a gestational age between 25.3 and 39.9 (median 34.9) weeks, and a weighed 742 – 4126 (median 1960) grams. Two were extremely low birth weight (<1000 grams), five were very low birth weight (between 1000 and 1500 grams) and more than fifty percent (n = 14) were low birth weight (between 1500 and 2500 grams). Nineteen were male. Infants with a wide variety of diagnoses were included, such as chromosomal abnormality, atrial septal defect, patent ductus arteriosus, peripheral pulmonary artery stenosis, Trisomy 21, respiratory distress syndrome, transient tachypnoea of the newborn and pneumothorax.

Three recruited neonates were receiving nasal continuous positive airway pressure (CPAP), two were conventionally ventilated with intermittent mandatory ventilation and two were on high frequency oscillation ventilators. No specific exclusion criteria were mentioned, and the research was conducted in the neonatal intensive care unit of the Akita University Hospital in Akita, Japan. Recordings were taken with simultaneous ECG to detect the reference heart rate, and were between ten hours and nine days in length, sampled every two milliseconds. Data acquisition (Axoscope9; Molecular Devices, United States of America) and analysis software (Clampfit 9.2; Molecular Devices) was employed. High-pass filtering removed noise from the piezoelectric recording, before template search analysis (a type of pattern recognition processing) was used to search the whole record for similar signals with a predefined representative S1 epoch regardless of amplitude. Then, using the spreadsheet application, S1 –S1 intervals were compared with corresponding R–R intervals captured by ECG. In comparison to the research completed by Nukaya and colleagues reported above, this investigation of piezoelectric-detected heart rate compared to simultaneous ECG revealed a similar correlation coefficient of 0.92. The analysed segments from which this was calculated were, however, one-minute-long sections picked out from times in which the study participants were not moving (Figure 9), and cannot necessarily be considered representative of total data.

Figure 9. Piezoelectric sensor output analysed. Sato et. al. Reproduced here with permission. Copyright © Karger Publishers 2010

Analysis of the full recordings of the infants over several hours to days showed that heart rate was accurately detected by piezoelectric technology 82.6% of the time compared to being detectable 91.8% of the time with ECG. Breastfeeding, ventilation and spontaneous infant movement were listed as key sources of interference. The authors felt that the detrimental influence of the high frequency oscillation signal could potentially be resolved by advanced signal-processing algorithms such as pattern recognition, or wavelet transforming analysis. Furthermore, their piezoelectric sensor was considered easy-to-use, durable, sterilisable and safe, without a risk of causing skin irritation compared to conventional monitoring methods. They postulated that with development their system could be used as a backup cardiorespiratory monitor for a more secure monitor system, or as a main cardiorespiratory monitor for a healthier infant not necessarily requiring full information (187).

Wang and colleagues provide the only study results of a piezoelectric sensor for neonatal heart rate detection with real-time output compared to ECG (189). After preliminary studies helped design an algorithm and an appropriate silicone base for their mattress-based sensors, five preterm infants (one male and four female) were studied for ten minutes each. These infants were all preterm and weighed between 1532 and 2112 grams. No specific exclusion criteria were reported, and the study was conducted in a single centre, the neonatal intensive care unit of the Tohoku University Hospital in Japan. A flexible, synthetic film piezoelectric sensor sheet was developed, resting on a silicone rubber base. The thickness of this base was approximately 5mm, and after being placed in a thin vinyl case it was positioned on the cot bed underneath the bedcover sheet.

Heartbeat pulsations resulted in small, detectable deformations of the piezoelectric material, arranged within the device into four separate rectangular sensor strip areas each 5 x 28cm in shape. Only the components of the signal generated by fluctuation of pressure were transmitted and processed by filtering, conversion and amplification techniques. Wavelet multi-resolution decomposition was used to separate out pressure fluctuations due to respiratory efforts rather than the commonly-employed bandpass filtering method, because this was thought to be more accurate. An algorithm selected the strongest of the four piezolectric heart rate signals coming from each rectangular strip automatically.

Comparison of ECG and piezoelectric-detected heartbeats revealed that the rate of incorrect heartbeat recording using this novel technology (either an inappropriate recorded beat or missed beat) was 8.24%, and arose primarily due to infant movement or weakness of the heartbeat vibration. Whilst the authors felt that this may be a clinically acceptable level of accuracy (189), limiting the study to a small group of low birthweight infants means that the findings may not be generalisable to other infants (for example newborns <1500 grams who may have weaker heartbeat signals or more robust infants displaying larger and more frequent spontaneous movements).

Studies of other novel technologies

Only one study each used laser Doppler vibrometry and transcutaneous electromyography. Electromyography utilised skin electrodes similar to those used in ECG; it was tested by Kraaijenga and colleagues on over thirty preterm infants with a gestational age between 26 and 32 weeks who were being treated with nasal CPAP or nasal oxygen (184).

Patients were one to seven days old, and those with congenital anomalies were excluded from the single centre study conducted at the Department of Neonatology, Emma Children's Hospital, Academic Medical Center, Amsterdam, The Netherlands. Measurements were performed using three skin electrodes (two electrodes were bilaterally placed at the costo-abdominal margin in the nipple line and one at the sternum) which were connected to a portable 16-channel digital physiological amplifier. The signal was band-pass filtered from 40 Hz to 160 Hz prior to a gating technique being employed to isolate cardiac-relevant signal components for heart rate counting. Analyses were performed using Polybench software. Although transcutaneous electromyography determined heart rate with a high degree of accuracy in comparison to conventional ECG (mean difference -0.3 bpm, 95% limits of agreement -5.3 to 4.7 bpm), it can be easily argued that for heart rate monitoring the technology offers limited advantage over current practice given that similar transcutaneous electrodes (subject to the same pros and cons) are required.

Marchionni and colleagues studied non-contact Doppler vibrometry which used a single-point laser beam 1.5 – 2 metres away directed toward the anterior left chest walls of premature infants in order to detect minute movements of their praecordium occurring with each heartbeat (188). Twenty infants (seven female) with a mean weight of 1111 grams were studied principally to test the technology for the assessment of heart rate. All testing was completed within the Neonatal Intensive Care Unit of the Università Politecnica delle Marche in Ancona, Italy. The technique was unaffected by a transparent crib wall (160). The study setup (Figure 10) was also capable of detecting respiratory-related signals.

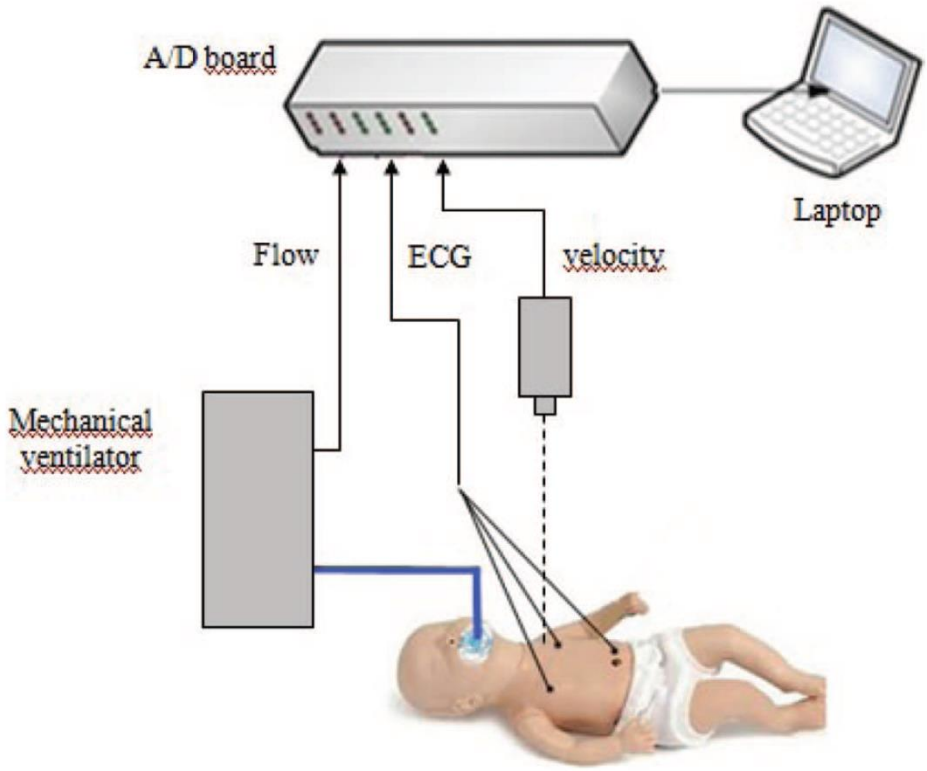


Figure 10. Laser Doppler Vibrometry setup. Marchionni et. al. Reproduced here with permission. © AIP Publishing 2013

For each subject, Lead II ECG and Laser Doppler Vibrometer (Polytec, PDV100, GmbH, Germany) traces were simultaneously recorded (length not reported) with an analog-to-digital 12-bit acquisition board with anti-aliasing filters (ADI Instruments, PowerLab 4/25T) also utilised for signal acquisition. Laser Doppler heart rate values were obtained through post-hoc, wavelet-based algorithm construction, with selection of parameters to best fit the gold standard data.

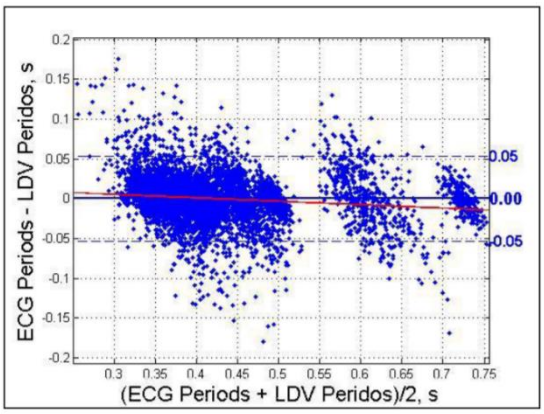


Figure 11. Bland Altman analysis comparing heart rate extracted by Laser Doppler Vibrometry and ECG. Marchionni et. al. Reproduced here with permission. Copyright © AIP Publishing 2013

Bland Altman analysis (Figure 11) revealed that laser Doppler heart rate values had a SD of approximately eight bpm when compared to ECG values. The authors concluded that their study demonstrated some level of uncertainty with respect to laser Doppler-acquired heart rate (which was quantified as 6% of the average heart rate), and that in the future it would likely be possible to reduce the dimensions, complexity and cost of such systems.

3.4.3 Methodological quality of included studies

The results of the QUADAS-2 tool, used to assess the methodological quality of included studies, are presented in Figure 12.

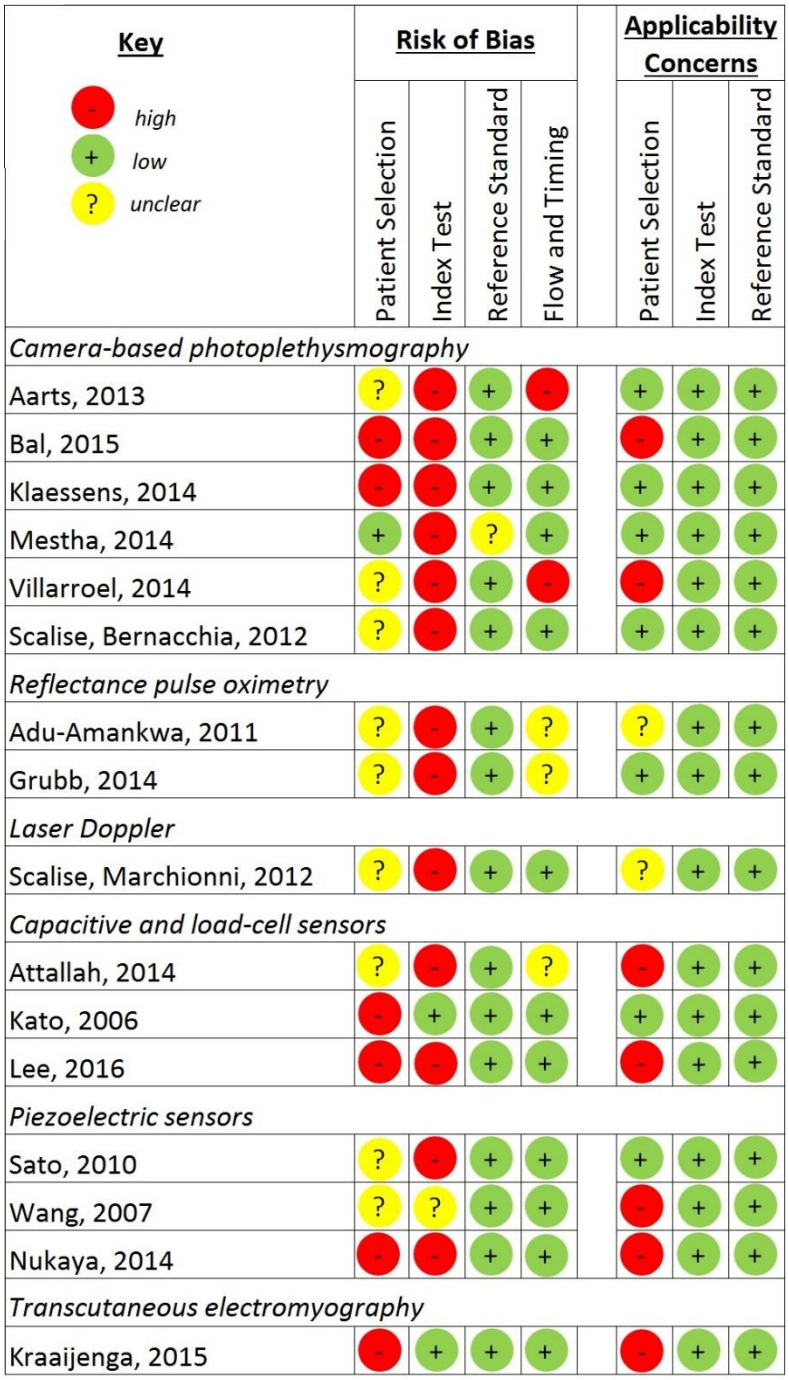


Figure 12. Methodological quality of included studies.

One of the main limitations identified was that patient selection was a potential source of bias. Only one of the articles specified randomised patient selection (186), and most of the articles did not describe how patients were selected (160, 173-176, 178-182, 184, 185, 187-189). In addition, it was deemed that some studies used restrictive inclusion criteria without suitable explanation.

All of the studies applied the index and reference tests simultaneously. However, many studies analysed the index test results after obtaining results of the reference test, especially studies of photoplethysmography (160, 177, 178, 180-182, 185, 186, 188). This process was deemed to increase the risk of bias.

Post-hoc data exclusion and selective data analysis also affected the methodological quality of several studies. Some studies did not report data for all patients (176, 178) whereas others excluded data arising affected by a poor trace (175, 177, 180, 182) or when movement, apnoea or arrhythmia occurred (185, 187).

Almost all studies reported and appropriately used a suitable reference standard. However, some studies were unclear in specifying which reference standard (for example, ECG, pulse oximetry) was used and/or whether the same reference standard tool was applied to all studied infants (178, 180). Another notable source of bias includes the practice of re-recruiting or re-recording the same patient, affecting three studies (174, 176, 185).

With regard to the QUADAS-2 category of applicability, some novel technologies were trialled on a very specific subgroup of infants. Five studies trialled their devices only on preterm neonates (173, 177, 179, 184, 189), one obtained data only from sleeping infants (174) and one focused exclusively on intubated patients (181). Whilst most studies had small numbers of recruited participants, several publications were able to demonstrate appropriate demographic variability in their selected population (175, 182, 185).

3.4.4 Findings

Results of the analysis

Data extracted for statistical analysis and synthesis from the included studies are presented in in Figure 13. Many of the studies did not provide sufficient data to derive mean difference and/or SD in bpm for cross-comparison. Considerable heterogeneity exists between the statistical reporting methods employed, both across the assorted technologies investigated and between different individual studies utilising the same basic technological approach.

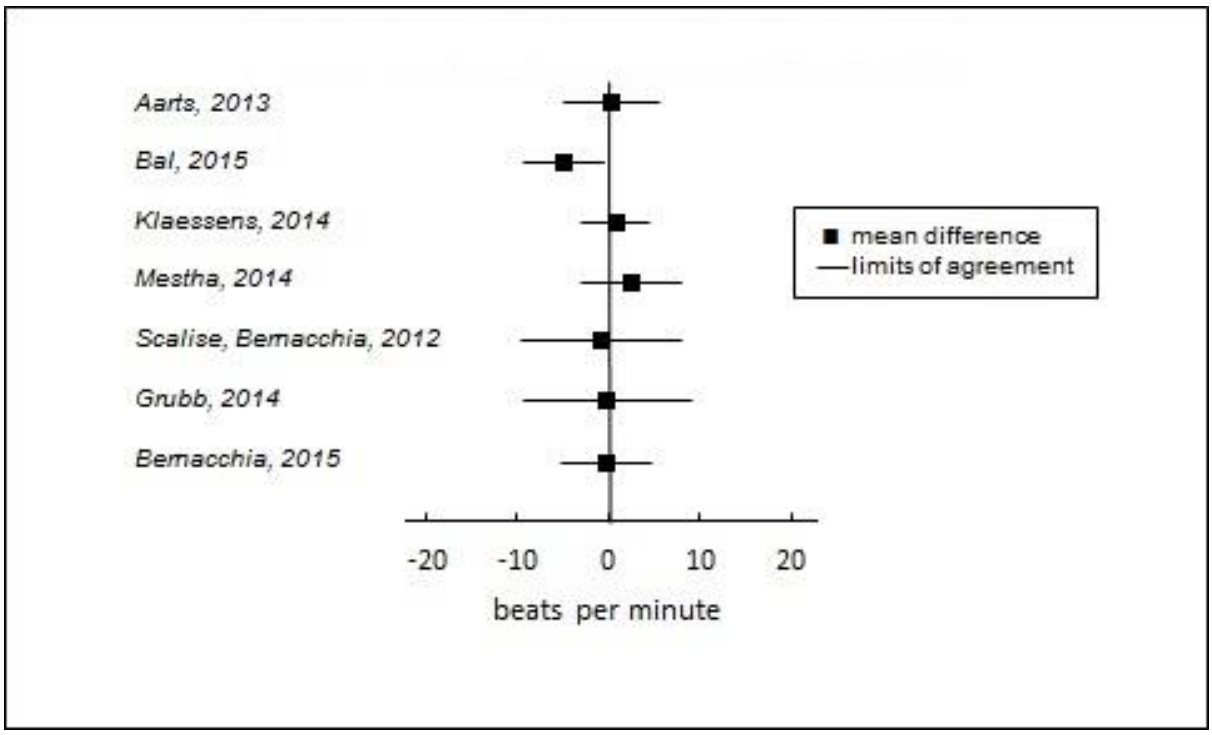


Figure 13. Mean difference and 95% limits of agreement between studied technology heart rate and reference heart rate.

The mean difference and limits of agreement between studied technology and reference device heart rate tended to be less than ten bpm. Studies with greater accuracy evidenced by tighter limits of agreement investigated the use of camera photoplethysmography; they tended to outperform studies of other technologies such as reflectance pulse oximetry, which highlights the strengths of this camera-based method.

Summary of Findings

We identified six novel technologies for heart rate monitoring in neonates and infants. Each modality had its own limitations; movement artefact in particular was a limitation mentioned in most of the studies reviewed. Ambient light was also a limitation in several of the studies assessing camera-based photoplethysmography. An analysis of the

risks of bias and applicability of each study has been presented in Figure 12. The published data has been summarised and presented in Figure 13.

3.5 Discussion

3.5.1 Strengths and Limitations of the Review

A comprehensive review of the published literature has been conducted, following the systematic approach outlined in the QUADAS-2 methodology. Criteria for study inclusion have been uniformly applied. Sixteen articles describing trials comparing novel technologies for heart rate monitoring in neonates and infants, across five different modalities were identified. A key strength of the review is the cross-disciplinary nature of the search, identifying scientific papers from medical, biomedical and engineering journals.

The most salient limitations of our review arise from the nature of the included articles. All of the included works describe small-scale, pilot studies of technology. Many of these can be accurately described as being still in a developmental phase. Significant risk of bias affected methodological quality of these studies across multiple domains. Results were not reported in a comparable fashion across studies, making accurate comparison of included works in order to identify the most promising novel technology difficult.

