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Validity and reconstruction of the intra-arterial blood pressure waveform measured with a catheter-manometer system in critically ill neonates

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Master thesis

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Abstract

Background: Adequate blood pressure (BP) measurement, as part of comprehensive hemodynamic monitoring, is important to assess the circulation in critically ill neonates. Continuous BP measurement via an intra-arterial catheter-manometer system (CMS) is the gold standard method in neonatal care. However, validity of these measurements may be affected by the dynamic response (DR), a characteristic of the CMS. Inadequate DR of the system may lead to under- or overestimation of BP values and changes in wave shape.

Objective: The aim of this study was twofold: to assess the validity of the neonatal arterial waveform and to propose and evaluate a method for the reconstruction of distorted waveforms based on DR measurements.

Design/methods: Computer simulations of neonatal BP measurement with CMS were performed to assess the effect of varying DR on BP values and wave shape. To measure DR in a clinical setting, newborns admitted to the neonatal intensive care unit (NICU) with an umbilical or peripheral arterial line were included. During routine catheter flushing, we calculated DR from the pulse exercised on the system by closure of the flush valve. We created a measurement-specific method for waveform reconstruction based on DR of the CMS. The method was validated using computer simulations and applied to our clinical data using calculated DR. Measured and reconstructed waveforms were compared based on pressures and wave shape parameters.

Results: Computer simulations showed effects of DR on wave shape. Systolic pressure (P_S) and pulse pressure (PP) were affected in case of inadequate DR. Mean blood pressure (MBP) was not affected. To measure DR at the NICU, 15 patients with a total of 21 arterial lines were included from which 553 flush moments were recorded and DR could be calculated in 73% of the cases. We created a method for reconstruction of distorted waveforms based on measured DR. Validation with simulations showed decrease in both wave shape and pressure errors. Application of the reconstruction method improved validity of the distorted BP signal showed mainly changes in wave shape parameters. P_S and PP showed changes of -1 mmHg (IQR -2 – 0 mmHg).

Conclusion(s): Dynamic response of CMS for neonatal arterial waveform measurement affects mainly wave shape. MBP measurement remains reliable. Ps and PP may be affected by inadequate dynamic response, though errors are generally not clinically relevant. From measured DR, we created a measurement-specific reconstruction method which may aid in obtaining more valid neonatal arterial pressure waveforms.

List of abbreviations and symbols

ABBREVIATIONS

APW	Arterial pressure waveform
AUC	Area under the curve
BP	Blood pressure
BW	Birth weight
CMS	Catheter-manometer system
CO	Cardiac output
DA	Ductus arteriosus
DN	Dicrotic notch
DR	Dynamic response
FO	Foramen ovale
GA	Gestational age
HR	Heart rate
IQR	Interquartile range
LV	Left ventricle
MAD	Median absolute deviation
MBP	Mean blood pressure
MTC	Manometer-tipped catheter
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
NIBP	Non-invasive blood pressure
PDA	Patent ductus arteriosus
PRAM	Pressure recording analytical method
R	Pearson's correlation coefficient
RMSE	Root mean square error
SGA	Small for gestational age
SBF	Systemic blood flow
SV	Stroke volume
SVR	Systemic vascular resistance

SYMBOLS

a	Cross-sectional area
A	Amplitude
CV_{MAD}	Coefficient of variation estimated by the ratio of the MAD
d	Catheter diameter
dP/dt_{max}	Maximal slope of the APW
ζ	Damping coefficient
η	Fluid viscosity
f_n	Natural frequency in Hz
φ	Phase angle
H	Transfer function
I	Friction
K	Stiffness
L	Catheter length
λ	Overdamping exponential decay constant
M	Mass
P	Pressure
P_D	Diastolic blood pressure
P_S	Systolic blood pressure
PP	Pulse pressure
Q	Flow
R	Resistance
ρ	Fluid density
s	Laplace constant
T	Duration
ω	Frequency in rad/s
ω_n	Natural frequency in rad/s

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1 Introduction

In the Netherlands, approximately 2.5% of newborns are admitted to the neonatal intensive care unit (NICU). This corresponds to about 4000 children a year, of which 5% will not survive the first 28 days of life [1]. Furthermore, patients admitted to the NICU are at risk of impaired neurodevelopmental outcome, especially in case of extreme prematurity, perinatal asphyxia or treatment with extracorporeal membrane oxygenation [2, 3]. Hypotension and the development of shock are associated with both short-term mortality and long-term adverse outcome [4-8]. Hemodynamic compromise may occur in (preterm) infants due to immaturity of the cardiovascular system and problems in transition from intra- to extrauterine life, as well as the development of sepsis and the presence of congenital heart disease [9]. Adequate hemodynamic monitoring is an important aspect of care in the NICU, especially to prevent neonatal shock. Early recognition of hemodynamic compromise may guide patient-specific treatment and thereby improve outcome in neonates. However, assessment of a newborn's hemodynamic status remains challenging [9, 10].

Despite technological advancements in for example cardiac output (CO) measurements for the adult, assessing the hemodynamic status at the NICU is still mainly based on clinical signs and symptoms. Techniques developed for hemodynamic monitoring in the adult are not readily adaptable to (preterm) infants due to size constraints and the immaturity of the cardiovascular system, which may differ from the adult circulation [9, 11]. Furthermore, this patient group is heterogeneous in both etiology and presentation of hemodynamic instability, thereby complicating diagnosis and treatment strategy [12].

Mean blood pressure (MBP) is the most frequently used parameter for the assessment of hemodynamic status at the NICU [13, 14]. Blood pressure measurement via an intra-arterial catheter is the current gold standard method in neonatal and pediatric care [15]. In the intensive care setting, a fluid-filled catheter-manometer system (CMS) can be introduced in the radial, ulnar or posterior tibial artery, or, in neonates, the umbilical artery [15, 16]. This allows for continuous monitoring of the full arterial blood pressure wave (APW), from which pressures such as MBP, diastolic and systolic blood pressure and pulse pressure (*PP*) are calculated. Blood pressure is indicative of tissue perfusion, cardiac function, fluid status, endocrine function and overall level of illness [15]. However, blood pressure does not directly reflect systemic blood flow (SBF) as this is dependent on systemic vascular resistance (SVR) as well [17]. The full pressure waveform may contain additional clinically relevant information as it is a complex signal resulting from various physiologic factors such as stroke volume (SV), vascular compliance and systemic vascular resistance [18, 19]. Consequently, a reliable arterial wave shape is of importance to enable advanced waveform analysis, possibly leading to more hemodynamically relevant information to be derived from the arterial waveform. Moreover, valid blood pressure monitoring is key for adequate assessment of hemodynamic status in the current clinical setting.

Although intra-arterial BP measurement via a CMS is considered to be the most accurate method of BP assessment in general clinical practice, several factors such as air bubbles in the catheter can lead to incorrect translation of pressure values and wave shape from patient to monitor [15, 20-23]. This translation is mainly affected by the dynamic response, a characteristic of the CMS [24]. According to this dynamic response, diastolic pressure, systolic pressure and pulse pressure can be both under- or overestimated. To prevent inadequate assessment of neonatal hemodynamic status as a result of invalid blood pressure measurement, it is of great importance to identify the system's dynamic response and its effects on the measured arterial blood pressure waveform. Furthermore, inadequate dynamic response of the CMS may give rise to distortions in the signal or decrease waveform complexity, both of which impede the usefulness of the wave shape for advanced hemodynamic monitoring.

In 1981, Gardner described the effects of the dynamic response on the arterial blood pressure waveform and its requirements for adequate measurement. These findings, however, cannot be readily translated to the heterogeneous neonatal population as the effects of dynamic response on arterial pressure measurement depend on the heart rate and systolic rise time [24]. Van Genderingen et al. determined several pressure errors induced by varying dynamic response for critically ill newborns. However, they did not take into account the heterogeneity of the neonatal population either [20]. They therefore do not provide a comprehensive view on the effects of dynamic response on neonatal arterial waveforms. Furthermore, the generally accepted method for assessment of dynamic response is not applicable in neonates. Consequently, little is known about dynamic response of catheter-manometer systems for blood pressure measurements in the neonatal population and thereby on validity of the neonatal arterial blood pressure waveform.

1.1 Aim of the study

Although the use of a CMS is considered the gold standard method for blood pressure measurement in neonates, its validity may be affected by a characteristic of the system called the dynamic response. BP values may not always be accurate, possibly leading to inadequate diagnosis or treatment strategies. Furthermore, validity of the arterial pressure waveform is of importance to enable further research on the relationship between wave shape and hemodynamic status.

There is of yet no comprehensive view on whether the dynamic response provides problems for BP measurement in neonates. The aim of the current study was therefore to assess the validity of CMS based intra-arterial BP measurement in the NICU, by evaluating the effect of varying dynamic response on pressure values as well as the wave shape, and determining the actual dynamic response of intra-arterial catheter-manometer systems in situ at the NICU. To improve validity of these measurements, a secondary aim was to develop a reconstruction method for distorted intra-arterial BP measurement.

1.2 Thesis outline

The outline of this thesis is as follows: in **chapter 1,** a general introduction and outline of the thesis is provided. **Chapter 2** introduces the theoretical framework of this study. In **chapter 3**, simulation study to evaluate the effect of dynamic response on the neonatal arterial waveform is discussed. **Chapter 4** discusses dynamic response measurement of arterial lines during routine care at the NICU. In **chapter 5,** we attempt to use the measured dynamic response parameters to reconstruct the true arterial waveform. **Chapter 6** discusses the clinical implications of the results described in the previous chapters. Lastly, **chapter 7** provides a general discussion of the results, recommendations, perspectives on future work and a general conclusion of this thesis.

2 Theoretical framework

2.1 Neonatal hemodynamics

2.1.1 *Fetal, transitional and neonatal physiology*

The fetal circulation differs from the circulation of the adult as the placenta is the organ of gas exchange in the fetus rather than the lungs [13]. Oxygenated blood from the placenta is directed to the systemic circulation via the foramen ovale (FO) between the left and right atria and the ductus arteriosus (DA) between the pulmonary artery and aorta. Consequently, the lungs are predominantly bypassed and both the left and right ventricle (RV) contribute to the systemic circulation in parallel [14, 25-27]. This parallel circulation is characterized by a low-resistant placental circulation and high pulmonary vascular resistance (PVR), so blood flow through the pulmonary circulation is low [9].

As the postnatal pulmonary and systemic circulations are in series and the lungs are the organs of gas exchange, the cardiovascular system needs to undergo major changes in the transition from intra- to extrauterine life. The differences between the fetal and neonatal circulation are shown in Fig. 2.1 A and B, respectively. With the first inhalation, the pulmonary vessels dilate and PVR decreases substantially, increasing pulmonary blood flow (PBF). This leads to an increase in pulmonary venous return, which results in the functional closure of the FO as pressure between the two atria reverses. As the low-resistance placental circulation is cut off with umbilical cord clamping, SVR rises [9, 27]. In healthy term infants, the DA constricts within the first 24 hours after birth as a result the rise in partial oxygen tension among other things [28, 29].

2.1.2 *Pathophysiology of low cardiac output and neonatal shock*

The vast majority of term neonates smoothly experience the transitional period. In contrast, adaptation to extrauterine life may be hindered by organ system immaturity in (extremely) preterm infants [18]. Premature neonates often present with low SBF, which is associated with adverse outcome such as cerebral injury [30]. This may result from several mechanisms. First,

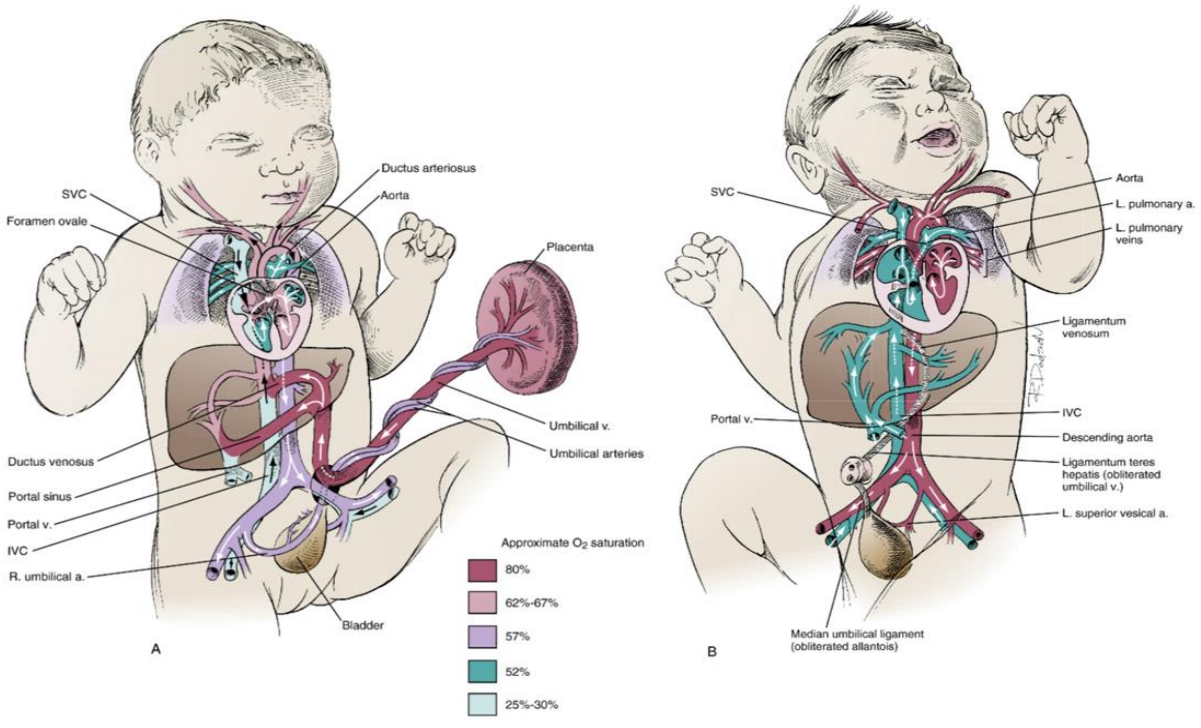

Figure 2.1: Fetal (A) and neonatal (B) circulation with various oxygen percentages depicted [27]

the immature myocardium contains less contractile elements and is more sensitive to changes in afterload than the mature myocardium. This limits the ability of the heart to overcome the increase in SVR after umbilical cord clamping. Furthermore, decrease in PVR is delayed which impedes a rise in CO [13, 19]. This may also limit functional FO closure [31]. When the ductus arteriosus remains patent (PDA), which occurs more often in premature and small-for-gestational-age (SGA) neonates, the transitional fall in PVR and rise in SVR may lead to left-to-right shunting, which in turn results in pulmonary overflow and decreased SBF [9].

Shock is a state in which oxygen delivery cannot meet oxygen demand, resulting in tissue hypoxia. This can occur in (extremely) premature neonates in the transitional phase, but in other circumstances such as sepsis, asphyxia, necrotizing enterocolitis (NEC) as well. For example, a delayed decrease of PVR and the resulting persistent pulmonary hypertension in the newborn (PPHN) is associated with neonatal shock in (nearly) term infants [19]. Initially, neuroendocrine compensatory mechanisms are in play which direct the blood flow towards the vital organs – brain, heart and suprarenal glands in neonate – at the expense of other organs [8, 19]. The second (compensated) phase of shock may be recognized by clinical signs such as decreased urine output and cold extremities, as perfusion of nonvital organs is reduced [13]. However, neonatal shock is often not recognized before onset of the uncompensated phase, which is when systemic hypoperfusion and hypoxia occur. When left untreated, this will eventually lead to multiorgan failure and death [19, 32]. Interestingly, the cortex may not function as a 'vital organ' in very preterm infants, as vasodilation does not occur in response to decreased cerebral blood flow [11]. This further demonstrates the need for early recognition of neonatal shock.

This illustrates the importance of adequate hemodynamic monitoring at the NICU, especially in preterm infants. One of the main goals of (advanced) hemodynamic monitoring is to be able to recognize shock early, within the compensated phase or earlier and obtain insight into the pathophysiology of shock to guide individualized treatment, thereby reducing adverse outcome.

2.2 Current clinical practice of hemodynamic monitoring at the NICU

In the neonatal population, medical professionals mainly rely on clinical assessment of hemodynamic status in newborns. To evaluate SBF, a combination of clinical signs and symptoms and biochemical parameters is often used. This includes BP, serum lactate concentration, capillary refill time (CRT), skin color and urine output. These parameters often lack predictive ability, reproducibility and objectivity, and clinical thresholds and guidelines for intervention are largely based on expert opinion and have no or little scientific basis [9, 12, 33, 34].

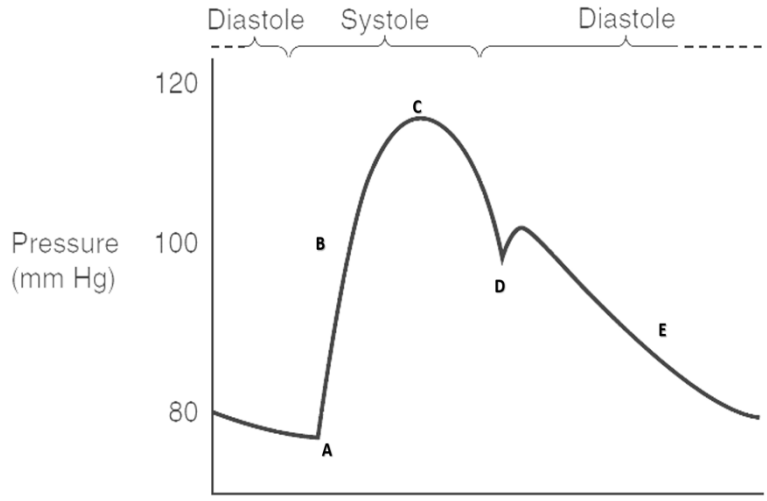

Figure 2.2: Schematic representation of the arterial pressure waveform at the level of the aortic arch of one cardiac cycle, with A = end-diastolic pressure; B = systolic upstroke; C = peak systolic pressure; D = dicrotic notch; E = diastolic downstroke. Adapted from [28]

2.3 The neonatal arterial pressure waveform

At the NICU, BP can be measured noninvasively and intermittently using a cuff or invasively via a peripheral arterial catheter – often placed in the radial or posterior tibial artery – or an umbilical arterial catheter. Intraarterial catheterization is indicated when frequent arterial blood sampling is required, for continuous BP monitoring or in case of an exchange transfusion. It allows for continuous monitoring of the arterial pressure waveform, of which a schematic representation is given in Fig. 2.2 [16, 28]. From this curve, several pressure readings are derived, such as systolic, diastolic and mean blood pressures. However, as the APW has a complex physiological basis and is determined by among other things SV, contractility and SVR, more information than just these single pressure readings may be hidden in the arterial curve [29, 35].

A schematic representation of the APW at the aortic root is depicted in Fig 2.2. The ejection of blood from the left ventricle causes a fast rise in pressure in the aorta, resulting in an upstroke (B) in the arterial waveform from diastolic (A) to systolic peak pressure (C). The pressure then drops and the onset of the diastolic part of the APW starts just after aortic valve closure, which is represented by the dicrotic notch (D). This is followed by a downstroke, representing diastolic relaxation (E) [28, 36].

