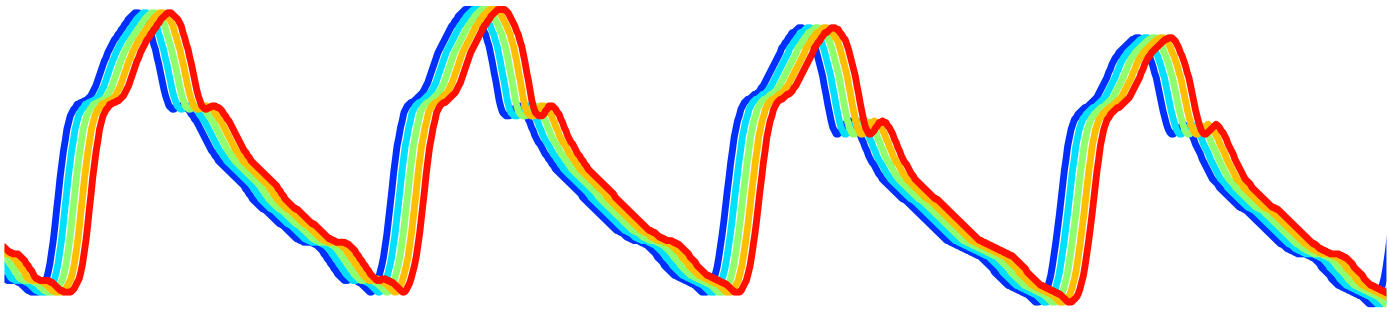
# MASTER'S THESIS

# ARTERIAL BLOOD PRESSURE CURVE ANALYSIS IN CARDIOGENIC SHOCK COMPLICATING MYOCARDIAL INFARCTION

Author: Soray Dülger, BSc.

Graduation committee
Prof. dr. R.H.J.A. Slart
Prof. dr. J.P.S. Henriques
Dr. ir. F.H.C. de Jongh
Dr. D.M. Ouweneel
Drs. B.J.C.C. Hessink-Sweep

*Academic Medical Center, Amsterdam*
*University of Twente, Enschede*
November 9, 2017



**TECHNICAL MEDICINE MASTER'S THESIS:**

# ARTERIAL BLOOD PRESSURE CURVE ANALYSIS IN CARDIOGENIC SHOCK COMPLICATING MYOCARDIAL INFARCTION

Author: Soray Dülger

UNIVERSITY OF TWENTE.

# Acronyms

| | |
|---|---|
| ***(p)PCI*** | (primary) Percutaneous coronary intervention |
| ***AIx*** | Augmentation index |
| ***AMI*** | Acute myocardial infarction |
| ***AUC*** | Area under the curve |
| ***BMI*** | Body-mass index |
| ***BS*** | Beatscope |
| ***CABG*** | Coronary artery bypass grafting |
| ***CAD*** | Coronary artery disease |
| ***CD*** | Cardiac death |
| ***CI*** | Cardiac index |
| ***CO*** | Cardiac output |
| ***CPO*** | Cardiac power output |
| ***CS*** | Cardiogenic shock |
| ***ECG*** | Electrocardiogram |
| ***HF*** | High frequency |
| ***HR*** | Heart rate |
| ***HRV*** | Heart rate variability |
| ***IABP*** | Intra-aortic balloon pump |
| ***ICU*** | Intensive care unit |
| ***iNOS*** | Inducible nitric oxide synthase |
| ***IQR*** | Interquartile range |
| ***LAD*** | Left anterior descending artery |
| ***LF*** | Low frequency |
| ***LM*** | Left main artery |
| ***(r)LVET*** | (relative) Left ventricular ejection time |
| ***LV*** | Left ventricle |
| ***MAP*** | Mean arterial pressure |
| ***MI*** | Myocardial infarction |
| ***NSTEMI*** | Non ST-elevation myocardial infarction |
| ***OHCA*** | Out-of-hospital cardiac arrest |
| ***PCPW*** | Pulmonary capillary wedge pressure |
| ***PPV*** | Pulse pressure variation |
| ***PWV*** | Pulse wave velocity |
| ***PWV*** | Pulse wave velocity |
| ***RAS*** | Renin-angiotensin system |
| ***RCA*** | Right coronary artery |
| ***RCx*** | Ramus circumflexus |
| ***RDNP*** | Relative dicrotic notch pressure |
| ***STEMI*** | ST-segment elevation myocardial Infarction |
| ***SVV*** | Stroke volume variation |
| ***SV*** | Stroke volume |
| ***SVR*** | Systemic vascular resistance |
| ***VLF*** | Very low frequency |

# Abstract

*Introduction:* Cardiogenic shock (CS) is the most common cause of death in patients with acute myocardial infarction. CS is defined by insufficient organ perfusion, caused by cardiac dysfunction. In-hospital mortality rates of CS patients are dramatically high, approximately 50 percent. CS is diagnosed based on the presence of hypotension, cardiac failure and some additional clinical findings suggesting decreased organ perfusion. The current definition of CS does not provide a grading that gives insight in the severity or "stage" of CS. Such a grading could guide medical therapies in the acute representation of CS, such as the timing of placement of mechanical assist devices. Since the arterial pressure pulse is determined by the pumping function of the heart and the bodies vasculature, the blood pressure curve might give additional insight in CS severity. The aim of this study is to gain insight in the value of the blood pressure curve morphology of predicting outcome in CS patients.

*Methods:* An algorithm is developed to calculate various pressure, time slope, area, blood pressure variability and frequency related parameters. This thesis consists of three sub studies. In study I, the reliability and reproducibility of the parameters are investigated with blood pressure measurements during elective procedures in the catheterization lab. A subset of reliable parameters is chosen. In study II, these parameters are used to investigate blood pressure curve morphology differences in AMI patients that were treated with primary PCI and submitted to the ICU. In this retrospective cohort study, differences were investigated between the 'cardiac death' group, 'non-cardiac death' group and 'survival' group. Factor analysis is performed to investigate correlation between parameters. In study III, the change of blood pressure curve parameters in time is investigated prospectively in STEMI patients treated with primary PCI.

*Results:* Based on study I, only the parameters that are not related to anacrotic and dicrotic notch were regarded reliable, since the anacrotic -and dicrotic notch related parameters showed large variation due to poor detection. With study II, thirteen parameters show a significant relation with either 30-day mortality or cardiac recovery in CS patients. These are: time to maximum slope, upstroke time, downstroke time, heart rate, left ventricular ejection time, systolic area under the curve, shock index, age adjusted shock index, stroke volume, cardiac output, cardiac power output, cardiac index and cardiac power index. Factor analysis revealed that all parameters are more or less correlated with each other, but can be reduced to three subgroups. These groups are: 1) shock index and area under the curves; 2) CO, CPO and SV; 3) Age adjusted shock index and heart rate. Heart rate, LVET and shock index were the strongest predictors of outcome and cardiac function. Though, these parameters could not be combined in multivariate analysis, due to multi-colinearity. Only age, in combination with one of these parameters, give a significant multivariate model with independent parameters. No significant changes in blood pressure curve morphology is seen over time in STEMI patients, except for a small decrease in diastolic pressure and MAP.

*Conclusion:* 'Shock index', 'LVET', 'HR', 'SV', 'CO', 'CPO', 'CI', 'time to maximum slope', 'upstroke time' and 'downstroke time' are parameters that have potential to create a CS grading. Based on the current patient cohort, a complete CS grading cannot be developed yet.

# Voorwoord

Na tien maanden stage op de onderzoeksafdeling van de interventie cardiologie van het AMC, mag ik mijn studie afronden met deze thesis. Deze thesis is tot stand gekomen naar aanleiding van mijn afstudeerstage op de afdeling interventie cardiologie van het AMC in Amsterdam. Tijdens deze stage heb ik metingen mogen uitvoeren bij spoed patiënten met een hartinfarct en kennis mogen maken met de (acute) kliniek op de hartkatheterisatie. Ook heb ik mee mogen krijgen wat de impact van een hartinfarct is voor patiënten en familie. Ik wil alle patiënten die mee hebben gedaan met het onderzoek bedanken.

Dagmar, enorm bedankt voor je betrokkenheid en hulp gedurende mijn stage! Fijn dat je altijd open stond voor vragen. Dankzij jouw databases zat er de nodige vaart in het onderzoek.

Jose, bedankt voor je kritische blik en tijd die je nam om mee te denken met het onderzoek en de focus op klinische relevantie. Leuk om een medisch begeleider gehad te hebben die zo enthousiast is over klinisch onderzoek. Ook bedankt voor je eerlijke en directe feedback.

Frans, elke paar weken hebben we samen gezeten om de (technische) voortgang te bespreken. Je grote hoeveelheid aan kritische vragen zette altijd goed aan het denken en heeft geholpen om het onderzoek richting te geven.

Ook wil ik mijn intervisiegroep en Bregje bedanken voor de gezellige intervisies met mandarijnen en koekjes. Ik vond het fijn om ervaringen te delen en af en toe terug te keren naar onze “thuisbasis” Enschede ;)

Wim Rohling bedankt voor je hulp met het gebruiksklaar maken van de meetapparatuur en data extracties. Ook bedankt voor al je uitleg op het cathlab en handige tips aan het begin van het onderzoek.

Martijn en Juliëtte, jullie ook bedankt voor de hulp met het werkend krijgen van de meetapparatuur en de begeleiding toen Dagmar in Japan zat. Ook alle andere onderzoekers van de cardio wil ik bedanken voor de gezelligheid in de pauzes en al het lekkers.

Ik wil ook graag mijn huisgenoten in Gouda bedanken voor de gezelligheid tussen het afstuderen door!

# Table of contents

# Introduction

## Cardiogenic shock

Cardiogenic shock (CS) is the most common cause of death in patients with ST-segment elevation myocardial infarction (STEMI) hochman[2]. After introduction of early revascularization with primary percutaneous coronary intervention (pPCI) or emergency coronary artery bypass grafting (CABG), outcomes of STEMI patients have dramatically improved [3]. With pPCI it is aimed to achieve immediate reperfusion in the infarct related artery[4]. Although CS incidence has declined with pPCI, it still occurs in 5-8 % of all acute myocardial infarctions (AMI's) with approximately 50 % mortality [2,5]. CS is more common amongst patients with STEMI. It was observed that CS developed in ~7.5% of patients with STEMI and in 2.5% of patients with non-ST-segment elevation myocardial infarction (NSTEMI)[6-8].

CS is a condition with inadequate end-organ perfusion. It represents the final common pathway of large numbers of pathologic conditions, leading to marked impairment of cardiac output and consequently inadequate end-organ perfusion. CS is initiated by a severe reduction in cardiac output, lowering perfusion of the coronary arteries, which may already be compromised by atherosclerotic lesions. This leads to ischemia, further worsening of myocardial performance, and hence the perpetuation of a vicious cycle within the heart. This cycle is presented in figure 1. Further myocardial necrosis and/or stunning may result from distal embolization and/or reperfusion injury when fibrinolytics therapy or primary PCI is undertaken, or from reocclusion of the infarct artery. Right ventricular failure may be the primary cause of CS, but more commonly is a contributing factor. Inflammatory mediators are frequently elevated in CS and have a negative inotropic effect (lower cardiac contractility). In addition, cytokines lead to the production of high levels of nitric oxide (NO) through induction of inducible nitric oxide synthase (iNOS). This may result in a state of inappropriate vasodilation, worsening hypotension, and lactic acidosis[2]. Consistent with these observations, approximately 20% of patients in the SHOCK trial demonstrated findings characteristic of the systemic inflammatory response syndrome. These include low systemic vascular resistance, fever, leukocytosis, and elevated inflammatory markers[9]. The diagnosis of CS is based on the presence of hypotension, low cardiac output, hypoperfusion, and congestion. There are various diagnostic criteria for CS, each relying on invasive hemodynamic measurements obtained from a pulmonary artery catheter, in addition to clinical findings. Currently, there is no gold standard available, but criteria used in the SHOCK trial are generally accepted. CS is present when there is ventricular failure with electrocardiogram (ECG) evidence of total recent coronary occlusion complicated by shock, defined by[10]:

- Hypotension;
- Systolic blood pressure <90 mm Hg for at least 30 minutes or the need for supportive measures to maintain a systolic blood pressure >90 mmHg;
- Evidence of decreased organ perfusion (cool extremities, urine output < 30 ml per hour);
- Confirmatory hemodynamic or radiographic features: Cardiac index <2.2 L/min per square meter of body surface area; Pulmonary capillary occlusion pressure >15 mm Hg; Pulmonary congestion on chest X-ray.

The current definition does not provide a measure of shock severity. It is likely that CS is a gradient phenomenon that develops from mild to severe shock. A proper CS classification might give more insight in the development of CS and guide therapy of CS patients. The arterial pressure is mainly determined by the heart, the arterial vasculature and vascular resistance. Since the diagnosis of shock relies on assessment of the arterial pressure for a large part, the morphology of the arterial pressure may provide a CS grading.

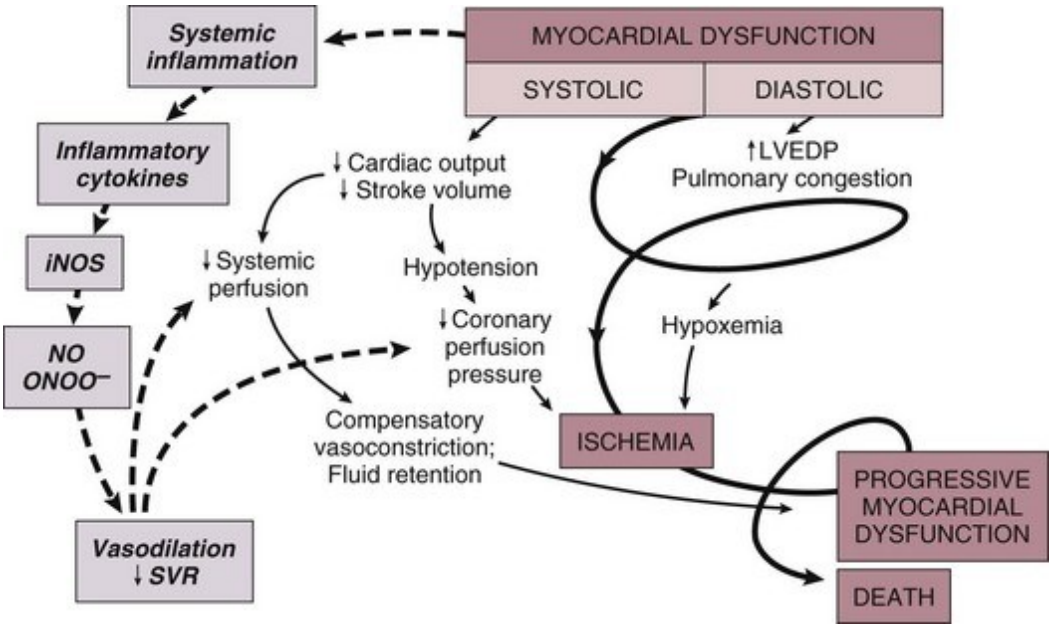



*Figure 1 Pathophysiologic cycle in cardiogenic shock*[11]

# Arterial pressure curve

## Origin of the arterial pressure waveform

The arterial pulse, palpable at for example the radial or carotid artery, is the result from the cyclic change of pressure exerted on the arterial walls by the circulating blood. Blood pressure is a term that is used worldwide and is mostly presented in the form of two values: systolic and diastolic pressure. However, there is more to blood pressure than these two values, which becomes clear if blood pressure is determined continuously as seen in figure 2.

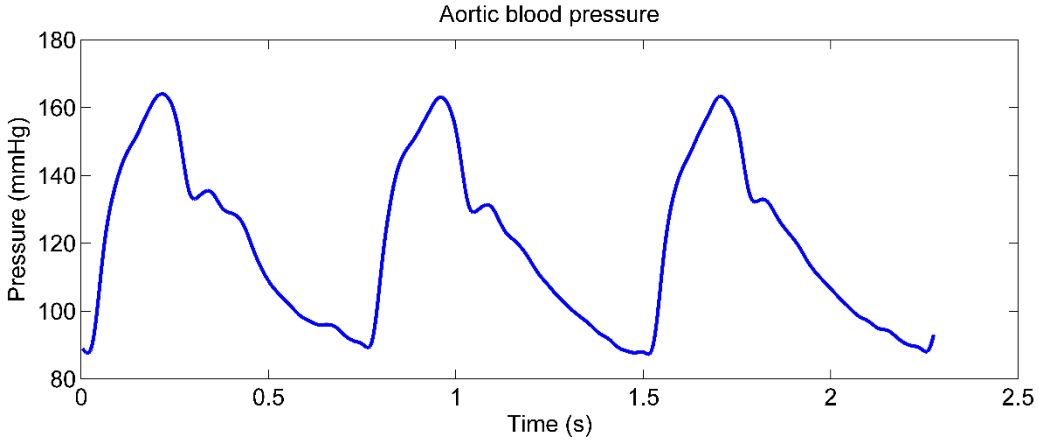



*Figure 2. Continuous blood pressure recording measured in or near one of the coronary ostia.*

The left ventricle (LV) ejects blood into the aorta. When the LV contracts, isovolumetric contraction causes pressure inside the ventricle to increase until pressure inside the ventricle exceeds the pressure inside the aorta. At this point, the aortic valves open and blood ejects from the left ventricle into the aorta, causing steep increase of arterial pressure. The point of maximal slope (dp/dt max) is correlated to left ventricular contractility[12]. The anacrotic shoulder, that is, the rounded part near the top of the waveform, reflects primarily volume displacement.[13,14] The peak pressure point is also called systolic pressure. At this point, pressure inside the ventricle still exceeds pressure in the aorta

and blood keeps flowing from the left ventricle into the aorta. When pressure inside the ventricle exceeds the pressure of the aorta, the aortic valve closes. This point, called the dicrotic notch, is characterized by a dip after the systolic maximum[15] (see figure 3) , caused by aortic valve closure and subsequent retrograde flow. The dicrotic notch marks the end of systole and the beginning of diastole. After the dicrotic notch, pressure inside the arteries decreases until the next ventricular contraction causes the pressure to rise again.

With ejection of blood inside the aorta, a forward running (from aortic root to periphery) pressure wave is generated. As suggested by Westerhof et al. this pressure wave reflects on every location of impedance change all along the vascular tree, for example at bifurcation points[16]. The summation of all reflections results in a backward running wave (from periphery to aortic root). The pressure measured at a certain point along the vascular tree will thus be the superposition of the reflected wave on the forward wave[17], which is called the augmentation of pressure. The position and amplitude of the systolic -and dicrotic notch pressure thus depends on the timing of these forward and backward waves. The timing of the backward wave is largely dependent on speed at which the pressure wave

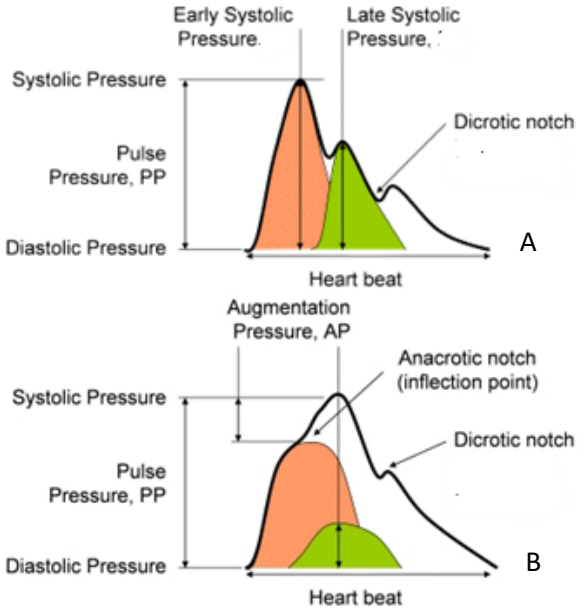



*Figure 3. Visualization of augmentation of the aortic pressure waveform. In orange: the forward running pressure wave, in green the backward running pressure wave. In the resulting pressure waveform the backward running wave is superimposed on the forward running wave. In figure A the reflected wave is superimposed on the down sloping part of the forward wave (relatively low PWV), mostly seen in younger people. In figure B the reflected wave arrives relatively early (high PWV), mostly seen in older people.*

travels through the arterial system, called pulse wave velocity (PWV). PWV is mainly determined by the stiffness of the vessel.

Besides wave reflection, also the duration of systole influences systolic pressure. With a short duration of systole, the reflected wave will appear relatively late compared to a long duration of systole, assuming pulse wave velocity is the same. In figure 3 an example is shown of the difference in blood pressure curve morphology between a late (3A) and an early arriving backward running wave (3B).

## Continuous measurement of arterial pressure

The arterial pressure can be measured invasively and non-invasively. The aortic blood pressure can be measured invasively by an external pressure transducer connected to a fluid filled catheter system. Invasive arterial pressure measurements in this research are measured with an external pressure transducer (Namic Perceptor manifold, Navilyst medical, New York, USA) with a sampling frequency of 240 Hz and a spatial resolution of 0.2 mmHg. The catheter is inserted through a sheath placed in the femoral or radial artery. The proximal end of the catheter is placed in the aorta ascendens, in or near one of the coronary ostia to provide the cardiologist access to the coronary arteries (see figure 4A). Blood pressure is recorded on the MacLab ComboLab 6.8 Z600 acquisition system (GE-Healthcare, Little Chalfont, UK).

The arterial pressure can be measured in a non-invasive manner using the volume clamp method[18]. For this research, non-invasive blood pressure measurements are performed with the Nexfin (Edwards Lifesciences), that uses the volume clamp method with the use of a finger cuff (see figure 4B).[19] The volume clamp method is based on the development of the dynamic pulsatile unloading of the finger arterial walls. The main components of the finger cuff are an inflatable air bladder, and a plethysmograph consisting of a light source (infrared light light-emitting diode) and a light detector (infrared photodiode). The air bladder is connected to the front-end unit via an air hose and both components of the infrared plethysmograph via a cuff cable. In this method the diameter of an artery under a cuff wrapped around the finger is kept constant (clamped) at a certain diameter, the 'set-point', in spite of the changes in arterial pressure during each heartbeat. Changes in diameter are detected by means of an infrared photo-plethysmograph built into a finger cuff. If during systole an increase is detected in arterial diameter the finger cuff pressure is immediately increased by a rapid pressure servo-controller system to prevent the diameter change. Finger cuff pressure equals intra-arterial pressure when the volume- clamp method is active at the proper unloaded diameter of the finger artery. The output of the Nexfin represents the brachial artery pressure reconstructed from the finger arterial pressure by a generalized waveform.