3.5.2 Applicability of Findings to the Review Question

Because only studies where novel technologies had been trialled on a neonatal and/or infant population in comparison to an established gold-standard were included, findings are considered applicable to the review question.

3.6 Author's Conclusions

3.6.1 Implications for Practice

The ongoing innovation of technological solutions for assessment of heart rate in young children is highly encouraging, with potential for significant effects on clinical practice. Non-contact methods for heart rate assessment have the advantage of minimising noxious stimuli and infection pathways for vulnerable preterm infants. However, due to the limitations of the studies and trialled heart rate assessment methods described in this systematic review, none of the novel technologies can be recommended as being suitable for widespread clinical implementation at this stage.

3.6.2 Implications for Research

Several of the novel technologies, particularly photoplethysmography and ballistocardiography, suffered from poor signal accuracy due to movement of the neonate/infant (160, 174, 177, 178, 180-182, 185, 186, 188). Methods for minimising movement artefact have previously been developed to improve oximeter-based heart rate assessment in newborns (192). It is clear that overcoming inaccuracy due to movement artefact is an area of high research importance for these novel heart rate monitoring technologies.

Trial methodology and hence clinical applicability of future studies could be improved by inclusive patient selection criteria, larger sample sizes and standardised reporting of results with inclusion of all relevant data are needed. Real-time assessment of heart rate using the novel method is highly desirable in order to demonstrate its capability in practice rather than simulated conditions. Future studies should also compare novel methods against each other, to ascertain the most promising technological approach.

Chapter Four: Evaluation of a Digital Stethoscope for Assessment of Heart Rate in Newborns and Infants in the Neonatal Intensive and Special Care

4.1 Background and Rationale

Heart rate is a vital sign of critical importance in the assessment of neonates and young infants. It is a central parameter of routine neonatal monitoring because of its role in identifying and managing medical disorders that may affect neonatal cardiac function (193).

Prompt and accurate assessment of the heart rate of newborns also provides important information about cardiorespiratory function and is useful in guiding resuscitation (29, 137). A key component of neonatal resuscitation guidelines such as the European Resuscitation Council Newborn Life Support Guidelines 2015 (194), World Health Organization 2012 Guidelines on Basic Neonatal Resuscitation (137), and Australian Resuscitation Council Neonatal Guidelines 2010 (195) is the counting of heart rate of the neonate.

However, prompt and accurate assessment of heart rate with pulse oximetry or ECG may take some time to establish (136). A 2012 single centre study of twenty deliveries demonstrated that pulse oximetry took on average more than two minutes to establish heart rate (96). Another study showed that the time to acquire newborn heart rate using ECG exceeded one minute in more than 75% of cases (100).

There is also significant inaccuracy in heart rate obtained umbilical cord palpation and manual auscultation of the heart. In a study of vigorous newborn infants in the delivery room, cord pulse assessment and auscultation underestimated the ECG-derived heart rate by an average of fourteen and 21 bpm respectively; in addition, umbilical cord palpation was unsuccessful in determining heart rate in 19% of cases (80). A study of medical staff assessing the heart rate of a neonatal simulation manikin using stethoscopes found auscultation to be so inaccurate that 28% of assessments would have prompted incorrect management during resuscitation or stabilisation (83). Accuracy of neonatal heart rate determination may not be easily improved through training. A study where some medical staff received a resuscitation training intervention prior to repeating simulated neonatal auscultation to determine heart rate found there was no significant increase in this group's accuracy compared to others who did not undergo the intervention (196).

Smart devices are electronic devices which are generally connected to other devices or networks. They include smartphones, which are smart devices that enable mobile communication and computation in a handheld-sized device, facilitating computing at the point of care (197). In recent years there has been a rapid and widespread uptake of smart device technology in developed as well as developing countries (198). Current smart devices possess a tremendous amount of computational ability in a highly portable and affordable form. This provides the opportunity for a new generation of diagnostic tools based on smart devices that could significantly improve monitoring and treatment of infants and children worldwide (199).

A low-cost digital stethoscope that connects to smart devices (200) to monitor and record neonatal chest sounds in an electronic format has been developed, as well as prototype software that is able to process the recorded data and provide information regarding neonatal and infant heart rate in real-time. This device could directly address the issues requiring prompt and reliable assessment of neonatal heart rate noted above.

Smartphone applications for use in healthcare are becoming increasingly common (201). The many advantages of using smartphone-based healthcare applications in medical practice include mobile communication, provision of access to various clinical resources at the point of care, and secure access to real-time patient monitoring systems and to electronic medical records for better patient care. However, challenges of smartphone-based healthcare also exist, such as limited battery life, small screen size, risk of erroneous data input, computer viruses, loss or theft, and adverse impacts on physician-patient interactions (197). Reliance on critical software applications can only be considered well-placed if the technology is robust. Therefore, it is important that smartphone applications used for healthcare purposes are rigorously evaluated and refined prior to widespread clinical use.

4.2 Objectives

This study had three main objectives. Firstly, a key goal was to evaluate the performance of a real-time heart rate algorithm used by a digital stethoscope and smart device-based software in providing accurate and precise assessment of neonatal heart rate compared to an established gold standard, in patients in the neonatal intensive and special care setting. Secondly, it was important to test the usability of the electronic stethoscope and smart device application in clinical settings.

Thirdly, the study aimed to obtain audio recordings of chest sounds to develop and refine algorithms built to determine heart rate in real time.

4.3 Methods

4.3.1 Study Design and Approval

This was a prospective observational study in which a cohort of infants admitted to the special care nursery or neonatal intensive care unit of the Royal Women's Hospital in Melbourne, Australia were opportunistically recruited to participate. Written informed consent was obtained from a parent or guardian of the child and recorded on a signed consent form.

Prior to consent being obtained, written information about the study including the purpose of research, potential benefits and risks, ethics committee approval and data use policy was provided to the parent(s)/guardian(s) and read by them. The Human Research and Ethics Committees of the Royal Women's Hospital, Melbourne, Australia approved the study (RWH Project Number 13/45).

4.3.2 Setting

The setting was the neonatal intensive and special care nursery of the Royal Women's Hospital a large perinatal tertiary hospital located in the city of Melbourne in Australia. This neonatal intensive and special care unit has 60 neonatal beds. As a tertiary obstetric centre, both high and low-risk pregnancies and deliveries are attended to by the obstetric, newborn and midwifery teams at the Royal Women's Hospital. The hospital sees more than 9,000 deliveries every year (202). These deliveries occur inside dedicated birthing suite and operating theatre rooms. Supervised normal vaginal

deliveries, inductions of labour, instrumental deliveries and emergency and elective Caesarean sections are all performed. There are over 1400 admissions to the NICU each year of whom approximately three hundred are very low birth weight infants (<1500 grams at birth).

Within the neonatal intensive and special care nursery, almost all infants are routinely monitored using conventional technologies such as pulse oximetry and/or ECG. Staff are well-trained and familiar with applying these monitoring devices. This makes it the ideal setting in which to trial a new device for newborn and infant heart rate detection against gold standard devices which are utilised in both neonatal inpatient care as well as in delivery room assessment. Trialling new technologies for measurement of heart rate for children in this age group has been performed before in the neonatal intensive and special care with other novel devices, such as camera-based photoplethysmographs (175, 177, 178, 185, 186), reflectance pulse oximetry devices (180, 182) and a variety of sensor-based solutions (179, 187, 189, 203).

4.3.3 Participants

Participants were newborns and infants admitted to the neonatal intensive and special care nursery of the Royal Women's Hospital in Melbourne, Australia and who were being monitored using three lead ECG. Those with cardiac arrhythmias, extremely preterm individuals (< 26 weeks corrected gestation) where the unit policy for skin protection is to avoid monitoring with ECG leads and unstable infants receiving high frequency oscillatory ventilation were excluded. Infants supported by conventional ventilation, inotropic medications and non-invasive ventilation such as CPAP and heated and humidified nasal high flow therapy were eligible for inclusion in the study.

Given the absence of previous trials assessing the novel digital stethoscope device to be used in the study, a power calculation was not performed. Instead, the original aim was to recruit a minimum of fifty infants as a convenience sample. The demographic characteristics of infants included in the study are discussed below.

4.3.4 Procedures

Parent(s)/guardian(s) of eligible neonates and infants admitted to the neonatal intensive care unit or special care nursery of the Royal Women's Hospital were approached by a study team member who was a nurse or doctor with experience in neonatal care. Witnessed written consent from the legal guardian of the infant to be studied was obtained before any procedures were carried out. Recruitment occurred when study team members were available to discuss the study in person with parent(s)/guardian(s) in order to provide information and gain consent, and this occurred during regular business hours as well as after hours and on weekends.

After consent was obtained, the clinical team were consulted to determine whether the infant was suitable to study at that time. If not, the study was postponed until the clinical team were satisfied that the infant was stable and could safely tolerate the additional handling associated with the study.

Basic demographic data were collected on each infant. Information collected included birthweight, current weight, gestational age at birth, current gestational age, gender, relevant cardiorespiratory diagnoses and type of respiratory support being given to the patient.

Figure 14. Stethocloud™ v2 Digital Stethoscope connected to smartphone.

Study team doctors applied the Stethocloud™ v2 digital stethoscope head to the exposed precordium of supine infants. The digital stethoscope was connected to an Apple iPhone™ 5s, running the Neorate 0.1a software application (Stethocloud Pty Ltd; https://clinicloud.com) which displayed a real-time heart rate on the screen.

The digital stethoscope itself was composed of an electret (electrostatic capacitor-based) microphone, housed in a hollow metal stethoscope head with the same plastic diaphragm found in modern binaural stethoscopes. Wiring protected by plastic sheathing connected the microphone to the smartphone via the 3.5mm audio jack, the port commonly used for headphones and hands-free devices, shown in Figure 14.

Infants were simultaneously electrocardiographically monitored with a 3-lead ECG (Philips Intellivue MP70, Philips Healthcare, Andover, USA). The Neorate 0.1a software application was initiated once a stable ECG trace was obtained and it was run for approximately ninety seconds. In addition to displaying a calculated heart rate (averaging time of three seconds), the Neorate software application also collected the raw audio / sound captured by the digital stethoscope microphone, in the format of a waveform file (also known as a .WAV file).

At any given time during the videorecording, the ECG and smartphone displayed a number representing measured heart rate or on occasion, a signal indicating an inability to detect heart rate. To capture this information, a Samsung ST150F digital camera (Samsung Electronics Co. Ltd, Suwon, South Korea) was used to take a videorecording of the simultaneous displays of both the Apple iPhone™ 5s and ECG screens over the ninety second recording time. Cleaning of the stethoscope and smartphone device with 70% isopropyl alcohol was conducted between patient use.

Recordings were considered eligible to undergo further analysis based on our a priori definition of reliability; (a) Neorate application heart rate obtained within thirty seconds of activating the software on the iPhone and (b) a minimum of ten seconds of heart rate data output from the Neorate application during the ninety second recording period. If recordings did not meet these requirements, then their data was not included in the analysis. Spectrograms (also known as spectrographs) characterise the frequency, intensity and time length of audio sounds in a visual representation of data, facilitating further analysis and comparison.

Spectrogram generation using Audition CC software (© Adobe Systems, San Jose, California, United States of America) was utilised on an ad-hoc basis for a small number of recordings only, to illustrate interesting features such as cardiac murmur waveforms (see Figure 18 and relevant discussion below).

All video recordings were loaded onto secure computers. The videos obtained were reviewed and heart rate values were extracted every second by incrementally advancing and pausing the video in order to note down the numbers displayed on the captured digital stethoscope and ECG heart rate screen displays. ECG trace quality, rated good or poor, was also noted at the one-second intervals. This was done by both an independent offsite investigator, and in the same fashion by a separate second person who was a study team member, in order to ensure correct values were obtained. This process was considered important as a quality assurance check. Disagreements were resolved by reviewing the video in question.

A Microsoft™ Excel spreadsheet was used to tabulate the extracted values. The heart rate values obtained by the ECG and novel stethoscope device at the same point in time in the same recording were considered to be paired values. The spreadsheet also recorded each patient's demographic data, type of respiratory support the patient was receiving at the time of recording, and relevant cardiorespiratory diagnoses. In particular, infants with a history of cardiac murmur, clinically suspected cardiac lesions, and structural abnormalities found on echocardiogram had this information noted. Information about concentration of oxygen delivered to the patient was not collected and neither was information regarding inotropic drug infusion(s).

4.4 Statistical Analysis

Using the fifty included recordings, time in seconds from application activation to first digital stethoscope heart rate display was noted, with median and interquartile range (IQR) values calculated. Bland Altman analysis was conducted because this technique is based on the philosophy that the key to method comparison studies is to quantify disagreements between individual measurements in order to help the clinician interpret a measurement (204). Therefore, a Bland Altman plot was constructed to assess the level of agreement between the ECG heart rate and digital stethoscope heart rate. This method plots the difference between these two values against their average (205). An individual analysis of the mean difference between ECG and digital stethoscope heart rate was also constructed for each infant's recording.

4.5 Results

Sixty-five participants were recruited and consented, using the recruitment and consent process described above. Eight patients were discharged from the Royal Women's Hospital neonatal care unit prior to being recorded. Some of these eight infants were discharged home and others were transferred to external special care nurseries. Therefore, fifty-seven infants were studied. The number of recordings considered failed attempts according to our *a priori* definition was seven; for six infants, the digital stethoscope did not capture heart rate within thirty seconds of activation, and for one infant the digital stethoscope did not record greater than ten seconds of output, leaving fifty infants in total (Figure 15).

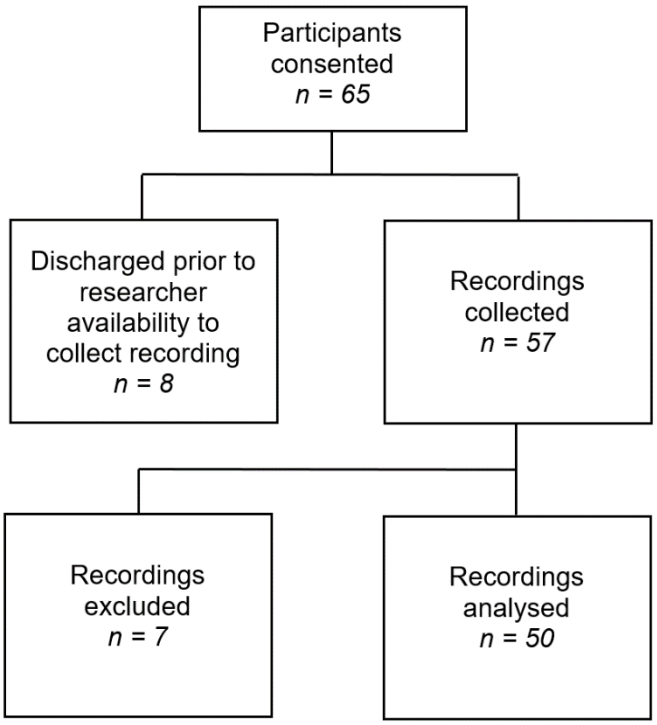


Figure 15. Participant recruitment and analysis for neonatal intensive and special care study.

A summary of the demographic profile of infants who had recordings analysed is shown in Table 2. Half of these fifty infants were female and half were male. Their weight ranged from 656 to 3690 grams. The median weight was 1891 grams. The corrected gestational age at time of recording ranged from 26.7 to 54.7 (median 34.1) weeks. Thirty-four per cent of included newborns were receiving respiratory support defined as conventional ventilation, continuous positive airway pressure or high flow nasal oxygenation. Forty-four per cent were receiving some form of respiratory intervention. Five infants were receiving low flow nasal prong oxygenation, seven were receiving nasal mask continuous positive airway pressure ventilation, three were intubated and conventionally ventilated, and seven were receiving high flow nasal prong therapy.

Study characteristics (N=23)	**Median [Range]**
Female sex, n (%)	25 (50%)
GA (weeks+days)	30^{+5} [23^{+5} to 39^{+4}]
Corrected GA (weeks+days) at time of recording	34^{+1} [26^{+5} – 54^{+5}]
Birthweight (grams)	1528 [485 – 3960]
Weight at time of recording (grams)	1891 [656 – 3690]
Respiratory Interventions	**n (%)**
Conventional ventilation (intubated)	3 (6)
CPAP	7 (14)
High flow nasal oxygenation	7 (14)
Low flow nasal oxygenation	5 (10)
None	23 (56)
Cardiac Lesions	**n (%)**
Patent Ductus Arteriosus	8 (16)
Tetralogy of Fallot	1 (2)
Isolated ventricular septal defect	1 (2)
Isolated valvular abnormalities	2 (4)
No lesion suspected	38 (76)

n=number of infants; sec=seconds; IQR=interquartile range; GA=gestational age

Results are n (%) or median (range)

Table 2: Demographics of infants analysed in the neonatal intensive and special care study.

Twenty-four per cent had known or clinically suspected cardiac lesions, the commonest of which was an isolated patent ductus arteriosus (n = 7). Other cardiac diagnoses included Tetralogy of Fallot (n = 1), ventricular septal defect with patent foramen ovale (n = 2), suspected tricuspid regurgitation (n = 1) and mitral valve thickening with atrial clot/vegetation (n = 1).

The seven infants with recordings that were deemed failed attempts did not differ significantly from the fifty infants recruited for the study with regard to their rate of cardiac pathology or need for respiratory support. Four of them (57%) were receiving respiratory/oxygenation support, two in the form of invasive ventilation through endotracheal tubes, one on high flow nasal prongs, one wearing low flow nasal prongs, and one receiving continuous positive airway pressure via nasal mask. Two had known/suspected cardiac lesions (both patent ductus arterioses). Their recorded weights were also similar, and ranged from 1130 grams to 3834 grams (median weight 1350 grams).

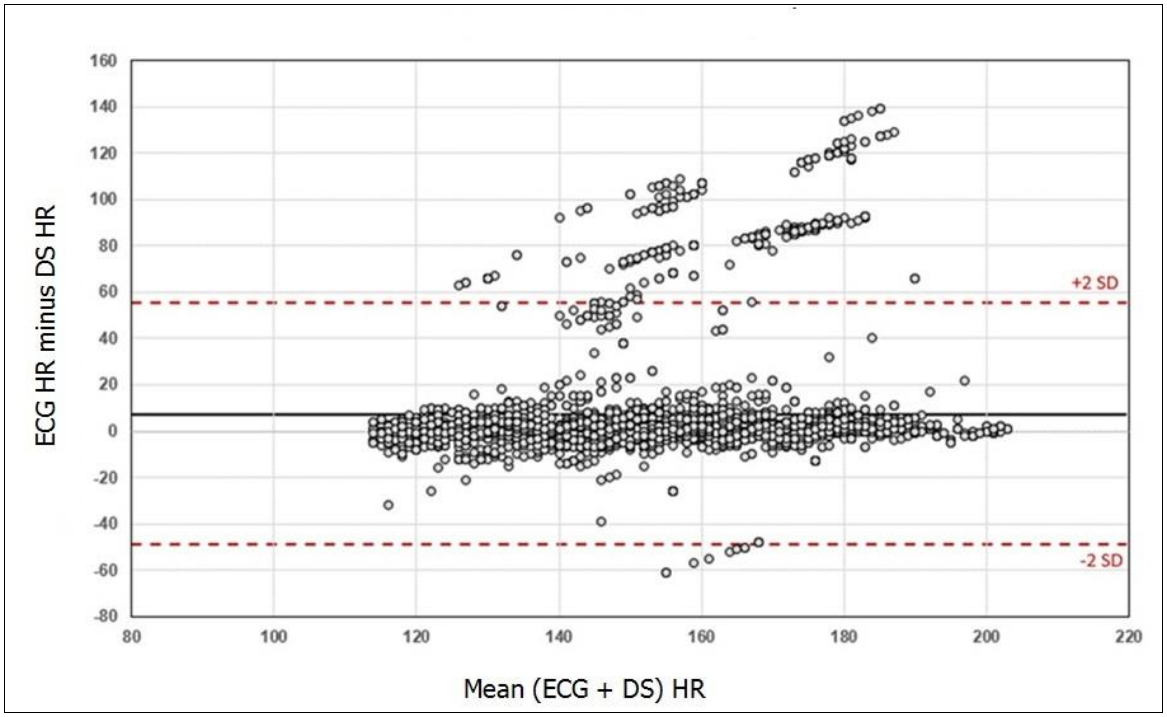


Figure 16. Neonatal intensive and special care study Bland Altman analysis.