2.3.1 *Advanced analysis of the arterial pressure waveform*

The APW may contain more clinically relevant information than solely pressure values [35, 36]. For example, the slope of the systolic upstroke reflects the pressure development during LV ejection and may therefore be related to myocardial contractility, as well as SVR [35-37]. Especially changes in peripheral dP/dt_{max} , which is the maximal slope of the systolic upstroke, and left ventricular dP/dt_{max} have been shown to correlate well with each other in adults [35, 38]. The diastolic component of the APW is largely a result of aortic compliance and radial expansion of the vessels that occurs during systole; during left ventricular ejection, blood is stored in the compliant aorta which is released during diastolic relaxation, creating the diastolic component of the APW [28]. Consequently, the shape of the diastolic part of the APW may be related to aortic compliance. Furthermore, the downstroke of the APW is related to SVR [36]. Being able to estimate SV and thus CO would provide a substantial and desirable advancement of hemodynamic monitoring. Many attempts have been made to derive SV and CO from the APW, of which area under the curve (AUC) analyses based on the Windkessel model have been most extensively studied [35, 39].

2.4 Invasive blood pressure measurement in neonates

Invasive blood pressure measurement is generally performed using a liquid-filled catheter-manometer system. Fig. 2.3 gives a schematic representation of the measurement mechanism. A catheter is introduced into the artery and filled with saline, which is connected to the transducer with an elastic diaphragm. In the figure, this is represented by a piston operating against a spring K, the elastic component. Blood pressure is presented to the tip of the catheter, leading to a displacement of volume within the catheter, causing a small amount of fluid to enter the

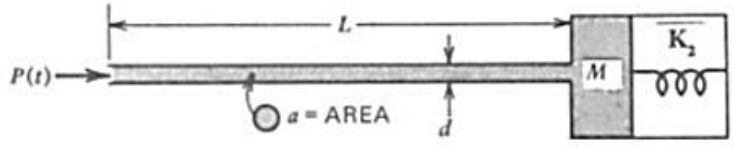

Figure 2.3: schematic representation of a liquid-filled catheter-manometer system with P(t) the applied (blood) pressure, a the area of the catheter, d the diameter, M the fluid mass in the catheter and transducer and K the elastic transducer diaphragm [23]

transducer. Resulting displacement of the elastic diaphragm is detected and translated to an electrical signal that is proportional to the blood pressure at the tip of the catheter [23].

Another way to measure blood pressure invasively is via a manometer-tipped catheter. This is considered to be a more accurate method than the CMS, as the transducer is placed directly into the catheter and there is no displacement of volume. However, this is currently not available in clinical practice [40].

2.5 Validity of invasive blood pressure measurement in neonates

Intra-arterial blood pressure recording via CMS is the current gold standard reference method for BP measurement [15]. It is deemed superior to noninvasive oscillometric blood pressure (NIBP) measurements as it allows for continuous monitoring of the full BP wave. Moreover, in their systematic review, Dionne et al. concluded that MBP, systolic pressure (P_S) and diastolic pressure (P_D) measurement by oscillometric methods are less accurate and precise than intra-arterial pressures, especially in small newborn infants in the lower pressure range [15]. It is generally known, however, that the intra-arterial blood pressure measurement via CMS is not free from difficulties or inaccuracies. Aside from risks such as ischemia, thrombosis and catheter-site infection, technical problems such as the need for calibration and the introduction of air bubbles affect measurement validity. The signal may be distorted by artifacts such as noise due to movement, but these are generally transient and easily detectable [41]. In contrast, characteristics of the catheter-manometer measurement system itself have a possibly long-lasting error-inducing effect on the arterial waveform. These characteristics, which are determined by the system's dynamic response (DR), dictate whether the arterial pulse is correctly translated from patient to a measured waveform [15, 24, 42].

2.5.1 *Dynamic response*

A CMS in situ can be approximated as a second-order dynamic system, which is characterized by the mechanical parameters elasticity (K), mass (M) and friction (I). Mathematically, this is described by the differential equation:

$$M\ddot{x} + I\dot{x} + Kx = P(t), \qquad \text{(Eq. 2.1)}$$

with x the displacement of the transducer diaphragm and $P(t)$ the resulting blood pressure.

In a CMS, elasticity is determined by the flexibility of the transducer diaphragm, mass is analogous to the mass of fluid moving in the system and friction is caused by pulsatile movement of the fluid within the catheter and tubing [24]. This is illustrated in Fig. 2.3. Displacement and release of a mass (M) suspended by a string with a certain elasticity (K) will cause the mass to oscillate. The frequency of oscillation is determined by both the mass and stiffness of the spring – the fluid mass within the CMS and stiffness of the transducer diaphragm, respectively.

This is the natural frequency (f_n) or resonant frequency of the system, and is determined by:

$$f_n = \frac{1}{2\pi}\sqrt{\frac{K}{M}}, \qquad \text{(Eq. 2.2)}$$

with f_n the natural frequency in Hz, M the fluid mass and K the spring or elastic diaphragm, given by:

$$K = \frac{A^2}{V_d}, \qquad \text{(Eq. 2.2)}$$

with A the diaphragm area and V_d the volume displacement in cubic millimeters when a pressure of 100 mmHg is applied.

Viscous drag resulting from friction (I) of the fluid entering the transducer leads to damping of the oscillation, thus determining how long it will last. Consequently, the dynamic response i.e. the characteristic behavior of a CMS is a result of friction as well. This effect is dictated by the damping coefficient (ζ), which is given by:

$$\zeta = \frac{16\eta}{d^3}\sqrt{\frac{3LV_d}{\pi\rho}}, \qquad \text{(Eq. 2.4)}$$

with η fluid viscosity, d catheter diameter, L catheter length, V_d transducer volume displacement and ρ fluid density [23].

In terms of the dynamic response parameters f_n and ζ, the CMS can be represented as a 2nd order dynamical system with the following differential equation:

$$\ddot{x} + 2\omega_n\zeta\dot{x} + \omega_n^2 x = \omega_n^2 P(t), \qquad \text{(Eq. 2.5)}$$

with $\omega_n = 2\pi f_n$ the angular frequency in rad/s.

2.5.2 *Effects on the arterial waveform and dynamic response requirements*

The combination of f_n and ζ will determine whether the patient's blood pressure is correctly translated to the waveform on the monitor. Ideally, the input to the transducer – the actual blood pressure – is the same as the output – the measured blood pressure. This requires for the output to have the same frequency components with the same relative amplitudes and phases as the input signal; no frequencies are either attenuated or enhanced by the transducer system. However, dependent on the combination of natural frequency f_n and damping coefficient ζ, frequency components of the true arterial waveform may be enhanced or attenuated [23].

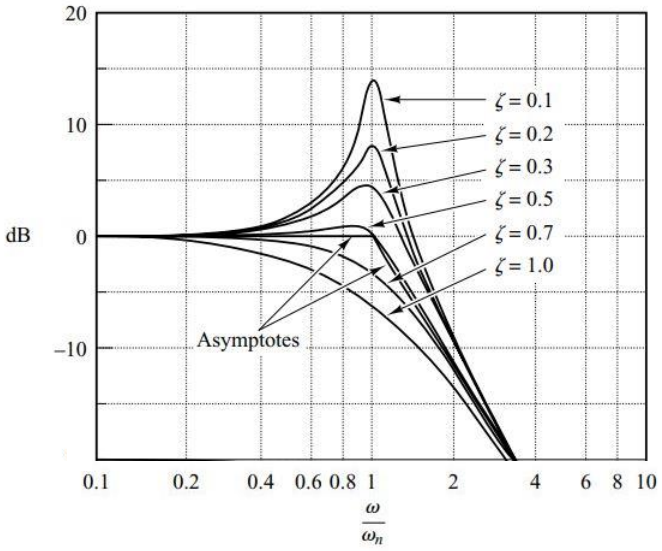

Figure 2.4: Log-magnitude curves of a 2nd order system given by Eq. for varying damping coefficients. ω = frequency component of the signal in rad/s; ω_n = natural frequency in rad/s; ζ = damping coefficient. Adapted from [43]

Figure 2.5: Schematic representation of the effects of dynamic response on the arterial waveform. Left: overdamped waveform; middle: valid waveform; Right: underdamped waveform [author's own data].

Frequency response is the steady-state response of a system to a sinusoidal input. Magnitude and phase of the response can vary as the input frequency is changed. The magnitude response of a second order system is shown in Fig. 2.4. As it is desired to have an output with the same frequency components as the input, a flat response up to a high frequency and thus a high natural frequency is preferential. As can be seen in Fig. 2.4, magnitude enhancement or attenuation at the natural frequency is dependent on the damping [43]. Dependent on the damping coefficient, the measurement system can be underdamped ($\zeta < 1$), critically damped ($\zeta = 1$) or overdamped ($\zeta > 1$).

With low underdamping, i.e. $\zeta < 0.5$, a peak occurs at the natural frequency (f_n or $\frac{\omega}{\omega_n}$) and surrounding frequencies are enhanced in amplitude, as is illustrated in Fig. 2.4. This causes artificial oscillations in the blood pressure signal, which is shown in the right waveform of Fig. 2.5. Frequencies above the natural frequency are attenuated, low frequencies retain their magnitude. With higher underdamping, amplitude enhancement at natural frequency decreases and evolves into attenuation. The left waveform of Fig. 2.5 illustrates that damping of frequencies leads to a loss of complexity in the signal and flattening of the pulse wave. These effects become more prominent with increasing damping coefficient. Note that underdamped systems can give lead to seeming overdamped waveforms as the left waveform of Fig. 2.5, when ζ approaches a value of 1. Ideally, damping is around 0.65 for the widest frequency response without any enhancement. For high natural frequency, however, damping is of less importance as the flat part of the frequency response may be large enough to attain all frequencies within the arterial waveform with the correct amplitude. This is illustrated by the middle waveform of Fig. 2.5 [23, 44].

In 1981, Gardner evaluated dynamic response requirements of blood pressure measurement with CMS in the intensive care setting. He described changes in the arterial waveform as a result of varying natural frequency and damping coefficients. High-fidelity patient data were processed through a catheter-transducer simulator that allowed a range of natural frequencies and damping coefficients. The processed data were visually compared to the original data and depending on the differences, the waveform was characterized as either 'overdamped', 'underdamped' or 'adequate'. These findings were summarized in a frequency/damping plot as shown in Fig. 2.6. The grey area indicates all combinations of f_n and ζ for which dynamic response was deemed adequate. We can see that the range of adequate damping coefficients increases with increasing natural frequency, which is in line with Fig. 2.4. From this publication onwards, the graph shown in Fig. 2.6 was considered to represent the generalized requirements for dynamic response of blood pressure measurement with CMS. However, as Gardner introduced this figure as the dynamic response requirement for a single patient, it may not necessarily be generalizable to all patients and waveforms. Furthermore, he showed that a patient with a rapid HR and high dP/dt_{max} required a higher f_n [24].

2.5.3 *Factors affecting dynamic response*

Dynamic response is determined by the mechanical properties of the CMS. Substituting Eq. 2.2 in Eq. 2.3, and taking into account that $M = La\rho$, we obtain:

$$f_n = \frac{A}{2\pi}\sqrt{\frac{1}{La\rho V_d}}, \qquad \text{(Eq. 2.6)}$$

with A the area of the transducer diaphragm, L and a the length and area of the catheter, respectively, ρ the fluid density and V_d the diaphragm displacement volume. Consequently, natural frequency depends on the transducer diaphragm area and the diaphragm displacement volume, which are properties that will remain the same if the same transducers are used. In contrast, the length and area of the catheter may be varied. For example, longer tubing will lead to a smaller natural frequency and consequently a higher chance of under- or overdamping of the waveform.

Considering Eq. 2.4, we can conclude that damping depends on several of the same factors as the natural frequency. Longer tubing and a more elastic diaphragm will lead to higher damping. Furthermore, damping is the result of viscous drag of the fluid against the catheter, so the damping coefficient is also dependent on the fluid viscosity. The introduction of air bubbles in the catheter will increase the volume displacement of the transducer, as air is compressible. This corresponds to a decrease in stiffness. Compliant tubing has the same effect, resulting in increased damping as well as a smaller natural frequency, leading to an overdamped waveform as illustrated in the left panel of Fig. 2.5 [23, 45].

2.5.4 *Dynamic response measurement*

Dynamic response of an arterial catheter can be assessed in vivo by the fast flush test. For this test, the pressure transducer should be connected to a pressure bag. By activating the fast flush system, the tubing and transducer system are suddenly filled with fluid at a high pressure, usually 300 mmHg. This sudden pressure change leads to the superimposition of a square wave on the blood pressure waveform, as is illustrated in Fig. 2.7.

This fast flush test essentially 'activates' the system. As a CMS can be considered a 2nd order dynamical system, this activation will prompt an oscillation at the system's natural frequency that comes to rest according to its damping coefficient. This damped oscillation is superimposed on the arterial waveform as well and allows for calculation of the natural frequency and damping

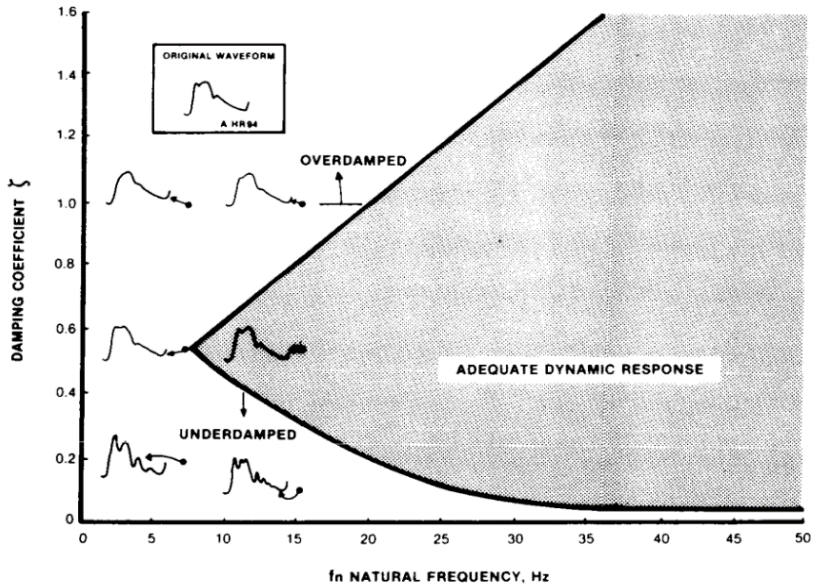

Figure 2.6: Dynamic response (f_n and ζ) requirements of blood pressure measurement via CMS for a single patient [21]

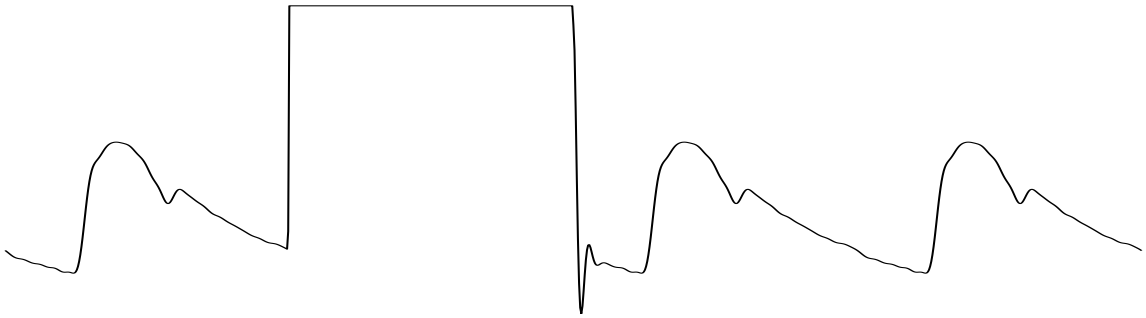

Figure 2.7: Schematic representation of the fast flush test, superimposing a square wave on the arterial pressure waveform [author's own data].

coefficient. In this way, the fast flush test gives an assessment of the measurement system's dynamic response and thus an indication of the validity of the arterial pressure waveform [44, 46, 47].

2.5.5 *Dynamic response of catheter-manometer systems in neonates*

The fast flush test measures the dynamic response of the full in vivo liquid-filled catheter-manometer system [46]. However, the technique is not applicable in neonates as it may perturb volume status of the patient. Van Langen et al. developed a flush-pulse test for evaluation of the dynamic response of arterial catheters in neonates. The transducer is not connected to a pressure bag but to an infusion pump. A flush-pulse is produced by opening and releasing the fast-flush valve, which in this case does not lead to a change in the net flow of infusion fluid as the flow rate is set by the infusion pump. However, there is an effect on the fluid column that is in-line with the tubing system, producing a flush-pulse that does not affect the patient's circulation but elicits a response as well. From the oscillating flush-pulse response superimposed on the patient's APW, the dynamic response of the catheter system can be derived [48].

Although Van Langen et al. validated their flush pulse method with in vitro measurements, it has of yet not been applied in clinical practice. Consequently, little is known about the actual dynamic response of CMS when they are used in neonates. Dynamic response may be different in neonates due to differences in developmental physiology. Although the dynamic response figures as presented by Gardner have since been used as generalized for all patients, he himself showed that the effect of a certain dynamic response is dependent on waveform characteristics and especially heart rate [24]. As the neonatal population significantly differs from the adult population in heart rate and in some cases in cardiovascular physiology, dynamic response requirements determined for adults cannot be readily translated to the neonatal population. Moreover, the neonatal population itself is highly variable so generalized dynamic response requirements may not even be achievable.

3 Effects of dynamic response of on the validity of the neonatal arterial pressure waveform – a simulation study

3.1 Introduction

In critically ill neonates, intra-arterial pressure recording via a catheter-manometer system is the gold standard method for continuous blood pressure measurement [15]. It is generally considered to provide the most accurate measurement and is therefore the preferred method in neonatal care [16]. Other methods of blood pressure measurement, such as the non-invasive oscillometric method and finger-cuff techniques, are validated with respect to the intraarterial blood pressure [15, 49, 50]. Since decades however, it has been generally known in the intensive care practice that the validity arterial pressure waveform measured via an indwelling liquid-filled catheter is subject to the measurement system's dynamic response [24]. The dynamic response is a characteristic of the CMS which dictates whether the fluctuations in blood pressure within the arterial tree are correctly translated to a measured waveform. To ensure valid measurement of the neonatal arterial waveform, it is therefore important to identify a CMS' dynamic response and its effects on measurement validity.