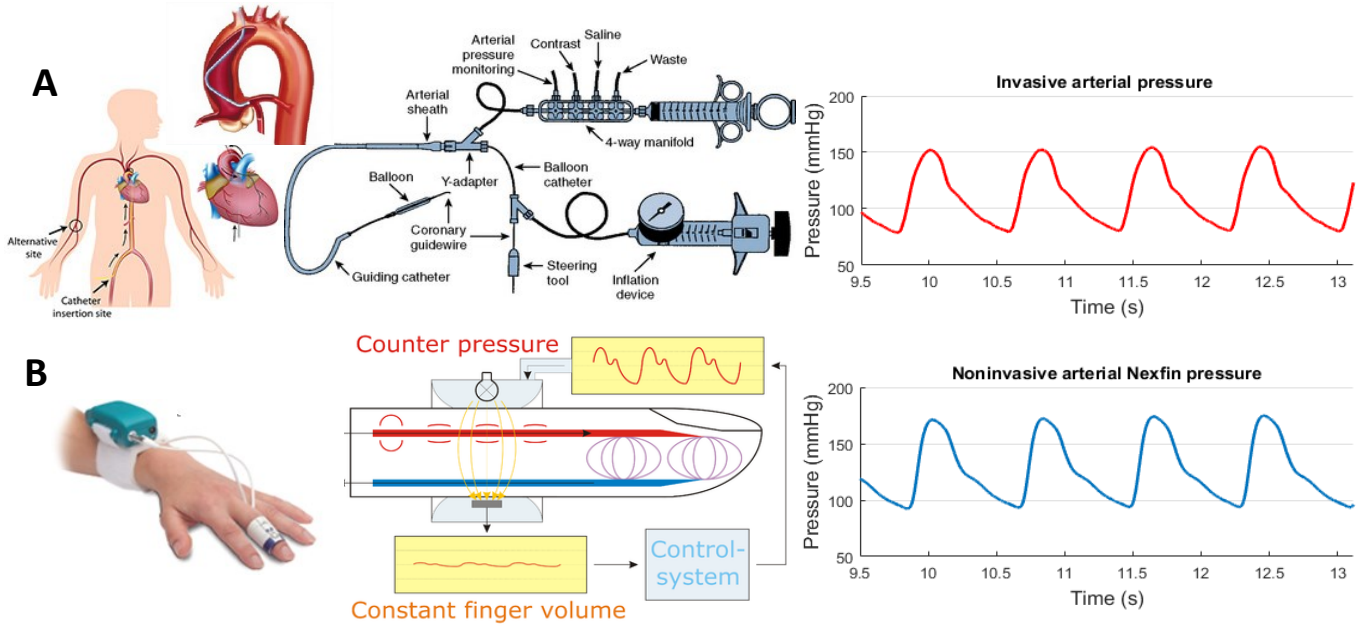



*Figure 4:* ***A:*** *Invasive blood pressure measurement during catheterization.* ***B:*** *Noninvasive brachial artery blood pressure measurement from an arterial finger pressure reconstruction.*

# Former research

Earlier research on blood pressure curve morphology in patients with acute myocardial infarction (AMI) has shown some potential markers for assessment of outcome after pPCI and in cardiogenic shock patients. Spyridopoulos et al. have shown that the shock index (heart rate/ systolic blood pressure) is a predictor of short -and long-term mortality following pPCI in elderly[20]. Stroke Volume Index (SVI) and StrokeWork Index (SWI), were found to be predictors of 30-day mortality in cardiogenic shock patients[21]. SVI and SWI were measured both before and after initial medical stabilization or early revascularization. SVI was calculated as (cardiac output/heart rate) * 1000/body surface area and SWI was calculated as (mean arterial pressure - PCWP) * stroke volume * 0.0136/body surface area. These results indicate the potential value of the blood pressure curve in cardiogenic shock to guide treatment. However, none of these studies have investigated the prognostic value of the blood pressure curve during pPCI. Spyridopoulos et al. investigated shock index post-PCI and found that shock index was a predictor of short -and long term mortality in CS patients (hazard ratio 2.1) and that there was a strong relation between shock index, age and mortality.

Fincke et al. state that cardiac power output is the strongest hemodyanamic independent predictor of in-hospital mortality (odds-ratio 0.55)[22]. Other independent predictors were cardiac power index (CPI), cardiac output (CO) and stroke volume(SV). Systolic and diastolic pressure had less predictive value of in-hospital mortality and left ventricular ejection fraction no predictive value. Their patient cohort included patients who had hemodynamic measurements beteen 6h before up to 12h after shock diagnosis. Assessment of parameters specifically during PCI could be of great interest to guide treatment, as will be investigated in this study. In addition, there are more parameters that could be interesting to evaluate in CS patients.

# Potential parameters

## Blood pressure variation

Literature reports that heart rate variability and blood pressure variability during surgery is associated with improved survival outcomes[23-26]. They suggest that heart rate variability (HRV) reflects an intact autonomic nervous system that is adapting appropriately to the stress of surgery. This implies that CS patients that are in a relatively worse hemodynamic state have may have less HRV.

Another measure associated with hemodynamic stability are pulse pressure variation (PPV) and stroke volume variation (SVV). PPV has been proven to predict fluid responsiveness. It is an indicator of the position on the Frank-Starling curve. Many studies have shown that PPV is much more accurate than cardiac filling pressures and volumetric markers of preload to predict hemodynamic effects

of volume loading. In this respect, PPV is increasingly used in decision-making process regarding volume expansion in patients with hemodynamic instability [27]. PPV is not an indicator of volume status or a marker of cardiac preload, but an indicator of the position on the Frank-Starling curve (figure 5). Patients that operate on the flat potion of the Frank-Starling curve are insensitive to cyclic changes in preload induced by mechanical inspiration. In these patients, PPV is low. PPV is high in patients operating on the steep portion of the preload/stroke volume curve. These patients are sensitive to cyclic changes in preload induced by mechanical inspiration. So far, this information has been used to predict fluid responsiveness in patients with shock. Though it could be useful in many other clinical situations, for example detecting hemodynamic changes during pPCI in patients with CS, or patients developing CS. Several studies have shown that monitoring and maximizing stroke volume by fluid loading is associated with improved postoperative outcome[27,28 29]. Increasing cardiac preload induces a rightward shift on the preload/stroke volume relationship and a decrease in PPV. Stroke volume is related with volume loading. A decrease in preload during pPCI, for example due to blood loss or vas-

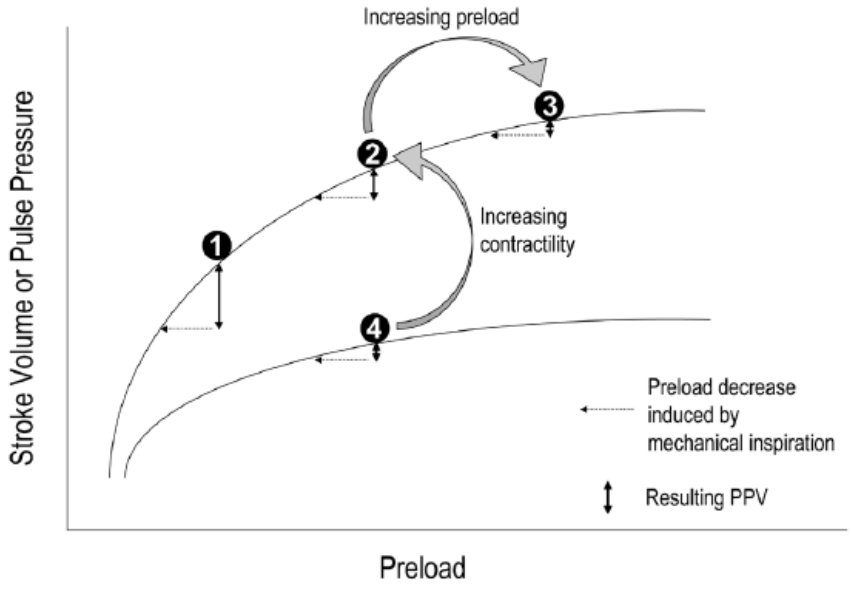



Figure 5: Determinants of pulse pressure variation. PPV is a marker of the position on the Frank–Starling curve, not an indicator of blood volume or a marker of cardiac preload. Increasing preload induces a decrease in PPV (from ❷ to ❸). PPV is minimal when the heart is operating on the plateau of the Frank–Starling curve (❸ and ❹). Decreasing preload induces an increase in PPV (from ❷ to ❶), also increasing contractility (from ❹ to ❷). [1]

odilation could induce an increase in PPV and have negative effects on hemodynamic stability and hence outcome. Some suggest that PPV can be used to track changes in cardiac contractility[29], because increasing left ventricular contractility increases the slope of the Frank-Starling curve. However, changes in PPV and contractility remains to be proven. Changes in preload or contractility detected by changes in PPV during PCI could give valuable information about the hemodynamic status of the patient.

To measure the PPV in a given patient, that patient must have consistent and demonstrable cardiopulmonary interactions. Requirements to measure PPV or SVV appropriately include that[30-32] :

- Patients should be in sinus rhythm during the assessment of PPV or SVV;
- patients should be intubated and be mechanically ventilated;
- Have no significant alternations to thorax compliance, such as an open chest;
- PPV and SVV should be measured within each respiratory cycle.

## Spectral analysis of blood pressure

Besides analysis of the blood pressure waveform in time domain, the blood pressure waveform can also be analyzed in the frequency domain, also called spectral analysis. Spectral analysis of a signal determines the strength of different frequency components (the power spectrum) of a time-domain signal. Hemodynamic compensation mechanisms during hemorrhagic shock to maintain cardiac output and blood pressure can be detected by analysis of the blood pressure curve in the frequency domain [33-35]. Analysis of the blood pressure curve change over time can be used to assess signatures created by physiological processes that influence blood pressure. In this way, changes in physiological processes may be observed before a significant shift in vital signs has occurred. When a patient develops shock, different compensation mechanisms may change the signal variability at different time scales.

Blood pressure and organ perfusion are controlled by a variety of cardiovascular control systems, such as the baroreceptor reflex and renin-angiotensin system, and by local vascular mechanisms such as shear stress-induced release of nitric oxide (NO) from the endothelium and the myogenic vascular response. Deviations in blood pressure activate these mechanisms in an attempt to restore blood pressure and secure organ perfusion. The response times at which different cardiovascular mechanisms operate differ. For example blood pressure control by RAS is slower than blood pressure control via the baroreceptor reflex. Because of these different response times, some cardiovascular control systems affect blood pressure more rapidly and others more slowly.

High frequency (HF) variability (0.15-0.4 Hz) has been associated with parasympathetic activity and respiration and increasing low frequency variability (0.06-0.15 Hz) has been associated with sympathetic activity[36]. The very low frequency band (VLF) lies in the frequency range 0.03-0.06 Hz and is thought to be associated with myogenic vessel tone.

### Sympathetic modulation of vascular tone

Sympathetic modulation of vascular tone arises from different individual vascular beds. Electrical stimulation of the lumbar sympathetic trunk results in a frequency response around 0.05-0.075 of skin blood flow in humans[24]. Sympathetic stimulation also results in an increase in power in the 0.075-0.15 Hz range in vascular beds other than the skin, such as the renal and mesenteric vascular beds[23,25]. These are also called Mayer waves. Sympathetic-mediated blood pressure Mayer waves depend on the response time of the vasculature and occur at frequencies between 0.075-0.15 Hz in humans. The initiation of sympathetic-mediated Mayer waves is not fully explained. Two theories have been proposed[26]. The pacemaker theory suggests that autonomic oscillators within the central nervous system generate periodic fluctuations in autonomic nerve activity that are translated into corresponding oscillations of arterial blood pressure and heart rate. However, the frequencies of central nervous system oscillators identified in most studies are different from the frequency of Mayer waves. [26] The seconds theory is called the baroreflex theory and implies that the arterial baroreceptor reflex exhibits a resonance frequency at the frequency of spontaneously occurring Mayer waves.[26]

### Myogenic vascular function

Myogenic mechanisms are intrinsic to the smooth muscle blood vessels, particularly in small arteries and arterioles. If the pressure within a vessel is suddenly increased, the vessel responds by constricting. Myogenic vasoconstriction is considerably slower than sympathetic-mediated vasoconstriction. Full myogenic vasoconstriction takes about one minute. Therefore, it is assumed that myogenic vascular function affects blood pressure variability at lower frequencies than sympathetic modulation of vascular tone does.[35] Stauss et al. recorded blood pressure in conscious normotensive rats under

control conditions and during infusion of calcium channel blockers, which inhibits myogenic vascular function.[7,8] Blockade of calcium channels significantly reduced very low frequencies in rats. Therefore, inhibition of VLF is thought to be the result of inhibition of myogenic vascular tone. Research to myogenic function ion humans is performed on dynamic autoregulation of cerebral blood flow. At frequencies below 0.15 Hz, changes in mean arterial pressure were followed by a similar change in total peripheral resistance as expected from myogenic vascular function.[56]

### Endothelial NO

The endothelial nitric oxide (NO) system is another vascular mechanism that influences blood pressure variability. A rise in blood pressure enhances endothelial shear stress and causes NO release from endothelial cells. NO diffuses to the adjacent vascular smooth muscle cells, where it elicits vasodilation.[57] In humans, blockade of the nitric oxide synthase significantly increased blood pressure in HF (0.15-0.4 Hz) range. [64] However, it is difficult to assess endothelial function in humans because HF blood pressure variability is largely influenced by respiration.

### Renin-angiotensin system

Regulation of blood pressure by the renin-angiotensin system (RAS) depends on the synthesis and release of renin and angiotensinogen. First, angiotensinogen needs to be converted to angiotensin II, thus it is expected that RAS affects blood pressure variability at lower frequencies that the sympathetic nervous system. Indeed, it has been suggested that RAS modulates VLF in dogs and rats. [66,32-34] Blood pressure variability in the VLF range increased when RAS was stimulated experimentally and that VLF activity could be blocked by angiotensin receptor antagonists. [69,70] In humans, the impact of RAS on blood pressure variability is scarce. In patients with stimulated RAS due to severe heart failure did not change overall blood pressure variability in LF and HF components. The VLF component was not studied. Whether RAS affects VLF in humans remains to be elucidated.

A summary of the different response mechanisms to regulate blood pressure and the corresponding frequency band is given in table 1.

*Table 1: Different frequency bands representing blood pressure variability and the corresponding mechanisms*

| **Blood pressure variability band** | **Frequency range** |
|---|---|
| **VLF** | 0.02-0.7 Hz |
| **LF** | 0.07-0.15 Hz |
| **HF** | 0.15-0.40 Hz |
| **Response mechanism** | **Frequency band** |
| Sympathetic modulation | LF |
| Myogenic vascular function | VLF and HF |
| Endothelial derived NO | Maybe HF |
| Renin-angiotensin system | Maybe VLF |

Scully et al. investigated that a change in these frequency bands give information about the physiological compensation -and decompensation phases during hemorrhagic shock development [33,37]. During progression of hemorrhagic shock, an increase in LF was seen in the compensation phase (increasing heart rate during blood pressure drop) and in increase in VLF was seen during the decompensation phase (decreasing heart rate and further decrease in blood pressure), prior to death. Similar mechanisms could be present in cardiogenic shock after AMI. The ratio of LF, VLF and HF could give information about the sympathovagal balance. It is hypothesized, that prior to revascularization there is increased sympathetic activity, because sympathetic hyperactivity is associated with vasospastic angina.[38]

# Objective

## Main objective

The objective of this research is to obtain an objective grading for cardiogenic shock based on the morphology of the blood pressure curve in STEMI -and cardiogenic shock patients. Some conditions that a proper grading should satisfy are:

- The parameters should be properly measured. Parameters should not be highly sensitive to signal disturbances;
- Parameter variations should not be too large in order to determine reliable cut-off values;
- There should be prominent differences between patients with different hemodynamic impairments.

The first condition that is important for investigating different parameters are that these parameters are properly measured. It has been investigated before that fluid-filled catheter wires that are used for invasive blood pressure measurements create signal disturbances[39]. Wire insertion and movement during cardiac catheterization might also create blood pressure signal disturbances. Some parameters may be more affected by catheter wire insertion than others. Furthermore, blood pressure parameters may vary over time during cardiac catheterization. It is assumed that parameters that show large variability over time in haemodynamically stable patients, are also less reliable to use in clinical decision making regarding CS patients.

The parameter variability during the procedure and parameter change with wire insertion is investigated during elective procedures in the cardiac catheterization lab. From these results, a set of consistent parameters are selected. The selected parameters are used to investigate blood pressure curve morphology in relation to outcome in the cardiogenic shock cohort. To investigate parameter changes over time before, after and <4 hours after revascularization, non-invasive blood pressure measurements are performed in STEMI patients.

In brief, this thesis consists of three main parts:

I. Assessment of parameter changes during elective procedures in the cardiac catheterization lab (Prospective observational cohort study)
II. Blood pressure curve morphology during cardiac catherization in acute myocardial infarction complicated by cardiogenic shock (Retrospective cohort study)
III. Change of blood pressure parameters over time in patients with acute myocardial infarction (Prospective observational cohort study)

# Methods

## Blood pressure waveform analysis

### Introduction

An automatic blood pressure waveform analysis method was developed by Wesselink[40]. The detection method is based on detecting local minima and maxima of the blood pressure signal and on bending points in the first and second derivative of the blood pressure signal. The detailed version of this waveform analysis is described in the Appendix.

## Characterization of the blood pressure curve

The waveform analysis is conducted off line using MATLAB (MATLAB R2017 A, The MathWorks Inc., Natick, MA, 2000). A custom, semi-automatic blood pressure analysis is performed on selected parts of the pressure signal. First, a section of blood pressure signal is (manually) selected. Then, all individual beats are determined. In each beat, five landmarks are determined, shown in figure 6. From the landmark points displayed in figure 6, different hemodynamic parameters shown in figure 7 and 8 are calculated that characterize the blood pressure curve. These parameters are divided in pressure, time, slope and area derived parameters and listed in table 3.

### Data selection and pre-processing

The selection of the blood pressure signals used for analysis in both studies of this thesis is described in the methods section of the respective study. The section of blood pressure signal should be at least 10 to 15 seconds long enabling calculation of the mean of approximately 10 to 20 heartbeats. If less beats were to be selected, the influence of noise and irregularities in the signal increases which could potentially lead to miscalculations. In theory, there is no limit to how long the selected data should be, if the signal is steady and regular. In this study it was chosen to select data to a maximum of 30-40 seconds.

Preprocessing of the selected data only consists of a polynomial Savitzky-Golay FIR smoothing filter with window 25 that was applied to the blood pressure signal to decrease high frequency noise originating from artifacts and from the low temporal resolution of the acquisition system, which is 0.2 mmHg.

With the detection method described in the appendix, the landmark points in figure 6 are calculated:

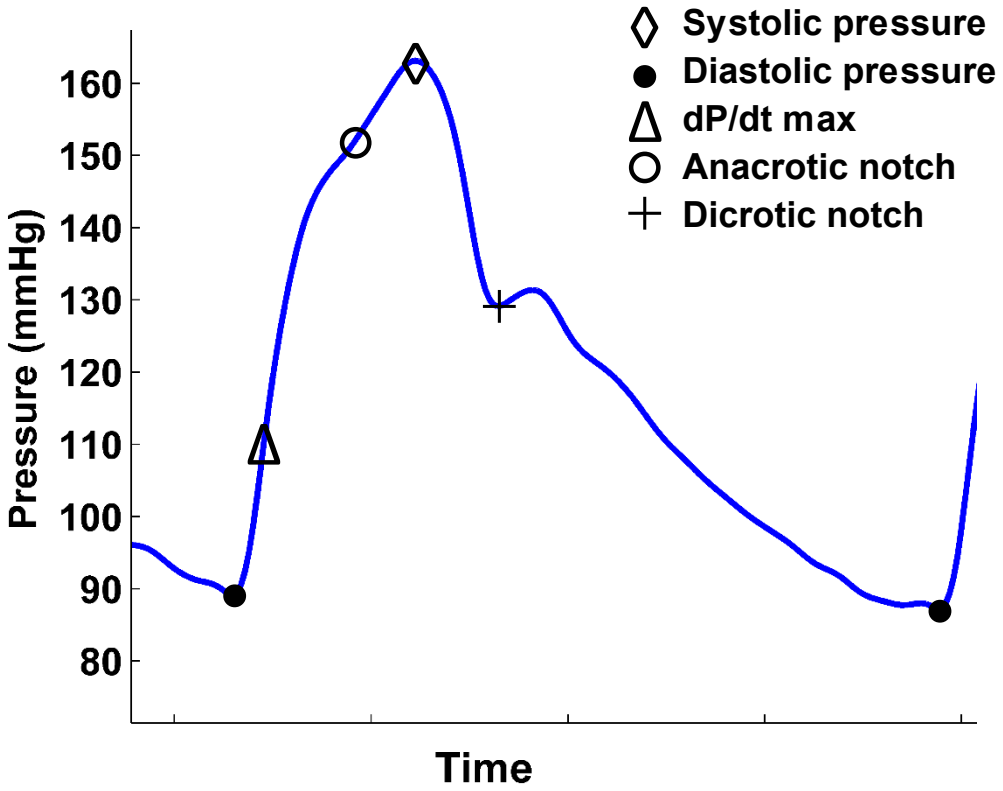



*Figure 6: Blood pressure curve with 5 markers for each beat. From left to right: Diastolic pressure. dp/dt max, anacrotic notch, systolic pressure, dicrotic notch.*

## Beatscope parameters

In addition to the parameters that are computed from the custom analysis, hemodynamic parameters determined with pulse contour analysis provided by Beatscope 1.1a (TNO) are computed. This is a software-version of the pulse contour analysis as conducted by the Nexfin (Edwards Lifesciences BMEYE, Amsterdam)[18]. Stroke volume (SV), cardiac output (CO) and other hemodynamic parameters as shown in table 2, are determined by the algorithm. In 'Study I', the algorithm is used to analyze the aortic blood pressure during elective procedures to determine the variability of each parameter, in 'Study II', the algorithm is used to analyze the blood pressure curve in cardiogenic shock patients and in 'Study III' the algorithm is used to analyze the non-invasively measured blood pressure curve in STEMI patients. Cardiac power output (CPO) is not calculated by this algorithm. CPO was calculated in retrospect with MAP and CO of the 'Beatscope parameters' as shown in table 2.