The Bland Altman analysis, shown in figure 16, compared 3972 paired data points compiled from fifty recordings and showed that the mean difference (±2SDs) between ECG and digital stethoscope heart rate was 7.4 (48.5) bpm. The median (IQR) time to first digital stethoscope heart rate display was 4.8 (1 to 7) seconds. Individual recording analysis, shown in Figure 17, demonstrated that 76% of recordings had a mean difference between DS and ECG heart rate of less than ten bpm and that only six recordings had a mean difference exceeding twenty bpm.

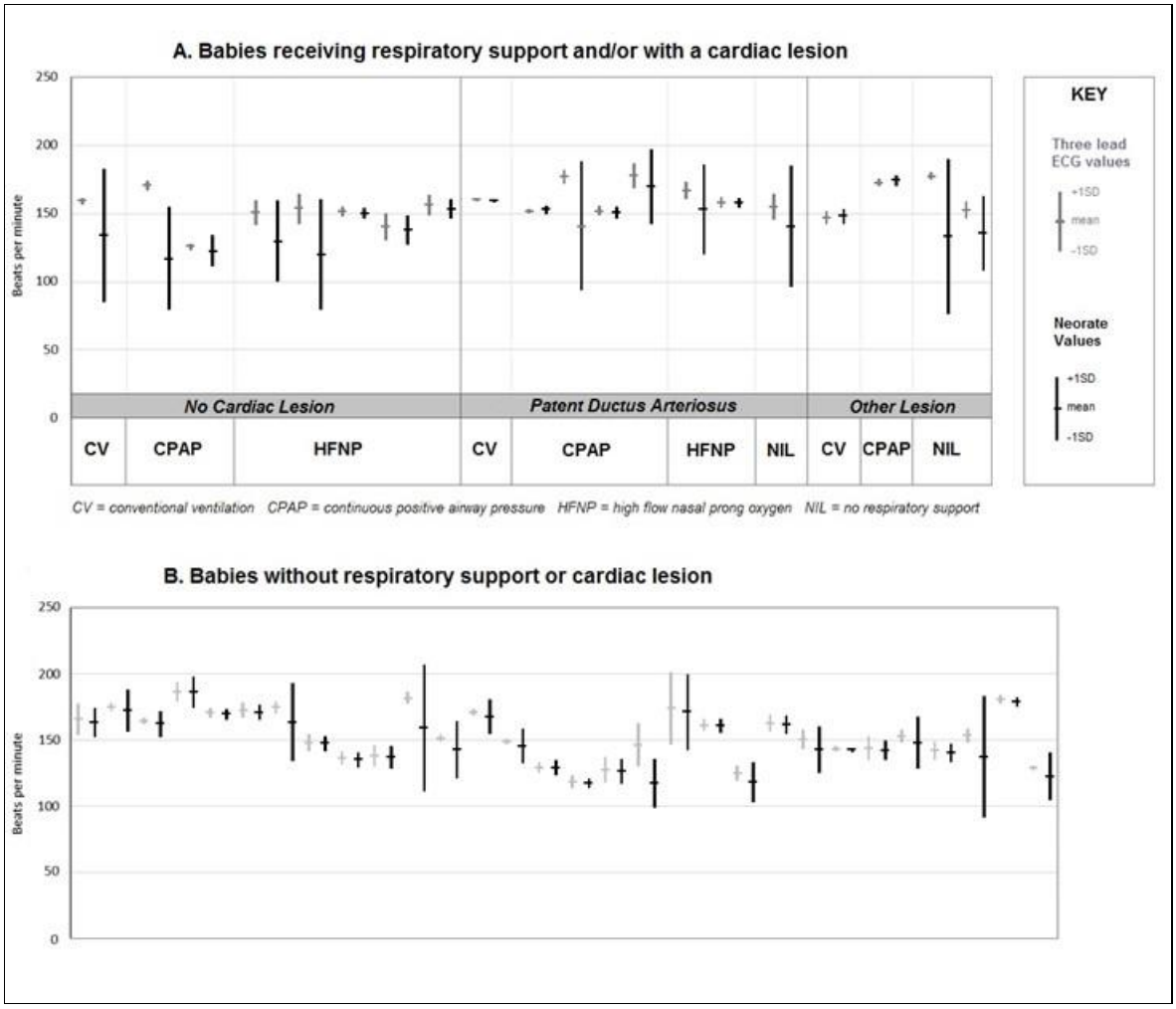


Figure 17. Heart rate values obtained from all individual recordings.

4.6 Discussion

Whilst an electronic stethoscope has been used to record neonatal bowel sounds (206), to the study team's knowledge this was the first time digital stethoscope technology for real-time heart rate analysis had been studied in newborn infants.

It was demonstrated that digital stethoscope and smart device technology can quickly establish neonatal and infant heart rate, usually taking less than five seconds. In regards to accuracy, it was found that the mean difference compared to ECG-derived heart rate was less than eight bpm.

Digital stethoscope technology in this study was more rapid than alternative methods of measuring newborn heart rate. For example, pulse oximetry generally takes longer than one minute to display heart rate (136) compared to digital stethoscope heart rate acquisition which occurs within ten seconds in most cases. Pulse oximetry is more accurate with a reported mean difference (±2SD) of -0.4 (±12) bpm compared with ECG (118). However, the accuracy of the digital stethoscope heart rate was greater than traditional rapid methods used to assess heart rate. Chest auscultation and umbilical cord palpation have been shown to underestimate ECG heart rate by 14 and 21 bpm respectively (80), and brachial and femoral pulse palpation are even more inaccurate (73). In contrast, the mean difference (SD) between digital stethoscope heart rate displayed on the smart device and ECG heart rate was 7.4 (24) bpm.

The study was limited by its sample size, opportunistic recruitment method and the characteristics of the recruited population. In particular, no participants had a heart rate less than one hundred bpm on ECG assessment, so conclusions about ability to detect bradycardia cannot be drawn. Strengths of the study included an *a priori* definition of device failure, a demographically diverse group of recruited infants and use of video footage which permitted objective, easily-extracted and well-recorded comparison data of device-detected heart rates.

For the purposes of this study, digital stethoscope heart rate output was considered inadequate if the device failed to capture heart rate within thirty seconds of activation or did not record more than ten seconds of output over the course of the recording. These limits were thought to constitute parameters for device performance that would be clinically relevant in its potential application in the delivery room and other settings.

Although no difficulties with quality of ECG trace were encountered, in twelve percent of infants, inadequate digital stethoscope heart rate output was obtained. Through post-hoc recording analysis, loss of contact of the stethoscope head with the precordium and accidental loosening of the wiring connection to the digital stethoscope head were identified as key reasons for this. These highlight potential challenges to the device's use that health care providers should be aware of. Other potential risks to successful software application use include interruption due to telephone calls to the smartphone, memory overload and timed screen lockout. Choosing a suitable smart device with appropriate settings can eliminate these risks, although other difficulties may not be so easily mitigated. The newly born infant in the delivery room may be wet, have a polyethelene sheet or bag applied for thermoprotection and/or be undergoing resuscitation resulting in chest wall movement, all of which have the potential to influence device failure rate. Assessing these factors can only be done through a study of this device and technology in the delivery room.

The Bland Altman analysis shown in Figure 16 depicts a series of outlying values where noted ECG minus digital stethoscope heart rate values were approximately half that of the infant heart rate. Reviewing videos of the digital stethoscope recordings identified these to be largely caused by occasional halving of the digital stethoscope heart rate compared to ECG heart rate, lasting for approximately five seconds during several recordings. This was suspected to be due to a software issue, as the software used algorithms that heavily rely on identification and clear differentiation of the S1 and S2 heart sounds to register a single heartbeat. Refining algorithms may therefore significantly improve accuracy. Interestingly, it was found that the presence of adventitious sounds from external noise sources, or from cardiac murmurs, was not

associated with inaccurate digital stethoscope heart rate. This may be due to the specific low frequency of neonatal heart beats (207) permitting filtering out of higher frequency sounds.

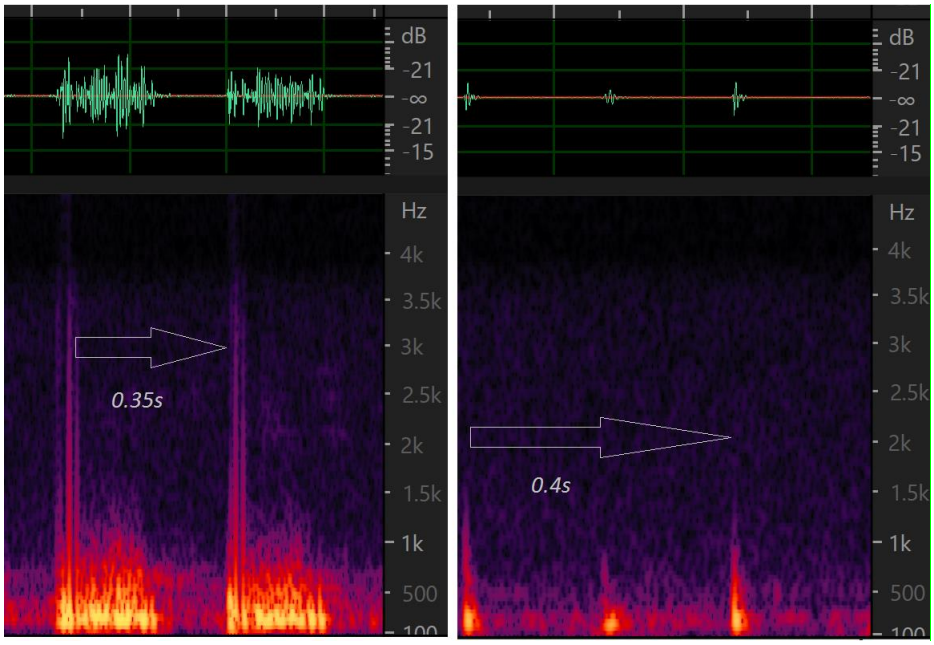


Figure 18. Spectrogram of an infant with a cardiac murmur from Tetralogy of Fallot (left) compared to spectrogram of an infant without a cardiac murmur (right).

There may be scope for automated murmur detection and heart rate variability analysis, which has been studied in neonatal and adult populations (207-210), to expand the clinical utility of this technology. As an example of what the device is capable of capturing, Figure 18 shows a spectrogram of heart sounds collected from an infant with a murmur related to Tetralogy of Fallot next to a spectrogram of heart sounds collected from an infant without a cardiac murmur, with R-R intervals marked on each. Spectrographs can be produced relatively quickly, for example at the time of a recording, and if found to correlate with a particular abnormality, may be useful in diagnosis or in monitoring. What is evident in Figure 18 is the noticeable presence of

higher intensity captured sound energy in the frequency range up to approximately 1.2 kilohertz in systole in the infant with Tetralogy of Fallot obscuring the second heart sound, not present in the infant without a murmur. Automated detection of such sound abnormalities, if developed, could potentially be used to screen neonates for the presence of cardiac murmurs. It may be possible in children to differentiate pathological murmurs from innocent ones using digital stethoscopes (211).

The relative portability and affordability of this digital stethoscope and smart device technology (200) make it attractive for global use, especially given the widespread uptake of mobile smartphones (198). This device may prove useful in low-resource hospitals or in the hands of those conducting postnatal infant checks in both developing and developed nations. Furthermore, detecting heart rate of newborns in the delivery room rapidly and accurately is of high clinical importance as heart rate is a critical sign which guides resuscitation (137). Therefore, this device may prove useful in the delivery room setting as well. However, to perform adequately in delivery scenarios, improvements are required. In the delivery room setting, device robustness is undoubtedly important. Furthermore, software modifications to improve accuracy prior to trials in the delivery room setting would certainly be advantageous. Delivery room trials should include both low-risk term and high-risk preterm infants born in both operating theatres and birthing suites.

4.7 Conclusion

In summary, the study findings showed that the digital stethoscope and smart device technology to measure newborn and infant heart rate was rapid and relatively accurate in stable infants in the neonatal intensive and special care setting. However, before wider clinical application of the device and software is recommended, improvement in precision is required, with software algorithm improvement being a key component of this. In addition, design improvements such as sturdier cable connections are required to minimise device failure rates and improve overall usability.

Chapter Five: Evaluation of a Digital Stethoscope for Assessment of Heart Rate in Newborns in the Delivery Room

5.1 Background and Rationale

Prompt and accurate assessment of a newborn's heart rate is very important in guiding decisions during neonatal resuscitation (29, 137). There are various ways to assess the heart rate clinically, including manual auscultation and pulse palpation at various sites such as femoral, brachial or umbilical cord (73, 82, 194). As these methods all have shortcomings, various electronic monitoring devices for obtaining heart rate have been used in the delivery room (99). Pulse oximetry is commonly used (89). However, some authors have noted an underestimation of heart rate using this technology (133). Others have documented substantial challenges in successful oximetry probe placement and connection to generate a reliable reading quickly enough to be able to guide decision-making in the crucial first couple of minutes of resuscitation (100). Continuous ECG represents the gold standard for accuracy in heart rate determination, and some studies have demonstrated it can be applied more quickly than pulse oximetry (96, 98). However, there is still a delay to reliable heart rate detection (100), and currently ECG is not commonly available in delivery rooms (82). Furthermore, leads cannot be easily applied in the sterile field or over the top of a polyethylene bag for preterm infants.

Using a digital stethoscope to obtain delivery-room newborn heart rate has theoretical advantages over traditional methods (99). As the stethoscope head is applied in the same fashion as when using a standard binaural stethoscope, it is a technology with a strong element of familiarity, that can be rapidly applied. An automated counting algorithm on an attached smart device may decrease bias and inaccuracy compared to standard methods.

Furthermore, the use of smart devices is widespread even in resource-limited settings, where cost may prohibit use of ECG or pulse oximetry (199). Therefore, using a digital stethoscope may improve speed and accuracy of newborn heart rate acquisition in both developing and developed world settings compared with other devices and methods commonly used in the delivery room.

The previous study of a digital stethoscope and smart device for infant heart rate detection in the neonatal intensive and special care setting demonstrated the rapidity of heart rate detection and real-time display which can be achieved by such a device, as well as its ease of use. However, the device was deemed to be too inaccurate for clinical application and refinement was recommended (183). In response to this, a transdisciplinary team was formed, allowing technology designers accompanied by doctors to enter the delivery room setting so as to better understand the challenges of this clinical environment. A number of changes to the device were made. The hardware was significantly altered, with a custom-made aluminium stethoscope head made to house the electret microphone, lined with material to insulate the microphone from noise that could be picked up through the casing rather than through the stethoscope diaphragm. Cable connections were improved to prevent issues of dislodgement and disconnection noted in the previous study. An audio pre-processing computer chip was added inside the stethoscope head to improve quality of sound data transmission to the smart device. Other additions included a lithium ion battery to power components and a light-emitting diode to signal to the user when the device was ready for use with sufficient battery charge.

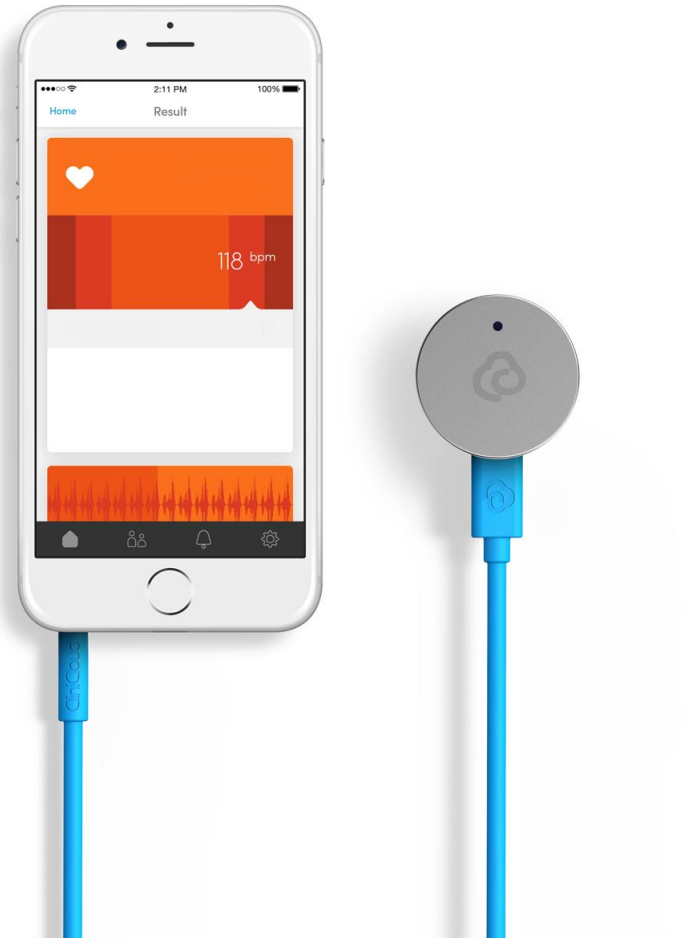


Figure 19. Clinicloud™ Digital Stethoscope connected to smartphone.

The smart device software was also revised. Algorithms were changed to improve filtering of extraneous noises picked up by the microphone in order to minimise the interference these sounds caused.

Accuracy of heart rate detection was also improved by implementing a dynamic rather than fixed method of determining the threshold for loudness of the S1 and S2 heartbeat components required for them to be counted as true beat components by the software, addressing a design fault thought to have contributed to the intermittent approximate halving of heart rates detected using the digital stethoscope in the previous study. Given the significant steps taken to improve the device as a whole, it was considered appropriate for a delivery room trial to proceed. In order to re-evaluate accuracy and robustness prior to use in higher-risk deliveries, this trial was limited to babies born by elective caesarean section.

5.2 Objectives

This study had two main objectives. The first goal was to evaluate the performance of the improved real-time heart rate algorithm used by the novel digital stethoscope and smart device-based software in providing accurate assessment of newborn heart rate in the delivery room compared to an established gold standard. Secondly, it was important to test the usability of the improved version of the electronic stethoscope and smart device application in this demanding clinical setting.

5.3 Methods

5.3.1 Study Design and Approval

This was a prospective observational study which recruited a cohort of newborn infants delivered by elective caesarean section at the Royal Women's Hospital in Melbourne, Australia. Written informed consent was obtained antenatally from a parent or guardian of the child and recorded on a consent form which was signed by them.

Prior to consent being obtained, written information about the study including the purpose of research, potential benefits and risks, ethics committee approval and data use policy was provided to the parent(s)/guardian(s) and read by them. The study was approved by the Human Research and Ethics Committees of the Royal Women's Hospital, Melbourne (RWH Project Number 13/45).

5.3.2 Setting

The setting was the Royal Women's Hospital, a large perinatal tertiary hospital located in the city of Melbourne in Australia. The hospital has more than 9 000 deliveries every year (202). Some study procedures were carried out inside the operating theatres, whilst recruitment and consent processes were undertaken inside the hospital but outside of operating rooms.

5.3.3 Participants

Participants were infants born by caesarean section at the Royal Women's Hospital in Melbourne, Australia. Infants delivered by planned elective caesarean section were eligible for inclusion. Also excluded were babies born at less than 34 weeks' gestation, and infants delivered urgently by caesarean section. The key reason for these exclusions was to ensure this trial tested the device in lower-risk deliveries in the operating room environment rather than in high-risk deliveries.

5.3.4 Procedures

Expectant parent(s) of eligible infants to be born at the Royal Women's Hospital were approached by a study team member with experience in neonatal care and resuscitation, in order to discuss the study and obtain consent for participation.

Written consent from the legal guardian of the infant to be studied was obtained prior to the study. Recruitment occurred when study team members were available to discuss the study in person with parent(s). This occurred during regular business hours as well as after hours and on weekends.