A CMS in situ can be considered a 2nd order dynamic system, of which the dynamic response is characterized by the natural frequency (f_n) and damping coefficient (ζ). Often, literature describes dynamic response requirements solely in terms of the natural frequency. The frequency content of the signal is not affected below the natural frequency and will be present in the measured signal with the same amplitude as in the original pulse. Geddes described that a natural frequency of at least the sixth harmonic of the HR is required for an adequate arterial waveform, but most literature suggests ten harmonics [23, 24]. Of course, the actual requirement depends on the desired fidelity. Gardner showed that dynamic response and thus the validity of the intra-arterial waveform is dependent on the interaction between natural frequency and damping coefficient, not solely on the f_n [24]. Frequencies around f_n may be enhanced according to ζ and frequencies above f_n are increasingly attenuated. A low natural frequency only allows for a small range of damping coefficients to ensure a valid waveform. Consequently, both f_n and ζ may be taken into account.

Since its publication in 1981, Gardner's natural frequency/damping coefficient plot, which was shown in Fig. 2.6 in Ch. 2, has been accepted as a generalized dynamic response requirements guideline for arterial blood pressure measurement via CMS in all patients. If f_n and ζ are known, this plot can show whether this specific dynamic response would result in an adequate arterial waveform. However, Gardner himself showed that the effect of a certain dynamic response is dependent on waveform characteristics and heart rate in particular [24]. Consequently, dynamic response requirements may not be generalizable to every patient. As the neonatal population considerably differs from the adult population in for example heart rate cardiovascular physiology, dynamic response requirements determined for adults cannot be readily translated to the neonatal population.

Van Genderingen et al. recognized this issue and attempted to evaluate dynamic response requirements of intraarterial catheters in neonates. From 21 critically ill newborns, they recorded high-fidelity arterial blood pressure waveforms which were processed through a computer simulated CMS. f_n and ζ were varied and the resulting processed waveform was compared to the original by calculating the percentage error of PP, P_S and P_D. Van Genderingen et al. propose a maximal pressure error of 2% for neonatal care, dictating that natural frequency should be at least 20 Hz, while only very small range of damping coefficients is acceptable for natural frequencies up to about 40 Hz. This imposes much more strict dynamic response requirements for CMS in neonates than the generally accepted guidelines assumed from Gardner [20, 24]. Though these dynamic response requirements were proposed for the neonatal

populations specifically, the heterogeneity of this patient group may pose an issue for the applicability of these guidelines. Arterial waveform measurement in an extremely preterm neonate with a heart rate of 180 bpm may require rather different values of f_n and ζ than in a term neonate with a generally lower heart rate. Consequently, generalized dynamic response requirements may not even be achievable in the neonatal population.

It is generally known that arterial pressure waveform measured with CMS is subject to erroneous measurement depending on the system's dynamic response [24]. However, little is known about the actual effect of various dynamic response on the neonatal arterial waveform. The goal of the current study was therefore to assess the effect of varying dynamic response on pressure values as well as wave shape in the neonatal population.

3.2 Methods

To evaluate the effect of dynamic response on the neonatal arterial waveform, we performed several computer simulations. We simulated various waveforms and processed these through a simulated catheter-manometer system with several combinations of natural frequency and damping coefficients.

3.2.1 *Simulation of the arterial blood pressure waveform*

The neonatal arterial blood pressure waveform was simulated in two ways. A realistic representation of the waveform was achieved by taking the sum of a series of cosine waves with frequencies that are the harmonics of the fundamental frequency – in this case the heart rate.

This is described by the equation:

$$P(t) = P_d + PP \sum_{k=0}^{M} A_k \cos(2\pi k f_0 t - \varphi_k), \qquad \text{(Eq. 3.1)}$$

with $P(t)$ the resulting arterial pressure waveform, P_d the diastolic pressure, PP the pulse pressure, $k = 0{:}M$ the harmonic frequency count, M the number of harmonics, A_k the amplitude, f_0 the fundamental frequency, t the time and φ_k the phase.

It has been suggested that up to six harmonics of the fundamental frequency, the heart rate, are required for adequate reproduction of the arterial waveform. For a good reproduction of the arterial waveform, up to six harmonics are required, but accuracy and signal complexity increases with each added harmonic [23]. We used Eq. 3.1 to simulate the arterial blood pressure waveform with up to 15 harmonics of the heart rate to ensure sufficient waveform complexity. With increasing harmonic frequency, the amplitude of the harmonic decreases.

Furthermore, we simulated the arterial blood pressure waveform in its most basic form as a reverse sawtooth wave with similar fundamental frequency and amplitude range to evaluate the effect of dynamic response on a simple representation of the arterial waveform.

3.2.2 *Simulation of a catheter-manometer system*

A CMS can be described as a 2nd order dynamical system with transfer function:

$$H_{CMS} = \frac{\omega_n^2}{s^2 + 2\zeta\omega_n s + \omega_n^2}, \qquad \text{(Eq. 3.2)}$$

with $\omega_n = 2\pi f_n$ the natural frequency in rad/s, ζ the damping coefficient and s the Laplace operator.

Table 3.1: Description of four different simulated arterial pressure waveforms.

	Type	HR (bpm)
Waveform 1	Complex waveform	140
Waveform 2	Reverse sawtooth	140
Waveform 3	Complex waveform	180
Waveform 4	Reverse sawtooth	180

Abbreviations: HR = heart rate; bpm = beats per minute

Table 3.2: Description of the four different dynamic responses

	f_n (Hz)	ζ
Setting 1	30	0.7
Setting 2	10	0.7
Setting 3	10	0.2
Setting 4	10	1.2

Abbreviations and symbols: f_n= natural frequency, ζ = damping coefficient

This function was implemented in Matlab (MATLAB R2018a, The MathWorks, Inc., Natick, Massachusetts, United States) to simulate a CMS. Subsequently, the time response of this simulated system to the original simulated arterial waveforms was computed, yielding a transformed arterial waveform as output. Varying f_n and ζ, the effects of changes in dynamic response on the output arterial waveform could be studied.

3.2.3 *Analysis*

To analyze the effect of dynamic response on different waveform types, we used four waveforms of which the basic characteristics are described in Table 3.1, with pressures set to $P_S = 60$mmHg and $P_D = 40$mmHg for each of the four waveforms. As illustrated in Fig. 3.1, these signals were processed through the simulated CMS to obtain a transformed arterial waveform. To assess the effect of dynamic response on these signals, f_n and ζ were given the values described as settings in Table 3.2. The resulting transformed waveforms were compared visually based on general wave shape, the presence, prominence, location and height of landmarks such as the dicrotic notch, and slopes of up- and downstrokes.

For a quantitative analyses of the effect of dynamic response on the neonatal arterial waveform, we used waveform 1. The signal was processed through the simulated CMS as shown in Fig. 3.1 with f_n varied from 1 to 50 Hz with increments of 1 Hz and ζ was varied from 0.1 to 2 with increments of 0.1. The original simulated and transformed waveforms were compared in terms of systolic pressure, diastolic pressure, pulse pressure, mean arterial pressure dicrotic notch pressure, systolic duration, dP/dt_{max} and systolic AUC (AUC_S). A short explanation of the calculation of these parameters is provided in the Appendix. Differences in these parameters between the original and transformed signal were analysed in both absolute values and percentages. Furthermore, the root mean square error (RMSE) between the two full waveforms was calculated. Percentage pressure errors of systolic pressure, diastolic pressure and pulse pressure for each combination of f_n and ζ were summarized in heat maps, as well as the waveform RMSE.

3.3 Results

3.3.1 *Visualizing the effect of dynamic response on different waveform types*

We simulated four types of waveforms, shown in Fig. 3.1. These waveforms were processed through a simulated CMS with varying f_n and ζ to assess the effect of dynamic response on

different types of waveforms. In all waveform types, the first dynamic response setting ($f_n = 30$ Hz, $\zeta = 0.7$), resulted in a good reproduction of wave shape and pressure values when assessed visually. With lower natural frequency, this deteriorated in all cases, especially affecting the steepness of the systolic upstroke and prominence of the dicrotic notch. Decreasing the damping coefficient led to oscillations in the waveforms, with a corresponding increase in systolic pressure, small decrease in diastolic pressure and thus overestimation of pulse pressure. Considering waveforms 2 and 4, the reverse saw tooth waves, an oscillation can be observed with low damping that is very similar to the effects seen in the more complex simulated waveforms 1 and 3. High damping, shown in the right most column of Fig. 3.1, results in the opposite effect to low damping; diastolic pressure is overestimated, and systolic pressure and pulse pressure are underestimated. Furthermore, the dicrotic notch is barely discernable in the transformed waveforms 1 and 3. Waveform 3 – with similar pressures to waveform 1 but a higher heart rate and longer systolic period – is affected by inadequate dynamic response to a greater extent than waveform 1 in both pressure errors and wave shape distortion. A similar result is seen in waveform 4 with respect to waveform 2; a higher fundamental frequency leads to a worse reproduction of the reverse sawtooth waveform.

3.3.2 *Quantifying the effect of dynamic response on the neonatal arterial waveform*

To quantify the effects of varying dynamic response, waveform 1 as given in Table 3.1 and Fig. 3.1 was processed through the simulated CMS with varying combinations of natural frequency and

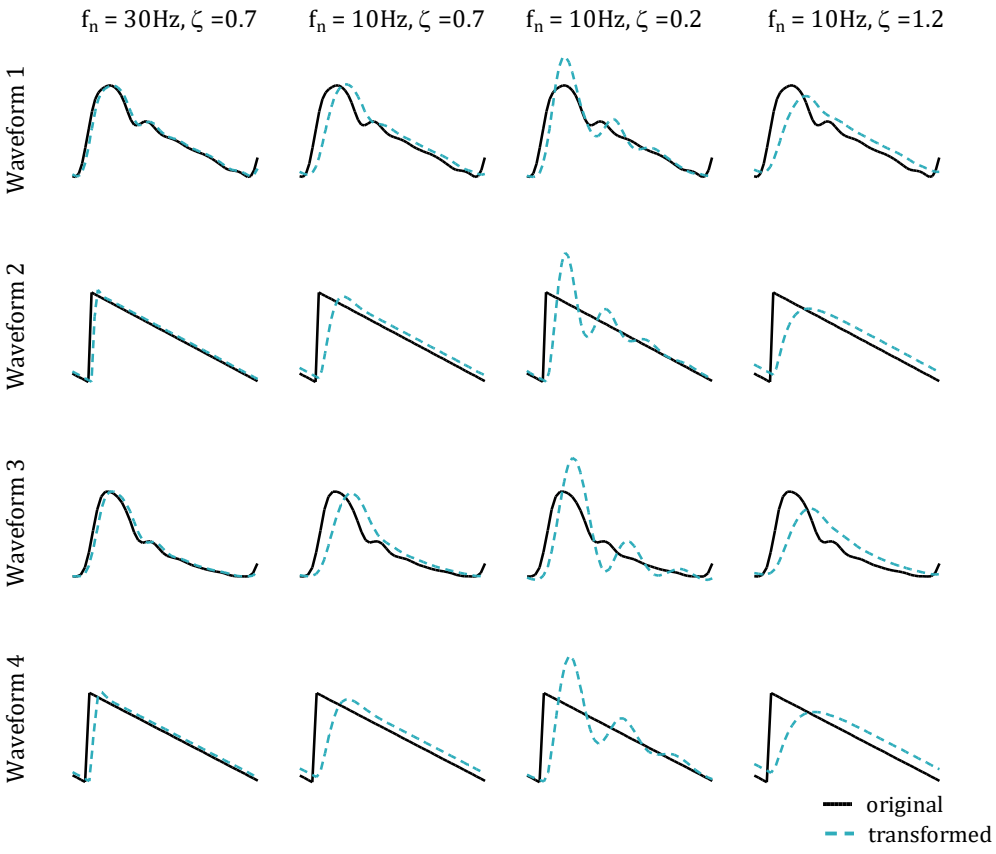

Figure 3.1: Effects of varying dynamic response (columns) on four different waveforms (rows). Waveform 1 is a complex waveform with heart rate of 140bpm; waveform 2 is a reverse sawtooth waveform with heart rate of 140bpm; waveform 3 is a complex waveform with heart rate of 180bpm; waveform 4 is a reverse sawtooth waveform with heart rate of 180bpm. The black lines represent the original simulated waveform, the dashed blue lines represent the transformed waveforms as a result of simulated dynamic response.

damping coefficient. Several baseline parameters calculated from this simulated waveform are given in Table A.1 in the Appendix.

In Fig. 3.2, four heat maps are shown, giving an overview of the percentage errors in systolic pressure (a), diastolic pressure (b) and pulse pressure (c) and the RMSE between the full waveforms (d) for a wide range of f_n and ζ. In Figs. 3.2 a, b, and c, a wedge-shaped area can be discerned containing the darkest color and thus corresponding to a low percentage error. For pulse pressure, this area is smallest as in this case, the erroneous effects on diastolic and systolic pressure are combined. The figures illustrate that with greater natural frequency, the range of damping coefficients yielding low errors increases.

Mean blood pressure errors are not included in Fig. 3.2, as these were less than 0.29 mmHg or 0.6% in all simulated combinations of f_n and ζ. This is illustrated in Table A.2 in the Appendix, which shows the maximal absolute and percentage errors in nine combinations of f_n and ζ, for systolic pressure, diastolic pressure, pulse pressure and mean blood pressure. Low natural frequency, in this case 10 Hz, led to the highest errors especially in the case of low damping ($\zeta = 0.2$) with errors of 11, -1 and 34% for P_S, P_D and PP, respectively. For overdamping with $\zeta = 1.2$, these errors were smaller with values of respectively -4, 3 and -17%. With increasing frequency, these errors decreased. For $\zeta = 0.7$, errors were small in all cases, with maximal error of -2% for pulse pressure.

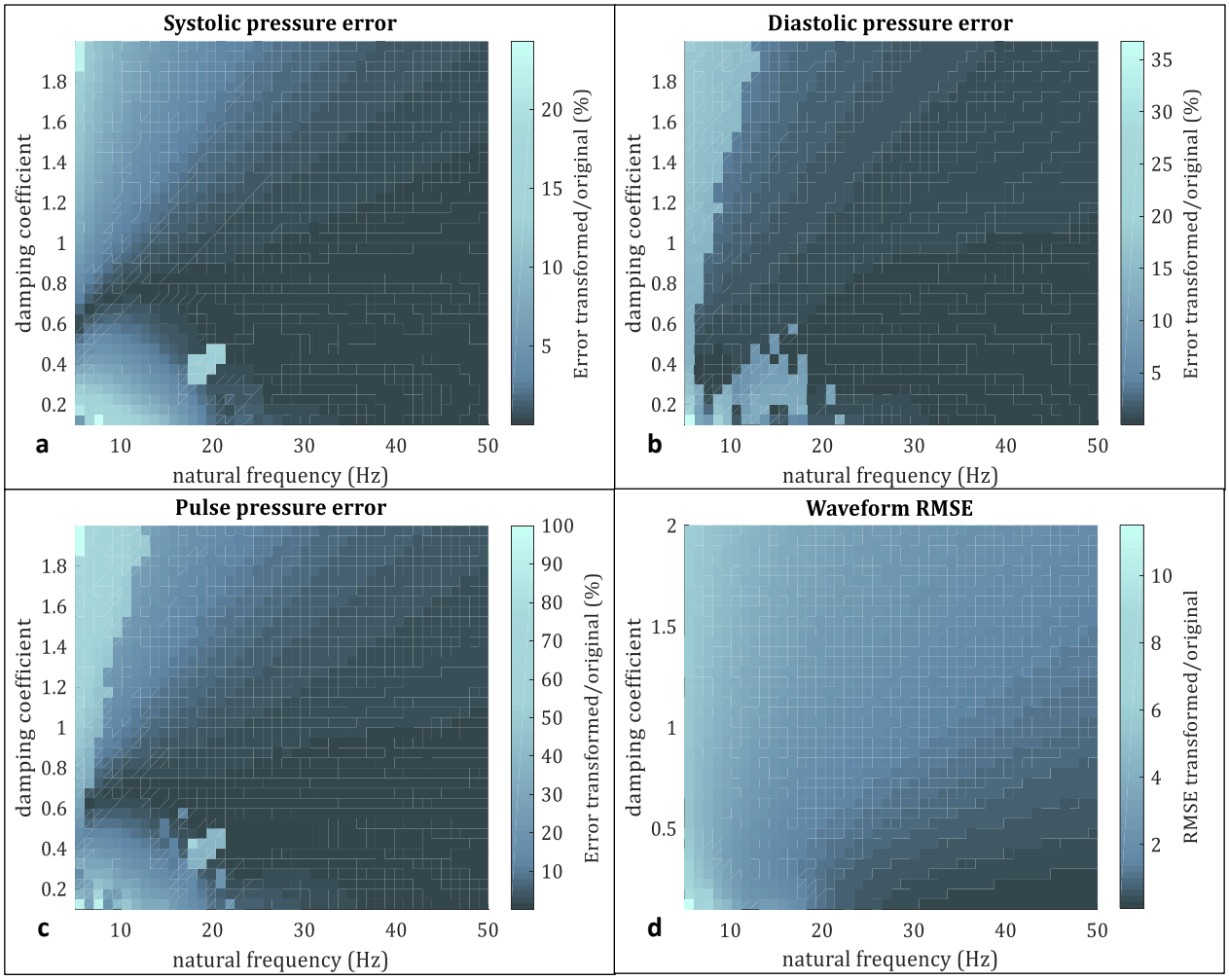

Figure 3.2: Heat maps of percentual errors in systolic pressure (a), diastolic pressure (b) and pulse pressure (c) and heat map of root mean square error (RMSE) of the full waveform (d) for varying dynamic response. Note that each figure has its own color bar.

Fig. 3.2 d shows the heat map of RMSE calculated between the original simulated waveform and the transformed waveforms for varying dynamic response. This figure shows a wedge-shaped area as well, though less prominent and placed more towards the high-frequency/low-damping part of the figure than in Figs. 3.2 a,b and c. RMSE becomes increasingly higher with decreasing frequency. Furthermore, a higher damping factor generally yielded higher RMSE. Numerical values of RMSE for several combinations of f_n and ζ are given in Table A.3 in the Appendix.

dP/dt_{max}, the slope of the systolic upstroke, is decreased with nearly 50% in the case of low natural frequency and high damping and the systolic area under the curve is affected even more extensively. The effects on dicrotic notch pressure are less than $\pm$ 14%. Location of the dicrotic notch and thus the area under the systolic part of the curve and duration of the systolic period, however, were not calculable in case of low frequency and high damping, as there was no discernible notch in the downstroke of the signal. T_S and P_{DN} were most affected by a DR of $f_n = 10$ Hz, $\zeta = 0.2$ with maximal percentage errors of 77% and -11%, respectively. For this system, AUC_s error was 49% while it was 60% for a natural frequency of 20 and low damping. For $\zeta = 0.7$, independently of natural frequency, all percentage errors of AUC_s, T_S and P_{DN} had absolute values smaller than 20%. These numerical results of errors in waveform parameters for varying dynamic response are given in Table A.4 in the Appendix.

3.4 Discussion

The goal of this study was to assess the effect of varying dynamic response on pressure values as well as shape of the neonatal arterial waveform, by using computer simulations. Inadequate dynamic response led to noteworthy changes in wave shape, for both excessive and insufficient damping. Inadequate dynamic response led to erroneous measurement of mainly systolic pressure and pulse pressure. MBP was not notably affected by inadequate dynamic response.