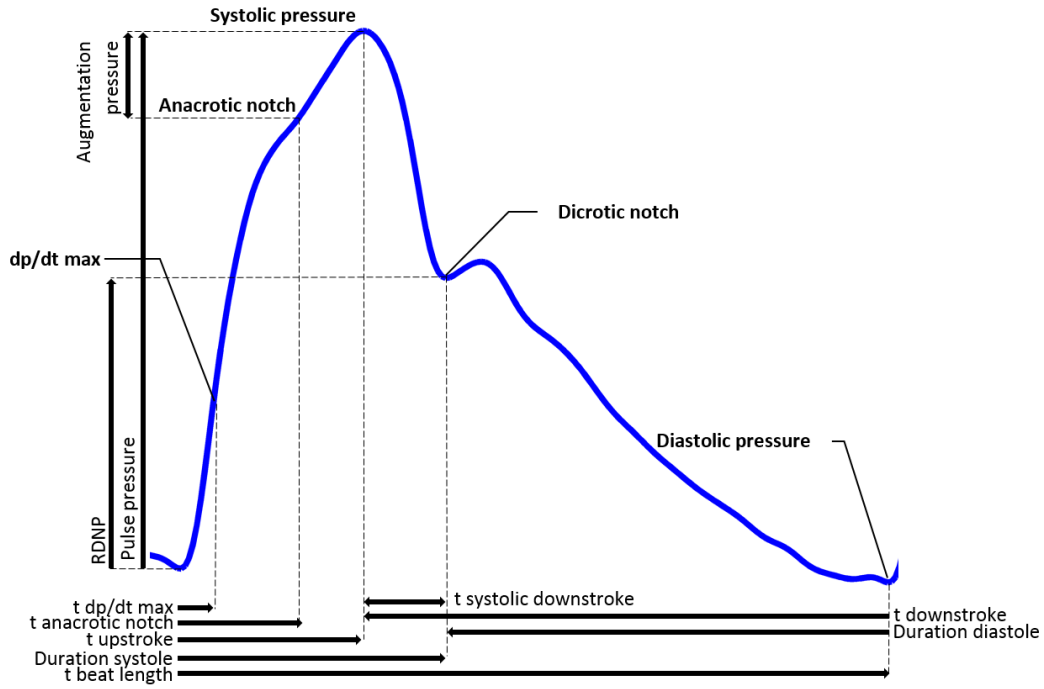



*Figure 7: Pressure and time derived parameters*

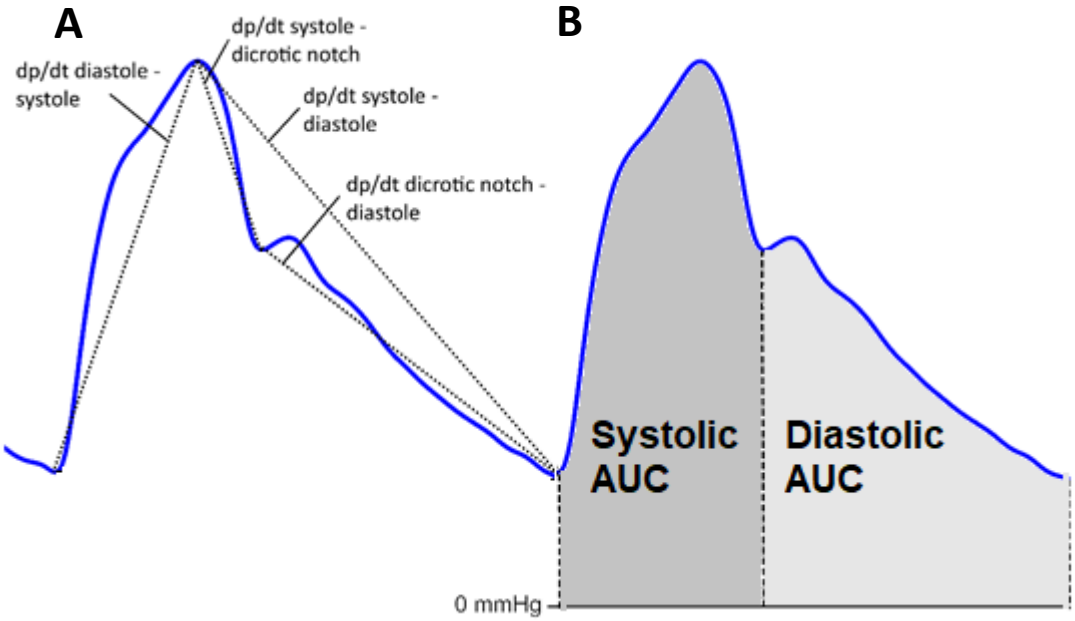



*Figure 8: Slopes and areas. A: Mean slopes between diastole and systole and diastole/systole and dicrotic notch. B: Systolic and diastolic AUC. Total AUC = systolic AUC+ diastolic AUC.*

*Table 2: Parameters determined by the Nexfin.*

| BEATSCOPE (BS) PARAMETERS | UNITS |
|---|---|
| BS SYSTOLIC PRESSURE | mmHg |
| BS DIASTOLIC PRESSURE | mmHg |
| BS MAP | mmHg |
| BS HEART RATE | Bpm |
| BS LVET | s |
| BS STROKE VOLUME | ml |
| BS CARDIAC OUTPUT | L/min |
| BS SYSTEMIC VASCULAR RESISTANCE | Dynes.s/cm$^5$ |
| BS CARDIAC INDEX | L/min/m² |
| CARDIAC POWER OUTPUT (CPO) * | mmHg.L/min |

** CPO is no output of 'Beatscope'. CPO was calculated in retrospect using MAP and CO of the 'Beatscope parameters':* $CPO = \frac{MAP * CO}{451}$

## Calculation of mean values

Of every blood pressure waveform parameter, the mean value was calculated after discarding 5% of the values of each parameter to exclude potential outliers. 2,5% of the total amount of beats, rounded up a whole number, of both the highest and lowest values are excluded for every parameter. The resulting values are used to calculate the mean value.

# Pulse pressure variation, stroke volume variation and heart rate variability

## Pulse pressure variation, stroke volume variation and heart rate variability

Pulse pressure variation and stroke volume variation are computed from a blood pressure signal of at least 30 seconds within a respiratory cycle. Figure 9 illustrates a blood pressure signal with the maximum and minimum pulse pressures and stroke volumes annotated.

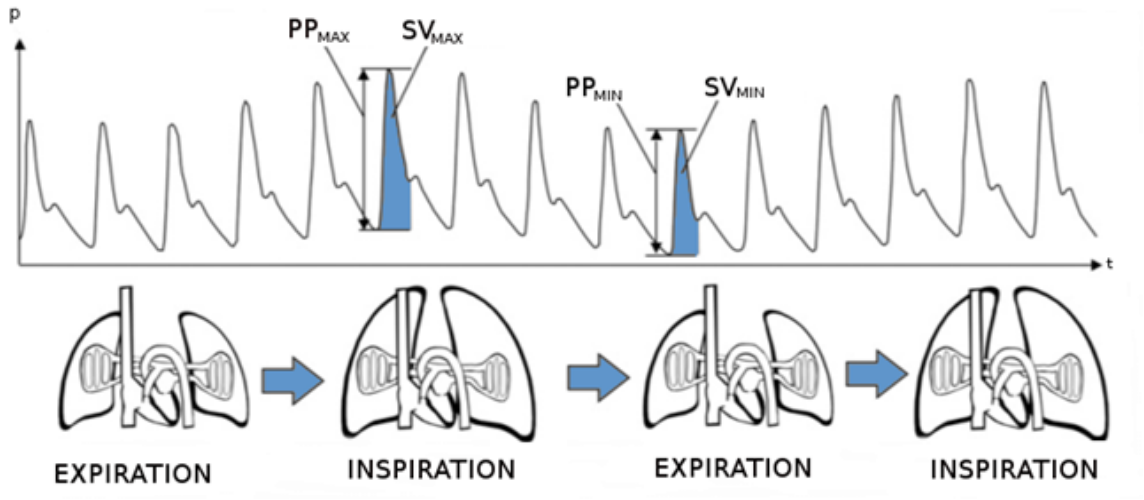



*Figure 9: Maximum and minimum pulse pressure and stroke volume illustrated during the respiratory cycle.*

Heart rate variability is calculated with the minimum and maximum the inter-beat interval (IBI) within every respiratory cycle. The exact computation of the variability of pulse pressure, stroke volume and IBI is explained below.

# Computation of parameter variation

To account for the degree of coupling between respiration and its influence on pulse pressure variation, a method is used to quantify the coupling of the phase of the respiration band in the blood pressure signal (0.15-0.4 Hz) to the amplitude of the pulse pressure signal.

For optimal evaluation of pulse pressure variation, stroke volume variation and heart rate variability, the respiratory cycle should be measured simultaneously. A simultaneously measured respiratory signal is not available. To get an estimation of the respiratory cycle, the blood pressure curve is first

band pass filtered with 0.15-0.4 Hz and divided by the mean to minimize noise (figure 8A and 8B). The pulse pressure, stroke volume or heart rate signal is obtained from beat to beat analysis and resampled to the same sampling frequency of the blood pressure signal (figure 8C).
This gives the two signals of interest:

- An estimation of the respiratory cycle: $ABP_{0.15\text{-}0.4\ Hz}$ $(ABP_{resp}(t))$
- Continuous pulse pressure/stroke volume/heart rate signal $(S_A(t))$

The time series of the phases of the estimated respiratory signal is obtained from the standard Hilbert transform and denoted as $\theta_{ABP_{resp}}(t)$. The time series of the amplitude envelope is obtained by computing the absolute value of the Hilbert transform of $S_A$. The phase time series and amplitude time series are then combined to $[\theta_{ABP_{resp}}(t), S_A(t)]$, which gives the amplitude of the amplitude of $S_A$ (which is either pulse pressure, stroke volume or heart rate) at each phase of the respiration band. The variation of the parameter in $S_A$ is then calculated within each phase of the respiratory cycle with the maximum and minimum values of $S_A$ in every phase. For example pulse pressure variation (PPV) is calculated for every estimated respiratory cycle and averaged for all respiratory cycles with the following formula:

$$PPV(\%) = \frac{PP_{max} - PP_{min}}{(PP_{max} + PP_{min})/2} \times 100$$

The computational steps are illustrated in figure 10 for computation of PPV. Stroke volume variation (SVV) and heart rate variability (HRV) are calculated in a similar way. For SVV:

$$SVV(\%) = \frac{SV_{max} - SV_{min}}{(SV_{max} + SV_{min})/2} \times 100$$

And for HRV:

$$HRV(\%) = \frac{HR_{max} - HR_{min}}{(HR_{max} + HR_{min})/2} \times 100$$

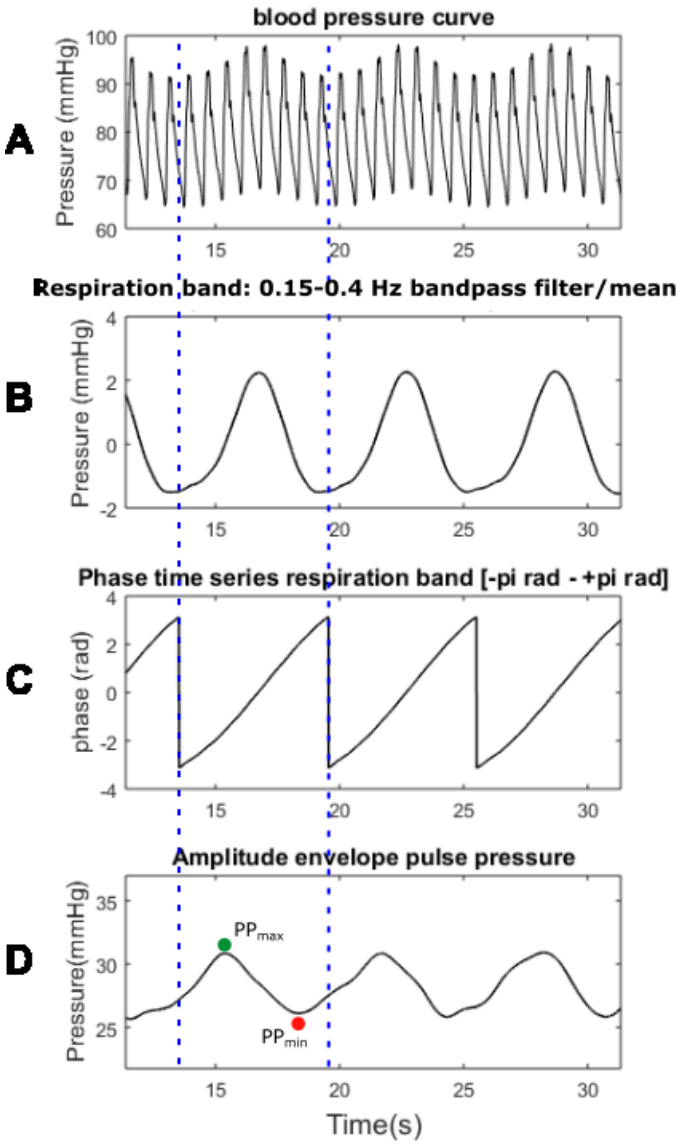



*Figure 10: Process of calculation of parameter variation*
*A: The blood pressure signal.*
*B: Estimation of the respiratory cycle ($ABP_{resp}$)*
*C: Phase time series of the respiratory cycle ($\theta_{ABP_{resp}}(t)$)*
*D: Amplitude envelope of the pulse pressure with maximum and minimum pulse pressure within one respiratory cycle.*

## Spectral analysis of blood pressure

The ratio of VLF, LF and HF will be assessed to investigate the sympathovagal balance. Multitaper spectral analysis with a resolution bandwidth of 4 is used to obtain a power spectral density plot. Power spectral density plots are made for a ~5-minute epoch prior to revascularization and a ~5-minute epoch after revascularization. Spectral analysis is only performed on continuous blood pressure

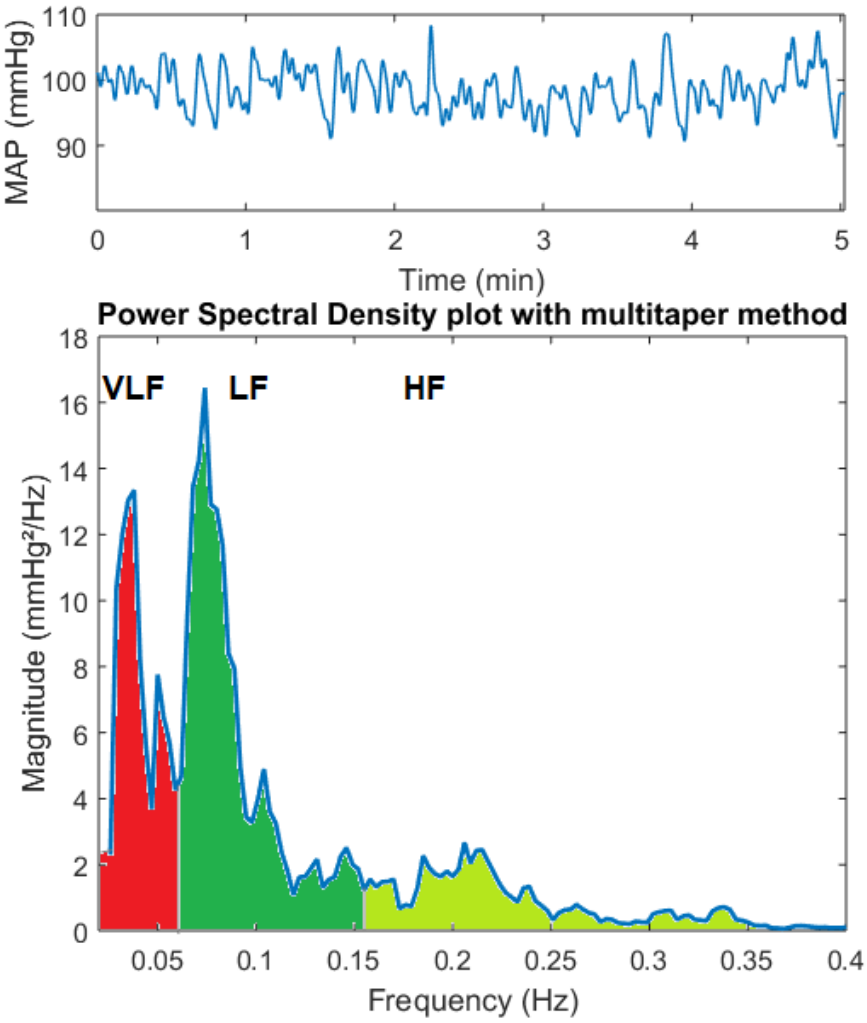



*Figure 11: **Upper** figure: Nexfin mean arterial pressure signal. **Lower** figure: Power spectral density plot displaying the time-frequency analysis of a Nexfin mean arterial pressure signal. The red area represents the power in the VLF range (0.02-0.06 Hz), associated with myogenic vascular function. Myogenic vasoconstriction causes in increase in the VLF band. The dark green area represents the power in the LF range (0.06-0.15 Hz), associated with sympathetic modulation and myogenic vascular function. The light green area represents the HF range (0.15-0.4 Hz), associated with respiration and endothelial-derived NO.*

measurement measured non-invasively with the Nexfin during pPCI of STEMI patients. Since one period of VLF takes about one minute (myogenic vasoconstriction takes about one minute), and at least five periods are needed to perform reliable spectral analysis, at least five minutes of data is needed for proper analysis.

The sympathovagal balance is assessed from the mean arterial pressure (MAP). The beat-to-beat MAP is first interpolated and resampled to 5 Hz. Sympathovagal balance is computed with the following formula:

$$Sympathovagal\ Balance\ (SVB) = \frac{VLF + LF}{HF} = \frac{MAP_{\sim 0.03-0.06\ Hz} + MAP_{\sim 0.06-0.15\ Hz}}{MAP_{\sim 0.15-0.4\ Hz}}$$

The frequency boundaries in Hertz are estimations of the VLF, LF and HF bands. For every patient, frequency cut-off values are chosen manually since some differences are present between subjects.

## Summary of parameters

Table 3 lists all parameters that are calculated with the semi-automatic detection method and the added blood pressure variation related parameters.

*Table 3: List of parameters used to study blood pressure curve morphology*

| | |
|---|---|
| **Pressure derived parameters** (shown in figure 5) | |
| Systolic pressure | Maximal pressure during systole |
| Diastolic pressure | Minimal pressure preceding ventricular ejection |
| Mean arterial pressure (MAP) | $MAP = (2 * Pdia + Psys)/3$ |
| Pulse pressure | $Systolic\ pressure - \ diastolic\ pressure$ |
| Augmentation pressure | $Systolic\ pressure - \ anacrotic\ notch\ pressure$ |
| Dicrotic notch pressure | Pressure of dicrotic notch |
| Relative dicrotic notch pressure (RDNP) | $Dicrotic\ notch\ pressure - \ diastolic\ pressure$ |
| Pulse Pressure Variation | $100 * (PP_{max} - PP_{\min})/((PP_{max} + PP_{min})/2)$ |
| Stroke Volume Variation | $100 * (SV_{max} - SV_{\min})/((SV_{max} + SV_{min})/2)$ |
| Heart Rate Variability | $100 * (HR_{max} - HR_{\min})/((HR_{max} + HR_{min})/2)$ |
| **Time derived parameters** (shown in figure 5 ) | |
| t systolic downstroke | $t\ dicrotic\ notch - \ t\ upstroke$ |
| t dp/dt max | Time of dp/dt max |
| t anacrotic notch | Time to anacrotic notch |
| t upstroke | Time to systolic pressure |
| t downstroke | Time from systolic maximum to following diastole |
| Heart rate (HR) | $\frac{60}{t\ beat\ length}$ |
| Duration systole (LVET) | Time to dicrotic notch |
| Duration diastole | $t\ beat\ length - \ LVET$ |
| Relative t upstroke | $\frac{t\ upstroke}{t\ beat\ length}$ |
| Relative t dp/dt max | $\frac{t\frac{dp}{dt}max}{t\ beat\ length}$ |
| Relative LVET | $\frac{LVET}{t\ beat\ length}$ |
| Relative t anacrotic notch | $\frac{t\ anacrotic\ notch}{t\ beat\ length}$ |
| Duration systole / duration diastole | $\frac{LVET}{t\ beat\ length - LVET}$ |
| **Slopes** (shown in **figure 6A**) | |
| dp/dt max | Maximal slope during upstroke |
| dp/dt diastole - systolic max | Slope from diastolic to systolic pressure |
| dp/dt systolic max - diastole | Slope from systolic pressure to following diastolic pressure |
| dp/dt systolic max - dicrotic notch | Slope from systolic pressure to dicrotic notch |
| dp/dt dicrotic notch - diastole | Slope from dicrotic notch to diastolic pressure |
| RDNP / LVET | $RDNP\ /\ LVET$ |
| RDNP / t upstroke | $RDNP\ /\ t\ upstroke$ |

| | |
|---|---|
| **Areas** (shown in **figure 6B**) | |
| AUC | Absolute systolic + diastolic AUC |
| Systolic AUC | Shown in 6 B |
| Diastolic AUC | Shown in 6 B |
| I**ndexes** | |
| Dicrotic notch index | $\frac{Relative\ dicrotic\ notch\ pressure}{Pulse\ pressure} * 100$ |
| Augmentation index | $\frac{Relative\ anacrotic\ notch\ pressure}{Pulse\ pressure} * 100$ |
| Shock index (SI) | $\frac{Systolic\ pressure}{HR}$ |
| Age Adjusted Shock Index (AASI) | $\frac{Age}{shock\ index}$ |
| Relative dicrotic notch pressure index (RDNPI) | $\frac{HR}{Relative\ dicrotic\ notch\ pressure}$ |
| **Frequency derived parameters (figure 8)** | |
| Sympathovagal balance (SVB) | $\frac{MAP_{\sim 0.06-0.15\ Hz} + MAP_{\sim 0.02-0.06\ Hz}}{MAP_{\sim 0.15-0.4\ Hz}}$ |

# I. Parameter changes during elective procedures in the catheterization lab

## Introduction

When blood pressure curve parameters are used to investigate differences in outcome of STEMI patients with and without cardiogenic shock, these parameter differences should be substantially different from the parameter variability in patients with (relatively) good cardiac function. The blood-pressure curve is mainly determined by the heart, the arterial vasculature and vascular resistance[41] . Though, the shape of the blood pressure curve partly depends on the signal quality. The amount of damping of the cardiac catheter system varies through a PCI procedure and influences different parameters determined from the blood pressure curve[42].

To evaluate the reliability of different parameters, parameter variation of a large subset of parameters to characterize blood pressure curve morphology is investigated in patients undergoing elective procedures. During catheterization procedures, coronary guide wires, balloon dilatation catheters and stents are inserted through the catheter. The influence of wire insertion on different parameters will be investigated, since it is hypothesized that some parameters may be more affected by wire insertion than others.

The aim this study is to find a reliable set of parameters to investigate blood pressure curve morphology in cardiogenic shock -and STEMI patients. A set of blood pressure parameters are investigated in blood pressure measurements in elective procedures in the catheterization lab. Blood pressure parameters that show a relatively small variability through time or due to wire are considered more reliable.

## Methods

### Inclusion -and exclusion criteria

Inclusion criteria are: patients undergoing elective procedures in the catheterization lab (i.e. percutaneous coronary intervention, coronary angiography). Exclusion criteria are: patients with atrial fibrillation; known severe congenital heart defects; severe aortic regurgitation; patients under age 18; patients are unable to give informed consent.

### Data selection

During elective procedures in the catheterization lab, continuous blood pressure measurements are recorded simultaneously both invasively -and noninvasively. Blood pressure was measured invasively with an external pressure transducer (Namic Perceptor manifold, Navilyst medical, New York, USA), connected to a fluid filled catheter system. The proximal end of the catheter is placed in the aorta ascendens, in or near one of the coronary ostia to provide the cardiologist access to the coronary arteries. Blood pressure is recorded on the MacLab ComboLab 6.8 Z600 acquisition system (GE-Healthcare, Little Chalfont, UK). This signal acquisition system applies no filtering to the blood pressure signal. Non-invasive blood pressure recordings are recorded simultaneously with the Nexfin (Edwards Lifesciences BMEYE). The Nexfin monitor is a CE-marked device which uses the volume clamp method as first described by Penaz and later developed by Wesseling et al. to measure blood pressure noninvasively at the finger. With the use of a finger cuff, digital blood pressure was measured between the distal and proximal interphalangeal joints of the middle finger. The finger pressure is transformed to a brachial artery pressure signal by the Nexfin.