If the parent(s) consented to the study, a researcher attended the birth to set up the equipment and measure the heart rate with two devices. As soon as the infant was brought to the warming bed by the midwife, neonatal ECG leads (Kendall, Medtronic, Minneapolis, MN, USA) were applied and connected to a handheld ECG monitor (IntelliVue X2, Philips, Suresnes, France). The ECG monitor has an averaging time of two seconds. Then the smart device application for the Clinicloud Digital Stethoscope (NeoRateRT, Clinicloud, Melbourne, AUS) was started. This calculates the heart rate each second by averaging the heart beats of the last five seconds, and evaluates signal quality. The signal quality evaluation was based on the regularity of the detected heart sound. In case of low signal quality, the value for the heart rate was displayed in red and if no regular heart rate could be detected, 'N/A' was displayed. The display screens of both devices (ECG and digital stethoscope smart device) were video-recorded. As soon as all devices and the video were running, the stethoscope head was put onto the infant's chest left of the sternum to auscultate the heart (Figure 20). The time the stethoscope was put on and taken off the chest was recorded. Crying was clearly audible on the video and the time crying started and finished was documented.

Figure 20. Clinicloud™ Digital Stethoscope applied to infant's praecordium.

Heart rate was recorded for sixty seconds after the first displayed value on the digital stethoscope smart device. If there was no heart rate displayed after thirty seconds, the attempt was considered to have failed. After the allotted time the devices were disconnected and the baby was wrapped and transferred to the mother as per standard care.

Basic demographic data were collected on each infant. This included birthweight, sex, gestational age at birth, and details of any resuscitation provided. The video recordings were then analysed post-hoc by comparing the displayed values of the two devices every second.

Given the absence of previous delivery room trials assessing this iteration of the digital stethoscope device (or indeed any digital stethoscope device), a power calculation was not performed. Instead, a convenience sample of paired recordings of thirty infants was chosen to provide clinically meaningful data.

5.4 Statistical Analysis

The Bland-Altman method (205) was used to compare the heart rates derived from the digital stethoscope and ECG devices. The correlation between the two modalities was assessed using a Pearson's r statistic. Data was first analysed using all data points available and subsequently after the exclusion of data during crying periods, defined as during and within five seconds of crying. All data was analysed using R statistical software, version 3.3.1.

5.5 Results

In the study period, consent was obtained for 44 patients, although seven were subsequently excluded from analysis for the following reasons: ECG unsuccessful in obtaining heart rate (n=3), equipment unavailable (n=3), researcher unable to attend birth (n=1).

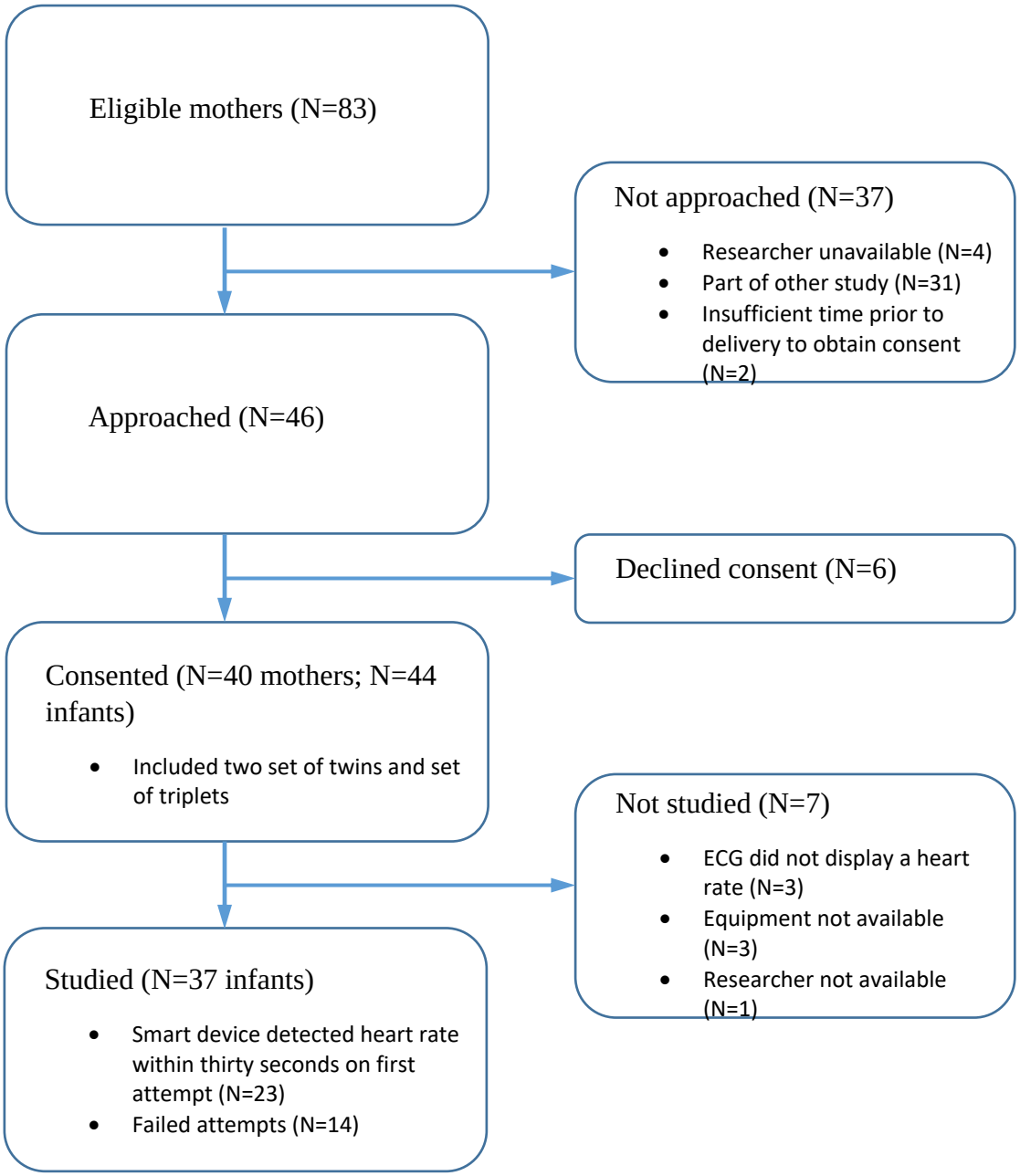


Figure 21: Participant recruitment and analysis for delivery room study.

Thirty-seven video recordings were taken and underwent analysis as described above. The demographic characteristics of these infants is shown in Table 3 below. Almost half were male, and the median gestational age was 39 weeks (range 34.3 to 40.1 weeks). Median weight was 3.23 kilograms, with all babies weighing greater than two kilograms at birth.

Study characteristics (N=37)	Median [IQR]
Male sex, n (%)	17/37 (45.9%)
GA (weeks+days)	$39^{0/7}$ [$37^{3/7}$ to $39^{2/7}$]
Weight (grams)	3230 [2895 to 3645]
Apgar at 1 minute	9 [9 to 9]
Apgar at 5 minutes	9 [9 to 9]
Time to stethoscope on chest, from birth (sec)	85 [65 to 123]
Time to start recording, from birth (sec)	89 [69 – 128]
Time until heart rate displayed, from digital stethoscope activation (sec)	7 [5 – 11.5]

n=number of infants; sec=seconds; IQR=interquartile range; GA=gestational age

Median values and IQRs are depicted for most variables. Sex is depicted as total number and percentage of male participants.

Table 3. Study characteristics of included infants.

The digital stethoscope was able to detect a heart rate at first attempt (ie. within half a minute of application) in 23 of 37 infants (62%). In comparison, at the time the video was started (roughly 10 to 15 seconds after application of the ECG electrodes), the ECG had heart rate data available in 24 of the 37 infants (65%). The fourteen infants for whom the digital stethoscope did not display a heart rate were all crying before and/or during the initial thirty seconds of placing the digital stethoscope on the infant's chest. More specifically, 89% of the data points where the digital stethoscope displayed no signal (N/A) in the initial thirty seconds of a recording were during or within five seconds of crying episodes.

The 23 infant recordings where the DS displayed a heart rate were included in further detailed analysis, including the Bland Altman analysis. Their demographic characteristics (outlined in Table 4) were not statistically significantly different from the original included thirty-seven infants.

Study characteristics (N=23)	Median [IQR]
Male sex, n (%)	12/23 (52.2%)
GA (weeks+days)	$38^{4/7}$ [$36^{6/7}$ to $39^{2/7}$]
Weight (grams)	3210 [2639 to 3495]
Apgar at 1 minute	9 [9 to 9]
Apgar at 5 minutes	9 [9 to 9]
Time to stethoscope on chest, from birth (s)	93 [79.5 to 185.5]
Time to start recording, from birth (s)	89 [69 – 128]
Time until heart rate displayed, from digital stethoscope activation (s)	7 [5 – 11.5]

n=number of infants; sec=seconds; IQR=interquartile range; GA=gestational age

Median values and IQRs are depicted for most variables. Sex is depicted as total number and percentage of male participants.

Table 4. Study characteristics of newborns included in the Bland Altman analysis.

For these 23 neonates, the digital stethoscope and smart device took a median (IQR) of 7 (5 to 11.5) seconds after application to display a heart rate. All instances where greater than ten seconds was required to detect a heart rate using the novel technology were in crying infants.

Of the 1380 available paired data points for the 23 infants (60 seconds each), the ECG failed to display a heart rate in seven and the digital stethoscope in 229 instances, 189 (or 83.3%) of which were during or within five seconds of crying episodes.

Digital stethoscope heart rate was highly correlated to ECG heart rate ($r=0.8508$; $p<0.0001$), when examining all available paired data points, as shown in Figure 22. If crying periods were excluded, the correlation between the two modes was stronger ($r=0.9320$; $p<0.0001$), as shown in Table 5.

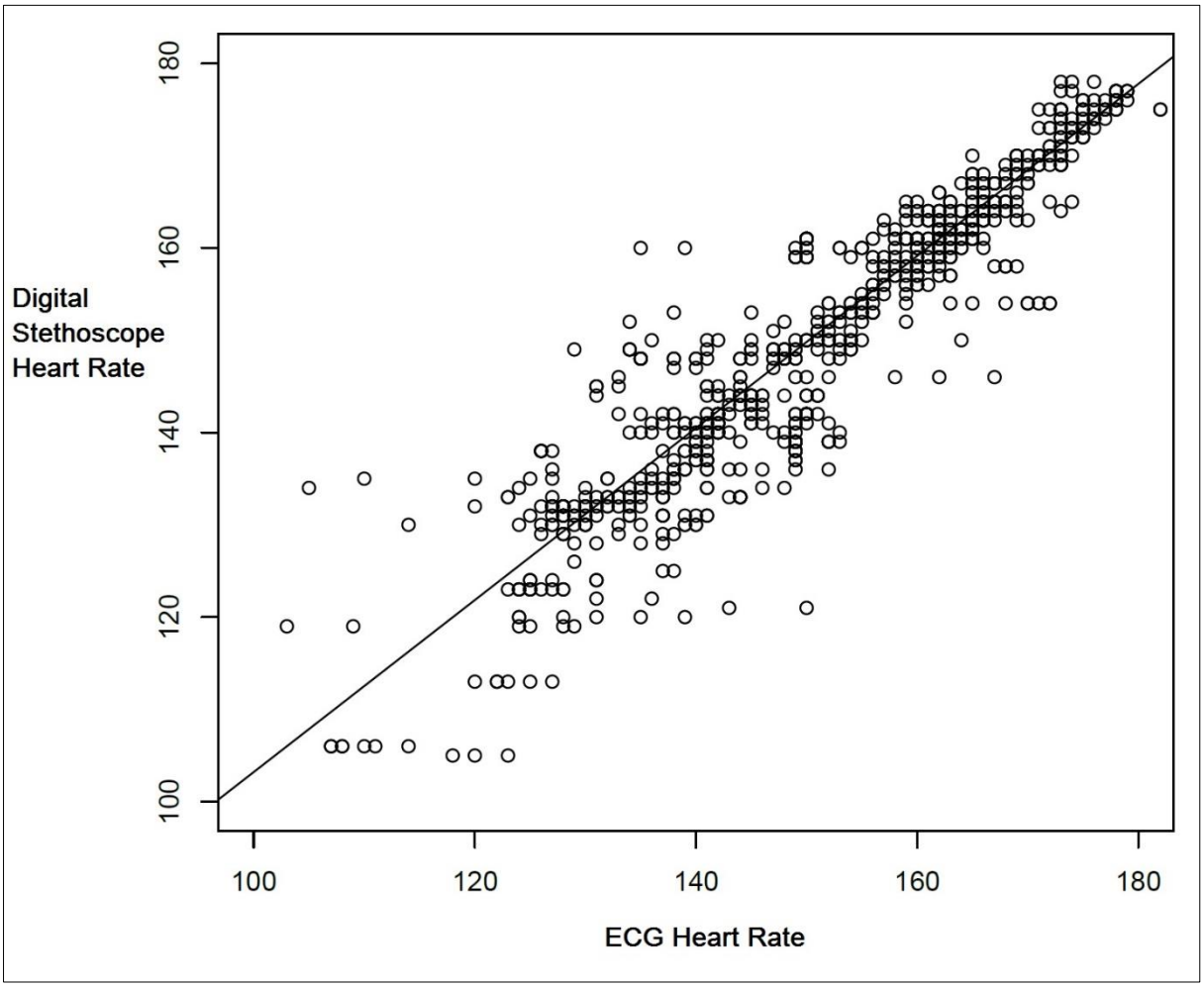


Figure 22: Correlation Between Digital Stethoscope and ECG heart rate (all data points).

Pearson's correlation between ECG and the DS	
All data points	*Non-Crying Periods*: After exclusion of crying and five seconds after crying
r=0.8508 (p<0.0001)	r=0.9320 (p<0.0001)

Table 4: Pearson's correlation between ECG and Digital Stethoscope heart rate

The median difference (IQR) between digital stethoscope heart rate and ECG heart rate was 1 bpm (-2 to 3). After excluding data from crying periods, the median (IQR) difference was 1 bpm (-1 to 3). Bland-Altman analysis revealed a mean difference (±2SD) between the two devices of 0.2 (-18 to +18) bpm including crying periods (Figure 23), and 1.0 (-11 to +12) bpm excluding crying periods (Figure 24).

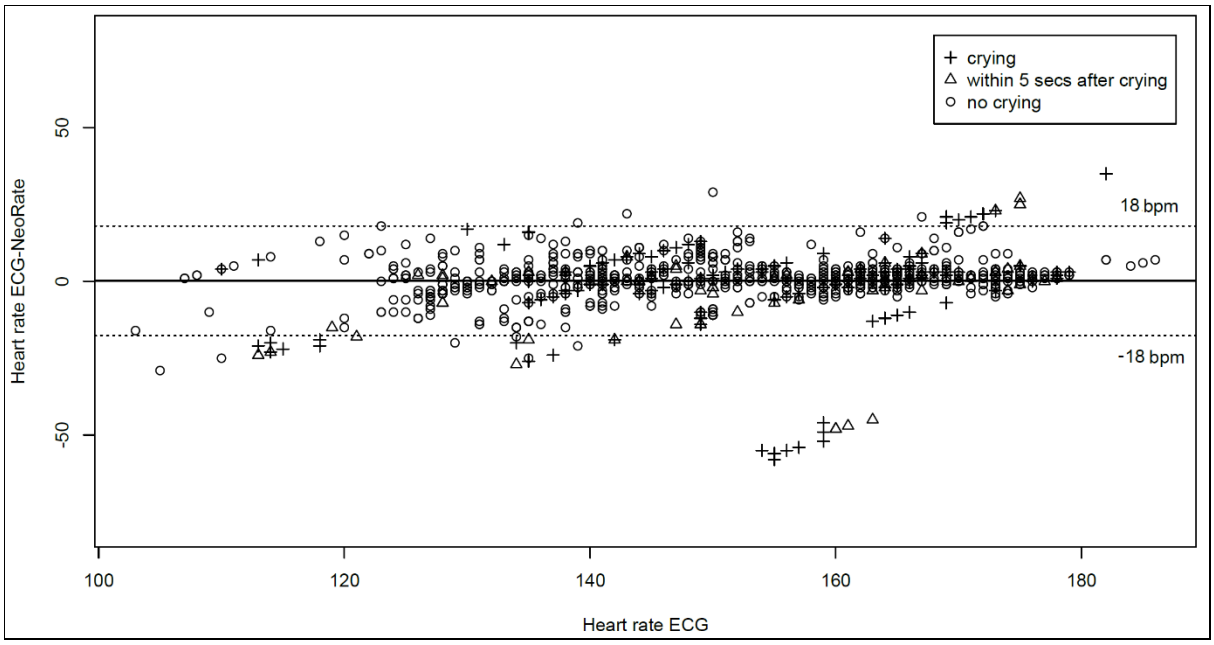
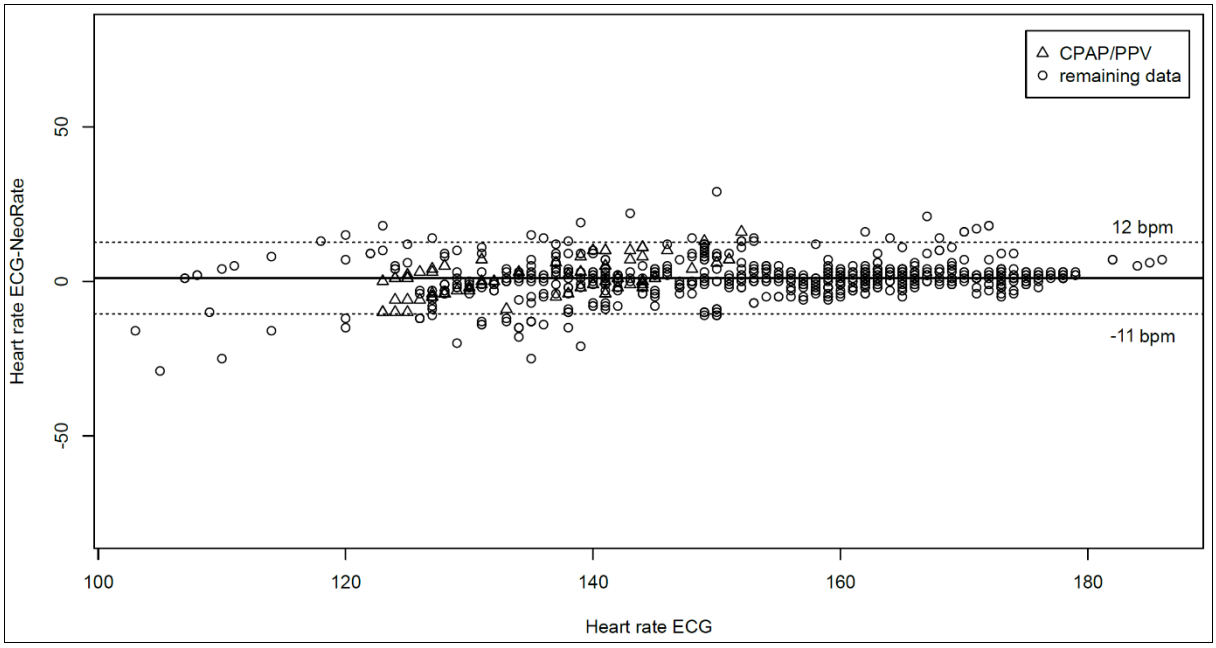


Figure 23: Bland Altman plot – all paired data points.



CPAP=continuous positive airway pressure; PPV=positive pressure ventilation

Figure 24: Bland Altman plot – data points during/within five seconds of crying excluded.

Two infants required positive pressure ventilation in the form of either continuous positive airway pressure delivered by face mask, or intermittent positive airway pressure also delivered by face mask. In these newborns, the digital stethoscope device was able to detect a heart rate for more than 90% of the 60-second recording time despite concurrent provision of positive pressure therapy. Although the number of data points was much lower, the heart rate values displayed by the digital stethoscope were of similar accuracy as those seen in infants who were not crying.

Most digital stethoscope heart rate values displayed were unaffected by poor signal quality. In fact according to the smart device application, less than five percent of displayed values were of poor signal quality; half of these were associated with crying periods.