3.4.1 *Visualizing the effect of dynamic response on different waveform types*

We analyzed the effect of specific values of dynamic response on simulated waveforms with various heart rates – two complex waveforms providing a realistic representation of the arterial waveform with HR = 140 bpm and HR = 180 bpm and two simplified waves with the same frequencies. Decrease of f_n led to a worse reproduction of all waveforms. With a high ζ, narrowing of *PP* and a n indiscernible and less prominent dicrotic notch was observed. Low damping led to widening of *PP* and additional oscillations in the signal. These effects were present in all four simulated waveforms to a variable extent. Waveforms with a HR = 140 bpm were less distorted than those with higher HR. As the heart rate determines the fundamental frequency of a signal, higher HR will result in higher frequencies to be present in the signal with larger amplitudes than for lower HR, thereby requiring a larger f_n for a valid signal.

Since its publication, arterial blood pressure measured with CMS has been validated against Gardner's plot providing generalized dynamic response requirements. Devasahayam et al. aimed to build on Gardner's knowledge on dynamic response by providing numerical error values summarized in heat maps similar to ours in Fig. 3.2. They found that a blood pressure signal with a higher heart rate was more prone to errors, which is in line with our findings [24, 51]. Van Genderingen et al. recognized that the generally higher HR within the neonatal population could invalidate the use of Gardner's plot for dynamic response requirements in newborns. They proposed requirements based on calculated errors in neonatal arterial waveforms [20, 24]. Even within the neonatal population, however, HR can be highly variable between for example an extremely premature newborn and a term neonate. We have demonstrated that two different blood pressure signals that would not be uncommon in our NICU would yield different arterial waveforms in case of the same inadequate dynamic response. Consequently, even within the neonatal population the effects of dynamic response are not uniform and any attempt of generalization of its effects or requirements may be futile.

We analyzed the prominence and placement of the dicrotic notch, an incisura in the downstroke of the waveform marking the division between systole and diastole. It is used as a visual marker for an adequate waveform; if the dicrotic notch is visible, the waveform is deemed adequate. With very low d, however, an incisura may be present in the signal while P_S and PP are overestimated. Interestingly, when applying the same dynamic response to a reverse sawtooth wave, oscillations arise in the downstroke that are strikingly similar to the oscillations visible in the underdamped complex waveforms, even though there was no incisura in the original wave. Possibly, the incisura was not the dicrotic notch but rather a result of resonance of the systolic upstroke. Consequently, dicrotic notch presence does not suffice as a criterium for a valid arterial waveform. Schwid et al., though not analyzing CMS, similarly found that waveform distortion between central and radial pressures resulted in an incisura that was not related to the dicrotic notch [52].

3.4.2 *Quantifying the effect of dynamic response on the neonatal arterial waveform*

We quantified the effects of varying dynamic response on P_S, $P_D PP$ and MBP derived from a simulated neonatal arterial waveform. Several waveform parameters and the RMSE between the full waveforms were analyzed as well. Dynamic response had no effect on MBP. Maximal percentage errors of P_D were 3% in case of low f_n and high ζ. In Fig 3.2, showing error heat maps, we observed small areas in which P_D error was higher, which occurred only for very low f_n and extreme values of ζ. Consequently, we conclude that the validity of MBP and P_D are not considerably affected by the system's dynamic response. This was different for $P_S$and PP. A simulated underdamped system with low $f_n$and low ζ led to the largest errors in these parameters, followed by overdamping and $\zeta = 0.7$. With increasing f_n, these effects decreased. This was also observed in the heat maps showing a wedge-shaped area of small errors pointed towards low fn. Consequently, the effect of dynamic response on the validity of $P_S$and PP is dependent on the combination of f_n and ζ. Errors in $P_S$and PP measurements are largest for lowf_n, low ζ systems. In clinical practice in the NICU, MBP is the most often used parameter in the assessment of hemodynamic status. We have shown that MBP is largely unaffected by inadequate dynamic response of a CMS and can therefore safely be used for assessment of the circulation. Pulse pressure, though used less often than MBP, is an important factor in the assessment of adequate circulation as it is related more closely to cardiac output. Our results show that pulse pressure calculated from the arterial waveform measured with CMS may not always be valid due to inadequate dynamic response of the system, especially in case of very low f_n and ζ.

We also aimed to quantify the effect of varying dynamic response on several wave shape parameters. The steepness of the systolic upstroke dP/dt_{max} has been suggested to be indicative of myocardial contractility. As steepness is proportional to the signal's frequency content, a low natural frequency may affect the systolic upstroke. Our results were in correspondence with this hypothesis; with lower natural frequency and especially with high damping, the systolic upstroke considerably lost in steepness. For $f_n = 10$ Hz and $\zeta = 1.2$, dP/dt_{max} decreased up to 46%. In contrast, low damping could result in a small increase in steepness, showing that adequate dynamic response is of importance to be able to use dP/dt_{max} reliably in more advanced analyses. The effects of inadequate dynamic response were even larger for low-frequency overdamping when looking at the parameters that are calculated by making use of the dicrotic notch, P_{DN}, $T_S$and the area under the systolic part of the arterial curve, as the dicrotic notch was not discernible for this specific dynamic response. Low damping led to considerable signal distortions as well, with high percentual errors for systolic duration and $AUC_S$of 77% and 60%, respectively. This indicates that wave shape is mainly affected by inadequate dynamic response and greatly impacts the reliability of methods of cardiac output estimation that are based onAUC_S, such as arterial pulse contour analysis.

3.4.3 *Study limitations*

We studied the effects of varying dynamic response on neonatal arterial waveforms by making use of computer simulations. We simulated both the waveforms and the catheter-manometer systems with varying dynamic response. As simulations are a simplification of the real world, our results may not fully represent the effects of dynamic response of CMS in situ on the arterial waveform in a newborn patient. Ideally, the blood pressure waveform would be measured by a manometer-tipped catheter – as a high-fdielity gold standard – simultaneously with CMS measurement, while varying the CMS' dynamic response. However, dynamic response of CMS cannot be manually changed precisely. More importantly, the invasiveness of the gold standard would provide ethical difficulties. Furthermore, modelling a CMS as a 2nd order dynamical system has been generally accepted and validated [53].

In our study, we have shown that heart rate is of influence on the extent to which the arterial waveform is distorted by inadequate dynamic response. Hence we have stated that the heterogeneity of the neonatal population – which among other things constitutes in variable heart rate in heart rate – limits the possibility for generalized dynamic response requirements within critically ill newborns. However, we also only considered four waveform types and calculated errors in only one. Theoretically, we would need to analyze all possible arterial waveforms with varying shapes, pressures and frequency content to get complete knowledge on the actual effects of dynamic response on any arterial waveform. Some signals may be more complex than others and with changes in heart rate, the shape of the waveform may change as well.

3.4.4 *Future perspectives*

Ideally, we want to know the effects of dynamic response on any possible arterial waveform. However, analysis of all variations of these signals provides a nearly impossible task. As we have seen that heart rate has a considerable effect on the dynamic response effects, error calculations for various ranges of heart rate may provide enough information on effects of inadequate dynamic response. This could easily be realised using the simulations described in this study. Additionally, the dynamic response of the measurement system would need to be measured and compared with the effects calculated in our simulations. Although it is useful to know the values of the errors that could induced by the catheter-system, it is also of importance to evaluate the causes of inadequate dynamic response. Furthermore, it would be even more beneficial if it were possible to correct for dynamic response errors. Measurement of dynamic response and evaluating the possibility to correct for dynamic response induced errors should be important aspects of further research.

3.4.5 *Conclusions*

Using computer simulations, we have shown that an inadequate dynamic response of a CMS can considerably affect wave shape, systolic pressure and pulse pressure. As these effects are influenced by the heart rate, they are not uniform within any patient group let alone in the heterogeneous neonatal population. Although we have shown that inadequate dynamic response can theoretically lead to pulse pressure errors up to 34%, the clinical implications of these results on can only be evaluated by actually measuring dynamic response in a clinical setting. For future research, it may be relevant to evaluate the possibility for reconstruction of arterial waveforms that are distorted by dynamic response.

4 Validity of intra-arterial blood pressure waveform recordings via a catheter-manometer systems in critically ill neonates based on dynamic response measurements

4.1 Introduction

In the NICU, patients are catheterized with an arterial line for hemodynamic monitoring in case of cardiorespiratory instability, need for continuous blood pressure monitoring, frequent blood sampling and exchange transfusion [16, 21]. In the previous chapter, we showed that the neonatal arterial waveform can be affected by the dynamic response of the measurement system, in both pressure values and wave shape. However, the dynamic response is not routinely measured in the NICU and the clinical implications of these possible dynamic response effects are still unknown.

In adults, dynamic response of a catheter manometer system can be measured by the fast flush test. As a CMS behaves like a 2nd order dynamic system, so an 'activation' of the system by for example a sudden increase in pressure will prompt the system to oscillate at its natural frequency and come to rest as a result of its damping coefficient. For the fast flush test, the CMS is connected to a pressure bag and opening of the flush valve will briefly expose the system to a high pressure. After the flush, the system returns to its baseline with a damped oscillation. From the oscillation, the natural frequency and damping coefficient can be derived [44, 46, 47]. However, as this method requires a relatively large fluid of volume to enter the circulation with each test, the method is not applicable in neonates. The fluid load could disturb the patients' circulation, especially in low birth weight infants [48].

Van Langen et al. therefore developed the flush pulse test; a method for dynamic response testing safe for the neonatal population. In the NICU, the flush system of the pressure transducer is not connected to a pressure bag but to an infusion pump. Opening and closure of the flush valve will therefore not lead to the introduction of a large amount of fluid in the circulation. However, there is an effect on the fluid column that is in-line with the tubing system, producing a flush-pulse that does not affect the patient's circulation but elicits a response as well. From the oscillating flush-pulse response superimposed on the patient's APW, the dynamic response of the catheter system can be derived [48].

Although Van Langen et al. validated their flush pulse method with in vitro measurements, it has not yet been applied in clinical practice. Consequently, the clinical applicability and feasibility of this method at the NICU are as of yet unknown. The actual extent to which neonatal arterial blood pressure measurements via CMS are in practice affected by their dynamic response has rarely been investigated, due to the absence of adynamic response measurement method deemed safe for the neonatal population.

A limitation of all methods for dynamic response testing to date is their applicability to only underdamped systems [24, 46, 48]. In literature, a CMS in situ has generally been described as an underdamped system [24, 42]. For example, dynamic response measurements of several in-dwelling catheter transducer systems in adults by Gardner showed damping coefficients of 0.32 or lower in 16 of 17 cases [24]. Similar results have been found for both umbilical and radial artery catheters in the neonatal population [20, 54, 55]. Consequently, characterization of overdamped systems seems redundant. In our experience at the NICU, however, many arterial lines do not seem underdamped, as additional oscillations are rarely seen in the signals and the dicrotic notch is not always clearly discernible. The results of the study by Van Langen et al. also showed multiple overamped arterial lines. Consequently, characterization of overdamped systems may provide relevant information as well.

To obtain a comprehensive view on the range of dynamic responses in the NICU, the goal of the current study was to use the flush-pulse technique in routine neonatal care to assess dynamic response of intra-arterial CMS. A secondary aim was to evaluate the feasibility of the flush-pulse method in routine clinical care at the NICU. Furthermore, we aimed to develop a method to be able to characterize critically damped and overdamped systems as well.

4.2 Methods

4.2.1 *Subjects and measurements*

In July and August 2021, patients admitted to the NICU with an intra-arterial line were included in the study. Exclusion criteria were planned removal of arterial line within 24 hours and high-frequency oscillatory ventilation. Patients receiving multiple arterial lines in subsequent epochs due to for example luxation or clinical deterioration were included multiple times. Measurements were performed from moment of inclusion until removal of the catheter or discharge to another hospital.

For included patients, nursing staff was instructed to register all moments of routine catheter flushing on the monitor that patients were connected to. No additional medical actions concerning the patients were required for this study. Registration of flushing moments and arterial blood pressure readings were collected in a data warehouse.

4.2.2 *Calculations and analysis*

For calculation of dynamic response, the flush-pulse test as described by Van Langen et al. was used, in which closure of the flush valve after routine flushing superimposes a flush pulse response on the arterial waveform [48]. Segments of 10 minutes surrounding the registered flushing moments were selected and analyzed visually to identify the end of flushing, corresponding to closure of the flush valve and thus the flush pulse response. As the flush-pulse response is superimposed on the arterial waveform, it is not always readily discernible from the original signal. To overcome this problem, the first time derivative of the blood pressure recording was taken, leading to a relative increase in pulse amplitude with respect to the amplitude of the arterial waveform. The derivative of the pulse response is characterized by f_n and ζ identically to the original pulse. From the first derivative of the measured signal, the pulse response was identified. Next, the pulse response was categorized according to Table 4.1. We visually determined whether an oscillation or an exponential decay was present, corresponding to respectively an under- or overdamped waveform, or whether no oscillation or pulse was discernible from the signal. The latter could be the case when the pulse is applied within the systolic rise period, as high frequency components of the arterial waveform are amplified as well. It could also be caused by artifacts, for example due to movement artifacts that we could not eliminate by filtering as this might affect the pulse response. According to this scoring system, we decided whether dynamic response could be derived from the data segment and which dynamic response calculation method should be used.

Table 4.1: Scoring system for the type of dynamic response: underdamped (1), overdamped (2) or indiscernible (3)

	Pulse response characteristics
1	Clearly discernible damped oscillation
2	Clearly discernible exponential decay *and* No oscillation
3	No discernible damped oscillation or exponential decay *and/or* Pulse applied during systolic upstroke

Assuming a second order underdamped system ($\zeta < 1$), the pulse response is given by:

$$P(t) = Ae^{\frac{-2\pi f_n \zeta t}{\sqrt{1-\zeta^2}}} \sin(2\pi f_n t + B) + C, \quad \text{(Eq. 4.1)}$$

with $P(t)$ the resulting pulse, f_n the natural frequency in Hz, ζ the damping coefficient, t the time vector in seconds and A, B and C being constants. To obtain f_n and ζ, the function in Eq. 4.1 was fitted to the measured pulse response.

In case of an overdamped system ($\zeta > 1$) there will be no oscillation so the above mentioned method for dynamic response calculation cannot be used. The system reacts differently to activation, and the response acts as a decaying exponential, rather than a decaying exponential multiplied with a sine function. Consequently, it is possible to fit the non-oscillatory pulse response to the function:

$$P(t) = ke^{-\lambda t}, \quad \text{(Eq. 4.2)}$$

with k a constant and λ the exponential decay constant, which is the overdamped dynamic response coefficient characterizing an overdamped system. For overdamped systems, dynamic response is not given by f_n and ζ but λ, which is a function of both the system's natural frequency and damping. With increasing damping, λ decreases, yielding a slower exponential decay. The opposite happens with increased natural frequency. A low natural frequency and high damping yields a small overdamped dynamic response coefficient which can thus be considered a worse dynamic response than high value for λ.

Aside from dynamic response, the heart rate and mean blood pressure were also calculated from the 10-minute data segment. f_n and ζ or λ were calculated from the resulting flush pulse responses.

4.2.3 *Statistical analysis*

Data are reported as median and interquartile range (IQR). To evaluate the relative variability of dynamic response over time, the coefficients of variation (CV_{MAD}) estimated by the ratio of the median absolute deviation (MAD) to the median were calculated per arterial line, separately for the under- and overdamped situations [56]. Furthermore, the course of dynamic response over time was explored by linear regression. The relationship between dynamic response and patient characteristics was also explored by linear regression. In the case of the placement of multiple consecutive arterial lines in the same patient, the dynamic response measurements between these lines were compared. Differences in dynamic response were evaluated by Mann-Whitney U or Kruskal-Wallis tests, when appropriate. Goodness of fit was reported in Pearson's correlation coefficient R and P-value. A P-value < 0.05 was considered statistically significant.

4.3 Results

4.3.1 *Subjects*

In this study, 15 patients were included with a total of 21 arterial lines. Baseline characteristics are shown in Table 4.2. As can be seen, some patients had more arterial lines. Of these arterial lines, the characteristics are shown in Table 4.3.

4.3.2 *Dynamic response measurements*

In the study, a total of 515 flushing moments were registered, of which 506 (98%) were performed after blood sampling. The remaining 2% of flushes were in context of inadequate curve, alarms indicating obstruction, introduction of a new system or unknown. In 374 cases (73%), we were able to calculate the dynamic response, corresponding to a median 70 (IQR 65 – 83%) per arterial line. In 15 of 21 arterial lines, at least 10 flushing moments yielded

Table 4.2: Patient characteristics

	$N = 15$
Female (n (%))	5 (33)
Gestational age (weeks + days)	36 + 4 (26 + 6 – 38 + 4)
Birth weight (g)	2248 (1020 – 2974)
Number of arterial lines (n)	1 (1 – 3)

Abbreviations and symbols: N = sample size, n = number of arterial lines, g = grams. Female gender is reported as number and percentage. Gestational age, birth weight and number of arterial lines are reported as median (interquartile range)

Table 4.3: Arterial line characteristics

	$N = 21$
Line placement	
- Radial artery	10 (48%)
- Umbilical artery	7 (33%)
- Ulnar artery	3 (14%)
- Unknown	1 (5%)
Time in situ (days)	6 (4 – 9)

Abbreviations and symbols: N = sample size. Results are reported as number (percentage)

Table 4.4: Calculated dynamic response parameters

Underdamped systems ($N = 334$)		*Overdamped systems ($N = 40$)*	
f_n	14.4 (11.9 – 15.6)	λ	87 (79 – 99)
CV_{MAD,f_n}	0.11 (0.09 – 0.14)	$CV_{MAD,\lambda}$	0.05 (0.04 – 0.08)
R_{f_n}	−0.09 (−0.45 – 0.12)	R_λ	0.08 (−0.03 – 0.37)
ζ	0.88 (0.45 – 0.93)		
$CV_{MAD,\zeta}$	0.05 (0.05 – 0.23)		
R_ζ	−0.09 (−0.23 – −0.04)		

Abbreviations and symbols: N = sample size, f_n = natural frequency in Hz, CV_{MAD} = nonparametric coefficient of variation, ζ= damping coefficient, reported in median (interquartile range), R = Pearson's correlation coefficient. Results are reported in median (interquartile range)

a dynamic response calculation, which was at least 50% of all recorded flushes in all cases. 89% of calculations yielded an underdamped dynamic response with calculated f_n and ζ and 11% overdamped with λ. The resulting dynamic response measurements are summarized in Table 4.4 and given per arterial line in Tables A2.1 and A.5 in the Appendix, for respectively underdamping and overdamping. Although most cases were underdamped with $\zeta < 1$, the value of ζ was generally high, with a median value of 0.88. Fig. 4.1 shows all underdamped dynamic response measurements with damping coefficient versus natural frequency. There is a clear concentration of measurements at ζ between 0.8 and 1 and f_n between 10 and 20 Hz. All except two dynamic response measurements showed natural frequencies above 30 Hz. The patient's heart rate was calculated from the arterial waveform and compared to the natural frequency in case of the underdamped waveforms. In 5% of underdamped measurements, f_n was equal to or larger than the 10th harmonic of the heart rate. For the 6th harmonic, this was 39%.