Invasive aortic blood pressure is recorded simultaneously on the Nexfin. The invasive blood pressure signal is transmitted from an analog output channel of the measurement system of the catheterization laboratory to the analog input channel of the Nexfin. Both signals are recorded with a sampling frequency of 200 Hz.

During the procedure, blood pressure is recorded continuously. A measurement of 20 blood pressure beats without disturbances in the invasive pressure signal with wire insertion is measured, followed by a measurement of 20 beats without a wire inserted. Catheter wire insertion and removal is registered during the measurement. All data was analyzed in MATLAB R2016B.

For analysis of the frequency derived parameters, a data segment of at least five minutes is required since the time series signal should contain at least ~4/5 periods of the very low frequency band, which has 1,2 cycles per minute[43]. Therefore two time segments of five minutes are analyzed to investigate the change in frequency components in the LF, VLF and HF band. For the frequency analysis, only the non-invasive measurements are used, since the invasive measurements contain too many disturbances for spectral analysis (from e.g. contrast, wire insertion and removal etc.).

## Data analysis

To investigate parameter variability during elective procedures, three blood pressure segments are selected in the beginning, the middle and the end of the invasive -and non-invasive measurements, see figure 12. The parameters in table 3 are calculated from 20 beats in every blood pressure segment and averaged to compute the mean. A limited set of parameters was selected, since many parameters are related to each other. Afterwards, the standard deviation is computed for the means of every data segment. The coefficient of variation is calculated and visualized in boxplots for every parameter to assess the amount of variation of each parameter on a standardized scale. The coefficient of variation is calculated as follows: $(Coefficient\ of\ variation = \frac{STD}{mean})$ . For variation between the data segments with and without a wire inserted, the coefficient of variation is computed equally using two data segments.

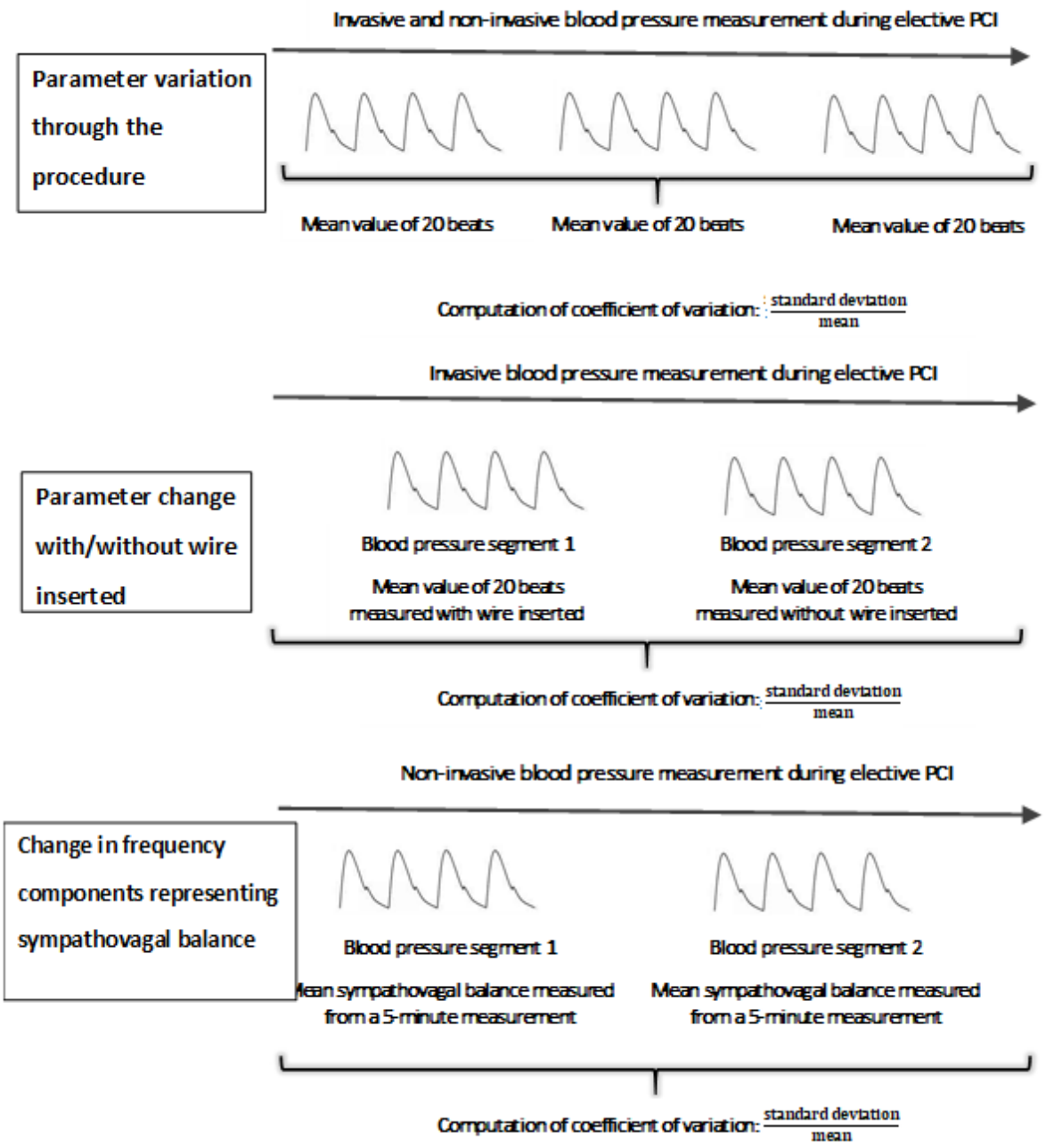



*Figure 12 Blood pressure selection to investigate parameter variability over time during elective procedures. Relative standard deviation (coefficient of variation) is computed by computing the standard deviation of the means of blood pressure segment 1, 2 and 3 divided by the mean. The relative standard deviation represents the amount of change of every parameter through the blood pressure measurement. This is done for both invasive and non-invasive measurements For assessment of the influence of wire insertion in invasive measurements, the relative standard deviations are computed for the mean of 20 beats measured with wire and without a wire inserted. The same is done to investigate the difference in frequency components, but for two non-invasive segments of 5 minute duration.*

**Pressure derived parameters**

| | |
|---|---|
| Systolic pressure | Maximal pressure during systole |
| Diastolic pressure | Minimal pressure preceding ventricular ejection |
| Mean arterial pressure (MAP) | $MAP = \frac{2 * Pdia + Psys}{3}$ |
| Pulse pressure | $Systolic\ pressure - \ diastolic\ pressure$ |
| Augmentation pressure | $Systolic\ pressure - \ anacrotic\ notch\ pressure$ |
| Dicrotic notch pressure | Pressure of dicrotic notch |
| Augmentation index | $\frac{Relative\ anacrotic\ notch\ pressure}{Pulse\ pressure} * 100$ |
| Pulse Pressure Variation | $100 * \frac{(PP_{max} - PP_{min})}{\left(\frac{PP_{max} + PP_{min}}{2}\right)}$ |
| Stroke Volume Variation | $100 * \frac{(SV_{max} - SV_{min})}{\left(\frac{SV_{max} + SV_{min}}{2}\right)}$ |

**Time derived parameters**

| | |
|---|---|
| t dp/dt max | Time of dp/dt max |
| t anacrotic notch | Time to anacrotic notch |
| t upstroke | Time to systolic pressure |
| t downstroke | Time from systolic maximum to following diastole |
| Heart rate (HR) | $\frac{60}{t\ beat\ length}$ |
| Duration systole (LVET) | Time to dicrotic notch |
| Duration diastole | $t\ beat\ length - \ LVET$ |
| Relative LVET | $\frac{LVET}{t\ beat\ length}$ |
| | |

**Slopes**

| | |
|---|---|
| dp/dt max | Maximal slope during upstroke |
| dp/dt diastole - systolic max | Slope from diastolic to systolic pressure |
| dp/dt systolic max - diastole | Slope from systolic pressure to following diastolic pressure |

**Areas**

| | |
|---|---|
| AUC | Relative systolic + diastolic AUC |
| Systolic AUC | Area under systolic curve |
| Diastolic AUC | Area under diastolic curve |

**Beatscope parameters**

| | |
|---|---|
| Stroke volume | Estimated stroke volume in mL |
| Cardiac output | Estimated cardiac output in L/min |
| Cardiac power output | Estimated cardiac power output in mmHg*L/min |
| **Frequency derived parameter** | |
| Sympathovagal balance (SVB) | $\frac{VLF + LF}{HF} = \frac{MAP_{0.06-0.15\ Hz} + \ MAP_{0.02-0.06\ Hz}}{MAP_{0.15-0.4\ Hz}}$ |

*Table 4: Parameters that are used for assessment of parameter variation.*

# Results

## Parameter variation over time

Blood pressure measurements were performed on 10 patients undergoing an elective PCI procedure. For the invasive measurements, the anacrotic notch pressure, time to anacrotic notch, augmentation index, diastole duration and pulse pressure variation show the largest variation between the three data segments. The relative standard deviations of the three data segments are illustrated for every parameter in Figure 13.

For the non-invasive measurements, variation is particularly seen in anacrotic notch pressure, time to anacrotic notch, diastole duration, augmentation index, time from diastole to anacrotic notch pressure, downstroke time and pulse pressure variation. An outlier is seen in the rLVET, AUC diastolic and AUC systolic parameters in one patient. These parameters show more variation in the non-invasive measurements compared to the invasive measurements. The relative standard deviations for all parameters are illustrated in figure 14.

## Parameter change due to wire insertion

In the invasive measurements, the largest variation between measurements with and without a wire inserted is seen in the time from diastole to maximum slope, diastole duration, anacrotic notch pressure, augmentation index, time to anacrotic notch, downstroke time and pulse pressure variation. The relative standard deviations are illustrated in figure 15. No relation is seen between the parameter change with and without a wire inserted.

*Figure 13: Boxplot illustrating parameter variation in invasive measurements. The x-axis represents the standard deviation relative to the mean (SD/mean) [dimensionless]. Every box represents the standard deviations computed from three data segments of each of the 10 patients. The width of each boxplot represents the amount of variation of the parameters.*

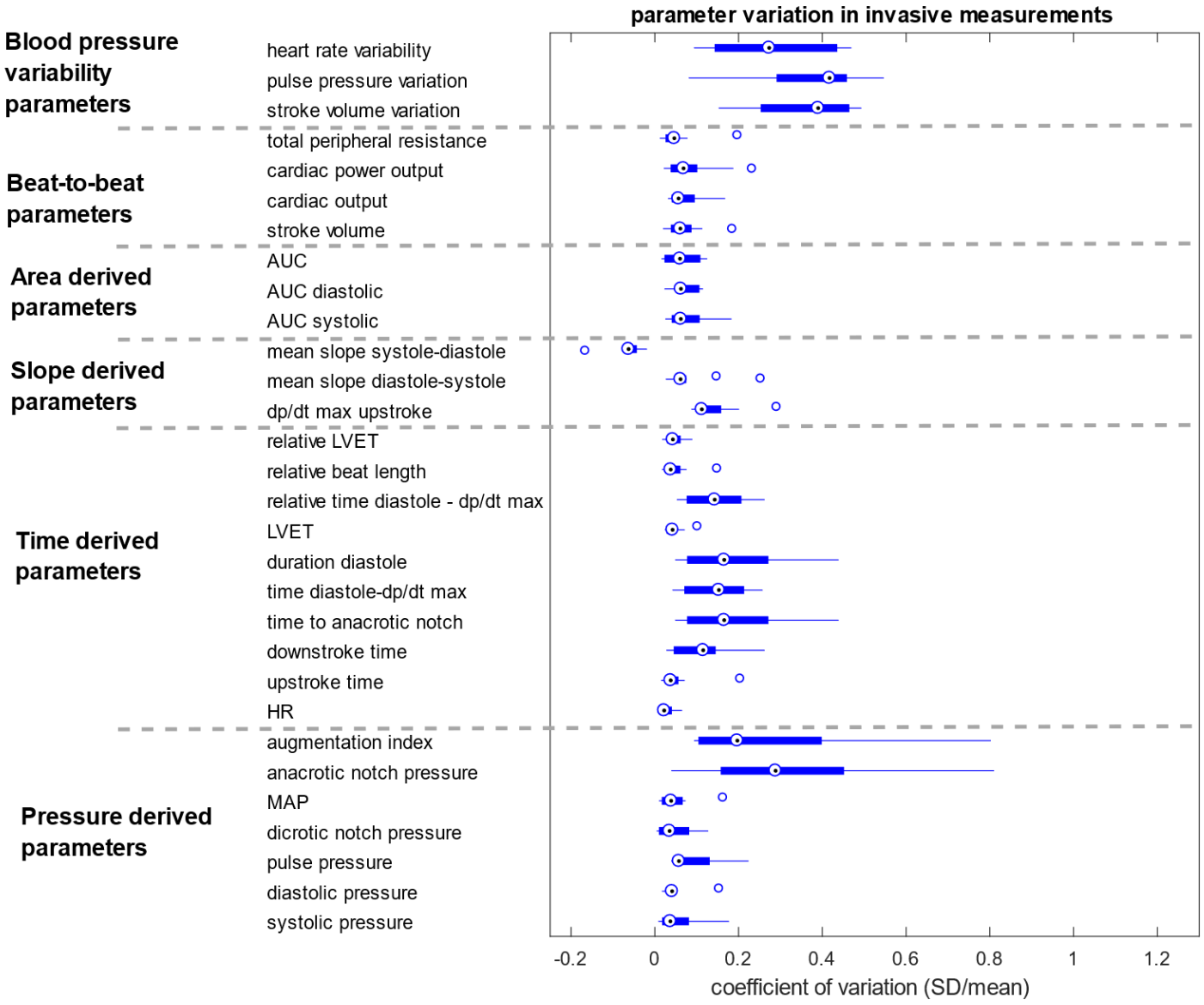


*Figure 14: Boxplot illustrating parameter variation in non-invasive measurements. The x-axis represents the standard deviation relative to the mean (SD/mean) [dimensionless]. Every box represents the standard deviations computed from three data segments of each of the 10 patients. The width of each boxplot represents the amount of variation of the parameters.*

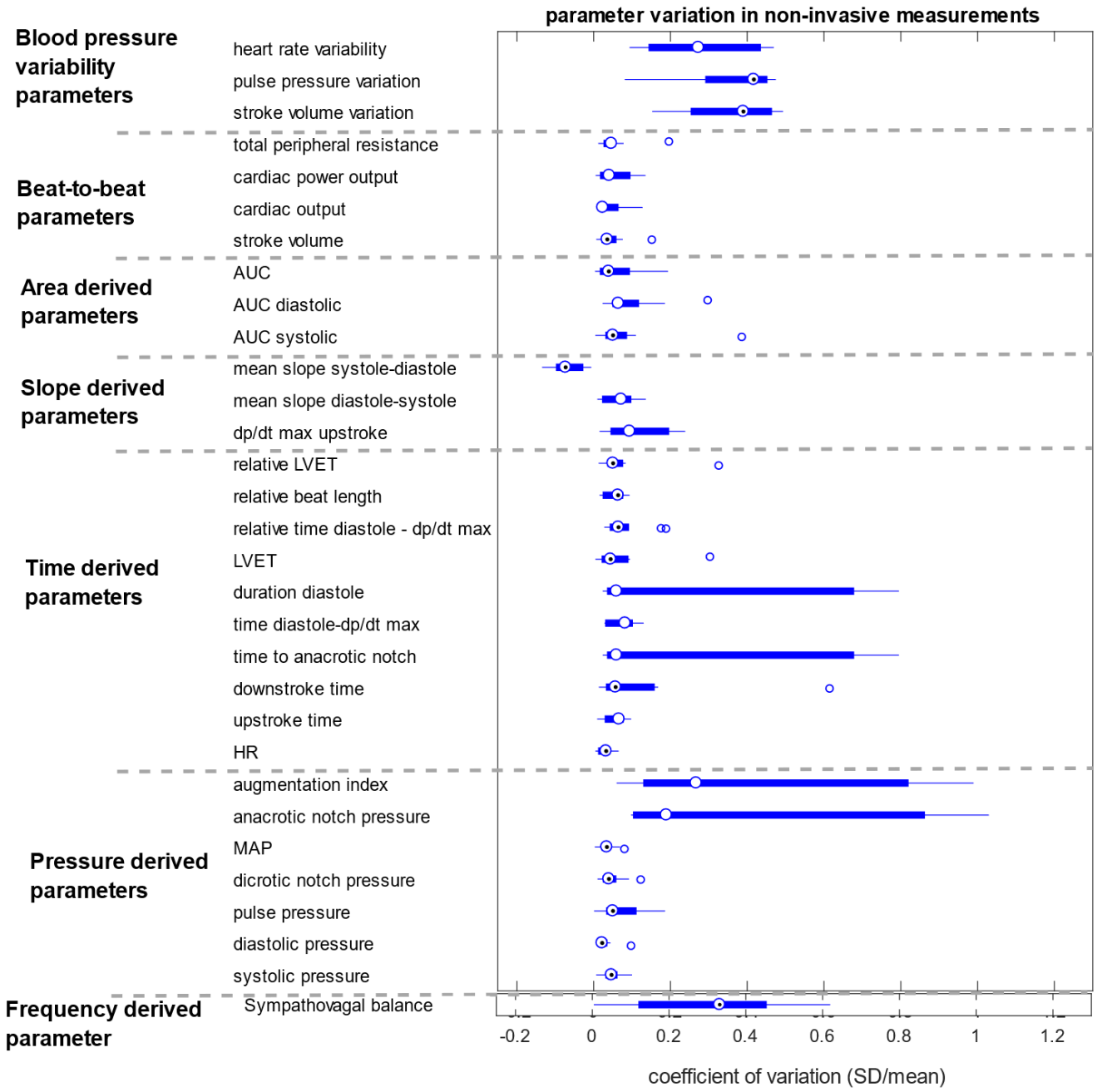
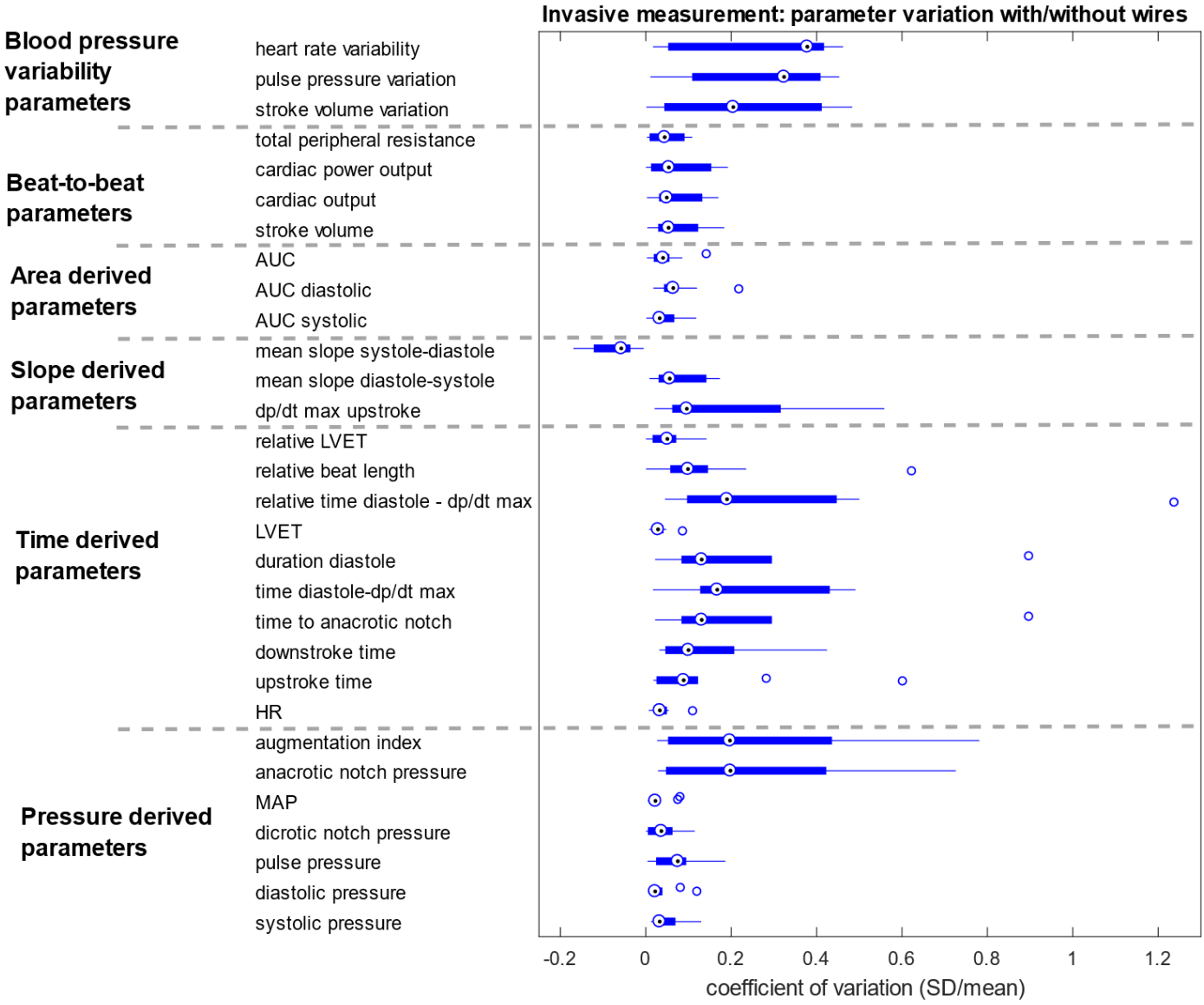


*Figure 15: Boxplot illustrating parameter variation between an invasive blood pressure measurement with and without a wire inserted. The x-axis represents the standard deviation relative to the mean (SD/mean) [dimensionless]. Every box represents the standard deviations computed from two data segments (with wire / without wire) of each of the 10 patients. The width of each boxplot represents the amount of variation of the parameters.*



# Discussion

The aim of this research was to investigate which parameters show the least variation over time and due to wire insertion, to select feasible parameters. This selection of stable parameters will be used to investigate blood pressure curve morphology in cardiogenic shock and STEMI patients. It was hypothesized that some parameters might vary more through time than others due to either variability in the actual blood pressure or due to varying signal quality. It was also hypothesized that the presence of a wire could induce a flow disturbance, inducing a change in parameter values. Also, it was hypothesized that wire removal or insertion might cause a change in parameters because of opening and closing of the y-connector at which catheterization materials (i.e. wires) are inserted into the catheter sheath, could induce a change in damping of the signal.

The parameters that show largest variation are almost all related to either the anacrotic notch (anacrotic notch pressure, augmentation index, time to anacrotic notch, diastole duration) or dicrotic notch (downstroke time, left ventricular ejection time, area under the diastolic and systolic curves). For the three data segments of the invasive measurements, largest variation was present in anacrotic notch pressure, time to anacrotic notch, augmentation index, time to diastole and pulse pressure variation. For the non-invasive measurements, the same parameters show most variation over time including downstroke time. In the non-invasive measurement an outlier is seen for the LVET, rLVET, diastolic area under the curve and systolic area under the curve. For the data segments with and without a wire inserted, similar parameters show a relatively large difference: time from diastole to maximum slope, diastole duration, anacrotic notch pressure, augmentation index, time to anacrotic notch, downstroke time and pulse pressure variation.