5.6 Discussion

In this study, a novel approach to measuring an infant's heart rate was evaluated in the delivery room setting. This is the first time digital stethoscope technology for real-time heart rate measurement has been studied in transitioning newborn infants in the delivery room. This is the environment where obtaining an accurate heart rate with minimal delay is perhaps most important for this vulnerable patient group.

Globally, approximately 5% of newborns require respiratory support for successful transition, and decisions in newborn resuscitation are generally based on the ascertained heart rate (29). A newborn's heart rate is commonly assessed via auscultation and palpation of the umbilical cord with pulse oximetry and ECG used adjunctively, but all of these methods in practice have notable shortcomings; application of pulse oximetry and ECG leads in a way that establishes an accurate trace is often time-consuming (96, 100), whilst auscultation and palpation methods, although rapid, are less accurate (80, 83).

This study demonstrated that although the digital stethoscope and smart device combination was unreliable in detecting infant heart rate during crying periods, it was quite accurate during non-crying periods. Crying sounds occur across a wide range of frequencies which may interfere with detection of heart rate despite software filtering processes. Conventional binaural stethoscopes are similarly affected. However, crying is a sign of successful transition and indicates that resuscitation is not required (212). Therefore, inaccuracy of a device employed to potentially guide resuscitation interventions is unlikely to detrimentally impact its usefulness if that inaccuracy is limited to crying periods.

The novel device underestimated heart rate by a mean of equal to or less than one beat per minute. Comparatively, chest auscultation and umbilical cord palpation have been shown to underestimate ECG heart rate by seventeen and 22 bpm respectively (80, 83). Pulse oximetry has also been shown to underestimate ECG-derived newborn heart rate over the first few minutes of life (133). It is reassuring to note that on average, the digital stethoscope and smart device pair do not systematically underestimate heart rate, as this phenomenon may lead to inappropriate escalation of resuscitative therapies with unwanted and unnecessary complications, such as pneumothorax from positive pressure ventilation (78).

During non-crying periods, more than 95% of novel device heart rate data points were within ±12 bpm of the corresponding ECG value. This is more accurate than auscultation, umbilical cord palpation and pulse oximetry, which in similar delivery room studies have demonstrated a greater range of deviation of the heart rate values compared to ECG values over the first several minutes of life (80, 100, 133). Analysis by demographic subgroups based on sex, gestational age and birthweight categories did not reveal any association with greater or lesser digital stethoscope accuracy.

The digital stethoscope and smart device combination only detected a heart rate within thirty seconds in 23 out of 37 infants. Thirty seconds was chosen as the target timeframe as detection within this period was thought to be suitably rapid from a clinical point of view and a clear improvement in comparison to other heart rate monitoring devices in use such as pulse oximetry and ECG. Although this 62% success rate leaves room for improvement, it is quite comparable to ECG success rates in detecting heart rate accurately in a similar timeframe as shown in this and other studies (96, 98).

Furthermore, all instances in which a heart rate was not detected in thirty seconds (or indeed in which it took longer than ten seconds to detect a heart rate) were in crying infants. Additionally, poor signal quality data points (where the smart device application displayed a heart rate in red-coloured numerals) were also associated with crying periods; 50% of them arose during or within five seconds of infant crying.

This updated version of the digital stethoscope hardware and smart device software, was an undoubted improvement upon the previous prototype. Despite being tested in the more challenging environment of the delivery room, the new iteration demonstrated clearly improved usability and accuracy without compromising rapidity. The ongoing use of a digital display comes with the potential benefit of immediately informing the whole resuscitation team of the heart rate whereas trends observed by a clinician using auscultation or cord palpation need to be passed on to the lead resuscitator which can take time and may not always be communicated quickly and effectively (213). Although this study was not conducted upon subjects being born in a high-risk setting, there were multiple instances in which an infant requiring positive pressure ventilation was studied. The digital stethoscope was able to detect a heart for more than 90% of the 60-second recording time in these circumstances, and the heart rate values detected were as accurate as previously described for non-crying periods despite noises generated by positive pressure ventilation. This is likely because of the intermittent nature of such noise as well as its relatively high-pitched frequency in comparison to heart sounds, allowing signal processing sound filters to more easily eliminate this as a potential source of interference (207).

The accuracy of the digital stethoscope in measuring neonatal heart rate through a polyethelene bag remain untested at this stage. Furthermore, no infants in this study were bradycardic; heart rates ranged from 100 to 180 bpm. Although it may seem reasonable to assume that the digital stethoscope and smart device would work well in non-crying, bradycardic infants needing respiratory support directly after birth, the accuracy, rapidity and usability of the digital stethoscope in this particular subgroup of patients needs to be evaluated.

5.7 Conclusion

The digital stethoscope and smart device under consideration in this study was able to be successfully used in the delivery room, and the device was more accurate than clinical assessment. Although the technology was less reliable during crying episodes it was more accurate and precise in non-crying periods compared to other methods of heart rate detection commonly used in this setting. With further research and development, the digital stethoscope may become a cost-efficient alternative method of obtaining an infant's heart rate in both resource-limited and developed delivery room settings.

Chapter Six: Summary, Recommendations and Future Directions

6.1 Background and Rationale

Heart rate is defined as the number of cardiac ventricular contractions, conventionally counted over one minute. Together with blood pressure, temperature and respiratory rate, heart rate is considered one of the four 'vital signs'. Whilst quoted normal ranges in children vary (47), it is widely agreed that heart rate outside the normal range is an important diagnostic sign in a number of conditions. These include traumatic injury (214), adverse drug effects, serious infection (18), malignancy (19), circulatory volume depletion (for example through dehydration), organ failure (6, 7), and raised intracranial pressure (15). Although these conditions can affect adults and children of all ages and heart rate is relevant in cases across the various age groups in such instances, the importance of determining heart rate in young infants in particular has also been explored. Tachycardia has, for example, been found to be the most specific indicator of severe congestive cardiac failure in a cohort of infants with heart disease (25).

Around five percent of newborns fail to make a smooth transition in cardiopulmonary physiology from the intrauterine state to that required for extra-uterine life. These infants require some form of resuscitative intervention, often ventilatory assistance (27, 28). In such cases, heart rate guides the decisions of when and how to intervene with positive pressure ventilation and/or external cardiac compressions. Recommendations for these resuscitative choices are outlined in international guidelines that are based on the best-available evidence (137, 194).

Heart rate features as the most important vital sign guiding early decision-making because the newborn heart has an immature myocardium, underdeveloped autonomic nervous system and vulnerability to oxygen supply interruption (32, 33) which means that without adequate cardiac output, the heart rate will quickly fall, further impairing cardiac output in a self-perpetuating and potentially life-threatening spiral. A beneficial upward spiral is also possible; with effective ventilation, the heart rate will usually rapidly improve (33). Because of the relatively fixed stroke volume of the neonatal heart, it is chiefly heart rate improvement that leads to better cardiac output and tissue perfusion to vital organs (23). It is therefore clear that for newborns, rapid and accurate assessment of heart rate is critically important. Several methods for determining neonatal and young infant heart rate exist, each with particular advantages and disadvantages.

6.2 Summary

6.2.1 Summary of Established Methods of Monitoring Newborn and Infant Heart Rate

Established methods of monitoring neonatal and infant heart rate include pulse palpation, auscultation, ECG monitoring and transmission pulse oximetry. Doppler technology, long-used in determining foetal heart rate (124, 125), has also been used to monitor newborn heart rate (128, 129). A useful distinction to draw is that some forms of heart rate detection are performed intermittently, such as pulse palpation and auscultation, whereas others such as ECG monitoring and pulse oximetry assess the rate continuously.

In the neonatal intensive and special care setting, 3-lead ECG and pulse oximetry are commonly utilised (105). Significant disadvantages of ECG and pulse oximetry lead application include skin damage in infants (215) which can predispose to serious infection, and negative emotional impacts on mothers causing interference with breastfeeding and bonding (150). Motion artefact, despite being reduced through advanced signal processing techniques (91), can still frequently impede device performance (92). Whilst these technologies are also used in the delivery room, there is a substantial time delay between beginning to apply the ECG or pulse oximeter and accurately displaying the heart rate (100, 136). Because of this and because of the lack of equipment in resource-poor settings, the intermittent assessment methods of auscultation and umbilical cord palpation are commonly used in the delivery room setting (99). Unfortunately, these methods of assessing heart rate are unreliable (73, 80). These drawbacks have contributed to the interest in and development of novel technologies to assess this vital sign.

6.2.2 Summary of Novel Methods of Monitoring Newborn and Infant Heart Rate

Novel methods for monitoring newborn and infant heart rate use different technologies which seek to overcome different particular challenges and are at varying stages of development. Methods include camera-based photoplethysmography (175, 177, 178, 181, 185, 186), reflectance pulse oximetry (180, 182), laser Doppler methods (188), capacitive and load-cell sensors (174, 176, 179), piezoelectric sensors (173, 187, 189), and transcutaneous electromyography (184).

Transcutaneous electromyography combines the monitoring of infant heart rate and respiratory rate with direct assessment of diaphragmatic activity (184). Whilst accuracy

in comparison to conventional ECG was high when tested in a cohort of preterm infants (184), the reliance on use of transcutaneous leads attached to the skin means there is little advantage for heart rate monitoring alone offered by this technology over conventional techniques such as ECG or pulse oximetry.

Camera photoplethysmography and laser Doppler methods on the other hand aim to overcome the need for attaching monitoring leads to the infant altogether. Because of the vulnerability of neonates (especially preterm newborns) to skin breakdown from the attachment of such monitoring leads (146), these technologies have been most often trialled in this group. Camera photoplethysmography determines heart rate by amplifying small changes in the colour of skin occurring due to each heartbeat which are seen by the camera and then counted post-hoc, whereas laser Doppler vibrometry uses a focussed laser beam to detect the minute movements of the thoracic wall occurring with cardiac activity (188). Although a systematic review of eligible scientific articles shows that camera photoplethysmography tends to outperform laser Doppler vibrometry with regard to accuracy for monitoring neonatal heart rate, the technology still faces major challenges posed by the extremely low strength of the colour-change signal, particularly under low lighting conditions, and by motion artefacts (216). Primarily because of the latter, the technology is unsuitable for use in the delivery room environment, where the infants most in need of heart rate monitoring are those undergoing resuscitation (29) which necessitates their frequent movement by the clinician.

Reflectance pulse oximetry, however, is designed specifically to be used in the delivery room (182). With significant modifications from transmission pulse oximetry technology, the reflectance version allows light emitting diodes and the sensor to be located on one planar surface of the probe whilst maintaining the capability to detect pulse rate and oxygen saturation. Over a hundred infants from newborn intensive and special care units have been involved in trials of reflectance pulse oximetry in the form of either an abdominal belt (180) or forehead sensor (182). Data from these stable infants shows a correlation between reflectance pulse oximetry-derived heart rate and that found by ECG acceptable for clinical purposes, but in both studies, large segments of data were excluded for various reasons. This makes it difficult to truly assess the proportion of time in which pulse oximetry devices are accurate versus unsuitably inaccurate. The results of further testing may shed light on this, as well as the aptness of the technology for use in the delivery room.

A variety of piezoelectric and capacitive sensors have been evaluated for infant heart rate detection, mainly to use for monitoring that occurs over an extended period of time in a stable setting, such as the intensive/special care or home environment. The aim of the development of such sensors is to provide a non-invasive clinical and research tool able to provide this monitoring in lieu of conventional methods requiring attachment of probes directly to the infant. Four studies used sensors physically located within the infant's mattress or bedding surface (176, 187, 189, 203), and two placed them underneath the legs of their cot (173, 174). However only one study, entirely limited to premature neonates, determined sensor-based heart rate in real time in comparison to ECG (189); the others performed post-hoc heart rate comparison, indicative of their technology being in a developmental phase.

Because all studied sensors relied upon the detection of tiny movements of the patient's body occurring due to the heart beating, they were adversely affected by other movements. Such interference was generated primarily by infant movement rather than that generated by passers-by (173, 189), which nonetheless limits delivery room applicability. The promise of advanced signal processing techniques provides some hope that interfering signals may be counteracted to an extent permitting clinical use in other settings (189).

A theme unifying the various non-contact novel heart rate determination methods is the susceptibility to movement artefact, a challenge likely to be much greater in the delivery room environment in comparison to other settings. Novel contact techniques such as reflectance pulse oximetry and transcutaneous electromyography also have limitations in terms of the number of studies which have trialled their use, and the usefulness offered over conventional heart rate detection methods.

6.2.3 Summary of Digital Stethoscope Research

Because of the need for rapid, accurate newborn and infant heart rate determination combined with the inadequacies of conventional and novel means of monitoring/assessment, alternate methods were considered worthy of investigation. Digital stethoscope technology has previously been used in young infants to assess heart sounds (217) and neonatal bowel sounds (206). Paired with a smart device with algorithmic software, a digital stethoscope was used to detect and display heart rate in real-time, which was directly compared to infant heart rate derived from 3-lead ECG (183).

Although the first generation digital stethoscope rapidly detected heart rate with a median time of less than five seconds to display, the proportional number of device failures in addition to a relatively high level of inaccuracy (mean difference 7.4 bpm, SD 24 bpm) meant that significant improvements were deemed necessary.

A refined version of the digital stethoscope with improved software was subsequently trialled in 37 low-risk deliveries in the delivery room setting. Enhancements to the technology likely led to improved accuracy (mean difference compared to ECG <1 bpm, 2SD ±12 bpm in periods unaffected by crying) without any important compromise in speed of data display.

6.3 Recommendations for Further Digital Stethoscope Research

A trial in higher-risk infants is yet to be undertaken and will be a crucial next step. Higher risk infants are more likely to be preterm, with lighter birthweights and a smaller thorax which may impact heart sound detectability. Preterm infants are more likely to experience bradycardia at birth and in early infancy (218). Ensuring the digital stethoscope can reliably detect this is fundamental to its clinical utility, especially in the delivery setting. A trial in high-risk infants will allow evaluation of how using the device impacts upon carrying out other resuscitative care tasks such as delivery of assisted ventilation, intubation, cardiac compressions, polyethylene bag application for warmth and vascular access / drug delivery. Assessing the effect of these interventions upon the digital stethoscope and smart device performance will also be important, not only for the neonatal carer but also for regulatory approval for clinical use of this technology, which is determined by legal frameworks that differ from jurisdiction to jurisdiction.

Research should be conducted on how the device should best convey heart rate to clinicians. It is unclear whether a visual display, audible heart sound, pre-recorded voice instructions based on the heart rate detected or a combination of these offers the best design for those using the device and for the infants it is applied to. Repeated studies of simulated resuscitation evaluating the time taken for neonatal teams to perform critical steps in the resuscitation pathway compared to internationally-recommended timeframes, such as the investigation performed by McKinsey and Perlman, could be used to help determine how the device and its means of communication with the clinical team is best optimised (219). This could be done using neonatal manikins with the capability of generating heart sounds at different rates. Wireless transmission of data from the stethoscope itself to the smart device could eliminate the need for electronic cables, potentially improving ease of use.

Overall, a cycle of continual improvement should be pursued. This involves device testing in real-world conditions, critical evaluation and reflection, intelligent redesign, and re-testing of the improved product. This necessitates a transdisciplinary team approach where engineers, designers, programmers and medical staff work closely together, keeping patients and their caregivers at the heart of their collective effort.

6.4 Future Directions for Novel Technology for Newborn and Infant Heart Rate Detection

A key element unifying the varied technological devices in use and development for monitoring heart rate in neonates and young infants is the use of computerised algorithms for processing the acquired signal. It has been demonstrated that improvements in algorithms leads to improved clinical utility (93).

Those technologies with algorithms better able to manage weak signals, movement artefact and other disruptive inputs, such as the improved version of the digital stethoscope and Mestha and colleagues' unique motion-compensation-enabled camera photoplethysmography, do demonstrate improved performance. It is likely, therefore, that the future direction of improving novel technologies lies in the optimisation of algorithms. In order to overcome obstacles and ensure safety, improvements should be both creative and robust.

The trial methodology of future studies should be improved compared to those studies already conducted. Inclusive patient selection, larger sample sizes, standardised reporting of results with inclusion of all relevant data is needed. Real-time assessment of heart rate using the novel method is highly desirable in order to demonstrate its capability in actuality rather than in simulated, post-hoc conditions.

Pursuing entirely new methods of newborn and infant heart rate assessment is a worthwhile goal, given that neither the established nor the emerging methods reviewed above are able to address all clinical needs and scenarios effectively. It may well be that improved contact-based methods will be best for assessing the heart rate immediately after birth, whereas non-contact methods will be ideal for heart rate monitoring in the neonatal unit or in other places such as the home environment. With the ongoing spread of smart device technology, these devices may transform healthcare (198) and enable better assessment of newborn and infant heart rate in both developed and developing world settings.

Reference List

1. Evans D, Hodgkinson B, Berry J. Vital signs in hospital patients: a systematic review. Int J Nurs Stud. 2001;38(6):643–50.

2. Cooper RJ, Schriger DL, Flaherty HL, Lin EJ, Hubbell KA. Effect of vital signs on triage decisions. Ann Emerg Med. 2002;39(3):223-32.

3. Brasel KJ, Guse C, Gentilello LM, Nirula R. Heart rate: is it truly a vital sign? J Trauma. 2007;62(4):812-7.

4. Stöhr EJ, González-Alonso J, Pearson J, Low DA, Ali L, Barker H, et al. Dehydration reduces left ventricular filling at rest and during exercise independent of twist mechanics. J Appl Physiol. 2011;111(3):891-7.

5. Webb SW, Adgey AA, Pantridge JF. Autonomic disturbance at onset of acute myocardial infarction. Br Med J. 1972;3(5818):89-92.

6. Rahman M, Shad F, Smith MC. Acute kidney injury: a guide to diagnosis and management. Am Fam Physician. 2012;86(7):631-9.

7. Figueiredo A, Romero-Bermejo F, Perdigoto R, Marcelino P. The end-organ impairment in liver cirrhosis: appointments for critical care. Crit Care Res Pract [Internet]. 2012 [cited 2016 Mar 3]; 2012(539412):1-13. doi:10.1155/2012/539412.

8. Young PJ, Saxena MK, Beasley RW. Fever and antipyresis in infection. Med J Aust. 2011;195(8):458-9.

9. Saper CB, Breder CD. The neurologic basis of fever. N Engl J Med. 1994;330(26):1880-6.

10. Leigh-Smith S, Harris T. Tension pneumothorax - time for a re-think? Emerg Med J. 2005;22(1):8-16.

11. Papiris S, Kotanidou A, Malagari K, Roussos C. Clinical review: severe asthma. Crit Care. 2002;6(1):30-44.

12. Fowler SJ, Lipworth BJ. Pharmacokinetics and systemic beta2-adrenoceptor-mediated responses to inhaled salbutamol. Br J Clin Pharmacol. 2001;51(4):359-62.

13. Glasgow JF, Middleton B. Reye syndrome - insights on causation and prognosis. Arch Dis Child. 2001;85(5):351-3.

14. Dunn LT. Raised intracranial pressure. J Neurol Neurosurg Psychiatry. 2002;73 Suppl 1:23-7.

15. Wan WH, Ang BT, Wang E. The Cushing Response: a case for a review of its role as a physiological reflex. J Clin Neurosci. 2008;15(3):223-8.

16. Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. J Invest Dermatol. 2000;115(2):149-53.

17. Grigoriou E, Boris JR, Dormans JP. Postural orthostatic tachycardia syndrome (POTS): association with Ehlers-Danlos syndrome and orthopaedic considerations. Clin Orthop Relat Res. 2015;473(2):722-8.

18. Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med. 2013;369(21):2063.

19. Tobias JD, Bozeman PM, Stokes DC. Postsepsis bradycardia in children with leukemia. Crit Care Med. 1991;19(9):1172-6.

20. Gerlach AT, Murphy CV. Dexmedetomidine-associated bradycardia progressing to pulseless electrical activity: case report and review of the literature. Pharmacotherapy. 2009;29(12):1492.

21. Ho JE, Larson MG, Ghorbani A, Cheng S, Coglianese EE, Vasan RS, et al. Long-term cardiovascular risks associated with an elevated heart rate: the Framingham Heart Study. J Am Heart Assoc. 2014;3(3):e000668.

22. Boudoulas KD, Borer JS, Boudoulas H. Heart rate, life expectancy and the cardiovascular system: therapeutic considerations. Cardiology. 2015;132(4):199-212.