In most arterial lines, variability in natural frequency, as quantified by CV_{MAD} was higher than in damping coefficient when DR was measured multiple times. Both f_n and ζ generally slightly decreased over time with median R of −0.09 (IQR − 0.45 – 0.12Hz for f_n and −0.23 – −0.04 for ζ). Overdamping did not occur in all arterial lines as shown in Table 4.5. Values of λ were variable

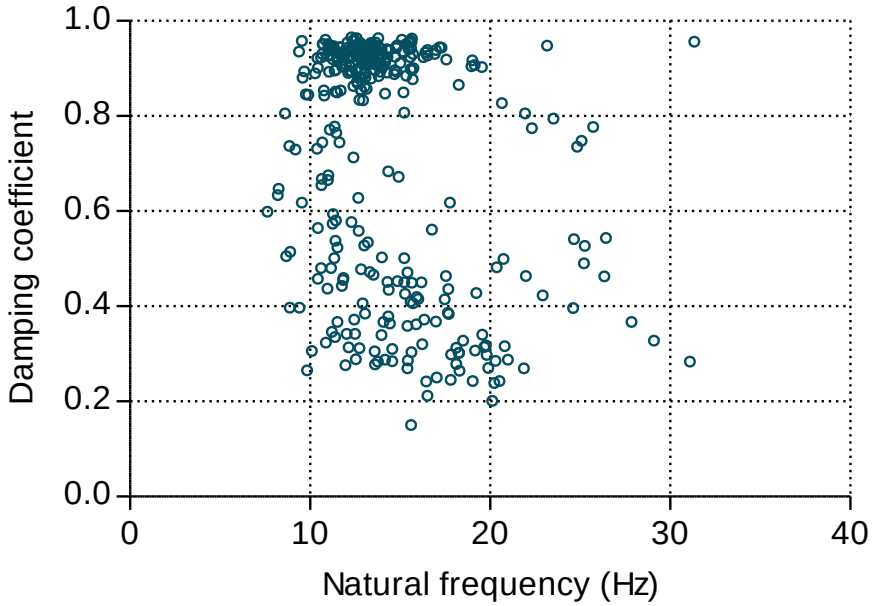

Figure 4.1: Underdamped dynamic response of CMS in situ measured with flush pulse response at the neonatal intensive care unit. Circles represent individual measurements.

between arterial lines, though coefficients of variation were generally low except for line 7, where λ was considerably lower than in other arterial lines and showed a $CV_{MAD,\lambda}$ of 0.37, whereas three lines had $CV_{MAD,\lambda}$ below 0.1. The values for R in Table A.6 in the Appendix show that λ could both increase or decrease over time and this varied between arterial lines.

The relationships between patient characteristics and the underdamped dynamic response parameters are shown in Fig. 4.2a, b, c and d. Median natural frequency and damping coefficient within a patient were related to birth weight (Figs. 4.2a and b) and gestational age (Figs 4.2c and d). The most prominent relationship is given by Fig 4.2c, showing a decrease in median natural frequency with increasing GA with $P = 0.001$ and goodness of fit of $R^2 = 0.56$. A similar but less strong relationship is seen between median f_n and birth weight. The relationship between these patient characteristics and damping coefficient were opposite to the natural frequency, with an increase in median damping coefficient with both increasing birth weight (Fig 4.2b) and gestational age (Fig 4.2d) Figs 4.2b and ζ also show that the range of damping coefficients decreased with higher birth weight and gestational age.

Of the 15 patients included in this study, 4 patients had 2 arterial lines within the study period. A single patient received 3 arterial lines. Comparison of f_n and ζ between arterial lines within the same patient resulted in a significant difference in f_n in Patient B. In both patients, the umbilical arterial line was replaced by a peripheral line. No other significant differences in dynamic response between consecutive arterial lines were found. The underdamped dynamic response characteristics of these 11 arterial lines are given in Table A.7 in the Appendix.

4.4 Discussion

To obtain a comprehensive view on the range of dynamic response at the NICU, we used the flush-pulse technique in routine neonatal care to assess dynamic response of intra-arterial CMS at the NICU. We were able to calculate dynamic response from the flush pulse response in 73% of recorded moments of flushing in our study of 15 patients with 21 corresponding arterial lines. In 89% of dynamic response calculations, CMS were found to be underdamped ($\zeta < 1$). In the remaining overdamped cases, we used a novel method to identify dynamic response, making use of the exponential decay constant. Dynamic response was found to vary over time within arterial

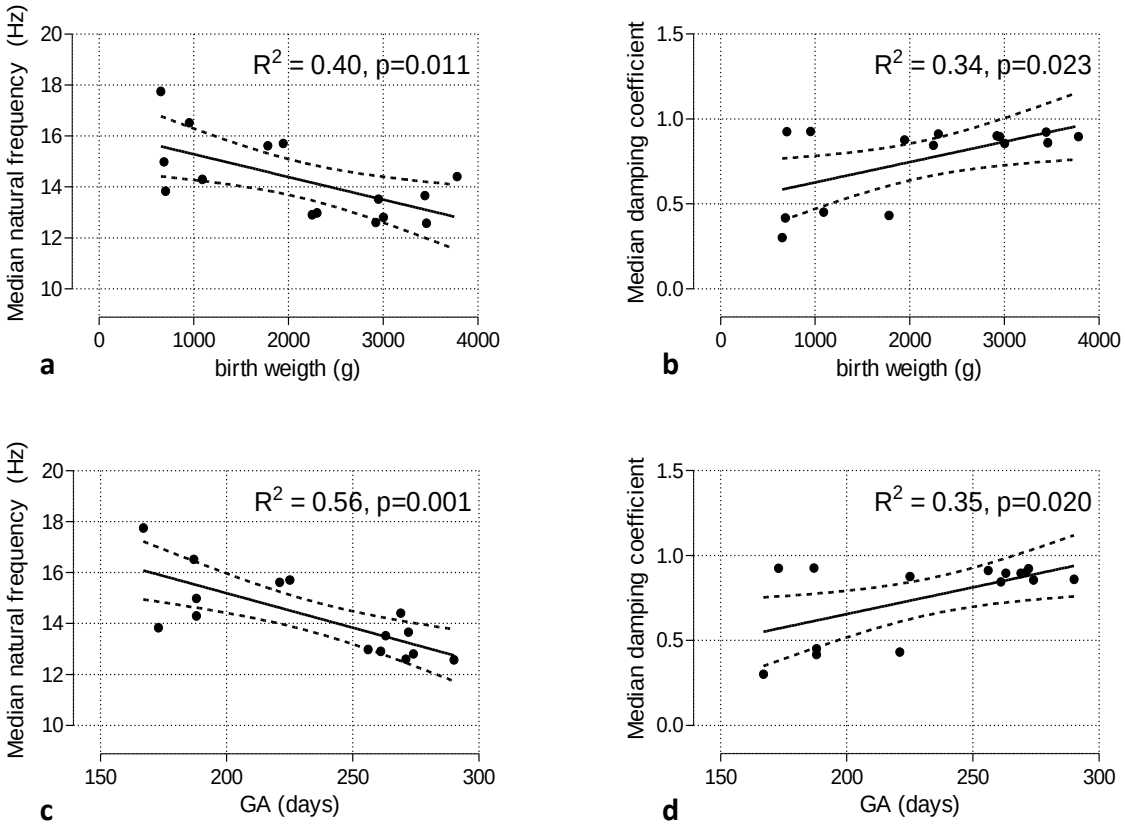

Figure 4.2: Linear relation between median natural frequency and patient's birth weight (a), median damping coefficient and patient's birth weight (b), median natural frequency and patient's gestational age (GA) (c), median damping coefficient and patient's gestational age (d). The black dots represent patients, the black continuous lines linear regression, the black dashed lines the 95% confidence intervals of the linear relationship. Goodness of fit is reported in R^2 and P-value.

lines. Though variable, natural frequency was generally low, indicating inadequate waveform reproduction. The damping coefficient was often high ($\zeta > 0.8$), likely leading to a seemingly overdamped waveform while the measurement system was underdamped.

4.4.1 *Dynamic response measurements*

Assuming that a natural frequency of at least the 6th harmonic of heart rate is required for adequate pressure waveform measurement, natural frequency with median 14.4 (IQR 11.9 – 15.6 Hz) was inadequate more than half of the time. With the requirement of a flat frequency up to at least 10th harmonic of the heart rate, as often mentioned in literature for sufficient signal complexity, natural frequency would have been inadequate in 95% of the cases. A necessary bandwidth of 30Hz has also been mentioned, which requirement was met in only 2 of the 334 underdamped measurements. Consequently, based on measurement of natural frequency only, dynamic response of CMS at the NICU is often inadequate and may lead to erroneous pressure recordings and wave shape distortion. Similar values for f_n have been found in studies using the fast flush test for evaluation of dynamic response in adults with arterial lines [24, 42, 53, 57, 58]. Van Langen et al. found similar values in a neonatal population as well [48].

Damping coefficients were generally high with median 0.88 (0.45 – 0.93), which can correspond to loss of waveform complexity and underestimation of systolic pressure and pulse pressure. Furthermore, we proposed a novel method to characterize overdamped system's as well, which resulted in calculation of overdamped dynamic response in 11% of all calculations. In literature, dynamic response measurements of CMS in situ have generally yielded low ζ. For example,

Gardner measured ζ of 0.32 or lower in 16 of 17 in-dwelling catheters [24]. In a study of damping coefficients by Rook et al., no oscillations and thus overdamped systems were found in 37% of patients and of the remaining underdamped systems, 69% of damping coefficients were below 0.4. Similar results have been found for both umbilical and radial artery catheters in the neonatal population [20, 54, 55]. This is not in line with our results, as we calculated considerably higher values of ζ. Dynamic response measurements described by Van Langen et al. showed more similarities, with damping coefficients below 0.4 in only 2 of 14 arterial lines [48]. All mentioned studies, however, were carried out over three decades ago.

Generally, high damping and overdamping are thought to be the result of the introduction of air bubbles in the catheter, but it is unlikely that this is more present in our patients than in other populations. Furthermore, CMS are flushed regularly in the intensive care setting. The damping characteristics of the system are affected by catheter diameter and length, diaphragm volume displacement and properties of the fluid. Diaphragm volume displacement is a function of diaphragm stiffness and area [23]. Though diaphragm area has been reduced in size in the last two decades of the 20th century, similar volume displacements were recorded in 1984 as our systems nowadays [22, 59]. Consequently, if differences between the amount of damping in CMS are a result of changes throughout the years, they are most likely found in the tubing. Currently, CMS transducers are placed at a certain length away from the patient in closed arterial blood sampling systems. This requires longer tubing, which causes higher damping.

Our study was performed in a neonatal population, whereas most dynamic response calculations reported in literature have been performed in adults. Hence the question arises whether the differences between adults and newborns may account for the discrepancy between our results and results presented in literature. Though our sample size was small and goodness of fit was not high in our analyses, our results indicated a relationship between dynamic response on one hand and gestational age and birth weight on the other, showing a decrease in f_n with increasing GA and birth weight. Possibly, birth weight and a combination of other factors related to gestational age influence the dynamic response of a CMS in situ. This would suggest that there is a patient- or measurement-specific factor affecting the characteristics of the CMS. The theoretical mechanism of this effect is difficult to grasp, as the system's f_n is thought to depend on system characteristics only. Possibly, there is an interaction at the interface of vessel and the indwelling catheter which is influenced by factors that change with (gestational) age, such as vessel diameter or blood pressure itself. There is a gap in knowledge on which characteristics of the patient, the CMS, the interaction between these and the environment influence the behavior of the full system and thus its dynamic response.

4.4.2 *Variability of dynamic response over time*

To our knowledge, this is the first study investigating variability of dynamic response over time. IQR and the non-parameteric equivalent of the coefficient of variation (CV_{MAD}) were used to assess variability of f_n, ζ and λ. IQR were generally wide in all three dynamic response parameters. For example, IQR of the damping coefficient was 0.42 – 0.93 in arterial line n, with a $CV_{MAD,\zeta}$ of 0.32, indicating high variability in the amount of damping of the system and thus the arterial waveform. Furthermore, in 12 arterial lines, the system was at times both under- and overdamped. Consequently, dynamic response is not stable over time. The causes of variability over time is unknown; degradation of system, caused by for example air bubbles or blood clots, could play a role but this would lead to a continuously worsening of dynamic response. Linear regression between dynamic response parameters and time, however, has shown that natural frequency did not necessarily decrease in all and damping could change either way as well. Instable dynamic response could have certain clinical implications. If an adequate signal becomes overdamped, the physician may interpret this as a decrease in tension, while the patient may have remained stable. Consequently, trend analysis of the arterial blood pressure waveform, whether used for pressure values or advanced hemodynamic parameters, may not be reliable.

4.4.3 *Limitations and future perspectives*

The results and considerations described above mainly illustrate the main limitation of this study; little is known about the underlying mechanisms determining the dynamic response of a CMS in situ. While it is useful to know that measured blood pressure and especially wave shape measured with an arterial line are not necessarily valid, finding the causes for inadequate dynamic response would be instrumental to facilitate development of solutions. Factors determining dynamic response could be found in a wet-lab setting, mimicking the (neonatal) circulation and measuring blood pressure by both a CMS and a high-fidelity manometer-tipped catheter in situ. By changing for example tube length and diameter, the effects of these and other parameters on dynamic response could be evaluated. Ideally, a method for the correction of arterial waveform measurement via CMS would be found.

While we obtained 374 calculations of dynamic response, our study population was still quite small. This limited statistical power and the possibility of drawing conclusions from our regression analyses. It will be straightforward to expand the study population in future research, as the flush-pulse response method of dynamic response calculation does not require any additional medical action. This also illustrates the potential for implementing this technique in clinical practice in the future to be able to evaluate a CMS' dynamic response in routine neonatal care.

4.4.4 *Conclusion*

To obtain a comprehensive view on the range of dynamic response at the NICU, we used the flush-pulse technique in routine neonatal care to assess dynamic response of intra-arterial CMS at the NICU. From our results we can conclude that blood pressure measurement via intra-arterial CMS at our NICU is characterized by high damping and predominantly low natural frequency. There was considerable variability of dynamic response over time. Much is still unknown, however, on the causes of these findings.

5 A reconstruction method for distorted neonatal arterial waveforms recorded with catheter-manometer systems based on dynamic response measurements

5.1 Introduction

Neonatal arterial blood pressure measurement via CMS maybe inadequate due to the system's dynamic response [20, 23, 24]. This can affect both the wave shape and derivation of pressure values such as pulse pressure. In chapter 3 we showed that mean blood pressure is least affected by the system's dynamic response, but especially systolic pressure and pulse pressure may have erroneous values in case of inadequate dynamic response. For assessment of a patient's hemodynamic status, adequate measurement of blood pressure is of importance. Furthermore, wave shape distortion may limit possibilities for more advanced analyses of the arterial waveform.

Several attempts have been made to counteract the effect of inadequate dynamic response and realize a more valid arterial waveform measurement via CMS. Early on, these methods were mainly aimed at increasing the damping coefficient, as inadequate damping has historically been the main problem in CMS [23, 24, 60]. For example an air bubble could be introduced to increase damping. However, this also increase stiffness of the transducer and thus decreases natural frequency, having the opposite effect on dynamic response [46, 60]. The ROSE damping device could increase damping while maintaining natural frequency [60]. The results described in chapter 3 illustrate, however, that higher damping is currently more of a problem in dynamic response at the NICU than underdamping, so methods aiming at damping increasing are futile. Furthermore, these methods are not measurement-specific and imprecise and may not eliminate all dynamic response errors. More advanced waveform correction methods have been scarce. The most promising method was proposed by Lambermont et al., who used measured damping coefficient and natural frequency in an equation to reconstruct waveforms from distorted measurements [61].

In chapter 3, we showed that the effects of dynamic response are not generalizable over the neonatal population. Consequently, a method for the reconstruction of distorted arterial waveforms should be specific for each measurement of dynamic response, as a generalized method would not take into account the variation in dynamic response effects. . A generalized method would not take into account the variability of dynamic response effects. Furthermore, chapter 4 illustrated that dynamic response is often variable within the same patient and arterial line, indicating that the method should be adaptable.

As a CMS can be described as a second order system with a transfer function based on f_n and ζ, in case of underdamped dynamic response and λ in the overdamped case, the calculation of dynamic response essentially gives all information on how the CMS works. Consequently, we know how the CMS operates with dynamic response and this information may also be used to correct for the effects given by this dynamic response. This would allow for a patient-, CMS- and measurement-specific way of reconstructing distorted arterial waveforms and provide more valid intra-arterial blood pressure measurement.

The goal of this study was therefore to propose and validate a novel reconstruction method to correct for dynamic response distortion in neonatal arterial waveforms measured with CMS using measured dynamic response parameters.

5.2 Methods

5.2.1 Subjects and measurements

For the creation and initial validation of the reconstruction method, we used the simulated complex waveforms with HR = 140 bpm and HR = 180 bpm as described in Ch. 3 and a set of 20 high-fidelity neonatal arterial waveform segments were extracted from a publication by Gevers et al. [62]. These arterial waveforms were measured using manometer-tipped catheters, which are not subject to the same dynamic response issues as CMS and therefore produce high-fidelity waveforms. For application of the reconstruction method, we used the clinically measured arterial waveforms and dynamic response parameters obtained in Ch. 4. For this purpose, a 30-second visually artifact-free waveform segment within 5 minutes after each flush was selected.

5.2.2 Design of a reconstruction method

For underdamped systems, a CMS in situ can be described as the following transfer function:

$$H_{CMS,u} = \frac{\omega_n^2}{s^2 + 2\zeta\omega_n s + \omega_n^2}, \quad \text{(Eq. 5.1)}$$

with $\omega_n = 2\pi f_n$ the natural frequency in rad/s, ζ the damping coefficient and s the Laplace variable. Depending on the values of ω_n and ζ, the system keeps low frequencies in the input signal stable and enhances or attenuates higher frequencies. Consequently, we aimed to create a function with the opposite effect, which can be obtained by taking the inverse of the transfer function given in Eq., resulting in:

$$H_{inv,u} = \frac{s^2 + 2\zeta\omega_n s + \omega_n^2}{\omega_n^2} * H_{filt,u}, \quad \text{(Eq. 5.2)}$$

with

$$H_{filt,u} = \frac{1}{as^2 + bs + 1}, \quad \text{(Eq. 5.3)}$$

a filtering transfer function with a and b chosen such that the $H_{inv,u}$ is a causal and stable function.

In case of overdamping, dynamic response is determined by the decay constant λ, with corresponding transfer function:

$$H_{CMS,o} = \frac{\lambda}{s + \lambda}. \quad \text{(Eq. 5.4)}$$

5.2.3 Validation of the reconstruction method

The simulated waveforms described in Ch. 3 were processed through a simulated CMS as described in Ch. 3, using the transfer function described in Eq. 3.2. Dynamic response was varied with $f_n = 10, 15, 25$ Hz and $\zeta = 0.2, 0.7, 1.2$, yielding 9 different combinations.