When visually analyzing the automatically detected anacrotic and dicrotic notch pressure in the patients showing large variation, it can be concluded that the anacrotic and dicrotic notch pressure are not detected accurately in these patients. Especially the anacrotic notch pressure is often falsely detected. Figure 16 shows examples of accurate and inaccurate marker placement for the anacrotic and dicrotic notch. Remarkably, these markers are not detected well when the anacrotic -and dicrotic notch are poorly visible. However, the detection algorithm does often detect an anacrotic and dicrotic notch, even when it is questionable whether these notches are visible. This could explain the large variation in anacrotic and dicrotic notch related parameters. Part of the variability in anacrotic and dicrotic notch related parameters is probably caused by a poorer detection of the anacrotic and dicrotic notch, rather than a physiological change of these parameters. This observation corresponds to the analysis of the used detection algorithm, showing that the anacrotic and dicrotic notch are well detected in respectively 62% and 67% in >90% of the recordings and that systolic and diastolic pressures are well detected in respectively 100% and 95% of the recordings[40]. However, this was only investigated in invasive pressure recordings, not in non-invasive recordings.

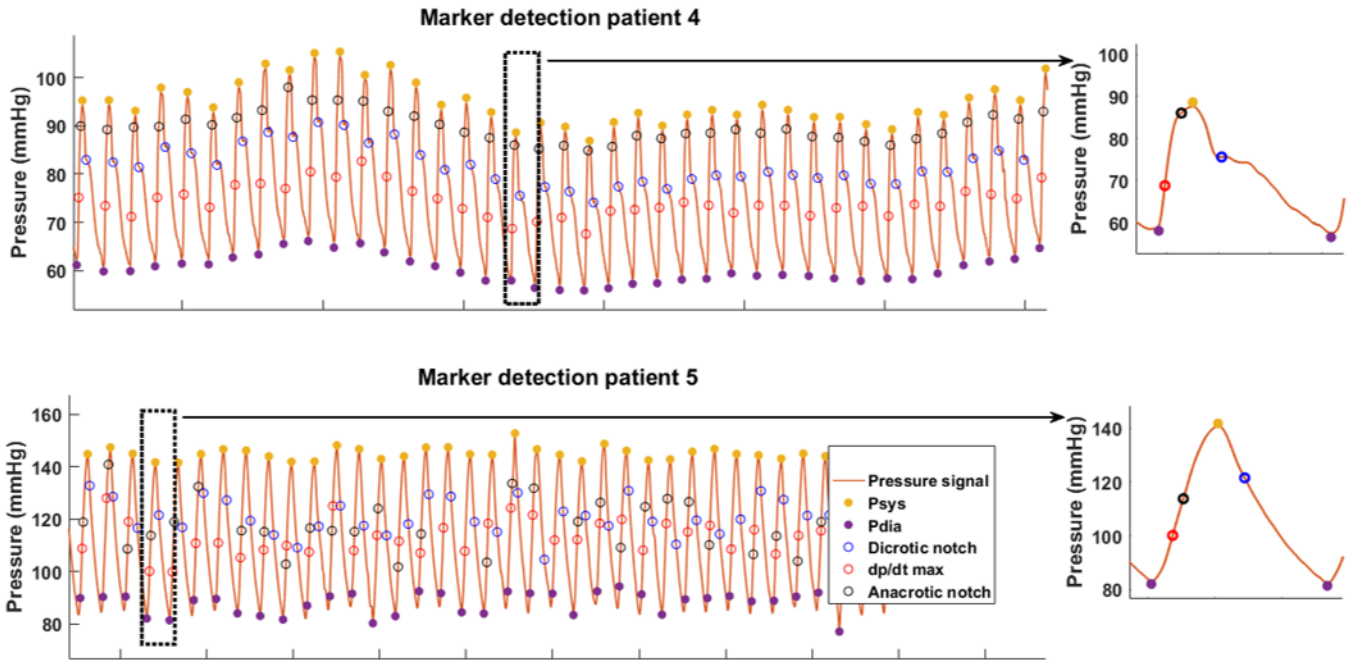



*Figure 16 : The **upper figure** shows an example of appropriate and consistent detection of the different markers. When looking at a close-up, different markers are clearly visible. The **lower figure** shows a measurement in which the anacrotic notch (black markers) and dicrotic notch (blue markers) are detected with high variability. A close-up of the blood pressure curve morphology reveals that anacrotic and dicrotic notch are barely visible.*

The dicrotic notch pressure related parameters show more variation over time in the non-invasive measurements compared to the invasive measurements. It seems that the detection algorithm sometimes has more difficulties in detecting the dicrotic notch pressure accurately in the non-invasive measurements. In one patient, the dicrotic notch is poorly visible, resulting in inaccurate detection of the dicrotic notch. This results in a large amount of variation in the dicrotic notch related parameters. LVET andand systolic and diastolic area under the curve related parameters mainly have an outlier in one patient. The systolic and diastolic are under the curve, as well as LVET are also both related to the dicrotic notch, are less vulnerable for the inaccurate detection.

When regarding the measurements with and without a wire inserted, similar parameters show a relatively large change, except for time from diastole to maximum slope. It was hypothesized that a parameter change might be caused by a change damping of the signal or signal quality after opening and closing of the y-connector. Remarkably, nearly the same parameters show a change compared to the differences seen in the three data segments over the entire measurement. It appears that especially the anacrotic notch is also not detected accurately in these measurements. Probably, the large differences in these parameters are neither caused by a change in damping nor by flow disturbance. Possibly, some variability is caused by wire insertion, but these differences are negligible compared to the parameter variability that is caused by poor marker detection of anacrotic and dicrotic notch.

PPV, SVV and HRV show relatively large variation. This could be caused by the fact that PPV and SVV measurement is validated in mechanically ventilated patients that have a respiratory cycle with a fixed rate. Also, respiration should be measured simultaneously to be sure that PPV and SVV are measured properly. The respiratory cyclus is estimated from the blood pressure curve in this analysis in patients that are not mechanically ventilated. This could cause erroneous measurements. Also, Larger heart rate variability is associated with better outcomes[23]. Hemodynamically instable patients might have a smaller heart rate variability/pulse pressure and stroke volume variation. Therefore, it

is kind of contradictory to exclude these parameters based on a large variation, since these measurements are performed on hemodynamically stable patients. Though, this study on pulse pressure -and stroke volume variation is valuable to compare the parameter values of the hemodynamically stable patients with the values of the hemodynamically unstable patients.

To improve analysis of variability of different parameters, the parameters that are not normally distributed should be analyzed using the median instead of the mean. This might improve the comparability of the variability of different parameters.

All parameters that are related to: the (relative) time from diastole to maximum dp/dt of the upstroke, diastole duration, time from diastole to dp/dt max, anacrotic notch pressure, time to anacrotic notch and augmentation index will not be used to investigate morphology in STEMI and cardiogenic shock patients. LVET, diastolic AUC and systolic AUC will be used for investigation of the blood pressure curve morphology in the invasive measurements of cardiogenic shock patients, because these parameter show acceptable variability. Attention should be paid when analyzing dicrotic notch related parameters in non-invasive Nexfin measurements, since the dicrotic notch is not always clearly visible and detectable in these measurements.

# Conclusion

In anacrotic notch related parameters, there is a substantial blood pressure variability in hemodynamically stable patients undergoing elective procedures. This variability is primarily caused by poor detection of the anacrotic notch, making all anacrotic notch related variables unreliable for investigation of the blood pressure curve morphology with the current detection algorithm.

Dicrotic notch related parameters are less reliable in non-invasive brachial artery pressure measurements with the Nexfin, compared to invasive measurements. These parameters show acceptable variability. However, care should be taken with the analysis of these parameters in invasive measurements.

# II. Blood pressure curve morphology in cardiogenic shock patients during catheterization

## Introduction

The aim of this study is to characterize the blood pressure curve morphology in patients with cardiogenic shock in relation to different outcome: cardiac death (CD), non-cardiac death (NCD) and survival. Blood pressure curve morphology is assessed prior to revascularization and post-revascularization and related to 30-day mortality for both groups. It is also investigated whether the change in blood pressure curve morphology from prior -to post revascularization is related to outcome. It is hypothesized that blood pressure parameters representing cardiac function, i.e. cardiac output, cardiac power output, stroke volume and left ventricular ejection time are lower in the cardiac death group/ non-survival group, compared to the survival group. It is hypothesized that a combination of blood pressure parameters other that the classic clinical blood pressure parameters has better predictive value for 30-day mortality than the classic clinical blood pressure parameters only.

## Methods

### Patient selection

The medical files of all patients that were admitted to the ICU after treatment of AMI with pPCI in the Academic Medical Center (AMC) Amsterdam from January 1, 2012 to December 31, 2016 are reviewed. Inclusion criteria are: patients with (successful) primary PCI for the treatment of AMI with admission to the ICU afterwards. Exclusion criteria are: complications during primary PCI (severe hemorrhage, ventricle-septum rupture, papillary muscle rupture); severe comorbidities (intoxications, severe sepsis, trauma); The inability to determine cardiac outcome (i.e. transfer to another hospital); Astma cardiale with no evident culprit vessel; Subjects under age 18.

For the analysis of the blood pressure variation related parameters (pulse pressure variation, stroke volume variation and heart rate variability), only patients that were mechanically ventilated during the procedure are included, since assessment of pulse pressure variation is mainly validated in mechanically ventilated subjects[44 1].

### Data selection

Of the selected patients, blood pressure recordings during pPCI, PCI procedure logs and post-procedural (intensive care) electronical records were collected. ICU data consists of hemodynamic support (vasoactive medication infusion rates, mechanical circulatory support, mechanical ventilation, renal replacement therapy) and the type of cooling protocol (no cooling, 32 degrees or 36 degrees).

Blood pressure was measured with an external pressure transducer (Namic Perceptor manifold, Navilyst medical, New York, USA) with a sampling frequency of 240 Hz and a temporal resolution of 0.2 mmHg. This transducer is connected to a fluid filled catheter system. The catheter was inserted through a sheath placed in the femoral or radial artery. The proximal end of the catheter is placed in the aorta ascendens, in or near one of the coronary ostia to provide the cardiologist access to the coronary arteries. Blood pressure is recorded on the MacLab ComboLab 6.8 Z600 acquisition system (GE-Healthcare, Little Chalfont, UK).

## Outcome definition

The primary endpoint of this study is 30-day survival. After AMI, some patients have cardiac recovery but do not survive due to other comorbidities like post-anoxic encephalopathy with bad neurological prognosis. Other patients do not survive because of progressive cardiac failure.

Three groups are created to compare outcome and blood pressure curve morphology: 'cardiac death' (CD), 'non-cardiac death' (NCD) and survival. The amount of vasoactive medication and mechanical circulatory assist prior to death is used to categorize the cardiac recovery and no-cardiac recovery group among the non-survivors.

Vasoactive medication such as inotropes to increase myocardial contractility and catcholamines to influence blood pressure, are used to support the cardiovascular haemodynamics and maintain cerebral perfusion. The use of this medication is restricted to the lowest possible dose as catecholamines and vasoconstrictive medication impair microcirculation, thereby decreasing end -organ tissue perfusion. Patients with a better cardiac function are likely to receive less vasoactive medication or mechanical circulatory support. Patients surviving 30 days post-PCI belong to the survival group. Patients that received low infusion rates of noradrenalin/adrenalin (< 0.5 mg/h) on the day of death belong to the 'non-cardiac death' group. Patients receiving high infusion rates of noradrenalin on the day of death or received mechanical circulatory support prior to the moment of death are labeled 'cardiac death'.

## Statistical methods

### Univariate analysis

All parameters are tested for normality by visual inspection of the histogram. To compare the survival/non-survival groups and cardiac recovery/no cardiac recovery group, the independent samples t-test is used to compare normally distributed continuous variables and the Mann-Whitney U test is used to compare not normally distributed continuous variables. To compare the CD, NCD and survival groups, ANOVA analysis is performed for normal distributed continuous parameters and Kruskal-Wallis test for not normal distributed parameters. Categorical variables (baseline characteristics) are compared between the three subgroups with the chi-square test.

### Survival analysis

Kaplan-Meier survival plots are generated for different parameters with $P<0.05$ on the univariate analysis to assess 30-day mortality rates for different cut-off values. Cut-off values with the most optimal sensitivity and specificity are determined with the use of Receiver-Operating-Characteristic curves.

### Multivariate analysis

Multivariate analysis is performed to assess whether a combination of blood pressure parameters measured during pPCI prior to revascularization is associated with 30-day mortality. Binary logistic regression analysis is performed on independent parameters with $p<0,05$ on the univariate regression analysis. Parameters were entered in the model stepwise with forward selection. Odds ratio's, 95% confidence intervals, P-values and Nagelkerke $R^2$ will be computed for each model.

Factor analysis based on principal component analysis is performed first, to reduce the amount of parameters in the multivariate analysis and prevent multi-colinearity.

# Results

Figure 17 represents the flow chart with exclusions -and inclusion per category. Between January 2012 and December 2016, 273 patients were identified that underwent primary PCI and admission to the ICU afterwards. Patients that were excluded due to complications during or after PCI, suffered from coronary artery dissection, tamponade, ventricular wall rupture, hemorrhagic shock or transfusion acquired lung injury. Patients were excluded due to severe comorbidities such as pre-existent dilated cardiomyopathy, Brugada-syndrome, pre-existent cardiac failure, sepsis or presence of aortic aneurysm. A total of 36 patients were excluded from analysis by a variety of other reasons. These other reasons were for example intoxications, hemodynamic instability after other surgery prior to PCI and congenital heart disease. Patients were excluded because 'no clear outcome' could be determined when patients were transferred to another hospital or when cardiac recovery was not clear. Ten patients were excluded because their hemodynamically unstable situation was primarily caused by acute cardiac failure without an evident culprit vessel present. Out of 273 patients, 165 patients were selected for blood pressure signal screening. No blood pressure signal was available in 51 patients because data export was not possible for data before 2012 (37 patients) and data export errors occurred in 14 patients in 2016, probably because of a software change that caused compatibility problems for data export. Signal quality was too poor for analysis in 11 patients. Most of these patients underwent manual or mechanical resuscitation during PCI, or intra-aortic balloon counter pulsation was used prior to revascularization, which severely deteriorates the blood pressure curve. A total amount of 103 patients were finally included in in the analysis.

Baseline, procedural, treatment and outcome characteristics for these patients are shown in table 5. The NCD group and survival group contained more smokers. In the CD group, vasoactive medication was more frequently used during the procedure and fewer patients were mechanically ventilated during the procedure. Patients in the NCD group and survival group, frequently had a medical history of stroke, whereas no patients in the CD group had a medical history of stroke. The median time to death is shorter in de cardiac death group (2 days), compared to the non-cardiac death group (6 days).

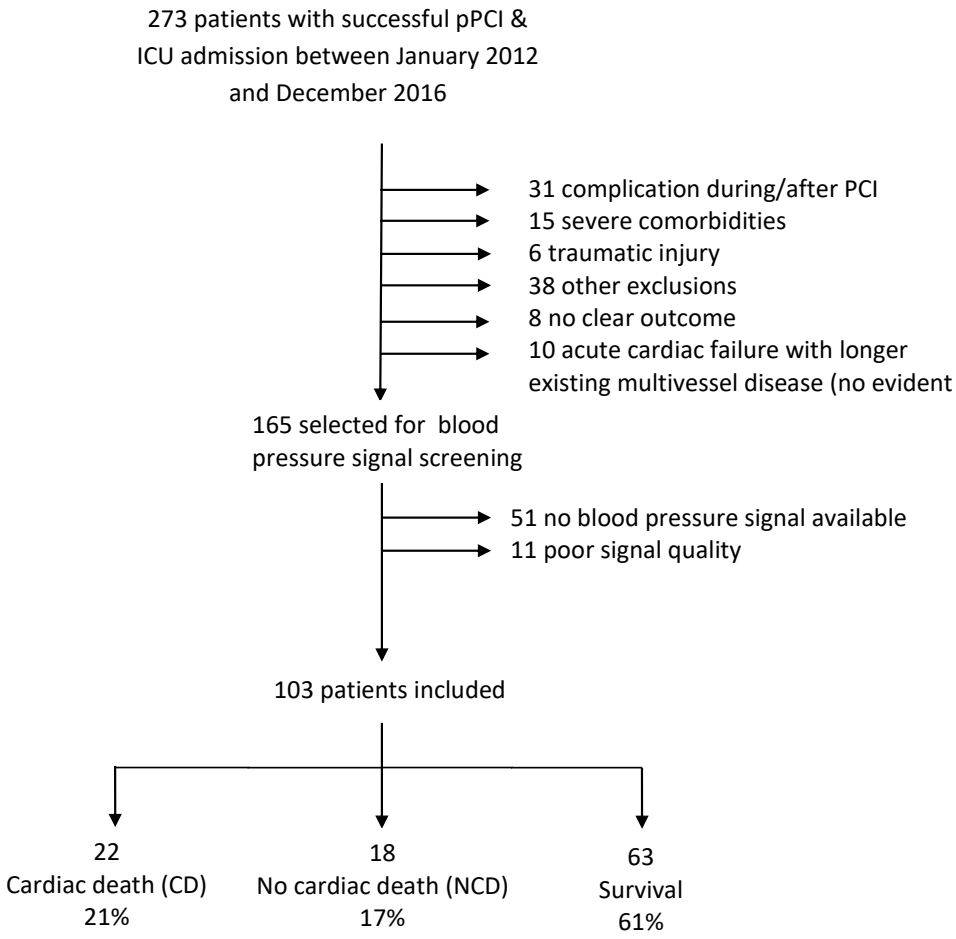



*Figure 17: Flowchart demonstrating the inclusion process of cardiogenic shock patients.*

## Blood pressure curve morphology prior to revascularization in relation to outcome

### Univariate analysis

Table 7 shows the results for the pressure, time and slope derived parameters, index parameters and Beatscope derived parameters prior to revascularization. P-values are shown when statistically significant (P<0,05).

Between the survival -and non-survival group, a statistically significant difference is seen in upstroke time, heart rate, left ventricular ejection time, area under the curve, diastolic and systolic area under the curve, shock index, age adjusted shock index and stroke volume.

The greatest difference is seen between the 'cardiac recovery' and the 'no cardiac recovery' group. Between these groups, the following parameters are statistically different: time to maximum slope, upstroke time, downstroke time, heart rate, left ventricular ejection time, systolic area under the curve, shock index, age adjusted shock index, stroke volume, cardiac output, cardiac power output, cardiac index and cardiac power index. The group that does not show cardiac recovery has smaller time to maximum slope, smaller upstroke and downstroke time, higher heart rate, shorter left ventricular ejection time, smaller systolic area under the curve, lower shock index, higher age adjusted shock index, smaller stroke volume, lower cardiac output and lower cardiac power output.

*Table 5: Baseline, PCI, treatment and outcome characteristics*

| | | Cardiac death (n=22) | No cardiac death (n=18) | Survival (n=63) | p-value |
|---|---|---|---|---|---|
| **Baseline characteristics** | | | | | |
| Male gender | | 18/22 (82%) | 13/18 (72%) | 53/63(84%) | Ns |
| Age (years) | | 61 ±10 | 63±9 | 58±10 | Ns |
| BMI | | 27 ± 5 | 26±2 | 26±4 | Ns |
| Diabetes | | 3/22 (14%) | 6/18 (33%) | 10/63 (16%) | Ns |
| Dyslipidemia | | 0/22 (0%) | 1/18 (6%) | 9/63 (14%) | Ns |
| Hypertension | | 8/22 (36%) | 8/18 (44%) | 16/63 (25%) | Ns |
| Smoking | never | 13/21 (62%) | 16/17 (94%) | 20/61 (33%) | 0,005* |
| | current | 6/21 (29%) | 1/17 (6%) | 28/61 (46%) | 0,004* |
| | previous | 2/21 (10%) | 0/17 (0%) | 13/61 (21%) | 0,046* |
| Family history of CAD | | 1/9 (11%) | 1/5 (20%) | 21/42 (50%) | Ns |
| Stroke | | 0/18 (0%) | 4/13 (31%) | 6/58 (10%) | 0,023* |
| Peripheral artery disease | | 2/17 (12%) | 1/11 (9%) | 9/40 (23%) | Ns |
| Previous MI | | 1/19 (5%) | 1/16 (6%) | 9/59 (15%) | Ns |
| Previous PCI | | 1/20 (5%) | 1/16 (6%) | 11/60 (18%) | Ns |
| Previous CABG | | 0/20 (0%) | 0/16 (0%) | 0/60 (0%) | Ns |
| Cardiac arrest | | 15/22 (68%) | 16/1889%) | 54/63 (86%) | Ns |
| **PCI characteristics** | | | | | |
| Culprit vessel | LM | 3/22 (14%) | 0/18 (0%) | 6/63 (10%) | Ns |
| | LAD | 11/22 (50%) | 8/18 (44%) | 30/63 (48%) | Ns |
| | RCx | 4/22 (18%) | 6/18 (33%) | 10/63 (16%) | Ns |
| | RCA | 4/22 (18%) | 4/18 (22%) | 17/63 (27%) | Ns |
| Multivessel disease | | 11/22 (50%) | 7/18 (39%) | 33/63 (52%) | Ns |
| Vasoactive medication | | 21/22 (95%) | 12/18 (67%) | 43/63 (68%) | 0,015** |
| Mechanical ventilation | | 15/22 (68%) | 16/18 (89%) | 60/63 (95%) | 0,022* |
| Mechanical support | IABP | 5/22 (23%) | 3/18 (17%) | 4/63 (6%) | Ns |
| | Impella | 9/22 (41%) | 2/18 (11%) | 13/63 (21%) | Ns |
| **Treatment: ICU** | | | | | |
| Mechanical ventilation | | 19/22 (86%) | 17/18 (94%) | 62/63 (98%) | Ns |
| Dialysis | | 5/22 (23%) | 4/18 (22%) | 6/63 (10%) | Ns |
| Cooling protocol | 32 degrees | 2/22 (9%) | 7/18 (29%) | 16/63 (25%) | Ns |
| | 36 degrees | 7/22 (32%) | 10/18 (56%) | 33/63 (52%) | Ns |
| **Outcome** | | | | | |
| Time to death (days) | | 2 [1 – 3] | 6 [2 – 9] | - | 0,010* |

BMI: body mass index; CAD: coronary artery disease; MI: myocardial infarction; PCI: primary percutaneous infarction; CABG: CABG: coronary artery bypass grafting; OHCA: Out of hospital cardiac arrest; LM: left main artery; LAD: left anterior descending artery; RCx: ramus circumflexus; RCA: right coronary artery; IABP: intra-aortic balloon pump; ICU: Intensive Care Unit; Ns: Not significant.