23. 23. Price JF. Unique aspects of heart failure in the neonate. In: Shaddy, RE, Ed. Heart failure in congenital heart disease. London: Springer; 2011. p. 21-42.

24. Harada K, Takahashi Y, Shiota T, Suzuki T, Tamura M, Ito T, et al. Effect of heart rate on left ventricular diastolic filling patterns assessed by Doppler echocardiography in normal infants. Am J Cardiol. 1995;76(8):634-6.

25. Ross RD, Bollinger RO, Pinsky WW. Grading the severity of congestive heart failure in infants. Pediatr Cardiol. 1992;13(2):72-5.

26. Mulholland EK, Olinsky A, Shann FA. Clinical findings and severity of acute bronchiolitis. Lancet. 1990;335(8700):1259-61.

27. Hillman NH, Kallapur SG, Jobe AH. Physiology of transition from intrauterine to extrauterine life. Clin Perinatol. 2012;39(4):769-83.

28. Wall SN, Lee AC, Niermeyer S, English M, Keenan WJ, Carlo W, et al. Neonatal resuscitation in low-resource settings: what, who, and how to overcome challenges to scale up? Int J Gynaecol Obstet. 2009;107 Suppl 1:S47-62, S3-4.

29. Wyllie J, Perlman JM, Kattwinkel J, Wyckoff MH, Aziz K, Guinsburg R, et al. Part 7: neonatal resuscitation: 2015 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. Resuscitation. 2015;95:e169-201.

30. Australian Resuscitation Council, New Zealand Resuscitation Council. Airway management and mask ventilation of the newborn infant - ARC and NZRC Guideline 2010. Emerg Med Australas. 2011;23(4):428-35.

31. Saladin KS. Human anatomy. 4th ed. London: McGraw-Hill; 2013.

32. Coté CJ, Lerman J, Anderson B. A practice of anesthesia for infants and children. 5th ed. Philadelphia: Saunders; 2013.

33. American Academy of Pediatrics, American Heart Association. Textbook of Neonatal Resuscitation. 7th ed. Chicago: American Academy of Pediatrics; 2016.

34. Friedman DM, Rupel A, Buyon JP. Epidemiology, etiology, detection, and treatment of autoantibody-associated congenital heart block in neonatal lupus. Curr Rheumatol Rep. 2007;9(2):101-8.

35. Bar R, Cohen M, Bentur Y, Shupak A, Adir Y. Pre-labor exposure to carbon monoxide: should the neonate be treated with hyperbaric oxygenation? Clin Toxicol (Phila). 2007;45(5):579-81.

36. Rennie JM, Kendall G. A manual of neonatal intensive care. 5th ed. Florida: CRC Press; 2013.

37. Lin PW, Stoll BJ. Necrotising enterocolitis. Lancet. 2006;368(9543):1271-83.

38. Griffin MP, Scollan DF, Moorman JR. The dynamic range of neonatal heart rate variability. J Cardiovasc Electrophysiol. 1994;5(2):112-24.

39. Griffin MP, Moorman JR. Toward the early diagnosis of neonatal sepsis and sepsis-like illness using novel heart rate analysis. Pediatrics. 2001;107(1):97-104.

40. Stone ML, Tatum PM, Weitkamp JH, Mukherjee AB, Attridge J, McGahren ED, et al. Abnormal heart rate characteristics before clinical diagnosis of necrotizing enterocolitis. J Perinatol. 2013;33(11):847-50.

41. Moorman JR, Carlo WA, Kattwinkel J, Schelonka RL, Porcelli PJ, Navarrete CT, et al. Mortality reduction by heart rate characteristic monitoring in very low birth weight neonates: a randomized trial. J Pediatr. 2011;159(6):900-6.e1.

42. Sullivan BA, McClure C, Hicks J, Lake DE, Moorman JR, Fairchild KD. Early Heart Rate Characteristics Predict Death and Morbidities in Preterm Infants. J Pediatr. 2016;174:57-62.

43. Pediatric basic and advanced life support [Internet]. United States of America: Department of Health and Human Services; 2011 [updated 26 Jun 2011 cited 15 Jan 2016]. Available from: https://chemm.nlm.nih.gov/pals.htm.

44. Nichols DG, Yaster M, Schleien C, Paidas CN. Golden hour: the handbook of advanced pediatric life support. 3rd ed. London: Elsevier; 2011.

45. Semizel E, Öztürk B, Bostan OM, Cil E, Ediz B. The effect of age and gender on the electrocardiogram in children. Cardiol Young. 2008;18(1):26-40.

46. Gemelli M, Manganaro R, Mamì C, De Luca F. Longitudinal study of blood pressure during the 1st year of life. Eur J Pediatr. 1990;149(5):318-20.

47. Fleming S, Thompson M, Stevens R, Heneghan C, Plüddemann A, Maconochie I, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet. 2011;377(9770):1011-8.

48. Moorman A, Webb S, Brown NA, Lamers W, Anderson RH. Development of the heart: (1) formation of the cardiac chambers and arterial trunks. Heart. 2003;89(7):806-14.

49. Gittenberger-de Groot AC, Bartelings MM, Deruiter MC, Poelmann RE. Basics of cardiac development for the understanding of congenital heart malformations. Pediatr Res. 2005;57(2):169-76.

50. Epstein JA. Cardiac development and implications for heart disease. N Engl J Med. 2010;363(17):1638-47.

51. Anderson RH, Webb S, Brown NA, Lamers W, Moorman A. Development of the heart: (2) Septation of the atriums and ventricles. Heart. 2003;89(8):949-58.

52. Campbell S. A short history of sonography in obstetrics and gynaecology. Facts Views Vis Obgyn. 2013;5(3):213-29.

53. Gavaghan M. Cardiac anatomy and physiology: a review. AORN J. 1998;67(4):802-22.

54. Whitaker RH. The normal heart: anatomy of the heart. Medicine. 2014;42(8):406-8.

55. Mahadevan V. Basic science: anatomy of the heart. Surgery (Oxford). 2015;33(2):47-51.

56. West JB, Luks A. West's respiratory physiology: the essentials. 10th ed. Philadelphia: Wolters Kluwer; 2016.

57. Beltrami AP, Urbanek K, Kajstura J, Yan S, Finato N, Bussani R, et al. Evidence that human cardiac myocytes divide after myocardial infarction. N Engl J Med. 2001;344(23):1750-7.

58. Mohrman DE, Heller LJ. Cardiovascular physiology. 8th ed. New York: McGraw Hill Medical; 2014.

59. Bers DM. Cardiac excitation-contraction coupling. Nature. 2002;415(6868):198-205.

60. Kawashima T, Sasaki H. Gross anatomy of the human cardiac conduction system with comparative morphological and developmental implications for human application. Ann Anat. 2011;193(1):1-12.

61. Anderson KR, Ho SY, Anderson RH. Location and vascular supply of sinus node in human heart. Br Heart J. 1979;41(1):28.

62. Klabunde RE. Cardiovascular physiology concepts. 2nd ed. Philadelphia: Lippincott Williams and Wilkins; 2011.

63. Kumar P, Denson SE, Mancuso TJ. Premedication for nonemergency endotracheal intubation in the neonate. Pediatrics. 2010;125(3):608-15.

64. Bayés de Luna A, Goldwasser D. Clinical arrhythmology. New Jersey: Wiley-Blackwell; 2011.

65. James TN. The internodal pathways of the human heart. Prog Cardiovasc Dis. 2001;43(6):495-535.

66. Temple IP, Inada S, Dobrzynski H, Boyett MR. Connexins and the atrioventricular node. Heart Rhythm. 2013;10(2):297-304.

67. Biondi B, Palmieri EA, Klain M, Schlumberger M, Filetti S, Lombardi G. Subclinical hyperthyroidism: clinical features and treatment options. Eur J Endocrinol. 2005;152(1):1-9.

68. Delacrétaz E. Supraventricular tachycardia. N Engl J Med. 2006;354(10):1039-51.

69. Waller BF, Gering LE, Branyas NA, Slack JD. Anatomy, histology, and pathology of the cardiac conduction system: Part II. Clin Cardiol. 1993;16(4):347-52.

70. James T. Structure and function of the sinus node, AV node and His bundle of the human heart: part I - structure. Prog Cardiovasc Dis. 2002;45(3):235-67

71. Boyden PA, Hirose M, Dun W. Cardiac Purkinje cells. Heart Rhythm. 2010;7(1):127-35.

72. Vorvick L. Pulse [Internet]. Bethesda, Maryland: United States National Library of Medicine; 2015 [updated 9 Mar 2017 cited 10 Mar 2017]. Available from: https://medlineplus.gov/ency/article/003399.htm.

73. Owen CJ, Wyllie JP. Determination of heart rate in the baby at birth. Resuscitation. 2004;60(2):213-7.

74. Eberle B, Dick WF, Schneider T, Wisser G, Doetsch S, Tzanova I. Checking the carotid pulse check: diagnostic accuracy of first responders in patients with and without a pulse. Resuscitation. 1996;33(2):107-16.

75. Handley AJ, Becker LB, Allen M, van Drenth A, Kramer EB, Montgomery WH. Single-rescuer adult basic life support: an advisory statement from the Basic Life Support Working Group of the International Liaison Committee on Resuscitation. Circulation. 1997;95(8):2174-9.

76. Tibballs J, Russell P. Reliability of pulse palpation by healthcare personnel to diagnose paediatric cardiac arrest. Resuscitation. 2009;80(1):61-4.

77. Sarti A, Savron F, Ronfani L, Pelizzo G, Barbi E. Comparison of three sites to check the pulse and count heart rate in hypotensive infants. Paediatr Anaesth. 2006;16(4):394-8.

78. Posner K, Needleman JP. Pneumothorax. Pediatr Rev. 2008;29(2):69-70.

79. Finer NN, Rich W, Wang C, Leone T. Airway obstruction during mask ventilation of very low birth weight infants during neonatal resuscitation. Pediatrics. 2009;123(3):865-9.

80. Kamlin CO, O'Donnell CP, Everest NJ, Davis PG, Morley CJ. Accuracy of clinical assessment of infant heart rate in the delivery room. Resuscitation. 2006;71(3):319-21.

81. Nelson CA, Spector JM. Neonatal resuscitation capacity in Nepal. J Paediatr Child Health. 2011;47(3):83-6.

82. Saugstad OD, Soll RF. Assessing heart rate at birth: auscultation is still the gold standard. Neonatology. 2016;110(3):238-40.

83. Voogdt KG, Morrison AC, Wood FE, van Elburg RM, Wyllie JP. A randomised, simulated study assessing auscultation of heart rate at birth. Resuscitation. 2010;81(8):1000-3.

84. Chitkara R, Rajani AK, Oehlert JW, Lee HC, Epi MS, Halamek LP. The accuracy of human senses in the detection of neonatal heart rate during standardized simulated resuscitation: implications for delivery of care, training and technology design. Resuscitation. 2013;84(3):369-72.

85. Abella M, Formolo J, Penney DG. Comparison of the acoustic properties of six popular stethoscopes. J Acoust Soc Am. 1992;91(4 Pt 1):2224-8.

86. Kruk ME, Rockers PC, Williams EH, Varpilah ST, Macauley R, Saydee G, et al. Availability of essential health services in post-conflict Liberia. Bull World Health Organ. 2010;88(7):527-34.

87. Sinex JE. Pulse oximetry: principles and limitations. Am J Emerg Med. 1999;17(1):59-67.

88. Moyle J. Pulse Oximetry London: BMJ Publishing Group; 2002 [2nd:[

89. Tin W, Lal M. Principles of pulse oximetry and its clinical application in neonatal medicine. Semin Fetal Neonatal Med. 2015;20(3):192-7.

90. Moyle JT. Uses and abuses of pulse oximetry. Arch Dis Child. 1996;74(1):77-80.

91. Goldman JM, Petterson MT, Kopotic RJ, Barker SJ. Masimo signal extraction pulse oximetry. J Clin Monit Comput. 2000;16(7):475-83.

92. Sahni R, Gupta A, Ohira-Kist K, Rosen TS. Motion resistant pulse oximetry in neonates. Arch Dis Child Fetal Neonatal Ed. 2003;88(6):F505-8.

93. Barker SJ. Motion-resistant pulse oximetry: a comparison of new and old models. Anesth Analg. 2002;95(4):967-72.

94. Goldstein MR, Liberman RL, Taschuk RD, Thomas A, Vodt JF. Pulse oximetry in transport of poorly perfused babies. Pediatrics. 1998;102(3):818.

95. O'Donnell CP, Kamlin CO, Davis PG, Morley CJ. Feasibility of and delay in obtaining pulse oximetry during neonatal resuscitation. J Pediatr. 2005;147(5):698-9.

96. Mizumoto H, Tomotaki S, Shibata H, Ueda K, Akashi R, Uchio H, et al. Electrocardiogram shows reliable heart rates much earlier than pulse oximetry during neonatal resuscitation. Pediatr Int. 2012;54(2):205-7.

97. Kc A, Wrammert J, Clark RB, Ewald U, Vitrakoti R, Chaudhary P, et al. Reducing perinatal mortality in Nepal using helping babies breathe. Pediatrics. 2016;137(6).

98. Katheria A, Rich W, Finer N. Electrocardiogram provides a continuous heart rate faster than oximetry during neonatal resuscitation. Pediatrics. 2012;130(5):1177-81.

99. Phillipos E, Solevag AL, Pichler G, Aziz K, van Os S, O'Reilly M, et al. Heart rate assessment immediately after birth. Neonatology. 2016;109(2):130-8.

100. Kamlin CO, Dawson JA, O'Donnell CP, Morley CJ, Donath SM, Sekhon J, et al. Accuracy of pulse oximetry measurement of heart rate of newborn infants in the delivery room. J Pediatr. 2008;152(6):756-60.

101. Fye WB. A history of the origin, evolution, and impact of electrocardiography. Am J Cardiol. 1994;73(13):937-49.

102. Kligfield P, Gettes LS, Bailey JJ, Childers R, Deal BJ, Hancock EW, et al. Recommendations for the standardization and interpretation of the electrocardiogram: part I: the electrocardiogram and its technology a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart

Rhythm Society endorsed by the International Society for Computerized Electrocardiology. J Am Coll Cardiol. 2007;49(10):1109-27.

103. Southall DP, Richards J, Mitchell P, Brown DJ, Johnston PG, Shinebourne EA. Study of cardiac rhythm in healthy newborn infants. Br Heart J. 1980;43(1):14-20.

104. Jones RW, Sharp C, Rabb LR, Lambert BR, Chamberlain DA. 1028 neonatal electrocardiograms. Arch Dis Child. 1979;54(6):427-31.

105. Murković I, Steinberg MD, Murković B. Sensors in neonatal monitoring: current practice and future trends. Technol Health Care. 2003;11(6):399-412.

106. Baird TM, Goydos JM, Neuman MR. Optimal electrode location for monitoring the ECG and breathing in neonates. Pediatr Pulmonol. 1992;12(4):247-50.

107. Kang-Ming C, Keng-Ming C. Pulse Rate Derivation and Its Correlation with Heart Rate. J Med Biol Eng. 2009(3):132.

108. Tabakov S, Iliev I, Krasteva V. Online digital filter and QRS detector applicable in low resource ECG monitoring systems. Ann Biomed Eng. 2008;36(11):1805-15.

109. Cloherty JP. Manual of neonatal care. 7th ed. Philadelphia: Lippincott Williams and Wilkins; 2012.

110. Bergum D, Skjeflo GW, Nordseth T, Mjolstad OC, Haugen BO, Skogvoll E, et al. ECG patterns in early pulseless electrical activity - associations with aetiology and survival of in-hospital cardiac arrest. Resuscitation. 2016;104(Jul):34-9.

111. Tham LP, Chan I. Paediatric out-of-hospital cardiac arrests: epidemiology and outcome. Singapore Med J. 2005;46(6):289-96.

112. Deasy C, Bernard SA, Cameron P, Jaison A, Smith K, Harriss L, et al. Clinical paper: epidemiology of paediatric out-of-hospital cardiac arrest in Melbourne, Australia. Resuscitation. 2010;81(9):1095-100.

113. Rosenberg EM, Cook LN. Electromechanical dissociation in newborns treated with extracorporeal membrane oxygenation: an extreme form of cardiac stun syndrome. Crit Care Med. 1991;19(6):780-4.

114. Dubin AM. Arrhythmias in the Newborn. NeoReviews. 2000;1(8):146.

115. Sacchetti A, Moyer V, Baricella R, Cameron J, Moakes ME. Primary cardiac arrhythmias in children. Pediatr Emerg Care. 1999;15(2):95-8.

116. Payne RA, Symeonides CN, Webb DJ, Maxwell SRJ. Pulse transit time measured from the ECG: an unreliable marker of beat-to-beat blood pressure. J Appl Physiol. 2006;100(1):136-41.

117. Di Fiore JM. Neonatal cardiorespiratory monitoring techniques. Semin Neonatol. 2004;9(3):195-203.

118. Singh JK, Kamlin CO, Morley CJ, O'Donnell CP, Donath SM, Davis PG. Accuracy of pulse oximetry in assessing heart rate of infants in the neonatal intensive care unit. J Paediatr Child Health. 2008;44(5):273-5.

119. Drew BJ, Califf RM, Funk M, Kaufman ES, Krucoff MW, Laks MM, et al. Practice standards for electrocardiographic monitoring in hospital settings: an American Heart Association scientific statement from the Councils on Cardiovascular Nursing, Clinical Cardiology, and Cardiovascular Disease in the Young: endorsed by the International Society of Computerized Electrocardiology and the American Association of Critical-Care Nurses. Circulation. 2004;110(17):2721-46.

120. Murray M. Antepartal and intrapartal fetal monitoring. 3rd ed. New York: Springer Publishing; 2007.

121. Chez BF, Harvey MG, Harvey CJ. Intrapartum fetal monitoring: past, present, and future. J Perinat Neonatal Nurs. 2000;14(3):1-18.

122. Freeman RK. Fetal heart rate monitoring. 4th ed. Philadelphia: Lippincott Williams and Wilkins; 2012.

123. Goodlin RC. History of fetal monitoring. Am J Obstet Gynecol. 1979;133(3):323-52.

124. Alfirevic Z, Stampalija T, Gyte GM. Fetal and umbilical Doppler ultrasound in high-risk pregnancies. Cochrane Database Syst Rev. 2013(11):CD007529.

125. Alfirevic Z, Stampalija T, Medley N. Fetal and umbilical Doppler ultrasound in normal pregnancy. Cochrane Database Syst Rev. 2015(4):CD001450.

126. Neipp C, Hernandez A, Rodes JJ, Marquez A, Belendez T, Belendez A. An analysis of the classical Doppler effect. Eur J Phys. 2003;24(5):497-506.

127. Deeg KH, Rupprecht T, Hofbeck M. Doppler sonography in infancy and childhood. Cham, Switzerland: Springer; 2015.

128. Dyson A, Jeffrey M, Kluckow M. Measurement of neonatal heart rate using handheld Doppler ultrasound. Arch Dis Child Fetal Neonatal Ed. 2016;102(2):116-9.

129. Goenka S, Khan M, Koppel R, Heiman H. Poster: Precordial Doppler ultrasound achieves earlier and more accurate newborn heart rates in the delivery room. American Academy of Pediatrics National Conference; Orange County, California: American Academy of Pediatrics; 2013.

130. Levick JR. An introduction to cardiovascular physiology. 5th ed. London: Hodder Arnold; 2010.

131. Abdulla R. The history of the stethoscope. Pediatr Cardiol. 2001;22(5):371.

132. WHO Generic essential emergency equipment List [Internet]. Geneva, Switzerland: World Health Organization; 2012 [updated 16 Dec 2016 cited 16 Jan 2017]. Available from: http://apps.who.int/medicinedocs/en/d/Js17374e/.

133. van Vonderen JJ, Hooper SB, Kroese JK, Roest AAW, Narayen IC, van Zwet EW, et al. Pulse oximetry measures a lower heart rate at birth compared with electrocardiography. J Pediatr. 2015;166(1):49-53.

134. Dawson JA, Morley CJ. Monitoring oxygen saturation and heart rate in the early neonatal period. Semin Fetal Neonatal Med. 2010;15(4):203-7.