High-fidelity waveforms extracted from Gevers et al. were also processed through the simulated CMS with random values of f_n between 5 and 25 Hz and ζ between 0.1 and 1.5 [62]. To calculate the dynamic response from the resulting transformed arterial waveform, the induction of a flush pulse to the system was simulated. A block pulse was superimposed on the waveform, before applying the CMS simulation. The first derivative was taken from the output signal to enable identification of the simulated flush pulse response. The resulting flush pulse response was visually characterized as either overdamped or underdamped according the scoring system described in Table 4.1 in Ch. 4.

When the response was classified as underdamped, the dynamic response parameters were calculated by fitting the pulse response to

$$P(t) = Ae^{\frac{-2\pi f_n \zeta t}{\sqrt{1-\zeta^2}}} \sin(2\pi f_n t + B) + C, \quad \text{(Eq. 5.5)}$$

resulting in a measured damping coefficient and f_n, giving the dynamic response of the system. In case of an overdamped pulse response Eq. 5.7 was used to obtain dynamic response parameter λ.

$$P(t) = ke^{-\lambda t} \quad \text{(Eq. 5.6)}$$

Depending on the type of system, over- or underdamped, the inverse transfer function was calculated by either Eq. 5.6 or Eq. 5.7 using λ or $f_n$and ζ, respectively.

5.2.4 *Calculations and analysis*

The delay between the waveforms was calculated using cross correlation and the output signal was shifted according to the delay to make sure the signals were aligned.
From the waveforms, pressure values P_s, P_d, PP, MBP and the RMSE of the full waveforms were calculated. Waveform parameter dP/dt_{max} was computed as well to evaluate wave shape distortion. A short explanation of the calculation of these parameters is provided in the Appendix.

For the initial validation, differences in these parameters between the transformed and original waveform were compared to the differences between the reconstructed and original waveform. After application of the reconstruction method to the clinically measured data, the reconstructed waveforms were compared to the measured waveforms based on the parameters described above. Before comparison, the delay between the waveforms was calculated using cross correlation and the output signal was shifted according to the delay to make sure the signals were aligned. Differences between parameters calculated from measured and reconstructed waveforms were analyzed by paired t-tests or Wilcoxon matched-pairs signed rank test, when appropriate. Furthermore, correlation between waveforms was assessed by the correlation coefficient R. A P-value < 0.05 was considered statistically significant.

5.3 Results

In Fig. 5.1, the initial results of validation of the reconstruction method are shown. A 140 bpm waveform (Figs. 5.1 a and b) and a 180 bpm waveform (Figs. 5.1 c and d) are shown, as well as the transformed waveforms after processing through a simulated CMS with dynamic response of $f_n = 10\text{Hz}, \zeta = 0.2$ (Figs. 5.1 a and c) and $f_n = 10\text{Hz}, \zeta = 1.2$ (Figs. 5.1 b and d). Furthermore, the corrected waveforms after application of the reconstruction method are shown in the dashed blue lines. In all four figures, we clearly see that the reconstructed and simulated waveforms are more alike in shape and pressures values than the simulated and distorted waveforms. The reconstructed waveforms do not fully follow the original, but there is a clear resemblance in upstroke, systolic peak, dicrotic notch and diastolic downstroke.

Errors between both the transformed and the original waveforms ($APW_t - APW_o$) and the reconstructed and the original waveforms ($APW_r - APW_o$) for 9 combinations of f_n and ζ are summarized in Table 5.1. In Table A1.1 in Appendix 8.1, several parameters of APW_o are summarized.

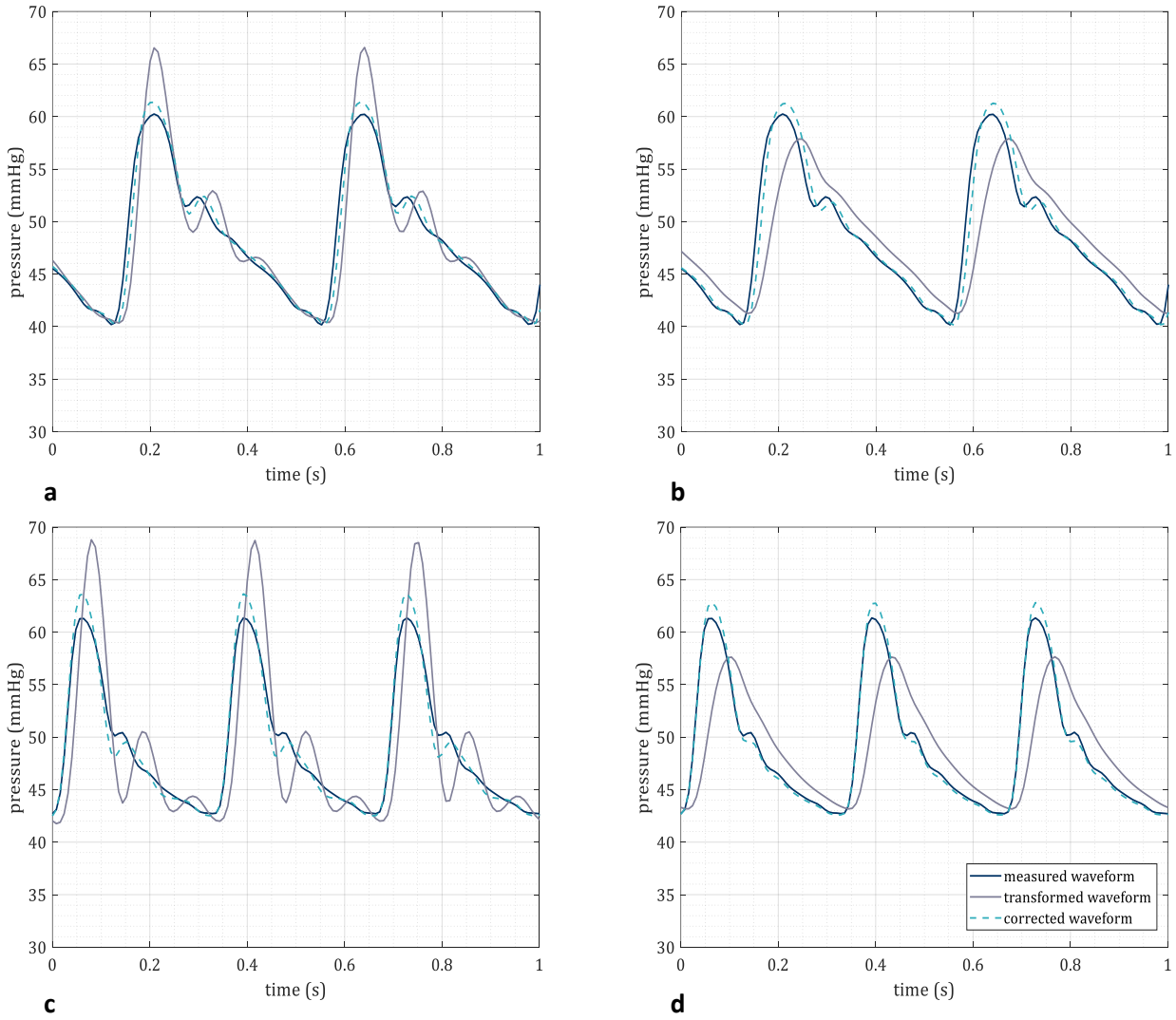

Figure 5.1: Initial validation of the proposed method for reconstruction of distorted waveforms based on dynamic response measurements with simulated waveforms with varying heart rates and varying dynamic response, respectively: (a) 140bpm and $f_n = 10Hz, \zeta = 0.2$, (b) 140bpm and $f_n = 10Hz, \zeta = 1.2$, (c) 180bpm and $f_n = 10Hz, \zeta = 0.2$, (d) 180bpm and $f_n = 10Hz, \zeta = 1.2$. The dark blue lines represent the simulated waveforms, the grey lines represent the transformed waveforms, distorted by simulated dynamic response and the dashed light blue lines represent the reconstructed signals.

For low damping ($\zeta = 0.2$) and high damping ($\zeta = 1.2$), all absolute differences in P_S, P_D, PP and dP/dt_{max} between the waveforms decreased with applying the reconstruction method to the transformed signal. This was not the case for $\zeta = 0.7$, for which errors slightly increased in some cases. For $f_n = 10Hz$ and $\zeta = 0.7$, for example, P_S error between APW_r and APW_o was -0.8 mmHg in contrast to 0.2 mmHg for $APW_t - APW_o$. An increase in error was also seen for Pd, Ps and PP with dynamic response of $f_n = 25$ Hz and $\zeta = 0.7$. Other errors were identical or slightly lower. Waveform RMSE decreased in all dynamic response settings except for $f_n = 25$ Hz, $\zeta = 0.2$, in which there was a slight increase of 0.6 to 0.7 after reconstruction. In Table 5.2, correlation between the transformed and original and reconstructed and original waveforms are

Table 5.1: Differences in waveform parameters between the transformed and the original simulated 140 bpm waveform and between the reconstructed and the original simulated 140 bpm waveform for varying simulated dynamic response.

ζ	*0.2*		*0.7*		*1.2*	
	$APW_t - APW_o$	$APW_r - APW_o$	$APW_t - APW_o$	$APW_r - APW_o$	$APW_t - APW_o$	$APW_r - APW_o$
$f_n\ (Hz)$	P_S error (mmHg)					
10	6.4	1.6	0.2	−0.8	−2.4	0.9
15	3.1	−0.1	0.2	0.2	−1.2	0.7
25	−0.6	0.1	−0.1	−0.2	−0.5	0.4
	P_D error (mmHg)					
10	3	0	0.5	0.4	1.1	0
15	−0.2	−0.1	0.4	0.4	0.7	−0.1
25	−0.3	−0.1	0.2	0.3	0.4	−0.1
	PP error (mmHg)					
10	6.2	1.6	−0.3	0.1	−3.5	0.9
15	3.3	0	−0.3	−0.3	−1.9	0.8
25	0.5	0.2	−0.2	0.4	−0.9	0.5
	dP/dt_{max} error (mmHg)					
10	51	31	−47	−11	−94	−21
15	62	26	−21	3	−66	−8
25	29	4	−5	5	−37	1
	Waveform RMSE					
10	2.9	1.0	3.3	1.2	4.0	1.8
15	1.8	0.9	2.3	1.0	3.1	1.5
25	0.6	0.7	1.4	0.9	2.1	0.7

Abbreviations and symbols: ζ = damping coefficient; f_n = natural frequency; APW_t = transformed arterial waveform; APW_o = original simulated arterial waveform; APW_r = reconstructed arterial waveform; P_s = systolic pressure; P_D = diastolic pressure; PP = pulse pressure; dP/dt_{max} = maximal slope of systolic upstroke; RMSE = root mean square error

Table 5.2: Linear correlation between the transformed and the original simulated 140 bpm waveform and the reconstructed and the original simulated 140 bpm waveform for varying simulated dynamic response

ζ	*0.2*		*0.7*		*1.2*	
	Correlation *(R)*					
	APW_t, APW_o	$APW_r APW_o$	APW_t, APW_o	$APW_r APW_o$	APW_t, APW_c	$APW_r APW_o$
10	0.92	0.99	0.85	0.98	0.76	0.95
15	0.96	0.99	0.93	0.99	0.86	0.97
25	0.99	0.99	0.97	0.99	0.94	0.99

Abbreviations and symbols: ζ = damping coefficient; f_n = natural frequency; APW_t = transformed arterial waveform; APW_o = original simulated arterial waveform; APW_r = reconstructed arterial waveform pressure

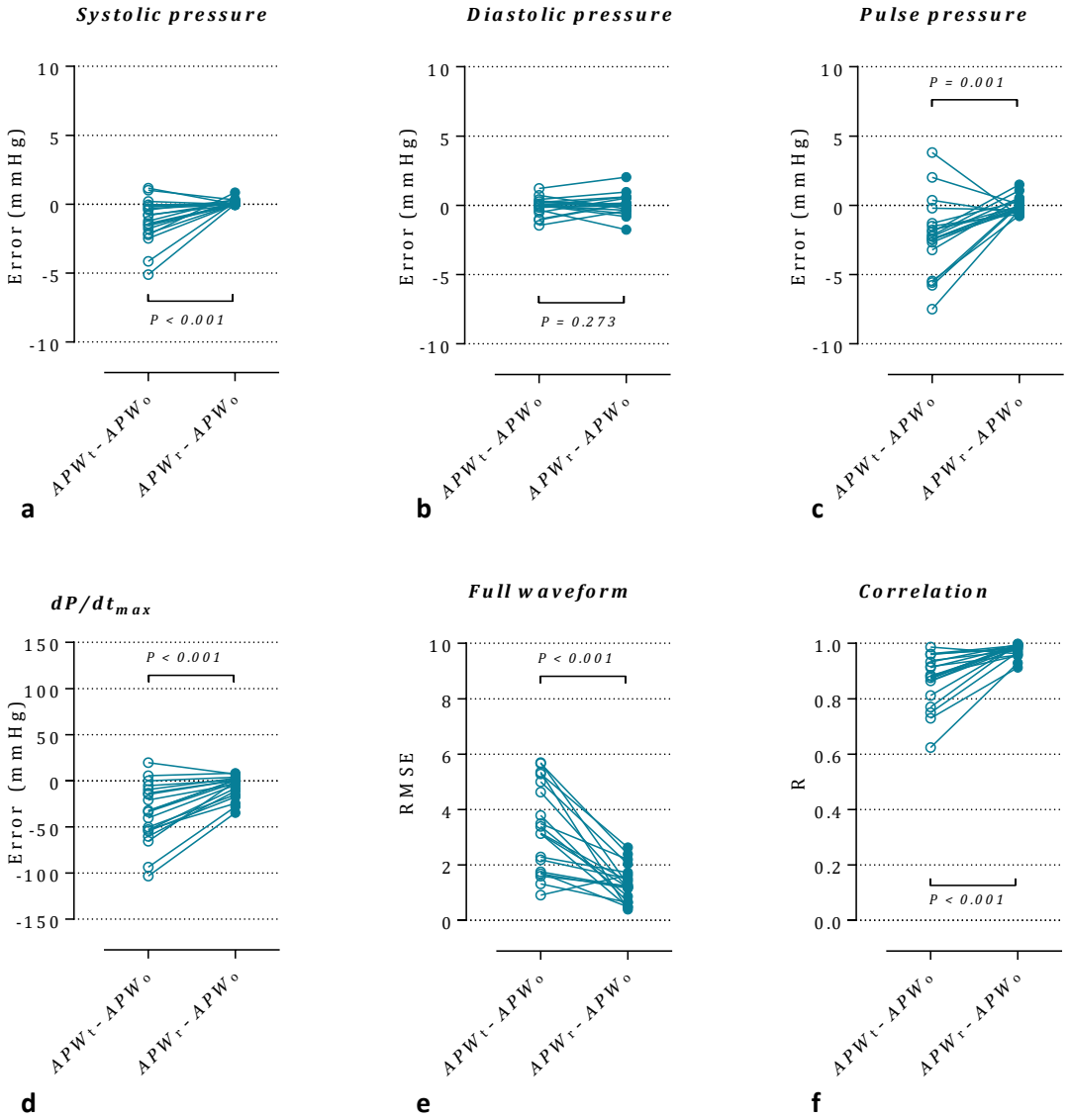

Figure 5.: The effects of the reconstruction method on errors in systolic pressure (a), diastolic pressure (b), pulse pressure (c) and dP/dt_{max} (d), full waveform RMSE (e) and correlation (f) for the 20 high-fidelity waveforms that were processed through a simulated CMS with random dynamic response parameters.

reported for the same values of dynamic response as Table 5.1. R increased after reconstruction in all dynamic response settings, except for $f_n = 25$ Hz, $\zeta = 0.2$, where correlation was 0.99 between both APW_t and APW_o and APW_r and APW_o.

Fig. 5.2 shows the effects of the reconstruction method on several parameters for the 20 high-fidelity waveforms that were processed through a simulated CMS with random dynamic response parameters. Systolic pressure error, which was up to -5 mmHg, significantly decreased after reconstruction as well as pulse pressure error (Fig. 5.2c) which had a maximal value of -7 mmHg. Diastolic pressure (Fig. 5.2b) did not change significantly after reconstruction and the absolute error value even increased slightly in some cases. For both dP/dt_{max} error (Fig. 5.2d) and full waveform RMSE (Fig. 5.2e), indicating effect of dynamic response on wave shape, the differences between $APW_t - APW_o$ and APW_r and APW_o were statistically significant in favor of the reconstructed waveforms. Correlation between waveforms (Fig. 5.2f) significantly increased with reconstruction.

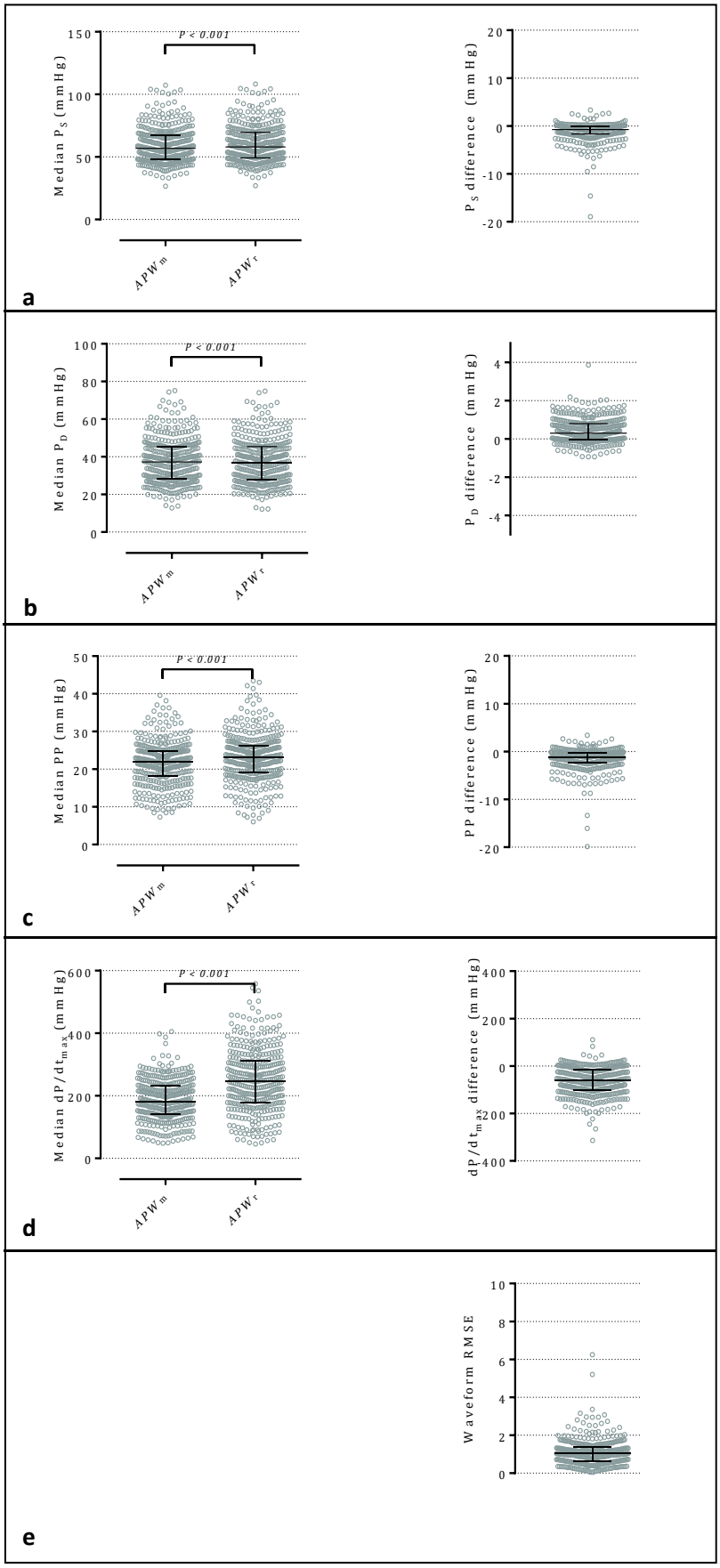

Figure 5.3: Differences in parameters between clinically measured waveforms (APW_m) and the reconstructed waveforms (APW_r) resulting from our reconstruction method based on measured dynamic response data. In the left column, scatter dot plots of P_S (a), P_D (b), PP (c) and dP/dt_{max} (d) are shown. The right panel shows the differences in these parameters between APW_m and APW_r and the full waveform RMSE (e). The black lines and bars represent median and interquartile range. Statistical significance of the differences are shown in P-value in the figures on the left.