## Blood pressure curve morphology post-revascularization in relation to outcome

### Univariate analysis

Table 9 shows the results for the pressure, time and slope derived parameters, index parameters and Beatscope derived parameters prior to revascularization. P-values are shown when statistically significant (P<0,05).

Between the survival -and non-survival group, significant difference is seen in heart rate, AUC, diastolic AUC, shock index and age adjusted shock index.

Similar to the results prior to revascularization, the greatest difference is seen between the 'cardiac recovery' and the 'no cardiac recovery' group. Between these groups, the following parameters are statistically different: heart rate, AUC, diastolic AUC, systolic AUC, shock index and age adjusted shock index, stroke volume variation and stroke volume. The group that does not show cardiac recovery has smaller area under the curves, lower shock index, higher age adjusted shock index, more stroke volume variation and smaller SV compared to the cardiac recovery group.

## Blood pressure curve morphology change pre-to-post-revascularization

### Univariate analysis

There is no significant relation between parameter change prior-to-post revascularization and outcome. With revascularization, there are only marginal differences seen in blood pressure curve morphology. There is a small increasing trend in the pressure -and area derived parameters, a decreasing trend in heart rate, and an increasing trend in shock index. Results are summarized in table 15 in the appendix.

## Survival analysis

Survival analysis is performed for pre-revascularization parameters. Kaplan-Meier survival plots for shock index, heart rate, cardiac output, stroke volume, LVET and diastolic AUC are illustrated in figure 18. Patients with shock index <0.9s have higher mortality rates than patients with a shock index $> 0.9\mathrm{s}$ (~60% vs. 25%). Patients with heart rate $> 91$ have higher mortality rates compared to patients with a heart rate $< 91$ ( ~55% vs. 25%). Patients with cardiac output of $< 4.2\ \mathrm{L/min}$ show higher mortality than patients with cardiac output $> 4.2\ \mathrm{L/min}$ (~50% vs. 25%). Patients with stroke volume less than $52\ \mathrm{mL}$ have higher mortality than patients with stroke volume $>\ 52\ \mathrm{mL}$ (~50% vs. 30%). The survival plots show that patients with LVET $<\ 0.29\mathrm{s}$ have higher mortality rates than patients $> 0.29\mathrm{s}$ (~65% vs. 30%). When patients have a diastolic AUC of $< 23\ mmHg * s$ generally have higher mortality rates than patients with a diastolic AUC of $> 23\ mmHg * s$ (~30% vs. 59%).

Cut off values, sensitivities, specificities and area under the curves are determined from ROC curves of the significant parameters in univariate analysis and shown in table 8. LVET and AASI have the highest sensitivies (84% and 85% respectively), but have relatively low specificities (45% and 50% respectively). Stroke volume has the highest specificity of 65% with an equal sensitivity of 65%.

## Factor analysis

Factor analysis is conducted on all parameters with P<0.05 in between either one of the subgroups prior to revascularization. This analysis revealed that all 13 statistically different parameters can be reduced to three subgroups. Table 6 in the appendix shows the component matrix containing correlation values with each subgroup for each parameter that was statistically significant in the univariate analysis. A total of 14 parameters that show a significant relation with 30-day mortality or cardiac recovery can be reduced to three independent subgroups (based on eigenvalue >1). Three subgroups

explain 79% of the total variance. These subgroups are primarily determined by 1) shock index and area under the curves; 2) CO, CPO and SV; 3) Age adjusted shock index and heart rate.

LVET and downstroke time are not very well correlated with any of the three subgroups but are both best correlated with shock index and area under the curves. Correlations of every parameter with each subgroup are summarized in table 13 in the appendix. Correlations of all parameters with each other are summarized in table 14 in the appendix.

## Multiple regression analysis

Based on the results from the univariate analysis and factor analysis, multiple regression analysis is performed on the pre-revascularization values of shock index combined with age, SV, CO, CPO and LVET to investigate their predictive value for 30-day-survival.

The results for the multivariate logistic regression analysis are shown in table 6. When age, SV, CO , CPO and LVET were separately included for logistic regression together with shock index, only the model including age and shock index had predictive value of 30-day mortality (P-value <0.05). Being one year older increases the likelihood of death within 30 days with 1.063. High shock index reduces likelihood of death within 30 days with 0.156. This model has the best predictive value, as expressed by Nagelkerke $R^2$ ($R^2$=0.259). This means that 26 % of the outcome (30-day mortality) can be predicted by shock index and age. Other parameters had a large 95% CI, even after removal of outliers. This indicates that a model including different parameters from the blood pressure curve is not stable. These findings suggest that the blood pressure curve derived are not independent predictors in relation to 30-day mortality.

A model using cardiac recovery as primary endpoint results in even weaker models with large 95% confidence intervals, probably because the cardiac death group is very small (N=22).

*Table 6: Analysis of the prognostic importance of blood pressure parameters on predicting 30-day mortality in STEMI patients that are submitted to the ICU.*

| **Parameter (prior to revascularization)** | | **Multivariate analysis (enter)** | | | | |
|---|---|---|---|---|---|---|
| | | B | OR (exp(B)) | 95% CI | p-value | $R^2$ |
| Model 1 | | | | | | 0.066 |
| | Shock index | -1.480 | 0.228 | 0.057 - 0.916 | 0.018* | |
| Model 2 | | | | | | 0.259 |
| | Shock index | -1.858 | 0.156 | 0.036-0.674 | 0.013* | |
| | Age | 0.061 | 1.063 | 1.018-1.110 | 0.006* | |
| Model 3 | | | | | | 0.100 |
| | Shock index | -1.176 | 0.309 | 0.07-1.33 | 0.114 | |
| | Stroke volume | -0.017 | 0.983 | 0.96-1.00 | 0.119 | |
| Model 4 | | | | | | 0.093 |
| | Shock index | -1.576 | 0.207 | 0.05-0.85 | 0.030* | |
| | Cardiac output | -0.160 | 0.852 | 0.68-1.02 | 0.163 | |
| Model 5 | | | | | | 0.073 |
| | Shock index | -1.369 | 0.254 | 0.06-1.04 | 0.057 | |
| | Cardiac power output | -0.447 | 0.640 | 0.17-2.36 | 0.520 | |
| Model 6 | | | | | | 0.112 |
| | Shock index | -0.944 | 0.389 | 0.09-1.63 | 0.195 | |
| | LVET | -6.454 | 0.002 | 0.00-1.49 | 0.064 | |

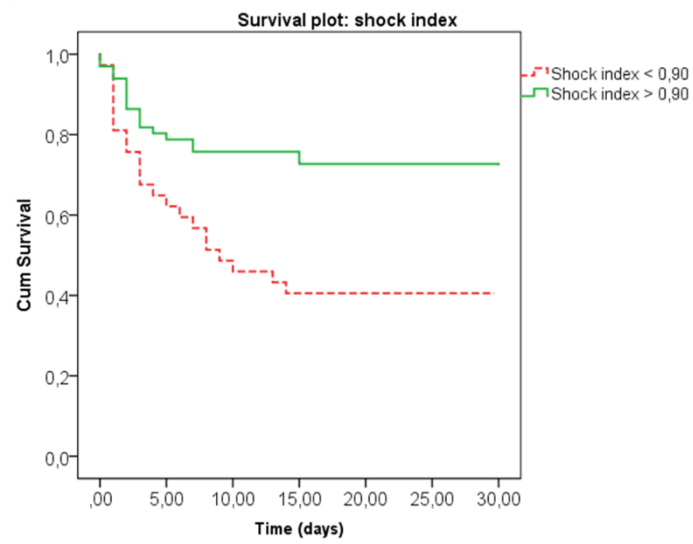
OR= Odds ratio; $R^2$: Nagelkerke $R^2$ (% of outcome predicted by the independent predictor)

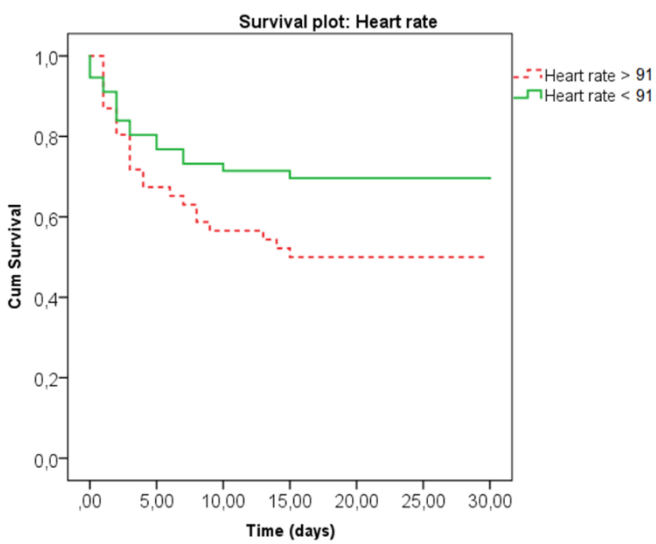
*Table 7: Results prior to revascularization*

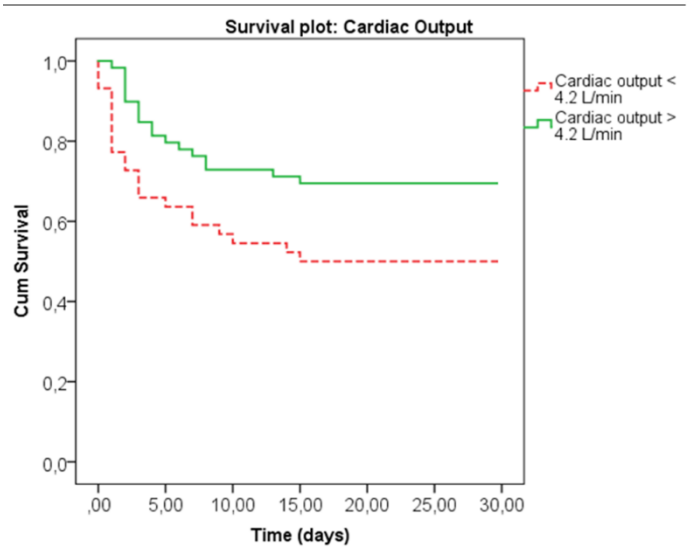
| | No survival no cardiac recovery | | No survival cardiac recovery | | Survival | | p-values | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | value | n | value | n | value | Between groups | Survival vs non-survival | Cardiac recovery vs no cardiac recovery |
| **Pressure derived variables** | | | | | | | | | |
| Systolic pressure (mmHg) | 22 | 86 ± 21 | 18 | 93 ± 29 | 63 | 91 ± 17 | ns | ns | ns |
| Diastolic pressure (mmHg) | 22 | 60 ± 13 | 18 | 60 ± 17 | 63 | 61 ± 14 | ns | ns | ns |
| MAP (mmHg) | 22 | 68 ± 15 | 18 | 71 ± 21 | 63 | 71 ± 14 | ns | ns | ns |
| Pulse pressure (mmHg) | 22 | 26 ± 12 | 18 | 33 ± 15 | 63 | 31 ± 14 | ns | ns | ns |
| **Time derived variables** | | | | | | | | | |
| t dp/dt max (s) | 22 | 0.049 [0.02 - 0.06] | 18 | 0.06 [0.04 - 0.08] | 33 | 0.06 [0.04 - 0.08] | ns | ns | 0.049 |
| t upstroke (s) | 22 | 0.154 ± 0.048 | 18 | 0.18 ± 0.05 | 63 | 0.19 ± 0.05 | 0.005 | 0.004 | 0.003 |
| t downstroke (s) | 22 | 0.107 [0.019 - 0.134] | 18 | 0.153 [0.118 - 0.184] | 63 | 0.134 [0.098 - 0.179] | 0.019 | ns | 0.008 |
| Heart rate (bpm) | 22 | 100 ± 20 | 18 | 90 ± 15 | 63 | 85 ± 16 | 0.002 | 0.003 | 0.001 |
| Duration systole(LVET) (s) | 22 | 0.28 ± 0.07 | 18 | 0.34 ± 0.07 | 63 | 0.34 ± 0.06 | 0.001 | 0.017 | 0.000 |
| relative t upstroke | 22 | 0.245 ± 0.055 | 18 | 0.256 ± 0.063 | 63 | 0.265 ± 0.057 | ns | ns | ns |
| relative t dp/dt max | 22 | 0.08 [0.05 - 0.10] | 18 | 0.07 [0.07 - 0.11] | 63 | 0.08 [0.05 - 0.12] | ns | ns | ns |
| relative LVET | 22 | 0.458 ± 0.083 | 18 | 0.505 ± 0.106 | 63 | 0.474 ± 0.082 | ns | ns | ns |
| **Slopes** | | | | | | | | | |
| dp/dt max (mmHg / s) | 22 | 334 [242 - 519] | 18 | 366 [260 - 463] | 33 | 326 [250 - 477] | ns | ns | ns |
| dp/dt diastole - systolic max (mmHg / s) | 22 | 38 [30- 47] | 18 | 43 [33 - 58] | 63 | 40 [34 -49] | ns | ns | ns |
| dp/dt systolic max - diastole (mmHg / s) | 22 | -38 [-46 - -30] | 18 | -43 [-58 - -33] | 63 | -41 [-50 - -33] | ns | ns | ns |
| **Areas** | | | | | | | | | |
| Absolute AUC (mmHg.s) | 22 | 10544 ± 3176 | 18 | 12135 ± 3374 | 63 | 13022 ± 3492 | 0.015 | 0.012 | ns |
| Absolute systolic AUC (mmHg.s) | 22 | 5.165 ± 1719 | 18 | 6663 ± 2568 | 63 | 6615 ± 1668 | 0.006 | 0.047 | 0.001 |
| Absolute diastolic AUC (mmHg.s) | 22 | 5.346 ± 2.055 | 18 | 5433 ± 2108 | 63 | 6369 ± 2401 | ns | 0.035 | ns |
| **Indexes** | | | | | | | | | |
| Absolute Myocardial oxygen supply/demand ratio | 22 | 1.1 ± 0.4 | 18 | 0.9 ± 0.5 | 63 | 1.0 ± 0.4 | ns | ns | ns |
| Shock index | 22 | 0.84 [0.63 - 1.2] | 18 | 0.99 [0.79 - 1.36] | 63 | 1.06 [0.911 - 1.28] | 0.01 | 0.012 | 0.004 |
| Age adjusted shock index | 22 | 76 ± 25 | 18 | 66 ± 17 | 63 | 55 ± 16 | 0.00016 | 0.000 | 0.005 |
| **Variability parameters** | | | | | | | | | |
| Pulse pressure variation (%) | 15 | 31.2 [8.1 - 24.8] | 16 | 10.3 [8.5 - 11.7] | 60 | 10.6 [6.3 - 20.1] | ns | ns | ns |
| Stroke volume variation (%) | 15 | 18.5 [7.5 - 30.6] | 16 | 9.7 [6.4 - 14.3] | 60 | 10.1 [5.6 - 28.5] | ns | ns | ns |
| Heart rate variability (%) | 15 | 3.7 [2.3 - 5.9] | 16 | 4.7 [2.6 - 10.5] | 60 | 3.2 [2.4 - 9.2] | ns | ns | ns |
| **Beatscope derived parameters** | | | | | | | | | |
| BS systolic pressure (mmHg) | 22 | 86 ± 21 | 18 | 93 ± 29 | 63 | 91 ± 17 | ns | ns | ns |
| BS diastolic pressure (mmHg) | 22 | 60 ± 13 | 18 | 59 ± 18 | 63 | 74 ± 15 | ns | ns | ns |
| BS MAP (mmHg) | 22 | 70 ± 16 | 18 | 74 ± 23 | 63 | 74 ± 15 | ns | ns | ns |
| BS Heart rate (bpm) | 22 | 99 ± 19 | 18 | 88 ± 19 | 63 | 84 ± 20 | 0.021 | 0.036 | 0.022 |
| BS LVET (s) | 22 | 0.29 ± 0.06 | 18 | 0.34 ± 0.07 | 63 | 0.35 ± 0.06 | 0.001 | 0.017 | 0.000 |
| BS Stroke Volume (ml) | 22 | 46 ± 22 | 18 | 61 ± 21 | 63 | 63 ± 25 | 0.014 | 0.03 | 0.004 |
| BS Cardiac output (L/min) | 22 | 4.0 ± 1.6 | 18 | 4.9 ± 1.7 | 63 | 4.9 ± 2.1 | ns | ns | 0.046 |
| BS Systemic vascular resistance (dynes.s/cm5) | 22 | 455 [1 - 1186] | 18 | 847 [1 - 1185] | 63 | 801 [1 - 1344] | ns | ns | ns |
| Cardiac Power Output (mmHg.L/min) | 22 | 0.63 ± 0.33 | 18 | 0.81 ± 0.39 | 63 | 0.79 ± 0.30 | ns | ns | 0.026 |
| Cardiac Index (L/min/m²) | 22 | 1.9 ± 0.7 | 18 | 2.4 ± 0.8 | 63 | 2.4 ± 1.0 | ns | ns | 0.046 |
| Cardiac Power Index (W/m²) | 22 | 0.32 ± 0.16 | 18 | 0.40 ± 0.18 | 63 | 0.39 ± 0.14 | ns | ns | 0.041 |

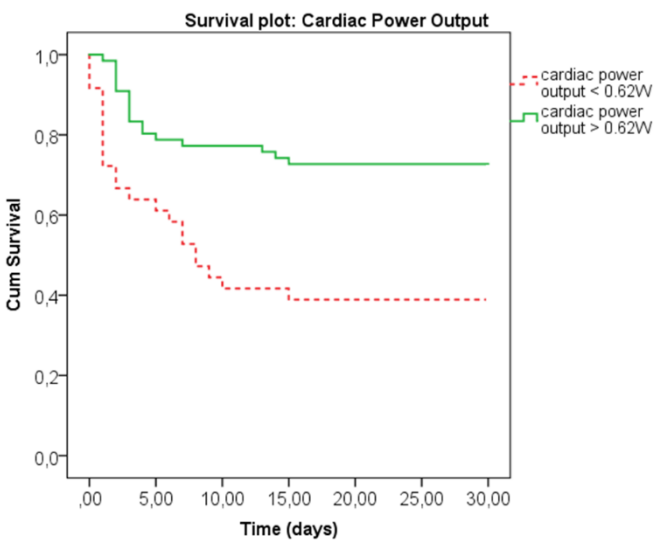
Values are presented as mean ± standard deviation or as medain [IQR].

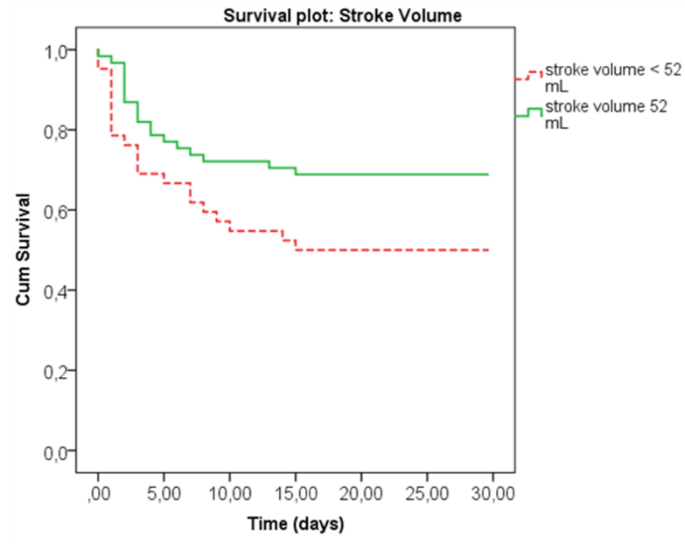
*Figure 18: Kaplan-Meier plots showing 30-day survival rates for shock index, heart rate, cardiac output, cardiac power output, stroke volume, LVET, cardiac power index and cardiac index.*

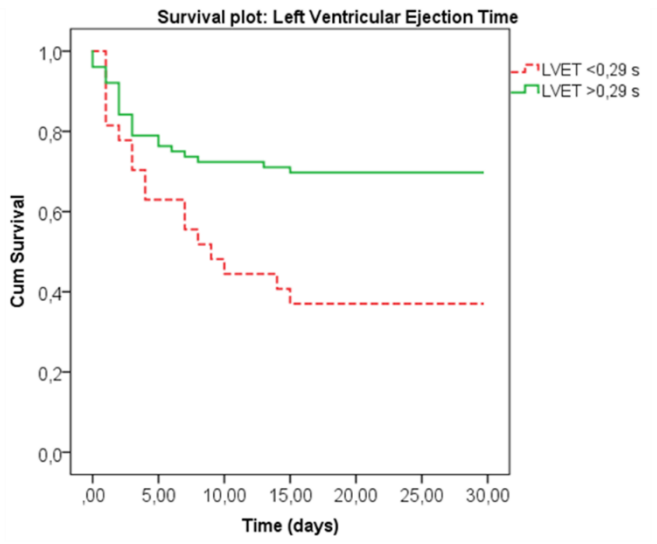


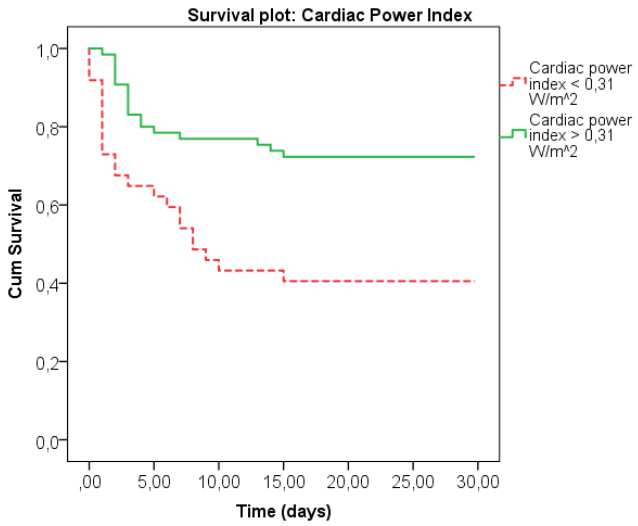





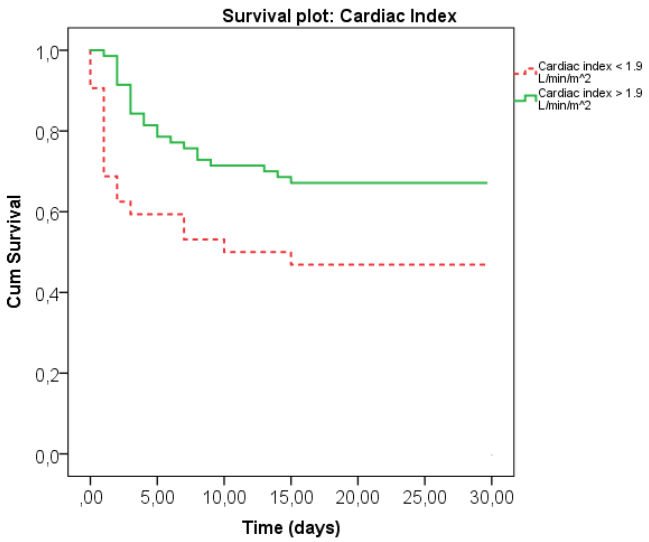




*Table 8: Cut-off values, area under the curves, sensitivities and specificities from ROC curves.*

| Parameter | Cut-off value | AUC | Sensitivity | Specificity |
|---|---|---|---|---|
| Shock index | 0.9 | 0.65 | 0.61 | 0.60 |
| Heart rate | 91 bpm | 0.62 | 0.71 | 0.48 |
| Cardiac output | 4.2 L/min | 0.58 | 0.66 | 0.53 |
| Cardiac Power Output | 0.62 W | 0.60 | 0.77 | 0.55 |
| Stroke volume | 52 mL | 0.64 | 0.65 | 0.65 |
| LVET | 0.29 s | 0.65 | 0.84 | 0.45 |
| Diastolic AUC | 22 mmHg·s | 0.62 | 0.61 | 0.58 |
| Cardiac index | 1.9 | 0.60 | 0.71 | 0.53 |
| Cardiac power index | 0.31 | 0.61 | 0.76 | 0.55 |
| Age adjusted shock index | 70 | 0.71 | 0.85 | 0.50 |

# Discussion

This exploratory study reveals some potential parameters for assessment of the severity of cardiogenic shock in relation to outcome. The shape of the blood pressure curve is defined by a large subset of parameters, in a way that has not been investigated before during cardiac catheterization.