135. Johnstone IC, Smith JH. Cardiovascular monitoring in neonatal intensive care. Infant. 2008;4(2):61-5.

136. McCarthy LK, Morley CJ, Davis PG, Kamlin COF, O'Donnell CPF. Timing of interventions in the delivery room: does reality compare with neonatal resuscitation guidelines? J Pediatr. 2013;163(6):1553-7.

137. WHO Guidelines on basic newborn resuscitation [Internet]. Geneva, Switzerland: World Health Organization; 2012. [updated 1 Jan 2017 cited 16 Jan 2017]. Avilable from: http://www.who.int/maternal_child_adolescent/documents/basic_ newborn_resuscitation/en/.

138. Guideline: Updates on Paediatric Emergency Triage, Assessment and Treatment: Care of Critically-Ill Children. Geneva, Switzerland: World Health Organization; 2016.

139. Chapman SM, Grocott MP, Franck LS. Systematic review of paediatric alert criteria for identifying hospitalised children at risk of critical deterioration. Intensive Care Med. 2010;36(4):600-11.

140. Katheria A, Rich W, Finer N. Electrocardiogram provides a continuous heart rate faster than oximetry during neonatal resuscitation. Pediatrics. 2012;130(5):e1177-81.

141. Teasdale D. Physiological monitoring In: Dixon M, Crawford D, Teasdale D, Murphy J, editors. Nursing the highly dependent child or infant. Chichester: Blackwell Publishing Ltd; 2009.

142. Rabi Y, Dawson JA. Oxygen therapy and oximetry in the delivery room. Semin Fetal Neonatal Med. 2013;18(6):330-5.

143. Fouzas S, Priftis KN, Anthracopoulos MB. Pulse oximetry in pediatric practice. Pediatrics. 2011;128(4):740-52.

144. Odman S, Oberg PA. Movement-induced potentials in surface electrodes. Med Biol Eng Comput. 1982;20(2):159-66.

145. Eichenfield LF, Hardaway CA. Neonatal dermatology. Curr Opin Pediatr. 1999;11(5):471-4.

146. Malloy-McDonald MB. Skin care for high-risk neonates. J Wound Ostomy Continence Nurs. 1995;22(4):177-82.

147. Murray JS, Noonan C, Quigley S, Curley MA. Medical device-related hospital-acquired pressure ulcers in children: an integrative review. J Pediatr Nurs. 2013;28(6):585-95.

148. Oranges T, Dini V, Romanelli M. Skin physiology of the neonate and infant: clinical implications. Adv Wound Care. 2015;4(10):587-95.

149. Dempsey MF, Condon B. Thermal injuries associated with MRI. Clin Radiol. 2001;56(6):457-65.

150. Roller CG. Getting to know you: mothers' experiences of kangaroo care. J Obstet Gynecol Neonatal Nurs. 2005;34(2):210-7.

151. Colville GA, Gracey D. Mothers' recollections of the Paediatric Intensive Care Unit: associations with psychopathology and views on follow up. Intensive Crit Care Nurs. 2006;22(1):49-55.

152. Als H, Duffy FH, McAnulty GB, Rivkin MJ, Vajapeyam S, Mulkern RV, et al. Early experience alters brain function and structure. Pediatrics. 2004;113(4):846-57.

153. du Prel J-B, Röhrig B, Blettner M. Critical appraisal of scientific articles: part 1 of a series on evaluation of scientific publications. Deutsches Arzteblatt International. 2009;106(7):100-5.

154. Cohen JF, Korevaar DA, Altman DG, Bruns DE, Gatsonis CA, Hooft L, et al. STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. BMJ Open. 2016;6(11):1.

155. Wade R, Corbett M, Eastwood A. Quality assessment of comparative diagnostic accuracy studies: our experience using a modified version of the QUADAS-2 tool. Research Synthesis Methods. 2013(3):280.

156. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155(8):529-36.

157. Ajami S, Teimouri F. Features and application of wearable biosensors in medical care. J Res Med Sci. 2015;20(12):1208-15.

158. Grifantini K. The telltale heartbeat : heart-rate monitors are taking new shapes. IEEE Pulse. 2016;7(1):35-8.

159. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L, et al. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. BMJ. 2015;351:h5527.

160. Marchionni P, Scalise L, Ercoli I, Tomasini EP. An optical measurement method for the simultaneous assessment of respiration and heart rates in preterm infants. Rev Sc Instrum. 2013;84(12):121705.

161. Mann C, Ward C, Grubb M, Teoh J, Crowe J, Hayes-Gill B, et al. Can we improve delivery room monitoring for newborns? A novel photoplethysmographic heart rate monitor evaluated among stable NICU infants. Arch Dis Child Fetal Neonatal Ed. 2011;96(Suppl 1):1.

162. Lemke R, Farrah M, Byrne P. Use of a new Doppler umbilical cord clamp to measure heart rate in newborn infants in the delivery room. The e-Journal of Neonatology Research. 2011;1(2):83-8.

163. Sikdar A, Behera SK, Dogra DP, Bhaskar H. Contactless vision-based pulse rate detection of Infants Under Neurological Examinations. Conf Proc IEEE Eng Med Biol Soc. 2015;2015:650-3.

164. Blohm ME, Obrecht D, Hartwich J, Mueller GC, Kersten JF, Weil J, et al. Impedance cardiography (electrical velocimetry) and transthoracic echocardiography for non-invasive cardiac output monitoring in pediatric intensive care patients: a prospective single-center observational study. Crit Care. 2014;18(6):603.

165. Noori S, Wlodaver A, Gottipati V, McCoy M, Schultz D, Escobedo M. Transitional changes in cardiac and cerebral hemodynamics in term neonates at birth. J Pediatr. 2012;160(6):943-8.

166. Grollmuss O, Demontoux S, Capderou A, Serraf A, Belli E. Electrical velocimetry as a tool for measuring cardiac output in small infants after heart surgery. Intensive Care Med. 2012;38(6):1032-9.

167. Gargiulo GD, O'Loughlin A, Breen PP. Electro-resistive bands for non-invasive cardiac and respiration monitoring, a feasibility study. Physiol Meas. 2015;36(2):N35-49.

168. Blanik N, Abbas AK, Venema B, Blazek V, Leonhardt S. Hybrid optical imaging technology for long-term remote monitoring of skin perfusion and temperature behavior. J Biomed Opt. 2014;19(1):16012.

169. Hafner N, Mostafanezhad I, Lubecke VM, Boric-Lubecke O, Host-Madsen A. Non-contact cardiopulmonary sensing with a baby monitor. Conf Proc IEEE Eng Med Biol Soc. 2007;2007:2300-2.

170. Yan Y, Li C, Yu X, Weiss MD, Lin J. Verification of a non-contact vital sign monitoring system using an infant simulator. Conf Proc IEEE Eng Med Biol Soc. 2009;2009:4836-9.

171. Ho CL, Fu YC, Lin MC, Chan SC, Hwang B, Jan SL. Smartphone applications (apps) for heart rate measurement in children: comparison with electrocardiography monitor. Pediatr Cardiol. 2014;35(4):726-31.

172. Trifunovic M, Vadiraj AM, van Driel WD, editors. MEMS accelerometers and their bio-applications. 13th International Thermal, Mechanical and Multi-Physics Simulation and Experiments in Microelectronics and Microsystems; 2012; Cascais, Portugal.

173. Nukaya S, Sugie M, Kurihara Y, Hiroyasu T, Watanabe K, Tanaka H. A noninvasive heartbeat, respiration, and body movement monitoring system for neonates. Artif Life Robotics 2014;19:414–168.

174. Lee WK, Yoon H, Han C, Joo KM, Park KS. Physiological signal monitoring bed for infants based on load-cell sensors. Sensors (Basel). 2016;16(3).

175. Scalise L, Bernacchia N, Ercoli I, Marchionni P, editors. Heart rate measurement in neonatal patients using a webcamera," IEEE International Symposium on Medical Measurements and Applications (MeMeA), 2012, 1–4 (2012). IEEE International

Symposium on Medical Measurements and Applications (MeMeA); 2012; Budapest: IEEE.

176. Kato T, Ueno A, Kataoka S, Hoshino H, Ishiyama Y, editors. An application of capacitive electrode for detecting electrocardiogram of neonates and infants. Annual International Conference Of The IEEE Engineering In Medicine And Biology Society; 2006; New York.

177. Villarroel M, Guazzi A, Jorge J, Davis S, Watkinson P, Green G, et al. Continuous non-contact vital sign monitoring in neonatal intensive care unit. Healthc Technol Lett. 2014;1(3):87-91.

178. Aarts LA, Jeanne V, Cleary JP, Lieber C, Nelson JS, Bambang Oetomo S, et al. Non-contact heart rate monitoring utilizing camera photoplethysmography in the neonatal intensive care unit - a pilot study. Early Human Development. 2013;89(12):943-8.

179. Atallah L, Serteyn A, Meftah M, Schellekens M, Vullings R, Bergmans JWM, et al. Unobtrusive ECG monitoring in the NICU using a capacitive sensing array. Physiol Meas. 2014;35(5):895-913.

180. Adu-Amankwa N, Rais-Bahrami K. Evaluation of a wireless cardio respiratory monitor for neonates. J Neonatal Perinatal Med. 2011;4(4):329-32.

181. Bal U. Non-contact estimation of heart rate and oxygen saturation using ambient light. Biomed Opt Express. 2015;6(1):86-97.

182. Grubb MR, Carpenter J, Crowe JA, Teoh J, Marlow N, Ward C, et al. Forehead reflectance photoplethysmography to monitor heart rate: preliminary results from neonatal patients. Physiol Meas. 2014;35(5):881-93.

183. Kevat AC, Dawson J, Davis PG, Kamlin COF. Evaluation of a digital stethoscope and smart device technology for assessment of heart rate in the newborn infant. Arch Dis Child Fetal Neonatal Ed. 2015;100(6):562-3.

184. Kraaijenga JV, Hutten GJ, de Jongh FH, van Kaam AH. Transcutaneous electromyography of the diaphragm: A cardio-respiratory monitor for preterm infants. Pediatr Pulmonol. 2015;50(9):889-95.

185. Klaessens JH, van den Born M, van der Veen A, de Kraats JS, van den Dungen FA, Verdaasdonk RM. Development of a baby friendly non-contact method for measuring vital signs: first results of clinical measurements in an open incubator at a neonatal intensive care unit. Proc SPIE, Advanced Biomedical and Clinical Diagnostic Systems. 2014;8935(12):1-7.

186. Mestha LK, Kyal S, Xu B, Lewis LE, Kumar V. Towards continuous monitoring of pulse rate in neonatal intensive care unit with a webcam. Conf Proc IEEE Eng Med Biol Soc. 2014;2014:3817-20.

187. Sato S, Ishida-Nakajima W, Ishida A, Kawamura M, Miura S, Ono K, et al. Assessment of a new piezoelectric transducer sensor for noninvasive cardiorespiratory monitoring of newborn infants in the NICU. Neonatology. 2010;98(2):179-90.

188. Scalise L, Marchionni P, Ercoli I, Tomasini EP. Simultaneous Measurement of Respiration and Cardiac Period in Preterm Infants by Laser Doppler Vibrometry. AIP Conference Proceedings. 2012;1457(1):275-81.

189. Wang F, Zou Y, Mami T, Tadashi M, Seiji C. Unconstrained cardiorespiratory monitor for premature infants. Int J Appl Electrom. 2007;25(1-4):469-75.

190. Cui WJ, Ostrander LE, Lee BY. In vivo reflectance of blood and tissue as a function of light wavelength. IEEE Transactions On Bio-Medical Engineering. 1990;37(6):632-9.

191. Gautschi G. Piezoelectric sensors. In: Gautschi G, Ed. Piezoelectric Sensorics. Berlin: Springer-Verlag; 2002. p. 73-91.

192. Hay WW, Rodden DJ, Collins SM, Melara DL, Hale KA, Fashaw LM. Reliability of conventional and new pulse oximetry in neonatal patients. J Perinatol. 2002;22(5):360-6.

193. Kramme R, Hoffmann K-P, Pozos RS. Springer handbook of medical technology. New York: Springer; 2011.

194. Wyllie J, Bruinenberg J, Roehr CC, Rüdiger M, Trevisanuto D, Urlesberger B. European Resuscitation Council guidelines for resuscitation 2015: Section 7 - resuscitation and support of transition of babies at birth. Resuscitation. 2015;95(Oct):249-63.

195. Australian Resuscitation Council, New Zealand Resuscitation Council. Assessment of the Newborn Infant: ARC and NZRC Guideline 2010. Emerg Med Australas. 2011;23(4):426-7.

196. Gazendam R, Voogdt K, Krage R, Wyllie J, Van Elburg R. Effects of training heart rate assessment in neonatal resuscitation: performance, confidence, stress Level. Pediatr Res. 2010;68:635.

197. Mosa ASM, Yoo I, Sheets L. A Systematic Review of Healthcare Applications for Smartphones. BMC Med Inform Decis Mak. 2012;12(1):67-97.

198. Steinhubl SR, Muse ED. Can mobile health technologies transform health care? JAMA. 2013;310(22):2395-6.

199. mHealth: new horizons for health through mobile technologies. Geneva, Switzerland: World Health Organization; 2011.

200. Lardinois F. StethoCloud: Australian college students build a digital stethoscope and mobile app to fight childhood pneumonia [Internet]. United States of America:

TechCrunch, AOL; 2012 [updated 6 Jul 2012, cited 9 Dec 2016]. Available from: https://techcrunch.com/2012/07/06/stehoclou/.

201. Ventola CL. Mobile devices and apps for health care professionals: uses and benefits. P T. 2014;39(5):356-64.

202. The Women's Annual Report 2016. Melbourne, Australia: The Royal Women's Hospital; 2016.

203. Atallah L, Serteyn A, Meftah M, Schellekens M, Vullings R, Bergmans JWM, et al. Unobtrusive ECG monitoring in the NICU using a capacitive sensing array. Physiol Meas. 2014;35(5):895-913.

204. Bland JM, Altman DG. Measuring agreement in method comparison studies. Stat Methods Med Res. 1999;8(2):135-60.

205. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet. 1986;1(8476):307-10.

206. Dumas J, Hill KM, Adrezin RS, Alba J, Curry R, Campagna E, et al. Feasibility of an electronic stethoscope system for monitoring neonatal bowel sounds. Conn Med. 2013;77(8):467-71.

207. Balogh AT, Kovacs F. Application of phonocardiography on preterm infants with patent ductus arteriosus. Biomed Signal Process Control. 2011;6(4):337-45.

208. Matic V, Cherian PJ, Widjaja D, Jansen K, Naulaers G, Van Huffel S, et al. Heart rate variability in newborns with hypoxic brain injury. Adv Exp Med Biol. 2013;789:43-8.

209. Aliefendioglu D, Dogru T, Albayrak M, Dibekmisirlioglu E, Sanli C. Heart rate variability in neonates with hypoxic ischemic encephalopathy. Indian J Pediatr. 2012;79(11):1468.

210. El-Segaier M, Lilja O, Lukkarinen S, Sörnmo L, Sepponen R, Pesonen E. Computer-based detection and analysis of heart sound and murmur. Ann Biomed Eng. 2005;33(7):937.

211. Lai LS, Redington AN, Reinisch AJ, Unterberger MJ, Schriefl AJ. Computerized automatic diagnosis of innocent and pathologic murmurs in pediatrics: a pilot study. Congenit Heart Dis. 2016;11(5):386-95.

212. Basic newborn resuscitation: a practical guide. Geneva, Switzerland: Maternal and Newborn Health Safe Motherhood Unit, World Health Organization; 1997.

213. Gelbart B, Hiscock R, Barfield C. Assessment of neonatal resuscitation performance using video recording in a perinatal centre. J Paediatr Child Health. 2010;46(7-8):378-83.

214. Holcomb JB, Salinas J, McManus JM, Miller CC, Cooke WH, Convertino VA. Manual vital signs reliably predict need for life-saving interventions in trauma patients. J Trauma. 2005;59(4):821-9.

215. Eichenfield LF, Frieden IJ, Mathes EF, Zaenglein AL. Neonatal and infant dermatology. 3rd ed. London: Elsevier Saunders; 2015.

216. Kumar M, Veeraraghavan A, Sabharwal A. DistancePPG: robust non-contact vital signs monitoring using a camera. Biomedical Optics Express. 2015;6(5):1565-88.

217. Finley JP, Warren AE, Sharrat GP, Amit M. Assessing children's heart sounds at a distance with digital recordings. Pediatrics. 2006(6):2322.

218. Hodgman JE, Hoppenbrouwers T, Cabal LA. Episodes of bradycardia during early infancy in the term-born and preterm infant. Am J Dis Child. 1993;147(9):960-4.

219. McKinsey S, Perlman JM. Resuscitative interventions during simulated asystole deviate from the recommended timeline. Arch Dis Child Fetal Neonatal Ed. 2016;101(3):244-7.

Appendix Items

Appendix Item 1. Details of search strategy for systematic review

MEDLINE Search (616 results) (undertaken 15/04/2016)

1. Exp infant

2. infant.mp. or infant/

3. neonatology.mp.

4. exp neonatalogy/

5. 1 or 2 or 3 or 4

6. heart rate.mp.

7. exp heart rate/

8. heart beat.mp.

9. 6 or 7 or 8

10. monitoring.mp.

11. exp monitoring, physiologic/

12. 10 or 11

13. 5 and 9 and 12

14. limit 13 to ("all infant (birth to 23 months)" and last 10 years)

EMBASE search (917 results) (undertaken 18/04/2016)

1. neonatology.mp.

2. exp infant/

3. infant.mp. or infant/

4. exp neonatology/

5. 1 or 2 or 3 or 4

6. heart rate.mp.

7. exp heart rate/

8. heart beat.mp.

9. 6 or 7 or 8

10. monitoring.mp.

11. exp monitoring, physiologic/

12. 10 or 11

13. 5 and 9 and 12

14. limit 13 to last 10 years

SCIE search via Web of Science (754 results) (undertaken 21/04/2016)

TOPIC: (neonat* OR infant OR newborn) AND TOPIC: (monitoring) AND TOPIC: (heart rate OR heart beat)

Timespan: 2006-2016

INDEXES: SCI-EXPANDED

Conference Proceedings Search via Web of Science (76 results) (undertaken 21/04/2016)

TOPIC: (neonat* OR infant OR newborn) AND TOPIC: (monitoring) AND TOPIC: (heart rate OR heart beat)

Timespan: 2006-2016

INDEXES: CPCI-S

Appendix Item 2: Main characteristics of studies included in systematic review

Aarts 2015

Patient Selection	• Sample size: 19 infants • Age: 25-42 weeks gestation; 3 days to 4 weeks old • Weight: 470 – 3810 grams • No exclusion criteria • Setting: 2 NICUs; Children's Hospital of Orange County, California, USA and Máxima Medical Center, Netherlands
Index Test	*Non-contact camera-based photo plethysmography* • Used a standard 300 pixel, 15 or 30 frame per second, 8 bit camera placed on a tripod at approximately 1 m distance • Recordings in ambient light only • MATLAB based graphical interface for non real-time heart rate extraction using an algorithmic approach which included motion detection
Reference Standard	• ECG and/or pulse oximetry
Flow and Timing	• 19 recordings, 0 patients recorded multiple times • Recordings one to five minutes in length

Results and Conclusions	• Reported on all available recording time data • Novel heart rate within 5bpm of reference standard >90% of the time for 13 infants, 50-90% of the time for 5 infants and <50% of the time for 1 infant • Dim ambient light levels and motion artefact increased inaccuracy; phototherapy and staphylococcal scalded skin syndrome likely improved novel device performance • Better hardware and algorithms needed to improve robustness

Mestha 2014

Patient Selection	• Sample size: 8 neonates • Age: 37-40 weeks gestation; 3 days to 4 weeks old • Weight: 2400-3620 grams • Preterm infants, neonates requiring ventilator support, and neonates on phototherapy for management of neonatal hyperbilirubinemia were excluded from the study • Setting: NICU at Manipal University Hospital, Manipal, India
Index Test	*Non-contact camera-based photoplethysmography* • Video of the neonates were recorded using commercial HD webcam, with image resolution of 640x480 at one hour post feeding state to minimize large subject movements.