In Fig. 5.3, the results of the application of our reconstruction method to clinical data are shown. In the left column, scatter dot plots of several parameters calculated from the measured waveform (APW_m) and $APW_r$are shown. In the right column, the difference in these parameters between APW_m and $APW_r$are given. Median and IQR of APW_m and APW_r were similar for both PP (Fig. 5.3c) and P_S (Fig. 5.3a). Paired t-tests showed that the APW_m and APW_r of these parameters were significantly different ($P < 0.001$), with median differences of -1 (IQR -2 – 0) for both P_S and PP. The largest differences were -21 mmHg for P_S and -18 mmHg for PP. Differences in P_D (b) were also statistically significant ($P < 0.001$) but smaller, with maximal difference of $6mmHg$. In Fig. 5.2d, the differences in dP/dt_{max} between APW_m and APW_r are shown, which were statistically significantly different ($P < 0.001$) with median 182 (IQR 141 – 234 mmHg) for APW_m and 247 (IQR 178 – 313 mmHg) for APW_r. In Fig. 5.3e. the RMSEs between the measured and reconstructed waveforms are depicted, with median 1 (IQR 1 – 1).

5.4 Discussion

Arterial pressure waveforms recorded via CMS in the neonatal population may be distorted due to characteristics of the measurement system. In the current study, we proposed a measurement-specific reconstruction method for distorted arterial pressure waveforms recorded via CMS in critically ill neonates, based on measurements of the system's dynamic response, both under- and overdamped. Using simulated waveforms, high-fidelity waveforms and computer simulations of CMS dynamic response, we were able to provide an initial validation of our reconstruction method. We showed that after reconstruction, the distorted waveforms became more similar to the original waveforms and differences in pressures and wave shape parameters decreased. This suggests that the application of our reconstruction method would lead to more valid arterial pressure waveform recordings via CMS.

Lambermont et al. proposed a similar method for APW correction using a transfer equation based on measured dynamic response parameters via the fast flush test in a porcine model [61]. They were able to validate their method by measuring APW via CMS and a manometer-tipped catheter (MTC), as measurements by MTC are not prone to errors induced by dynamic response. Their reconstructed pressure waves were very close to the pressure waves measured via MTC, with correlation coefficient of 0.99. However, they did not provide the actual errors between the CMS and MTC waveforms. Another solution for pressure errors induced by dynamic response was proposed by Devasahayan et al., using compensating filters to obtain a flat frequency response outside of the relevant bandwidth [51]. Though they did use knowledge on the system's characteristics to create their filters, they did not provide clear instructions on how to use these characteristics for the compensating filter. Interestingly, our results show that in case of medium damping ($\zeta = 0.7$), application of the reconstruction method may lead to a small increase in measurement errors in some cases. This is probably because the errors were already so small that the small de- or increase in these values are within acceptable ranges of errors. This indicates that application of the reconstruction method may only be warranted in case of actually inadequate dynamic response.

To evaluate the effects of our reconstruction method on arterial waveforms measured in clinical practice at our NICU, we applied the method to pressure data at which moments we also calculated dynamic response. For all measured parameters, statistically significant differences were found between the measured and the reconstructed group of APW, though differences in pressure values were generally small, indicating little effect of dynamic response and our reconstruction method. Consequently, for every day clinical practice, the effects of dynamic response may often be irrelevant and reconstruction is not necessary for adequate hemodynamic monitoring. In several cases however, errors in especially systolic pressure and pulse pressure were higher than 5 mmHg, which would be higher than the accepted error proposed in the Association for the Advancement of Medical Instrumentation (AAMI), European Society of Hypotension (ESH) and the International Organization for Standardization (ISO)

(AAMI/ESH/ISO) standard [63]. These standards are based on adult populations, however, and relevant errors may be different in the neonatal population.

Our results showed that the mainly the slope of the systolic upstroke (dP/dt_{max}) was affected by dynamic response, indicating that the reconstruction method would be of use to increase wave shape validity. Although the neonatal arterial waveform is currently not used for advanced hemodynamic analysis, we believe that the wave shape may contain hemodynamically relevant information. Consequently, our reconstruction method may be of great value in future research to obtain more insight from the neonatal arterial waveform.

5.4.1 *Study limitations*

Although our results suggest that a reconstruction method based on dynamic response characteristics of the measurement system increases arterial waveform validity, additional validation is required. We were not able to measure the actual undistorted arterial waveform and therefore are not certain that the reconstruction actually leads to a more valid pressure measurement. Our method for calculated the overdamped dynamic response parameter λ was not validated either and any inaccuracies in this method may induce additional errors to the waveform when used in the reconstruction method.

Furthermore, the validation that we performed did not make use of actual CMS, its dynamic response and the clinically used flush-pulse method for dynamic response calculation. As we did not have a gold standard reference method such as MTC, we relied on simulated data and high-fidelity data extracted from a published study [62]. Consequently, the CMS and flush pulse method needed to be simulated as well. On the one hand, these simulations could have induced inaccuracies as any simulation is a simplified representation of reality. On the other hand, it may have increased apparent validity of the reconstruction method as the signals were less prone to for example movement artifacts and the simulated flush pulse was generally easier to discern from the waveform than in clinical dynamic response measurements.

5.4.2 *Future perspectives*

Ideally, the reconstruction method would be validated by simultaneously measuring the blood pressure waveform via a manometer-tipped catheter and a fluid-filled CMS. The MTC would provide a gold standard measurement for the validation of the reconstruction method. However, any invasive research is not easily accepted and planned. The method may be more easily validated in adults, for example during cardiac catheterization. Wet lab experimentation using a circulation model with a pump could be a rather easy method of validation, providing both MTC and CMS measurements as well. This would also be a simple way to apply the reconstruction method to various circulatory situations as well as changes in the measurement system, such as the introduction of air bubbles.

As our previous studies on dynamic response of CMS were performed in the NICU, we initially focused the creation and validation of our reconstruction method on the neonatal population. Although effects of dynamic response may be less severe in adults due to generally lower heart rates, faulty pressure measurements may still have clinical implications and the proposed reconstruction method may therefore be of use in the adult ICU as well.

5.4.3 *Conclusion*

In the current study, we proposed a method for the reconstruction of neonatal arterial waveforms measured via CMS based on the system's dynamic response parameters in the case of both under- and overdamping. Though effects on pressure values were generally small, our results indicate an increase in waveform validity using this reconstruction method, but additional validation against a gold standard method of blood pressure measurement is still required.

6 Clinical implications

In the previous chapters, we have shown that blood pressure measurement in critically ill neonates via CMS is prone to errors by dynamic response, especially leading to distorted wave shape. These effects on wave shape may not have a direct implication in clinical practice, but more so on further research attempting to obtain more hemodynamically relevant information from the wave shape. In case of highly inadequate dynamic response, measurement of pressures may be affected, which may could have impact in every day clinical practice, dependent on the severity of the error. We will discuss the possible clinical implications of CMS dynamic response on blood pressure monitoring in the NICU.

In 2019, the Association for the Advancement of Medical Instrumentation (AAMI), European Society of Hypotension (ESH) and the International Organization for Standardization (ISO) collaborated on a universal standard for the validation of blood pressure measurement devices [63]. They stated a criterion of test versus reference BP measurements $\leq$ 5 mmHg with $SD \leq$ 8 mmHg for systolic and diastolic blood pressure. In our study, this would translate to an allowed error in systolic and diastolic BP measurement of up to 5 mmHg calculated from the measured arterial waveform. In our simulation study, this value was exceeded in systolic pressure with low natural frequency and damping. However, we have also shown that errors become larger with higher heart rate. A maximal error of 5mmHg for both systolic and diastolic pressure would allow for an error of 10mmHg in pulse pressure. This criterion was met in our simulations, though a pulse pressure error of 6.7 mmHg was found for low natural frequency and damping, which corresponded to a percentual error of 34%. This demonstrates the problem with these guidelines in the neonatal population; where an error of several millimeters mercury is irrelevant in adults with BP of 120/80 mmHg, it may lead to a 50% change pulse pressure in neonates. The AAMI/ESH/ISO standard does state age < 3 years as a 'special population', but does not provide any specific criteria for this patient group [63]. In their paper on dynamic response requirements of blood pressure measurements in neonates, Van Genderingen et al. employed a maximal inaccuracy of 2% for systolic pressure, diastolic pressure and pulse pressure [20]. This is a contrastingly strict criterion, as this could mean a maximal systolic pressure error of for example 1 mmHg, in case of a P_S of 50 mmHg. Moreover, even within the neonatal population a criterion may not be applicable to every patient due to heterogeneity of the population.

A more comprehensive way to look at this is considering which difference in BP would actually alert the physician to (think about) action – consequently, which difference in pressure would be clinically relevant. This is also difficult to determine, as the use of intra-arterially measured blood pressure differs per physician. Though there are several definitions of hypo-, hyper- and normotension in neonates, there is no consensus on which of these should be used in clinical practice.

The most used clinical sign for assessing the neonatal hemodynamic status is mean blood pressure [33]. In premature infants with BW between 500 and 2000 g, MBP generally ranges between 35 and 49 mmHg, P_S between 46 and 62 mmHg and P_D between 23 and 36 mmHg. BP increases with postnatal [16]. Generally, neonatal hypotension is considered as the MBP for which autoregulation is impaired but no clear threshold based on evidence is defined. In clinical practice, MBP below 30 mmHg or MBP below the neonate's gestational age in weeks is often considered as threshold – the circulation of a day-old patient of 28 weeks' gestation is deemed adequate when their MBP is above 28 mmHg [12, 16]. Another possible definition for hypotension is MBP below the 5th or 10th percentile of normative blood pressure for patients with similar gestational age, postnatal age and birth weight [16]. However, these definitions are not based on any (patho)physiological knowledge and proof of any relation to long-term outcome is lacking [64]. Furthermore, data of premature neonates by Alonzo et al. suggest that MBP exceeds the neonate's gestational age and increases with postnatal age as well [65].

Taking into account only MBP, which is thus mainly used in clinical practice, the effects of dynamic response are negligible. Consequently, clinicians can safely rely on MBP for assessment of hemodynamic status.

Next to only MBP, we observed that clinicians occasionally take into account pulse pressure as well, especially in case of (expected) circulatory distress. Yet this varies between and within specialists and residents. Considering *PP*, the impact of dynamic response may be clinically relevant. However, even more so than in MBP, clear guidelines on the use of pulse pressure in clinical practice are lacking. Distinguishing inadequate from adequate blood pressure and subsequent assessment of circulatory status is challenging. There are some small studies that report pulse pressure measurements in preterm neonates as 25 ± 6 mmHg, 24 ± 8 mmHg and 22 ± 12 mmHg, showing that 'normal pulse pressure' may have quite a large range [66-68]. However, normative data on pulse pressure do not tell when pressure is impactfully aberrant. A rule of thumb that may be used in clinical practice dictates that normal *PP* is about a third of systolic pressure and high *PP* is over half of systolic pressure. Pulse pressure would be low if it is less than 25% of P_S.

In Fig. 6.1, an example of a clinically measured neonatal waveform is shown before (a) and after reconstruction (b). Clearly, an increase in complexity of the signal is seen, but a change in pressure values as well. With some simple calculations, we obtain a pulse pressure of 24% of P_S in the original waveform in Fig. 6.1 a and 29% of P_S in the reconstructed waveform in Fig. 6.1b. The rule of thumb described above would indicate that the original measured pulse pressure was low but

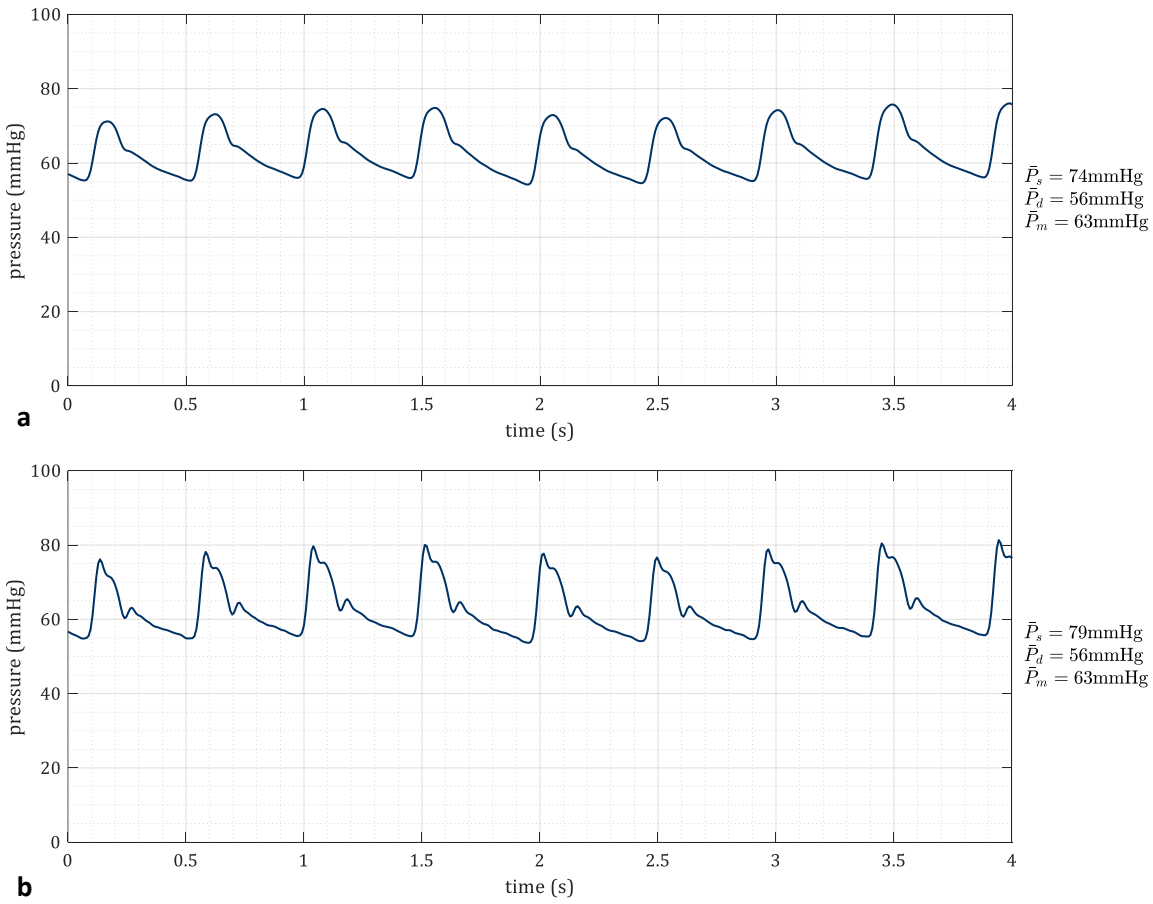

Figure 6.1: Example of a clinically measured neonatal waveform is shown before (a) and after reconstruction (b). On the right of each graph, several mean pressure values are shown: P_s = systolic pressure; P_d = diastolic pressure; P_m = mean blood pressure.

the reconstructed value adequate. Consequently, in this specific case, dynamic response and our reconstruction method are clinically relevant.

Ch. 4 illustrated that arterial lines are often subject to low natural frequency and high damping coefficient, indicating inadequate dynamic response. However, Ch. 5 illustrated that in general, our reconstruction method did lead to noteworthy changes in measured pressures, with median error of 1 (IQR −2 – 0) for both systolic pressure and pulse pressure. For most patients and arterial lines, the pressure errors induced by inadequate dynamic response of the CMS were thus not clinically relevant. Furthermore, there is no clear evidence showing which changes in (pulse) pressure would have any impact on the patient's hemodynamic status. It is therefore difficult to state for which dynamic response-induced errors the use of a reconstruction method in clinical practice is warranted.

We have also seen that dynamic response is highly variable over time within the same arterial line of the same patient. Consequently, in case of large changes in for example pulse pressure, it may be relevant to evaluate the CMS' dynamic response to make sure these changes are not caused by a decrease in measurement validity. Overall, however, our results indicate that MBP is not considerably affected by dynamic response. Pulse pressure may be affected to a clinically relevant degree in specific cases of highly inadequate dynamic response, while the general effects seem minor. In specific cases, application of a reconstruction method could therefore aid clinicians in clinical decision making by increasing validity of the arterial pressure waveform.

7 Discussion

Adequate blood pressure measurement, as part of comprehensive hemodynamic monitoring, is important to assess the circulation in critically ill neonates to evaluate the immature cardiovascular system and its development in the transition from intra- to extrauterine life. Hypotension and the development of shock are associated with adverse outcome [4-8]. Early recognition of hemodynamic compromise may guide patient-specific treatment and thereby improve outcome in neonates. Blood pressure measurement via CMS is the gold standard method in neonatal intensive care. However, the validity of measurements via CMS may be affected by a characteristic of the system called the dynamic response. The aim of this thesis was to assess the validity of CMS based intra-arterial BP measurement in the NICU, by evaluating the effect of varying dynamic response on pressure values as well as the wave shape, and determining the actual dynamic response of intra-arterial catheter-manometer systems in situ at the NICU. To improve validity of these measurements, we aimed to develop a reconstruction method for distorted arterial waveforms.