Classic pressure derived parameters on their own, do not give valuable information regarding cardiogenic shock severity, even though many clinical decisions rely on these parameters. Among all parameters, shock index, LVET and stroke volume are parameters that have best predictive value regarding outcome in cardiogenic shock. These parameters show a difference in mortality rate and time to death. Patients in the CD group have lower shock index, LVET and SV. Of course, LVET is inversely related with heart rate. Still, LVET has better predictive value in the current cohort than heart rate and relative LVET, which is divided by the beat length, is also lower in the CD group. Weissler et al. showed that in patients with nonvalvular heart disease and cardiac failure, ejection time was usually low relative to heart rate (compared to healthy individuals) but tended to fall within normal limits relative to stroke volume[45]. This supports the current finding of a short LVET being related to cardiac failure. It has been investigated before that mainly left ventricular haemodynamics are impaired

in cardiogenic shock patients compared to non-cardiogenic shock state[46]. Weissler et al. have also shown that the failing left ventricle is characterized by a prolongation in the systolic pre-ejection period and a reduction in the left ventricular ejection time while total electromechanical systole remains relatively unaltered[47]. These alterations in the phases of systole occur in the absence of a measurable change in ventricular depolarization time. The shortening in left ventricular ejection time is also correlated significantly with stroke volume and cardiac output[45]. Cardiac output and stroke volume are both lower in the NCD group, corresponding to the findings of Weissler et al. LVET shows some correlation with cardiac output and stoke volume, however this correlation is not very strong (0,12 and 0,54 respectively). When shock index and LVET are combined in a multivariate analysis, the model becomes unstable, suggesting that there is too much multi-colinearity present between LVET and shock index to be used in multivariate regression analysis.

Spyridopoulos et al. found that invasively measured shock index before pPCI is the strongest independent predictor of long-term outcome, especially in elderly patients. The current study confirms this. Especially a low shock index is related with increased mortality and shorter time to death. Though, shock index above 1,0 could also be present in a bad hemodynamic condition. This is illustrated in figure 19. Patients with a low shock index (systolic pressure/HR) have high heart rates and low systolic blood pressure. When blood pressure drops and during the compensatory phase of cardiogenic shock, heart rate and peripheral resistance increase to improve cardiac output and blood pressure[48]. When heart rate is high and blood pressure still low, this indicates that this compensation mechanism is not effective enough to improve blood pressure and thus perfusion. AMI patients with low blood pressure and high heart rate are at risk of developing progressive cardiac failure. Patients with a shock index > 1,0 may have low blood pressure and bradycardia. These patients probably reached the decompensated phase of cardiogenic shock and have high mortality risk[33]. It is important to realize that not only low, but also high shock index could reflect a bad hemodynamic condition.

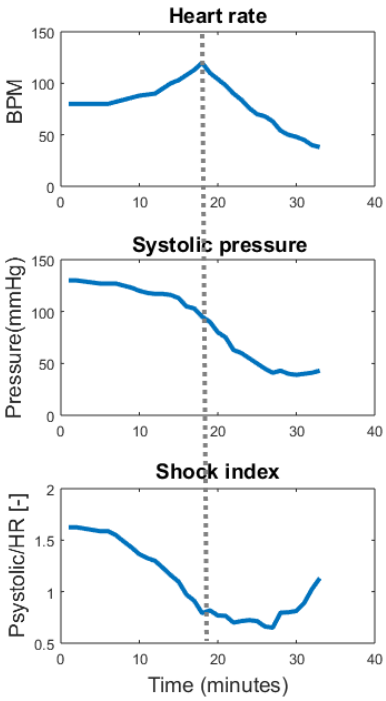


*Figure 19: Illustration of shock index change.*

Shock index and cardiac (power) output are parameters related to 30-day mortality and cardiac recovery, that do not have high correlation according to factor analysis. This suggests that these parameters play a key role in developing a cardiogenic shock grade. However, instable multivariate models when these blood pressure parameters are combined could imply that the correlation between blood pressure curve parameters is still too high to be used in a multivariate model. Even though factor analysis reveals that there are quite large differences in correlation between different blood pressure curve parameters.

Systolic, diastolic and total AUC and upstroke time are also different between the death -and survival groups and between cardiac recovery and no cardiac recovery group, since they are correlated to shock index. However, they do not have additive value in predicting outcome.

Multivariate analysis is very limited, since many of the parameters are correlated with each other. When different blood pressure parameters measured prior to revascularization are put together for multivariate analysis, the multivariate model becomes non-significant, probably due to multi-colinearity or too small patient groups. Only age, which is of course not derived from the blood pressure curve, has additive value in multivariate analysis. Age is already known to be related to higher mortality rates[5,49,50].

*Table 9: Results post revascularization*

| | No survival no cardiac recovery | | No survival cardiac recovery | | Survival | | p-values | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | value | n | value | n | value | Between groups | Survival vs non-survival | Cardiac recovery vs no cardiac recovery |
| **Pressure derived variables** | | | | | | | | | |
| Systolic pressure (mmHg) | 15 | 87 ± 32 | 17 | 95 ± 15 | 59 | 96 ± 21 | ns | ns | ns |
| Diastolic pressure (mmHg) | 15 | 60 ± 15 | 17 | 63 ± 12 | 59 | 64 ± 15 | ns | ns | ns |
| MAP (mmHg) | 15 | 68 ± 15 | 17 | 71 ± 21 | 59 | 71 ± 14 | ns | ns | ns |
| Pulse pressure (mmHg) | 15 | 27 ± 19 | 17 | 33 ± 9 | 59 | 32 ± 15 | ns | ns | ns |
| **Time derived variables** | | | | | | | | | |
| t dp/dt max (s) | 15 | 0,06 [0,04 - 0,07] | 17 | 0,05 [0,05 - 0,10] | 59 | 0,06 [0,04 - 0,08] | ns | ns | ns |
| t upstroke (s) | 15 | 0,151 ± 0,037 | 17 | 0,190 ± 0,050 | 59 | 0,189 ± 0,054 | 0.035 | ns | 0.009 |
| t downstroke (s) | 15 | 0,124 [0,093 - 0,163] | 17 | 0,149 [0,100 - 0,176] | 59 | 0,136 [0,096 -0,185] | ns | ns | ns |
| Heart rate (bpm) | 15 | 94 ± 19 | 17 | 84 ± 20 | 59 | 81 ± 19 | ns | ns | 0.028 |
| Duration systole(LVET) (s) | 15 | 0,31 ± 0,07 | 17 | 0,35 ± 0,08 | 59 | 0,35 ± 0,08 | ns | ns | ns |
| relative t upstroke | 15 | 0,25 ± 0,07 | 17 | 0,27 ± 0,07 | 59 | 0,26 ± 0,07 | ns | ns | ns |
| relative t dp/dt max | 15 | 0,08 [0,05 - 0,12] | 17 | 0,07 [0,07 - 0,11] | 59 | 0,08 [0,05 - 0,11] | ns | ns | ns |
| relative LVET | 15 | 0,48 ± 0,11 | 17 | 0,47 ± 0,09 | 59 | 0,45 ± 0,07 | ns | ns | ns |
| **Slopes** | | | | | | | | | |
| dp/dt max (mmHg / s) | 15 | 257 [178 - 456] | 17 | 361 [234 - 552] | 59 | 360 [254 - 493] | ns | ns | ns |
| dp/dt diastole - systolic max (mmHg / s) | 15 | 39 [17 - 58] | 17 | 44 [33 - 60] | 59 | 39 [32 - 48] | ns | ns | ns |
| dp/dt systolic max - diastole (mmHg / s) | 15 | -39 [-58 - -17] | 17 | -44 [-60 - -33] | 59 | -38 [-48 - -32] | ns | ns | ns |
| **Areas** | | | | | | | | | |
| Absolute AUC (mmHg.s) | 15 | 11623 ± 4296 | 17 | 13550 ± 2470 | 63 | 14370 ± 3623 | 0.032 | 0.031 | 0.012 |
| Absolute systolic AUC (mmHg.s) | 15 | 5767 ± 2330 | 17 | 6911 ± 2015 | 63 | 6936 ± 1660 | ns | ns | 0.020 |
| Absolute diastolic AUC (mmHg.s) | 15 | 5814 ± 2243 | 17 | 6592 ± 2015 | 63 | 7383 ± 2604 | ns | 0.034 | 0.048 |
| **Indexes** | | | | | | | | | |
| Absolute Myocardial oxygen supply/demand ratio | 15 | 0,99 ± 0,36 | 17 | 1,06 ± 0,43 | 63 | 1,09 ± 0,35 | ns | ns | ns |
| Shock index | 15 | 0,82 [0,73 - 1,18] | 17 | 1,08 [0,99 - 1,36] | 63 | 1,21 [1,03 - 1,39] | ns | 0.028 | 0.003 |
| Age adjusted shock index | 15 | 78 ± 31 | 17 | 53 ± 10 | 63 | 51 ± 20 | 0.000 | 0.006 | 0.000 |
| **Variability parameters** | | | | | | | | | |
| Pulse pressure variation | 8 | 20,6 [4,9 - 34] | 16 | 10,9 [7,7 - 19,6] | 57 | 12,4 [6,7 - 18,4] | ns | ns | ns |
| Stroke volume variation | 8 | 19,1 [6,7 - 48,5] | 16 | 6,3 [10,4 - 24,2] | 57 | 10,9 [5,9 - 17,5] | ns | ns | ns |
| Heart rate variability | 8 | 4,9 [3,5 - 22,5] | 16 | 3,4 [2,1 - 7,5] | 57 | 3,3 [2,3 - 9,3] | ns | ns | ns |
| **Beatscope derived parameters** | | | | | | | | | |
| BS systolic pressure (mmHg) | 15 | 87 ± 32 | 17 | 95 ± 16 | 63 | 96 ± 21 | ns | ns | ns |
| BS diastolic pressure (mmHg) | 15 | 60 ± 15 | 17 | 63 ± 12 | 63 | 64 ± 15 | ns | ns | ns |
| BS MAP (mmHg) | 15 | 71 ±22 | 17 | 77 ± 13 | 63 | 77 ± 16 | ns | ns | ns |
| BS Heart rate (bpm) | 15 | 91 ± 20 | 17 | 82 ± 18 | 63 | 79 ± 20 | ns | 0.046 | 0.049 |
| BS LVET (s) | 15 | 0,31 ± 0,06 | 17 | 0,34 ± 0,06 | 63 | 0,35 ± 0,08 | ns | ns | ns |
| BS Stroke Volume (ml) | 15 | 43 ± 24 | 17 | 59 ± 19 | 63 | 60 ± 25 | ns | ns | 0.019 |
| BS Cardiac output (L/min) | 15 | 3,8 ± 2,3 | 17 | 4,7 ± 1,7 | 63 | 4,2 ± 1,4 | ns | ns | ns |
| BS Systemic vascular resistance (dynes.s/cm5) | 15 | 3 [2 - 1341]] | 17 | 871 [2 - 1402] | 63 | 984 [1 - 1515] | ns | ns | ns |
| Cardiac Power Output (mmHg.L/min) | 15 | 0,66 ± 52 | 17 | 0,81 ± 0,33 | 63 | 0,83 ± 0,35 | ns | ns | ns |
| Cardiac Index (L/min/m²) | 15 | 1,9 ± 1,0 | 17 | 2,3 ± 0,9 | 63 | 2,1 ± 0,7 | ns | ns | ns |
| Cardiac Power Index (W/m²) | 15 | 0,32 ± 0,24 | 17 | 0,40 ± 0,17 | 63 | 0,36 ± 0,14 | ns | ns | ns |

Values are presented as mean ± standard deviation or as medain [IQR].

## Revascularization: effect on blood pressure waveform and relation to outcome

Revascularization in general has a very small (non-significant) positive effect on parameters related to systolic myocardial function. Revascularization has a slightly increasing effect on the classical pressure derived parameters and area derived parameters. Heart rate and heart rate related parameters decrease. As a result, the shock index increases. This effect could be due to the positive effect of revascularization or due to vasoactive medication administered during pPCI, since 76 out of 103 patients received vasoactive medication. Remarkably, patients in the CD group seem to have slightly less increase in parameters related to systolic function, whereas this group received vasoactive medication most frequently (95%) versus 67% and 68% in de NCD and survival group. However no significant difference is seen, this implicates that patients that receive vasoactive medication and show no improvement in hemodynamic pressure related parameters have worse outcome. The capacity of the cardiovascular function may be too severely impaired to adjust hemodynamics after revascularization. Cardiac function might be irreversibly damaged, so that revascularization has no effect in patients with severe cardiogenic shock.

The oxygen supply-demand ratios slightly increase in each subgroup. Interestingly, the smallest increase is present in the CD group. During systole, myocardial extravascular compression causes coronary flow to be near zero. Coronary flow is relatively high during diastole[51]. In 1972, Buckberg et al. showed that an index based on left ventricular and aortic pressures could predict subendocardial ischemia. They argued that the area between the diastolic aortic and left ventricular pressures represented the oxygen supply to the myocardium, and the area under the systolic left ventricular pressure curve represented the oxygen demand by the myocardium. Since the oxygen supply-demand ratios slightly increase with revascularization, this indicates that oxygen supply to the myocardium is also slightly increased. Also, the oxygen supply-demand ratio shows the smallest change in the CD group, indicating that revascularization might have less increasing influence on myocardial perfusion in patients that died due to cardiac failure. Though, the differences are marginal and non-significant. There is no significant difference seen between groups, but the CD group has less improvement (1%) compared to the NCD group (5%) and survival group (9%). Though, standard deviations are large, making the interpretation difficult. Furthermore, diastolic AUC as measured in this study overestimates myocardial oxygen supply, since the AUC of left ventricular pressure is not substracted from the diastolic AUC because ventricular pressure is not available.

Blood pressure variation related parameters show almost no increase. There is a slight increase in PPV, SVV and HRV in the CD group, mainly. This indicates that these patients shifted on the Frank-Starling curve by either a decreased preload or increased cardiac contractility. A decreased preload could be caused by blood loss during the procedure or due to diminished peripheral vasoconstriction. Increased cardiac contractility could either be due to improved cardiac function or effects of vasoactive medication. Since stroke volume and cardiac output are decreased, the latter is unlikely.

Not any of the investigated parameters showed significant difference in relation to 30-day mortality or cardiac recovery. Blood pressure curve morphology before revascularization apparently is of better predictive value for outcome than the difference before and after revascularization. Some patients show immediate recovery and others may suffer from revascularization injury. The timing of assessment of the difference in blood pressure parameters and administration of medication is important and probably has great influence on the results.

## Limitations

The current study is a retrospective cohort study which has several limitations.

Vasoactive medication was used in 76 out of 103 patients during pPCI. When choosing a blood pressure segment, procedure logs were used to avoid using a blood pressure segment directly after administration of vasoactive medication. However, the exact timing and amount of medication use is unknown, which has great influence on blood pressure[52]. Besides, vasoactive medication is often already administered by the ambulance or in the shock room.

Out of 103 patients, 98 patients were mechanically ventilated during pPCI. Mechanical ventilation influences cardiac output and blood pressure morphology by elevation of intrathoracic pressures during inspiration. Patients in de CD group, are less often mechanically ventilated (86%) versus the NCD (89%) and survival group (98%). Ventilator settings were unknown, whereas different ventilator settings (pressures, gases) cause different intrathoracic pressures, influencing the blood pressure curve morphology. This could influence the differences that are found between the groups.

For the proper assessment of pulse pressure variation and stroke volume variation, this parameter should be calculated for every respiratory cycle and averaged. For calculation of the parameters 'pulse pressure variation' and 'stroke volume variation' and 'heart rate variability', it is attempted to calculate pulse pressure variation within a respiratory cycle by adjusting a bandpass filter of 0.15-0.4 Hz on the blood pressure curve and regarding the resulting signal as being the respiratory signal. This method is not validated yet. Blood pressure measurements should be performed including an actually measured respiratory cycle to validate this technique to estimate the respiratory signal. Next, this method computing PPV and SVV variation should be validated.

Some information bias exists regarding the baseline characteristics and comorbidities. Sometimes very limited information is present in the non-survivor group, especially in very unstable patients that short time-to-death. This limitation has no impact on determining outcome in this study.

Resuscitation and IABP support severely affect the blood pressure signal. For this reason, patients that have received IABP during the procedure were excluded. Also a small amount of patients frequently had resuscitation with chest compressions during pPCI. Especially these patients are very hemodynamically instable and often died. To prevent inclusion bias, one would want to include these patients for assessment of the blood pressure waveform to create a CS grading.

Among the subjects that are included in the study, signal quality also differs through the measurement and in between subjects. Due to underdamping and overdamping, the blood pressure signal may contain excessive amplification of oscillations or a very dampened curve that does not represent the actual blood pressure signal appropriately[42].

## Clinical relevance

The haemodynamic measurement of cardiac function is of particular value for the kind of therapy, especially the initiation of circulatory assist or vasoactive medication. Mechanical circulatory assist devices provide haemodynamic support and most often are inserted post revascularization. Some patients suddenly become haemodynamically unstable after revascularization. Age adjusted shock index, shock index, LVET and cardiac output related parameters could be of value to determine the depth of cardiogenic shock, which is important for defining a high-risk procedure. These patients might need extra mechanical haemodynamic support or vasoactive medication before revascularization to prevent haemodynamic deterioration [53].

# Conclusion

Left ventricular ejection time, (age adjusted) shock index, stroke volume and cardiac output parameters that give information about the severity of cardiogenic shock with respect to 30-day mortality. When regarding cardiac recovery, these parameters as well as cardiac (power) output and cardiac (power) index are of predictive value. A complete CS grading is not yet developed based on these blood pressure curve morphology parameters only. Blood pressure curve parameters may be too much correlated to each other to develop a complete CS grading.

# III. Blood pressure changes over time in STEMI patients

## Introduction

The aim of this study is to investigate the blood pressure waveform morphology change during -and after pPCI in patients with ST-segment elevation myocardial infarction. Since some patients have a vasovagal response directly after revascularization, the shift in sympathovagal balance prior to revascularization and post revacularization in relation to TIMI grade flow is also assessed. 'TIMI Grade Flow' is a scoring system from 0-3 referring to levels of coronary blood flow assessed during PCI.

It is hypothesized that revascularization improves cardiac function -and or behavior of the vasculature and that these effects are reflected in the blood pressure curve, measured non-invasively. Also, it is hypothesized that revascularization might reduce sympathetic activity, reflected by a decrease in sympathovagal balance.

## Methods

### Patient selection

STEMI is defined as: new ST-segment elevation in at least two adjacent leads of ≥ 2 mm (0.2 mV) in men or ≥ 1.5 mm (0.15 mV) in women in leads V2-V3 and/or of ≥ 1 mm (0.1 mV) in other adjacent chest leads or the limb leads. A new left bundle branch block (LBBB) is considered the equivalent of STEMI. Exclusion criteria are: patients with atrial fibrillation, known severe congenital heart defects or severe aortic regurgitation. Also, patients under the age of 18 and patients unable to give informed consent are excluded from this study. A total of 18 patients were included who suffered from ST-segment elevation myocardial infarction and were referred to the catheterization laboratory of the Academic Medical Centre (AMC) for treatment with primary PCI.

Permission for this study has been granted from the Institutional Review Board with study number NL52819.018.15. Written informed consent was obtained from every patient.

### Measurement protocol

Non-invasive blood pressure measurements were performed during pPCI with the Nexfin device (Edwards Lifesciences). The Nexfin recordings were analyzed in MATLAB R2016B, MathWorks. Hemodynamic parameters were determined using pulse contour analysis provided by Beatscope 1.1a (TNO). The moment of first wire passage of the culprit lesion, all balloon inflations and deflations, administration of medication and moment of revascularization were registered by placing markers in the Nexfin pressure measurement during PCI.

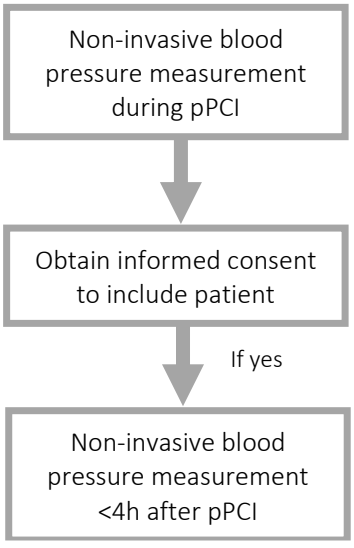



*Figure 20: Flow diagram of inclusion process for the prospective study*

Within four hours after PCI, a follow-up measurement is performed. For this measurement, patients were in a horizontal position with the left hand resting on the mattress. Non-invasive blood pressure recordings were conducted with a duration of 15 minutes.

### Data selection

To investigate beat-to-beat data from the non-invasively measured blood pressure recordings, a blood pressure segment of >20 seconds is selected before -and after revascularization. For follow-up measurements, at least 20 seconds of noninvasive blood pressure signal was selected from the middle of the recording. Pressure signals were selected such that they contain very few or no visible artifacts.

To investigate the frequency derived parameters in the VLF, LF and -HF range, blood pressure segments of approximately five minutes are analyzed to be able to appropriately measure these parameters (considering Rayleigh frequency). Five-minute periods are selected prior to revascularization, after revascularization and from the follow-up measurement.

To investigate the change in sympathovagal balance measured as $SVB = LF/HF$ before -and after revascularization and its relation with change in TIMI flow, two minutes of data is selected post revascularization. This is done since the biggest change in sympathovagal balance is expected directly after revascularization and a two minute data epoch is sufficiently long to measure LF.

The sympathovagal balance difference is computed as: $SVB_{difference} = SVB_{post\ revascularization} - SVB_{pre\ revascularization}$. The change in TIMI flow of the culprit vessel is defined as: $TIMI_{difference} = TIMI_{post\ revascularization} - TIMI_{pre\ revascularization}$.