	• normal NICU lighting without any additional modifications • Non real-time heart rate extraction using algorithmic approach
Reference Standard	• IntelliVue MP 20 Philips Neonatal monitor for reference rate, not specified whether ECG or pulse oximetry used
Flow and Timing	• 8 recordings, 0 patients recorded multiple times • Recordings 30 minutes in length
Results and Conclusions	• 10.5% of all available recording time data lost due to motion isolation • Mean difference 2.52, 1.96 SD of 5.48 (95% CI -2.96-8.0) • Future directions include validation on more subjects (>100) and improving estimation accuracy under low light conditions (or without visible light)

Villarroel 2014

Patient Selection	• Sample size: 30 pre-term infants • Infant 2 was 31 weeks corrected gestational age, weight 1200 grams; ages and weights of other patients not specified • No exclusion criteria specified • Setting: NICU at the John Radcliffe Hospital, Oxford, UK.
Index Test	*Non-contact camera-based photoplethysmography* • Video camera (JAI AT-200CL digital 3CCD progressive

	scan), with three separate CCD sensors to measure red, green and blue light intensity independently. • Authors developed software for implementing image acquisition, with processing on a Xilinx Spartan Field Programmable Gate Array (FPGA) board, using a workstation running the Fedora Linux Operating System. • Recordings made under a mixture of natural lighting and artificial lighting (mostly fluorescent)
Reference Standard	• ECG
Flow and Timing	• Recordings from only two of the patients reported • Each infant had multiple recordings made over 4 days • Recordings 0.89-7.32 hours, over 40 hours in total
Results and Conclusions	• Novel heart rate within 2 bpm of reference standard 81.2% of the time • Able to accurately assess heart rate for 80.3% of the valid camera data • Accuracy affected by three factors: • 1. Major changes in lighting conditions in the NICU. • 2. Variation in the baby's activity patterns. Small pre-term infants made irregular movements throughout the day, making it difficult to compute the frequency components of the heart rate and respiratory rate in the pulsatile reflectance waveform. • 3. The lack of visible skin area.

Scalise, Bernacchia 2012

Patient Selection	• Observations caried out on 7 NICU patients (3 males and 4 female), selected by NICU responsible • Sample size: 7 neonates • Age: 30-37 weeks gestation • Weight: 1030-3120 grams • No specific exclusion criteria • Setting: NICU of the 'G. Salesi' Children's Hospital
Index Test	*Non-contact camera-based photo plethysmography* • Used a standard digital webcamera WeC, (Microsoft LifeCam VX-3000). This WeC is based on a CMOS VGA sensor with a maximum video resolution of 640 x 480 pixels and a maximum frame rate of 30 frame-per-seconds • A large band light source illuminated the skin surface at which the web camera was directed • Video sequences generated by the camera were acquired by a property software developed in the LabView programming environment • All the video and physiological recordings were analyzed offline using custom software written in MATLAB.
Reference Standard	• ECG
Flow and Timing	• Each subject was measured 8 times (for a total monitoring time of 240 seconds) at rest.

	• Recordings 30 seconds each in length
Results and Conclusions	• 33 data sets reported (of 56 expected) • Pearson's coefficient of 0.94 • Mean difference between index and reference heart rate of 0.9 bpm, SD 4.5 bpm. • Artefact problems due to patient movement were infrequent because the preterm subjects were placed supine in the centre of crib. • Face detection algorithm needs to reduce uncertainty due to small movement of patient's head.

Adu-Amankwa 2011

Patient Selection	• Sample size: 25 neonates admitted to NICU • Age and weight of subjects unspecified • Patients were excluded if they had had chest or recent abdominal surgery • Setting: NICU of the Children's National Medical Center (CNMC), Washington DC, USA
Index Test	*Reflectance pulse oximetry* • Wireless sensor belt was placed around the abdomen. • Cardiac sensor is based on a plethysmographic technique utilizing infrared light – LED, developed by PGS Medical Research and Electronic Design

	• new sensor utilizes reflectance techniques, electronic filtering, and mechanical stabilization • Waveform data was recorded using a 4 channel analog Windaq system
Reference Standard	• pulse oximetry
Flow and Timing	• Breathing and heart rate waveform data were recorded from the wireless research monitor and from the existing NICU equipment (reference monitor) for a total of 90 minutes • Each file was then reviewed and 5 selections of at least 3 minutes duration wherein both monitors were displaying stable waveforms were compared for parity of peaks representing a beat. • Not specified whether all subjects included, nor whether any were recorded more than once
Results and Conclusions	• A 96% correspondence with deviation of ±2 beats per minute discrepancy between the Reference and PGS heart rate monitors • The wireless 2 sensor monitor described is an effective less invasive and easier method of collecting cardio respiratory data in the NICU.

Grubb 2014

Patient Selection	• Sample size: two groups, the first comprising 53 neonates of ≥ 32 weeks gestation with mean corrected gestational age of 33+2 weeks, mean age 6 days, and the second group of 24 neonates <32 weeks gestation, with mean corrected gestational age 31+1, mean age 12 days • Mean birth weight: 1.66 kilograms for ≥ 32 weeks gestation group,1.26 kilograms for <32 weeks group • Exclusion criteria were: newborns receiving phototherapy, those with extensive skin disease, receiving palliative care, where there were language or social barriers to obtaining consent, or patients that the attending physicians felt were too clinically unstable. • Setting: NICU, Nottingham University Hospitals NHS Trust, Nottingham, UK
Index Test	*Reflectance pulse oximetry* • Light source consisted of four 525 nanometer light emitting diodes (Marl, E1S02-3G0A7-02) arranged in pairs either side of a photodetector (Vartec, VTB8440B) to provide even illumination of the tissue beneath the sensor. • Detection consisting of an analogue front end, which used a transimpedance amplifier to amplify and convert the photocurrent to a voltage; data-logging was provided by a modified electrophysiological recorder (Monica Healthcare

	Ltd, AN24). • The digital signal processing comprising the lock-in detection utilizing a simple quadrature demodulator algorithm, followed by a 0.5–16 Hz band-pass filter, was implemented in MATLAB (version 7.12, MathWorks).
Reference Standard	• ECG
Flow and Timing	• 99 participants were recruited from the NICU. Technical problems resulted in no ECG data being logged in 22 of these recordings, although usable PPG data was present in 14 of these. • In the other eight PPG recordings, four suffered from poor signal quality because continued manipulation of the ECG electrodes to try and gain a good ECG signal caused excessive motion in the PPG sensor. • A further two were excluded because of internal electronic connection problems and two could not be aligned according to the protocol and were excluded but in fact still contained good quality signals. • Hence data from 77 participants were analyzed • Recordings were 20 minutes in duration
Results and Conclusions	• Data was excluded where the researchers physically adjusted either the PPG sensor or ECG electrodes. Additionally, moments where the ECG was of too poor quality to calculate a heart rate were excluded

	• For group 1, the median PPG reliability at ±3 bpm was 91.2%, and for group 2 91.4%. • Heart rate pairs from the two groups were aggregated giving a sensitivity (89.9%) and specificity (99.8%) of the device and extraction technique at a threshold of 100 bpm. • Motion artefact had the greatest effect on reliability • Approximately 10% of the data points are represented as outliers

Scalise, Marchionni 2012

Patient Selection	• Sample size: 20 neonates: 7 female and 13 male patients; only one patient was characterized by a hypotonic state. The mean weight was 1111 grams and 3 of the neonates were in incubators • Ages not specified • No exclusion criteria specified • Setting: Neonatal Intensive Care Unit (NICU) of the Università Politecnica delle Marche pediatric hospital G.Salesi of Ancona
Index Test	*Laser Doppler* • A laser Doppler vibrometer (Polytec, PDV100, GmbH, Germany) incorporating a Mach-Zender interferometer was used to measure the projection of the velocity of the measurement point along the optical beam direction

	• For each subject, ECG (obtained from the II-lead output), and VCG (velocity measured by the LDV) traces were simultaneously recorded. An analog-to-digital 12-bit acquisition board with antialiasing filters (ADI Instruments, PowerLab 4/25T), together with the chart 5 software, have been used to store the signals
Reference Standard	• ECG
Flow and Timing	• 20 recordings • Recording length not specified
Results and Conclusions	• Reported on all available recording time data • Mean difference between index and reference 0.2 bpm • Pearson's correlation coefficient is 96%. • This method can be used on uncooperative patients or with patients who have contraindications to the use of contact electrodes or transducers (such as the ECG electrodes or the oximeters probes). • Author's recommend avoiding direct and continuous eyes exposure to the laser beam

Atallah 2014

Patient Selection	• Sample size: 15 neonates • Age: not specified • Weight: approximately 750-2500 grams • No exclusion criteria • Setting: NISC of the Maxima Medical Centre in Veldhoven the Netherlands
Index Test	*Capacitive sensor array* • 8 sensors embedded in mattress • Camera used for some neonates to analyse body movements • Alternative to ECG that does not require adhesive gel electrodes
Reference Standard	• ECG
Flow and Timing	• 75 hours of data collected in total
Results and Conclusions	• Various analyses discussed. No statistical analysis provided • Instantaneous heart rate data very good where proper electrical coupling conditions were attained • 2-3 clothing layers on neonate led to bad contact between sensor and skin

Kato 2006

Patient Selection	• Sample size: 4 infants • Age: 10-133 days • Weight: 4690-7600 grams • No exclusion criteria • Setting: not specified
Index Test	*Capacitive Electrode (Electrographic potential)* • Potential measured through thin underwear • Subject laid in supine position on mattress bearing electrodes
Reference Standard	• ECG
Flow and Timing	• 4 infants, one had data recorded twice • Length and number of recordings not specified
Results and Conclusions	• No statistical analysis provided • Detection of signal through layers demonstrated • Detected waveform distorted when underwear present • Further development of method required if it is to be implemented.

Sato 2010

Patient Selection	• Sample size: 63 neonates in 3 groups; 27 eligible for heart rate assessment • Age: 25-42 (median 35) weeks gestational age • Weight: birth weights 742-4126g (median 2140) • No exclusion criteria • Setting: NICU, Akita University Hospital, Akita, Japan
Index Test	*Piezoelectric transducer sensor* • placed under folded towel under neonate • Filtering algorithm and template-based search for S1 peaks enabled comparison of S1-S1 intervals converted to a heart rate in beats per minute to the reference standard
Reference Standard	• ECG
Flow and Timing	• Sampled at 2 millisecond intervals for 10 hours-9 days continuously
Results and Conclusions	• Average correlation coefficient R = 0.92 for 1 minute assessments • During the long assessment, the heart rate detection rate by the sensor was 10% lower than that by ECG (82.6 ± 12.9 vs. 91.8 ± 4.1%; p = 0.001, n = 27), although comparable (90.3 ± 4.1 vs. 92.5 ± 3.4%, p = 0.081) in 70% (18/27) of neonates examined; sensor has an inherently high performance comparable to ECG

	• The lower heart rate detection rate was due to high frequency oscillation ventilation in 2 neonates, frequent body movements in 1 neonate and weak signal intensity in another

Wang 2007

Patient Selection	• Sample size: 5 infants for initial development then 5 for real-time testing • Age: premature infants • Weight: real-time testing grou: 1822±290 grams • No exclusion criteria • Setting: NICU, Center for Perinatal Medicine, Tohoku University Hospital
Index Test	*Polyvinylidene fluoride piezoelectric film sensor array* • Four sensors placed under bed cover sheet beneath child's body to detect pressure fluctuations. • wavelet multi-resolution decomposition method was used to separate out pressure fluctuations due to respiratory efforts • Real-time data processing algorithm programmed using LabVIEW™ • selected data from sensor with strongest signal for analysis

Reference Standard	• ECG
Flow and Timing	• Continuous monitoring, sampling rate 100Hz(10 milliseconds)
Results and Conclusions	• Shapes of responses of four sensors similar, but amplitudes vary (depends on position of infant in bed) • Heart beat mean error 8.24% • Errors attributed to body movement of infants and weakness of heart neat vibration

Nukaya 2014

Patient Selection	• Sample size: 1 infant • Age: preterm, low birth weight; 7 week old • Weight: 2840 grams • No exclusion criteria • Setting: NICU
Index Test	*Piezoceramic sensors on bed* • Heartbeat, respiration and movement separated from signal • Band pass filtering (3-13Hz for heartbeat)
Reference Standard	• ECG
Flow and Timing	• Continuous measurement for 60 minute period • 10ms sampling periods

Results and Conclusions	• Correlations: Heart rate correlation coefficient; R= 0.91 • Body movements identified by signals and large body movements prevented adequate detection of heart beat and respiration • External vibrations not found to affect detection

Kraaijenga 2014

Patient Selection	• Sample size: 31 preterm infants • Age: 29.6± sd 1.8 weeks gestation; 1-7 days old • Weight (birth): 1380±sd 350 grams • Patients with congenital anomalies were excluded • Setting: 1 NICU; Neonatal Intensive Care Unit of the Emma Children's Hospital, Academic Medical Centre, Amsterdam, The Netherlands
Index Test	*Transcutaneous Electromygraphy of the diaphragm* • Performed using three skin electrodes connected to a portable 16-channel digital physiological amplifier • The signal was band-pass filtered from 40 Hz to 160 Hz. • analyses were performed using Polybench software
Reference Standard	• ECG

Flow and Timing	• ECG and electromyography recorded for 1 hour on days 1, 3, 7 after birth • For each 1 hour recording, 6 intervals of 1 minute were selected for analysis.
Results and Conclusions	• Heart rate from electromyography had excellent correlation with reference method ($r = 0.98$, $P<0.001$) • Mean Difference -0.3 beats/min • Concluded that study demonstrates electromyography feasible and repeatable for preterm infants

LETTER

Evaluation of a digital stethoscope and smart device technology for assessment of heart rate in the newborn infant

As neonatal heart rate (HR) is a vital sign used to assess the need for and response to resuscitation,[1] measuring it rapidly, accurately and affordably is important to clinicians around the world. We aimed to assess the accuracy, speed and reliability of a novel low-cost digital stethoscope (DS) attached to a smartphone running real-time newborn HR detection software in determining the HR of clinically stable infants.

We studied infants >26 weeks' corrected gestation excluding those receiving high-frequency oscillation ventilation. We applied the Stethocloud V.0.2beta DS head to their exposed precordium. The DS was connected to an Apple iPhone 5s running Neorate 0.1a software (CliniCloud, Melbourne, Australia) which displayed a real-time HR (DS HR). Infants were simultaneously monitored with three-lead electrocardiography (Philips Intellivue MP70, Philips, Andover, USA). Video recordings captured both HR displays and data were extracted at 1 s intervals. We excluded seven of 57 recordings based on our a priori definition of reliability, data available within 30 s of activating the DS software and at least 10 s of output during the 90 s recording period.

Participants were a convenience sample obtained in the neonatal intensive care unit when a parent was available to provide informed consent. Corrected gestational age and weight at time of study ranged from 26.7 to 54.7 weeks and 656–3690 g, respectively. Thirty-four per cent had respiratory support via an endotracheal tube, continuous positive airway pressure or heated humidified high-flow nasal cannulae; 24% had cardiac lesions (table 1).

Table 1 Demographics of infants analysed

Demographics	
Female	50% (25)
Gestational age at birth (weeks+days)	30+5 (6+4)
Birth weight (g)	1303 (980)
Postmenstrual age at the time of recording (weeks+days)	34+1 (4+6)
Weight at the time of recording (g)	1891 (1240)
Respiratory interventions	
Conventional ventilation (intubated)	6% (3)
CPAP	14% (7)
HHHFNC	14% (7)
Low flow nasal oxygenation	10% (5)
None	56% (23)
Cardiac lesions	
Patent ductus arteriosus	16% (8)
Tetralogy of Fallot	2% (1)
Isolated ventricular septal defect	2% (1)
Isolated valvular abnormalities	4% (2)
No lesion suspected	76% (28)

Results are % (n) or median (IQR).
CPAP, continuous positive airway pressure; HHHFNC, heated humidified high-flow nasal cannulae.

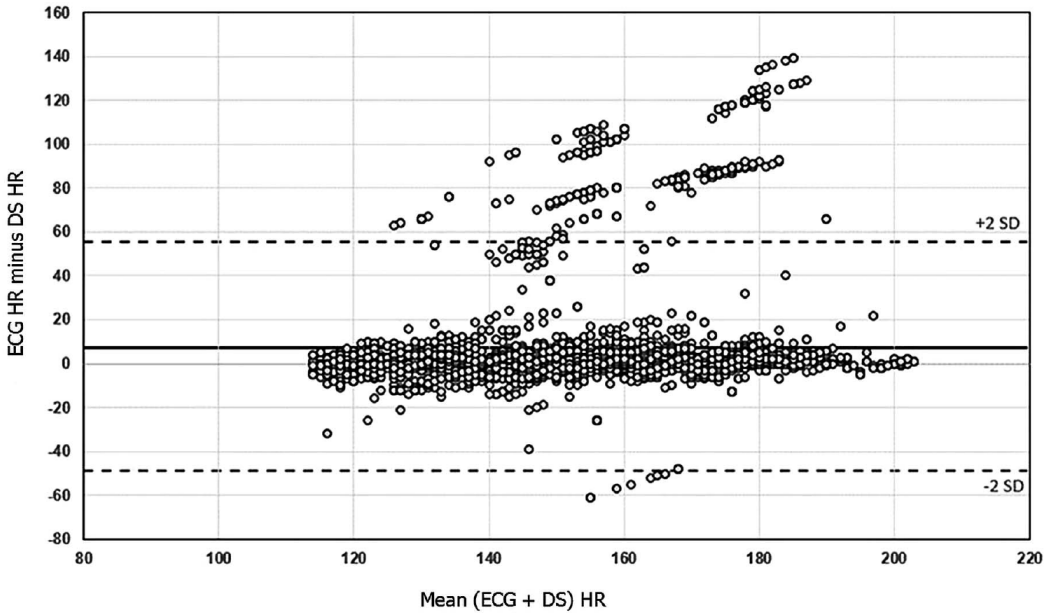


Figure 1 Bland-Altman analysis. DS, digital stethoscope; HR, heart rate.

A Bland–Altman plot constructed to assess agreement between ECG and DS HR compared 3972 paired data points (figure 1). The mean difference (SD) between ECG and DS HR was 7.4 (24) beats per minute (bpm). Only six recordings had a mean difference exceeding 20 bpm (data not shown). The median (IQR) time to first DS HR display was 2 (1–7) s.

To our knowledge, this is the first time DS technology for real-time HR measurement has been studied in newborns. Accuracy of DS HR is greater than chest auscultation and umbilical cord palpation which underestimate ECG HR by 14 and 21 bpm, respectively.[2] Pulse oximetry in comparison correlates more strongly with ECG but takes >1 min to establish a reliable HR,[3] whereas DS HR was displayed in <5 s on average. Figure 1 shows that for 8.6% of displayed values, DS HR is >20 bpm different to ECG, mostly due to underestimation of ECG HR. Such imprecision, despite occurring infrequently, represents a software algorithm flaw which renders the current device unacceptable for clinical use. Interestingly, we found external noises and murmurs were not associated with inaccurate DS HR. The lower frequency of neonatal heartbeats allows these high-frequency sounds to be filtered.[4]

A key limitation of the device is shown by the proportion of recordings excluded due to poor performance. Accidental loss of stethoscope contact with the precordium and loose wiring connections were major contributors. The DS and smartphone technology represent important developments in HR monitoring but further refinement is necessary before they are useful in clinical practice.

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REFERENCES

1 World Health Organization. *Guidelines on basic newborn resuscitation*. Geneva, Switzerland: WHO Press, 2012:p. 61.
2 Kamlin CO, O'Donnell CP, Everest NJ, *et al*. Accuracy of clinical assessment of infant heart rate in the delivery room. *Resuscitation* 2006;71:319–21.
3 McCarthy LK, Morley CJ, Davis PG, *et al*. Timing of interventions in the delivery room: does reality compare with neonatal resuscitation guidelines? *J Pediatr* 2013;163:1553–7.e1.
4 Balogh A, Kovacs F. Application of phonocardiography on preterm infants with patent ductus arteriosus. *Biomed Signal Process Control* 2011;6:337–45.

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