We showed that inadequate dynamic response can lead to noteworthy changes in wave shape. Decrease of natural frequency led to a worse reproduction of the arterial waveform. With a high damping factor, a corresponding dampening of the arterial waveform could be seen, with narrowing of the pulse pressure and less or no discernible dicrotic notch. With low damping, pulse pressure widened and additional oscillations appeared in the signals. Furthermore, we have shown that pressure errors are dependent on both f_n and ζ – a higher f_n will allow for a larger range of adequate damping coefficients. Changes in both pressure and wave shape due to dynamic response are considerably dependent on HR, with larger errors in waveforms with higher heart rates.

We used the flush pulse technique to evaluate dynamic response of CMS in routine care at the NICU, which yielded dynamic response measurements in nearly three quarters of all flushing moments. When arterial lines are flushed regularly, for example at least twice a day, it is possible to provide routine measurements of dynamic response parameters in the every-day clinical practice at our NICU. Furthermore, we were able to provide a measurement of overdamped systems as well, which to our knowledge has not been reported in previous literature. From our results we can conclude that blood pressure measurement via intra-arterial CMS at our NICU is characterized by predominantly low natural frequency and relatively high values of damping coefficient. Furthermore, variability of dynamic response over time was generally high. Combined with our findings on the effects of dynamic response, these results suggest that intra-arterial blood pressure measurement at the NICU may yield inadequate arterial waveforms. Knowledge on the causes of these dynamic response characteristics is limited.

To attempt to eliminate these negative effects of dynamic response on the neonatal APW, we created a method for the reconstruction of distorted blood pressure measurements. As this method is based on measured dynamic response parameters, it is measurement-specific. We provided initial validation that indicated improved waveform validity with the use of our reconstruction method, but additional validation against a gold standard method of blood pressure measurement is still required.

As discussed in Ch. 6, dynamic response only led to clinically relevant changes in pressure measurement in specific situations of highly inadequate dynamic response. Wave shape, which is not of importance in daily clinical practice, was more considerably distorted. However, there may be more clinically relevant information hidden in the complex arterial waveform than solely BP. The validity of such waveform analyses, however, would be hindered by inadequate wave shape induced by dynamic response. For example the pressure recording analytical method (PRAM), which has been validated in critically ill children, measures CO based on morphological analysis

of the arterial waveform [69]. Our results indicate that using a method such as PRAM could be based on distorted wave shape. Furthermore, numerous methods have been proposed to derive CO from the arterial pressure wave in adults, which are often based on dicrotic notch detection [29]. Though we only studied the neonatal population, dynamic response may be inadequate in other patients groups as well, which would limit the use of the arterial pulse contour analysis for hemodynamic assessment. Furthermore, many novel techniques for hemodynamic monitoring, are validated against the intra-arterial waveform measured with CMS as this is considered the gold standard method. This study shows that we should be apprehensive in using this technique as reference method, as it may not always provide an actual ground truth measurement.

7.1 Strengths and limitations

We have studied the possible effects of inadequate dynamic response on the neonatal arterial waveform. To our knowledge, dynamic response of CMS in the neonatal population has not been studied before in terms of both pressure measurement and waveform validity. Moreover, we measured dynamic response of CMS in a clinical setting and created a method for counteracting the distortions induced by inadequate dynamic response, thereby identifying the problem and directly proposing a solution. This comprehensive explorative approach poses a strength of the study.

Furthermore, in our clinical measurements of dynamic response, we were able to identify and characterize overdamped systems by proposing a novel dynamic response parameter, λ. In previous studies on dynamic response, CMS have been described as underdamped systems. Our study showed that neonatal CMS in situ may sometimes be overdamped as well. Characterization of overdamped systems by λ allowed for the measurement-specific reconstruction of these system's as well, which would not have been possible without the overdamped dynamic response coefficient.

In this thesis, we have stated multiple times that the neonatal population is highly heterogeneous. Throughout this research, we have attempted to take into account differences within the patient group in terms of for example heart rate, and have provided patient- and measurement-specific results. This is a strength especially in our reconstruction method. Previous attempts to solve for distortions imposed by inadequate dynamic response have rarely been measurement-specific, although the effects of dynamic response are not always generalizable and we showed in Ch. 4 that dynamic response is not stable within measurement systems and patients.

The characteristics of the population also constitute a difficulty in determining the clinical impact of our results. There is no consensus on the definitions of normal blood pressure, let alone which changes in pressure would be clinically relevant. Furthermore, some clinicians base their assessment of hemodynamic status on MBP alone, while others take into account pulse pressure as well. It is therefore not straightforward whether a certain pressure error may be allowed or when application of our reconstruction method would be of value.

Although we evaluated the effects of possibly inadequate dynamic response on the neonatal arterial waveform and were able to measure dynamic response in everyday clinical practice, we could not provide clear and definitive causes for inadequate dynamic response, the discrepancies between our measurements and those reported in literature and the variability of dynamic response parameters over time. This constitutes a gap in this research.

Moreover, our study is mainly limited by the absence of a ground truth measurement. We have evaluated possible effects of dynamic response based on simulated waveforms. Comparison of distorted waveforms with a gold standard would provide the actual effects of inadequate dynamic response. Furthermore, we validated our reconstruction method only on simulated data and simulation of CMS and additional validation with a true gold standard method is required.

7.2 Recommendations and future perspectives

Ideally, the our reconstruction method would be validated against the gold standard blood pressure measurement via an indwelling MTC, but this would be rather invasive research which is especially difficult in the neonatal population. Another option would be to construct a wet lab setting in which a simple circulation with a pump is simulated. In such a model, a MTC and a CMS could be introduced simultaneously, allowing for validation of the reconstruction method and additional validation of the flush-pulse method, as the fast flush test – the gold standard method for dynamic response measurement – could be applied as well. Furthermore, such a wet lab setting would allow for validation of the reconstruction method and evaluation of factors that affect dynamic response. For example, tubing length and diameter could be varied among other things and resulting dynamic response and its effects on blood pressure measurements could be evaluated.

Next to further analysis in a wet lab setting, improvement of the methods proposed in this thesis is required before it is ready for clinical implementation. In the current methodology, flushing moments are documented by nursing staff and subsequently, the flush-pulse responses are manually extracted from the data recordings and scored as under- or overdamped by the observer. These steps could be automized, for example by making use of machine learning methods that recognize specific patterns in data. Furthermore, goodness of fit of the flush-pulse responses to the dynamic response functions as described in Ch. 4 could be further improved.

These advancements would aid in possible future implementation of the reconstruction method in neonatal clinical practice. By routine measurement of dynamic response and subsequent application of a measurement-specific reconstruction method in the case of a clinically relevantly distorted waveform, blood pressure monitoring via in-dwelling CMS at the NICU could be improved which may expand knowledge on patients' hemodynamic status and aid in clinical decision making. Implementation of a reconstruction method could lead to increased validity of the full arterial waveform. This would allow for further analysis of the waveform, for example aiming to extract more hemodynamically relevant information. In this thesis, we have shown that inadequate dynamic response may significantly affect several aspects of the arterial wave shape, such as the steepness of the systolic upstroke, dP/dt_{max}, and the area under the systolic part of the curve. Such parameters could be indicative of for example ventricular function and cardiac output, respectively. Application of a reconstruction method which increases waveform validity would warrant further research in this area.

While this thesis focused on dynamic response of catheter-manometer systems for blood pressure measurement in neonates, the results are partly applicable to other populations as well. Though the effects of dynamic response may be larger in neonates due to their generally higher heart rates than older children or adults, CMS characteristics may still have clinically relevant impact on arterial waveform measurements in these populations as well, possibly warranting routine dynamic response measurement and the implementation of a reconstruction method. The findings described in this thesis are therefore not necessarily limited to the neonatal population.

7.3 Conclusion

Validity of arterial pressure waveforms measured with catheter manometer systems in critically ill neonates can be affected by the system's dynamic response, which can be easily measured in routine care at the NICU. Wave shape could be considerably affected, while the errors in pressure measurement were generally clinically irrelevant. From the measured dynamic response parameters, we created a measurement-specific method for the reconstruction of blood pressure signals distorted by inadequate dynamic response. Though further validation is required, the proposed reconstruction method may aid in obtaining more valid arterial pressure waveforms in critically ill neonates.

8 References

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Appendix

8.1 Supplementary tables

Table A.1: Baseline parameters of simulated waveform 1

Parameter	Value
Systolic pressure	60 mmHg
Diastolic pressure	40 mmHg
Pulse pressure	20 mmHg
Mean blood pressure	49 mmHg
Maximal slope (corrected for heart rate)	214 mmHg
Area under the systolic part of the curve	202 mmHg · s
Dicrotic notch pressure	52 mmHg
Systolic duration	139 ms

Table A.2: Absolute and percentual differences in pressure values between the transformed and the original simulated 140 bpm waveform for varying dynamic response

ζ	*0.2*		*0.7*		*1.2*	
	Absolute error	*Percentage error (%)*	*Absolute error*	*Percentage error (%)*	*Absolute error*	*Percentage error (%)*
f_n (Hz)	P_S (mmHg)					
10	6.4	11	0.2	0	−2.4	−4
20	0.6	1	0.0	0	−0.7	−1
40	0.1	0	−0.1	0	−0.2	0
	P_D (mmHg)					
10	−0.4	−1	−0.4	1	1.0	3
20	−0.2	−1	−0.2	1	0.4	1
40	0	0	0	0	0.2	1
	PP (mmHg)					
10	6.7	46	−0.3	−2	−3.5	−17
20	0.9	5	−0.3	−1	−1.2	−6
40	0.2	1	−0.2	−1	−0.4	−2
	MBP (mmHg)					
10	0.0	0	−0.1	0	0.1	0
20	−0.1	0	0.1	0	−0.1	0
40	0.1	0	−0.1	0	0	0

Abbreviations and symbols: ζ = damping coefficient; f_n = natural frequency; P_S = systolic pressure; P_D = diastolic pressure; *PP* = pulse pressure; MBP = mean blood pressure

Table A.3: Absolute and percentual differences in waveform parameters between the transformed and the original simulated 140 bpm waveform for varying dynamic response

ζ	*0.2*	*0.7*	*1.2*
	Absolute error	*Absolute error*	*Absolute error*
f_n (Hz)	RMSE		
10	2.9	3.2	4.0
20	0.9	1.7	2.5
40	0.3	0.9	1.4

Abbreviations and symbols: ζ = damping coefficient; f_n = natural frequency; RMSE = root mean square error

Table A.4: Absolute and percentual differences in waveform parameters between the transformed and the original simulated 140 bpm waveform for varying dynamic response

ζ	*0.2*		*0.7*		*1.2*	
	Absolute error	*Percentage error (%)*	*Absolute error*	*Percentage error (%)*	*Absolute error*	*Percentage error (%)*
f_n (Hz)	dP/dt_{max} (mmHg)					
10	58	27	−56	−26	−100	−46
20	60	29	−14	−7	−56	−26
40	11	5	−9	−4	−27	−12
	AUC_s					
10	98	49	32	17	*NC*	*NC*
20	115	60	−31	−14	−80	−40
40	−35	−16	31	17	−6	−3
	P_{DN} (mmHg)					
10	−5.6	−11	−0.3	−1	*NC*	*NC*
20	−3.2	−6	−0.3	−1	6.8	13
40	0.3	1	−0.3	−1	0.5	1
	T_s (mmHg)					
10	104	77	24	18	*NC*	*NC*
20	72	53	8	6	−48	−35
40	−8	−6	8	6	8	6

Abbreviations and symbols: ζ = damping coefficient; f_n = natural frequency; dP/dt_{max} = maximal slope in systolic upstroke; AUC_S = area under the systolic part of the curve; P_{DN} = dicrotic notch pressure; T_S = duration of systolic part of the curve; NC: not calculable due to indiscernibility of the dicrotic notch

Table A.5: Underdamped dynamic response measurements per arterial line

Line	N	$f_n(Hz)$	CV_{MAD,f_n}	R_{f_n}	ζ	$CV_{MAD,\zeta}$	R_ζ
a	1	12.8			0.86		
b	31	13.0 (12.2 – 14.0)	0.07	−0.07	0.89 (0.59 – 0.92)	0.05	−0.41
c	18	11.8 (11.0 – 15.6)	0.19	−0.09	0.73 (0.40 – 0.88)	0.28	−0.17
d	10	14.0 (12.0 – 15.5)	0.14	0.52	0.90 (0.86 – 0.94)	0.05	−0.16
e	59	12.6 (11.4 – 13.6)	0.09	0.02	0.86 (0.54 – 0.91)	0.09	−0.07
f	52	13.8 (12.9 – 17.4)	0.11	−0.17	0.93 (0.85 – 0.94)	0.02	0.19
g	17	14.2 (12.7 – 15.9)	0.29	−0.45	0.34 (0.29 – 0.56)	0.23	0.25
h	8	15.6 (11.6 – 16.9)	0.20	−0.01	0.43 (0.30 – 0.49)	0.30	0.16
i	1	15.7			0.88		
j	3	14.4 (12.8 – 14.6)	0.02	−0.53	0.90 (0.69 – 0.92)	0.05	−0.39
k	12	17.8 (13.5 – 18.7)	0.11	−0.23	0.42 (0.31 – 0.51)	0.26	−0.26
l	10	17.8 (17.2 – 19.7)	0.10	0.28	0.30 (0.27 – 0.39)	0.15	−0.12
m	25	12.7 (11.0 – 14.3)	0.13	0.31	0.90 (0.50 – 0.94)	0.06	−0.09
n	33	14.9 (12.8 – 16.3)	0.14	−0.23	0.91 (0.41 – 0.94)	0.05	0.36
o	1	13.5			0.95		
p	6	13.7 (13.5 – 14.1)	0.01	0.69	0.92 (0.92 – 0.94)	0.01	−0.58
q	19	12.6 (11.1 – 13.7)	0.11	0.12	0.90 (0.64 – 0.92)	0.05	−0.04
r	10	12.7 (11.6 – 13.7)	0.09	−0.67	0.93 (0.86 – 0.94)	0.03	−0.23
s	10	13.7 (10.4 – 16.4)	0.25	−0.59	0.71 (0.42 – 0.93)	0.32	−0.09
t	1	14.3			0.45		
u	7	16.5 (13.2 – 16.7)	0.06	−0.72	0.92 (0.64 – 0.93)	0.03	−0.07
Tot.	334	14.4 (11.9 – 15.6)	0.11 (0.09 – 0.14)	−0.09 (−0.45 – 0.12)	0.88 (0.45 – 0.93)	0.05 (0.05 – 0.23)	−0.09 (−0.23 – −0.04)

Abbreviations and symbols: N = sample size, f_n = natural frequency in Hz, reported in median (interquartile range), CV_{MAD,f_n} = nonparametric coefficient of variation of f_n, ζ = damping coefficient, reported in median (interquartile range), $CV_{MAD,\zeta}$ = nonparametric coefficient of variation of ζ, R = Pearson's correlation coefficient

Table A.6: Overdamped dynamic response measurements per arterial line

Line	N	λ	$CV_{MAD,\lambda}$	R_λ
a	7	84 (78 – 88)	0.04	0.44
b	5	100 (99 – 100)	0.01	−0.47
c	1	86		
d	5	103 (97 – 111)	0.09	−0.04
e	6	89 (86 – 93)	0.05	0.91
f	1	87		
g	4	55 (36 – 78)	0.37	0.16
i	1	43		
j	2	95 (91 – 100)		
m	6	78 (76 – 95)	0.04	−0.01
s	1	101		
t	1	43		
Tot.	40	87 (79 – 99)	0.05 (0.04 – 0.08)	0.08 (−0.03 – 0.37)

Abbreviations and symbols: N = sample size, λ = overdamped dynamic response coefficient, reported in median (interquartile range), $CV_{MAD,\lambda}$ = nonparametric coefficient of variation of λ, R = Pearson's correlation coefficient

Table A.7: Underdamped dynamic response of multiple arterial lines within the same patient

		Arterial line 1	Arterial line 2	Arterial line 3	P-value	
Patient A	*Line type*	Umbilical	Peripheral			
	f_n *(Hz)*	14 (12 − 17)	14 (13 − 18)		0.60	
	ζ	0.90 (0.73 − 0.94)	0.93 (0.82 − 0.94)		0.52	
Patient B	*Line type*	Umbilical	Peripheral			
	f_n *(Hz)*	13 (11 − 14)	15 (13 − 17)		0.01	(*)
	ζ	0.90 (0.48 − 0.94)	0.90 (0.39 − 0.94)		0.66	
Patient C	*Line type*	Umbilical	Peripheral			
	f_n *(Hz)*	13 (11 − 14)	14 (10 − 17)		0.80	
	ζ	0.93 (0.81 − 0.95)	0.71 (0.39 − 0.93)		0.17	
Patient D	*Line type*	Peripheral	Peripheral			
	f_n *(Hz)*	13 (12 − 14)	12 (11 − 16)		0.38	
	ζ	0.89 (0.59 − 0.92)	0.73 (0.38 − 0.90)		0.09	
Patient E	*Line type*	Peripheral	Peripheral	Peripheral		
	f_n *(Hz)*	14 (13 − 16)	18 (13 − 19)	13	0.13	
	ζ	0.34 (0.29 − 0.60)	0.42 (0.29 − 0.53)	0.92	0.54	

Abbreviations and symbols: f_n = natural frequency in Hz, reported in median (interquartile range), ζ = damping coefficient, reported in median (interquartile range). (*) indicates a statistically significant difference. A P-value < 0.05 is considered statistically significant.

8.2 Calculation of arterial waveform parameters

8.2.1 *Pressure values*

1. Detect onset of wave/systolic upstroke
    a. Slope sum function [70]
2. Detect systolic peak
    a. This is the local maximum after wave onset
    b. Find first positive to negative (2nd derivative < 0) zero crossing of the first derivative after wave onset
    c. Pressure at this time = systolic pressure
3. Diastolic pressure = pressure at onset of wave OR diastolic nadir:
    a. This is the local minimum before the inflection point
    b. Find last negative to positive (2nd derivative > 0) zero crossing of the first derivative before wave onset
    c. Pressure at this time = diastolic pressure
4. Pulse pressure: $PP = P_S - P_D$
5. Detect dicrotic notch [41, 71]
    a. This is a local minimum after systolic peak

    b. Determine searching window; $1/10^{th}$ of beat interval OR 40 ms (whichever is shortest) and half of beat interval OR 400 ms (whichever is shortest)
    c. Find secondary inflection point: second zero of second derivative where sign changes
    d. Find first zero crossing of first derivative after secondary inflection point
6. Mean pressure: take mean of one waveform; from onset of wave to onset of next wave, detected as described above

8.2.2 *Other waveform parameters*

1. Systolic part of the waveform is from onset of systolic upstroke to dicrotic notch (detected as described above)
2. Diastolic part of the waveform is from dicrotic notch to onset of next systolic upstroke (detected as described above
3. Total area: $AUC_{tot} = AUC_S + AUC_D$
4. Maximal systolic upstroke (dP/dt_{max}) is maximal slope from wave onset to systolic peak
5. Systolic duration (T_S) is the time from wave onset to the dicrotic notch of that wave.