Different TIMI flow scales are defined as[54]:

- TIMI 0 flow: no penetration of contrast beyond stenosis;
- TIMI 1 flow: penetration of contrast beyond stenosis but no perfusion of distal vessel;
- TIMI 2 flow: contrast reaches the entire distal vessel but either at a decreased rate of filling or clearing in comparison to the other coronary arteries;
- TIMI 3 is normal flow which fills the distal coronary bed completely.

### Statistical analysis

To test if there is a change in parameters over time, one-way repeated measures ANOVA test is used with the fixed factor 'patient' and variable factor 'time'. Hukey's post-hoc analysis is used to test for differences between timepoints prior to revascularization, post revascularization and the follow-up measurement.

To test if there is a relationship between the difference in sympathovagal balance and the difference in TIMI flow of the culprit vessel, the Mann-Whitney U test is used. The difference in sympathovagal balance is assessed between patients with TIMI flow difference of 3 and TIMI flow difference < 3.

## Results

Between april 2015 and july 2017, a total of 46 patients were measured during pPCI in the cardiac catheterization lab. The inclusion process is shown in figure 21. Of these patients, 28 subjects were excluded due to several reasons. Two of these patients did not have STEMI and in seven patients no culprit vessel was found. Two patients were excluded due to technical difficulties and ten patients could not be included because no informed consent was given. This was primarily due to transfer to the ICU while patients were unconscious and due to quick transfer to another hospital. From seven patients blood pressure curve data was not available anymore.

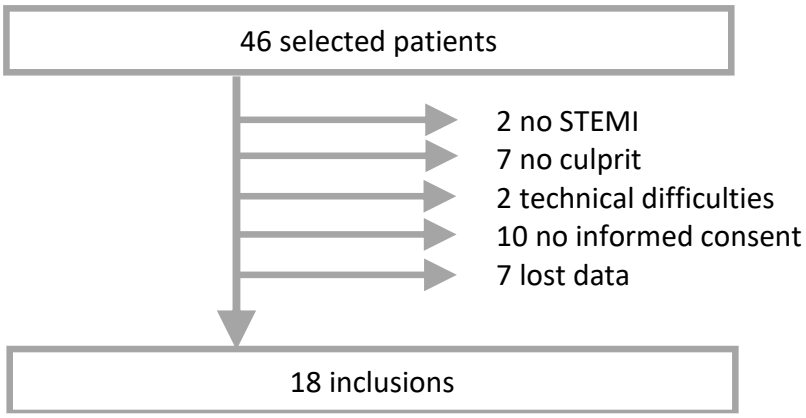



*Figure 21 : Inclusions and exclusions for blood pressure measurements in STEMI patients*

## Baseline characteristics

The baseline characteristics of the included patients (n=18) are listed in table 10. Most patients are male (83%). In half of the patients, the culprit vessel was the LAD. None of the patients received vasoactive medication or were mechanically ventilated.

*Table 10: Baseline, procedural and treatment characteristics of patients included in the prospective cohort study*

| | | **n=18** |
|---|---|---|
| **Baseline characteristics** | | |
| Male | | 15 (83 %) |
| BMI (kg/m²) | | 27 ± 6 |
| Age (years) | | 60 ± 14 |
| Diabetes | | 3 (17%) |
| Dislipidemia | | 8 (44%) |
| Current smoker | | 7 (39%) |
| Family history of CAD | | 9 (50%) |
| Stroke | | 2 (11%) |
| Peripheral artery disease | | 1 (6%) |
| Previous MI | | 1 (6%) |
| Previous PCI | | 1 (6%) |
| Previous CABG | | 0 (0%) |
| **PCI characteristics** | | |
| Culprit vessel | LM | 0 (0%) |
| | LAD | 9 (50%) |
| | RCx | 4 (22%) |
| | RCA | 5 (28%) |
| Multivessel disease | | 8 (44%) |
| **Treatment characteristics** | | |
| Vasoactive medication | | 0 (0%) |
| Mechanical ventilation | | 0 (0%) |

Values are presented as amount (% of total) or mean ± standard deviation. BMI: Body mass index (BMI); CAD: Coronary Artery Disease; MI: Myocardial Infarction; PCI: Percutaneous Coronary Intervention; CABG: Coronary artery bypass grafting; LM: Left main; LAD: Left anterior descending artery; RCx: Ramus circumflexus; RCA: Right coronary artery.

## Blood pressure parameter changes over time in STEMI

Results for all parameters are shown in table 11. The systolic pressure, diastolic pressure, mean arterial pressure and pulse pressure parameters show a small decrease after revascularization. During follow-up measurements an increase is seen. This difference is only statistically significant for diastolic -and mean arterial pressure between the timepoints before -and after revascularization.

As heart rate decreases with revascularization, most time derived parameters also decrease with revascularization. Again, during follow-up the time derived parameters tend to increase again. A significant difference is seen for upstroke time between the blood pressure measurement prior to revascularization and follow-up and for LVET between post revascularization and follow-up measurements. Heart rate tends to decrease with every timepoint.

The slope -and area derived parameters do not show significant changes, however there is a decreasing trend with revascularization.

The myocardial oxygen supply/demand ratio tends to increase with revascularization and unaltered during follow-up. Shock index barely changes. The sympathovagal balance decreases with revascularization and increases again with follow-up, suggesting that sympathetic activity decreases with revascularization, however no significant difference is found.

The classic clinical Beatscope parameters (systolic pressure, diastolic pressure, MAP, heart rate) show a decreasing trend with revascularization and an increase with follow-up. Only the diastolic pressure shows a significant change between blood pressure measurements pre -and post revascularization. All other parameters do not show a significant change. Stroke volume slightly increases with revascularization.

## Sympathovagal balance and change in TIMI flow

Results for sympathovagal balance post revascularization and sympathovagal balance difference are shown in table 12. The difference in sympathovagal balance varies among patients and does not show a clear increasing or decreasing trend in relation to TIMI flow difference post revascularization. Though not significant, the sympathovagal balance seems slightly lower post revascularization in patients that have a large difference in TIMI flow (patients that have TIMI = 0 prior to revascularization and TIMI = 3 post revascularization). This suggests that sympathetic activity relative to parasympathic activity is relatively low in patients with larger TIMI difference during pPCI. However, the difference is marginal. One patient that showed a vasovagal response directly after revascularization, has a decrease in $SVB_{difference}$ of -8,61, which is a large decrease in sympathetic activity directly after revascularization. This patient went from TIMI 0 to TIMI 3 flow grade as well. In figure 22 the sympathovagal balance differences are plotted against TIMI flow before revascularization of both zero and >1. From the figure it can be noticed that there is no clear relation between a sympathovagal balance shift and reflow change.

*Table11 : Results for prospective cohort st*udy in STEMI patients. Results are shown before revascularization, after revascularization and for follow up <4 hours after pPCI.

| | Pre-revascularization | | Post-revascularization | | Follow up < 4h | | p-values | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | value | n | value | n | value | Between groups | Between 1 and 2 | Between 1 and 3 | Between 2 and 3 |
| **Pressure derived variables** | | | | | | | | | | |
| Systolic pressure (mmHg) | 18 | 152 ± 6 | 18 | 146 ± 6 | 18 | 153 ± 7 | ns | ns | ns | ns |
| Diastolic pressure (mmHg) | 18 | 83 ± 3 | 18 | 80 ± 3 | 18 | 84 ± 3 | ns | 0.045 | ns | ns |
| MAP (mmHg) | 18 | 106 ± 3 | 18 | 102 ± 4 | 18 | 107 ± 4 | ns | 0.058 | ns | ns |
| Pulse pressure (mmHg) | 18 | 69 ± 6 | 18 | 66 ± 5 | 18 | 69 ± 6 | ns | ns | ns | ns |
| **Time derived variables** | | | | | | | | | | |
| t dp/dt max (s) | 18 | 0.06 [0.04 - 0.07] | 18 | 0.06 [0.05 - 0.07] | 18 | 0.06 [0.05 - 0.07] | ns | ns | ns | ns |
| t upstroke (s) | 18 | 0.14 [0.12 - 0.15] | 18 | 0.14 [0.12 - 0.16] | 18 | 0.16 [0.14 - 0.17] | 0.004 | ns | 0.011 | 0.005 |
| t downstroke (s) | 18 | 0.23 [0.19 - 0.26] | 18 | 0.21 [0.19 - 0.25] | 18 | 0.23 [0.21 - 0.24] | ns | ns | ns | ns |
| Heart rate (bpm) | 18 | 73 ± 4 | 18 | 70 ± 3 | 18 | 69 ± 2 | ns | ns | ns | ns |
| Duration systole(LVET) (s) | 18 | 0.38 ± 0.12 | 18 | 0.37 ± 0.01 | 18 | 0.39 ± 0.01 | 0.061 | ns | ns | 0.025 |
| relative t upstroke | 18 | 0.17 [0.15 - 0.21] | 18 | 0.16 [0.15 - 0.20] | 18 | 0.19 [0.16 - 0.22] | ns | ns | ns | ns |
| relative t downstroke | 18 | 0.28 [0.17 - 0.30] | 18 | 0.28 [0.18 - 0.31] | 18 | 0.29 [0.18 - 0.31] | ns | ns | ns | ns |
| relative t dp/dt max | 18 | 0.06 [0.06 - 0.08] | 18 | 0.07 [0.05 - 0.08] | 18 | 0.07 [0.06 - 0.08] | ns | ns | ns | ns |
| relative LVET | 18 | 0.45 ± 0.01 | 18 | 0.43 ± 0.02 | 18 | 0.45 ± 0.01 | ns | ns | ns | ns |
| **Slopes** | | | | | | | | | | |
| dp/dt max (mmHg / s) | 18 | 1088 ± 116 | 18 | 1041 ± 91 | 18 | 973 ± 105 | ns | ns | ns | ns |
| dp/dt diastole - systolic max (mmHg / s) | 18 | 82 ± 7 | 18 | 75 ± 5 | 18 | 79 ± 6 | ns | ns | ns | ns |
| dp/dt systolic max - diastole (mmHg / s) | 18 | -82 ± 7 | 18 | -75 ± 5 | 18 | -79 ± 6 | ns | ns | ns | ns |
| **Areas** | | | | | | | | | | |
| Absolute AUC (mmHg.s) | 18 | 78 ± 5 | 18 | 76 ± 5 | 18 | 81 ± 4 | ns | ns | ns | ns |
| Absolute systolic AUC (mmHg.s) | 18 | 40 ± 2 | 18 | 37 ± 2 | 18 | 42 ± 2 | ns | ns | ns | ns |
| Absolute diastolic AUC (mmHg.s) | 18 | 38 ± 3 | 18 | 39 ± 3 | 18 | 39 ± 2 | ns | ns | ns | ns |
| **Indexes** | | | | | | | | | | |
| Absolute Myocardial oxygen supply/demand | 18 | 0.86 [0.77 - 1.14] | 18 | 0.93 [0.80 - 1.27] | 18 | 0.93 [0.74 - 1.10] | ns | ns | ns | ns |
| Shock index | 18 | 2.2 ± 0.17 | 18 | 2.2 ± 0.15 | 18 | 2.3 ± 0.14 | ns | ns | ns | ns |
| Sympathovagal balance | 18 | 7.6 [3.3 - 9.7] | 18 | 6.3 [3.0 - 13.8] | 18 | 7.1 [4.8 - 9.0] | ns | ns | ns | ns |
| **Frequency derived parameters** | | | | | | | | | | |
| Very low frequency (mmHg^2/Hz) | 18 | 85.8 ± 17.0 | 18 | 86.4 ± 18.5 | 18 | 86.6 ± 15.8 | ns | ns | ns | ns |
| Low frequency (mmHg^2/Hz) | 18 | 29.7 ± 6.8 | 18 | 35.4 ± 11.3 | 18 | 28.6 ± 6.8 | ns | ns | ns | ns |
| High frequency (mmHg^2/Hz) | 18 | 5.3 ± 1.6 | 18 | 7.9 ± 3.3 | 18 | 5.1 ± 1.3 | ns | ns | ns | ns |
| **Beatscope derived parameters** | | | | | | | | | | |
| BS systolic pressure (mmHg) | 18 | 152 ± 6 | 18 | 146 ± 6 | 18 | 153 ± 7 | ns | ns | ns | ns |
| BS diastolic pressure (mmHg) | 18 | 83 ± 3 | 18 | 80 ± 3 | 18 | 84 ± 3 | ns | 0.045 | ns | ns |
| BS MAP (mmHg) | 18 | 108 ± 4 | 18 | 104 ± 4 | 18 | 109 ± 4 | ns | ns | ns | ns |
| BS Heart rate (bpm) | 18 | 73 ± 4 | 18 | 70 ± 3 | 18 | 69 ± 2 | ns | ns | ns | ns |
| BS LVET (s) | 18 | 0.31 ± 0.01 | 18 | 0.32 ± 0.01 | 18 | 0.31 ± 0.01 | ns | ns | ns | ns |
| BS Stroke Volume (ml) | 18 | 78 ± 3 | 18 | 80 ± 4 | 18 | 79 ± 4 | ns | ns | ns | ns |
| BS Cardiac output (L/min) | 18 | 5.7 ± 0.4 | 18 | 5.6 ± 0.4 | 18 | 5.5 ± 0.34 | ns | ns | ns | ns |
| BS Systemic vascular resistance | 18 | 1409 [1255 - 1896] | 18 | 1334 [1176 - 1902] | 18 | 1595 [1287 - 1868] | ns | ns | ns | ns |
| Cardiac Power Output (mmHg.L/min) | 18 | 1.4 ± 0.1 | 18 | 1.3 ± 0.1 | 18 | 1.3 ± 0.1 | ns | ns | ns | ns |

Values are presented as mean ± standard deviation or as median [IQR]; ns = not significant

*Table 12: Results for sympathovagal balance and TIMI flow difference*

| | TIMI flow before revascularization > 0 | | TIMI flow before revascularization = 0 | | P-values |
|---|---|---|---|---|---|
| | n | value | n | value | Between groups |
| **Frequency analysis** | | | | | |
| Sympathovagal balance difference (post - pre) | 8 | -0.6 [-2.7 - 4.8] | 10 | 0.3 [-4.6 - 3.9] | 0.929 |
| Sympathovagal balance post revascularization | 8 | 6.4 [2.9 - 11.8] | 10 | 5.9 [4.5 - 11.1] | 0.722 |

Values are presented as median [IQR].

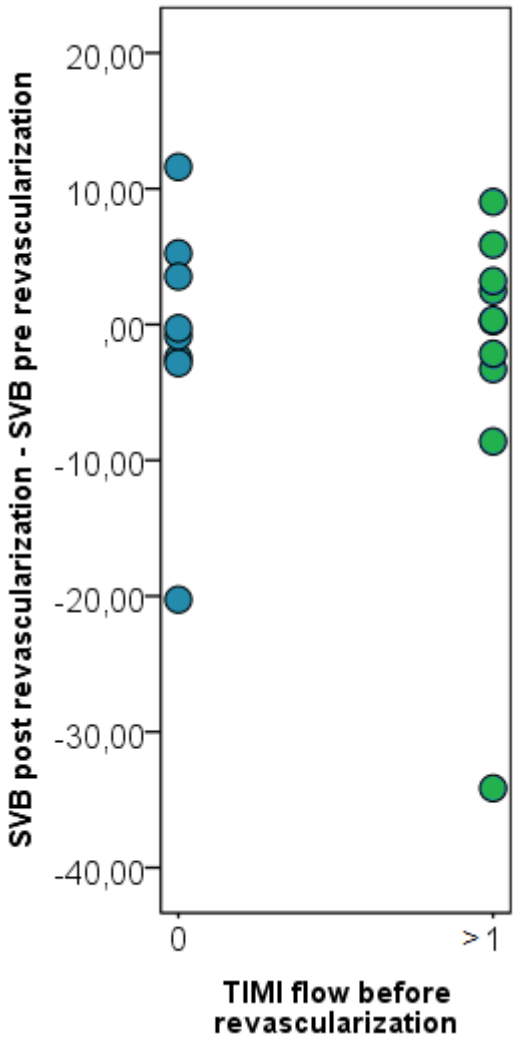



*Figure 22: Difference in sympathovagal balance in relation to TIMI flow before revascularization of 0 and >1.*

# Discussion

This study investigating blood pressure parameter changes over time shows that very few parameters change with revascularization and within four hours after PCI. Only diastolic pressure decreases significantly with revascularization, together with a decreasing MAP. After revascularization, many parameters decrease very slightly and increase again with the follow-up measurements (, except for heart rate. However, these changes are marginal. This indicates that the first hours after the beginning of STEMI, the hemodynamic changes that occur do not alter the blood pressure curve significantly. This is emphasized by the fact that the classic clinical pressure parameters are within quite normal peripheral pressure ranges. It could also indicate that pPCI limitedly effects hemodynamic parameters in the acute phase of MI.

From all parameters, only diastolic pressure (and MAP) significantly decrease with revascularization. The mean diastolic pressure only decreases with 3 mmHg, which is a very small decrease. Decrease of diastolic pressure indicates decrease of coronary filling, since perfusion of the coronary arteries happens during diastole[55]. Decreasing diastolic pressure might indicate less congestion within the heart and thus increased cardiac contractility. This is supported by the small increases in stroke volume and LVET and improvement of the myocardial oxygen supply/demand ratio. Cardiac output does not change while the heart rate decreases. The differences are marginal, but indicate that patients compensated for myocardial dysfunction by increasing heart rate to maintain sufficient cardiac output (before revascularization) and that cardiac function slightly improved after revascularization, reflected by increased stroke volume and decreased heart rate.

When the changes in revascularization are compared with the results of the shock cohort, it can be noticed that blood pressure changes relatively more in STEMI patients tha0t do not have CS, compared to hypotensive patients that are transferred to the ICU. This suggests that early revascularization of AMI has more improving influence on hemodynamics in the acute phase in patients that are not severely hypotensive compared to cardiogenic shock patients. STEMI patients that are not yet severely hypotensive seem to adapt better to reperfusion in the acute phase, since the myocardium has been damaged less.

It was unexpected that pressure related parameters would increase again with follow-up. This could be caused by post-procedural stress, since patients realized that they suffered from myocardial infarction. Often, family was present right before or during the follow-up measurement, some of them being emotional or concerned. Stress might cause the increased blood pressures. Heart rate and LVET show a small ongoing decreasing trend, as would be expected.

It was hypothesized that the sympathovagal balance computed from the frequency domain would decrease with revascularization, because it is expected that the patient are in distress before revascularization. Scully et al. have shown that sheep show increased VLF and LF activity, which is associated with increased sympathetic activity and decreased parasympathetic (HF) activity[33]. Boudou et al. have shown that patients with vasospastic angina have sympathetic hyperactivity[38]. It was expected that patients that suffer from ongoing myocardial infarction also have increased sympathetic activity as the patients hemodynamics is threatened by decreased myocardial perfusion. Since some patients show a vasovagal response directly after revascularization, it is expected that this response goes together with (relatively) increased parasympathetic activity and decreased sympathetic activity. There is only a small decrease in sympathovagal balance (from 7.6 to 6.3 when regarding the five-minute recordings), which is not significant. The difference is smaller than expected, but the small decrease in sympathovagal balance with revascularization emphasizes the hypothesis. The results of the frequency derived parameters could be influenced by signal disturbances. Less signal disturbances occurred during the Nexfin measurements because patients lied still during the procedure. However, physiocal that calibrates the Nexfin pressure signal interrupts the signal frequently. Also, finger/hand movement of the patient during the procedure could influence the pressure signal, this could not be controlled during the procedure.

The change in TIMI flow after revascularization was expected to be related to the change in sympathovagal balance. Patients that have a TIMI flow of 0 before revascularization and TIMI flow 3 after revascularization have the largest change in myocardial perfusion directly after revascularization. It is obvious that a larger hemodynamic change is expected in these patients. Since TIMI flow of 3 before -and after revascularization is an independent predictor of mortality, it would be interesting to investigate whether TIMI flow change is also related with a change in sympathovagal balance. Though, no relation at all is seen between sympathovagal balance change with revascularization and a TIMI flow

change of 3 compared to TIMI flow change < 3. Both patients that had TIMI 3 flow before PCI show a very small change in sympathovagal balance, which confirms the hypothesis that a small TIMI flow change goes together with a small change in sympathovagal balance. However, it is hard to draw conclusion from these results since only two patients had TIMI flow difference of zero. For this small pilot study, the two TIMI groups that are compared contain all kinds of culprit vessels. The type of culprit vessel and the size of the myocardium that is supplied by the culprit vessel, is of course of influence on the hemodynamic impairment. This might cause the varying results. To investigate the relation between TIMI flow and sympathovagal balance, a much larger cohort is needed to draw conclusions. Results of the study in this small cohort do not indicate a relation between TIMI flow change and sympathovagal balance. It should be noticed remarked that one patient that had an intense vasovagal response with heavy vomiting directly after the procedure, had a large decrease of sympathovagal balance of -8,61. This patient also had a TIMI flow difference of 3 after revascularization.

Shear stress of the vascular walls causes NO release from endothelial cells, finally resulting in vasodilation. This is associated with increase in the HF range. During cardiac catheterization, catheters are maneuvered through the radial and brachial artery to the heart. One could imagine that this might influence blood pressure regulation by endothelial derived NO and thus blood pressure variability in the HF range. This might influence a decrease of sympathovagal balance during cardiac catheterization, by increasing HF power.

LVET estimated by the custom analysis in Matlab and LVET estimated by Beatscope differ noticeably. Beatscope LVET is around 0,31, whereas Matlab LVET is around 0,38. As explained in study I, the custom Matlab analysis sometimes has difficulties with proper detection of the dicrotic notch, especially in the non-invasive Nexfin measurements. Since LVET dependent on dicrotic notch detection and the Beatscope detection method is validated, this difference could be explained by false detection of the dicrotic notch by the custom detection method.

Caution should be paid when comparing these non-invasively measured blood pressure to the results of the shock patients in study II, since they are measured with a different method on a different location. Peripheral pressure tends to be higher, since the reflected backwave arrives earlier on peripheral vessel sites, influencing dicrotic notch location and systolic/diastolic pressures. Blood pressure changes can be well compared because the same blood pressure measurement method is used on every timepoint. Though, blood pressure changes measured peripherally might be different from centrally measured blood pressure changes. Peripheral vasoconstriction will influence peripheral pressure differently than central pressures, depending on the patients vasculature.

Since the study cohort was small (n=18) and no patients died during follow-up, the non-invasively measured blood pressure morphology could not be related to patient outcome.

# Conclusion

During and after pPCI, limited changes in blood pressure are seen. Heart rate tends to decrease, together with an increasing LVET and SV. and Diastolic pressure tends to decrease with revascularization. Differences are marginal, but indicate a very little positive effect on hemodynamics during the acute phase of STEMI. Sympathovagal balance does not change significantly over time and during pPCI. From the current small cohort, no clear relation is found between sympathovagal balance and change in TIMI flow after revascularization, but a large decrease in sympathetic activity related LF power might be associated with a vasovagal response after revascularizaiton.

# General discussion

This explorative research provides information about the predictive value of different characteristics of the blood pressure curve for assessment of 30 day mortality and cardiac recovery. From 103 patients in the STEMI patients that were admitted to the ICU, shock index, heart rate, cardiac (power) output, stroke volume, LVET, diastolic AUC, cardiac (power) index and age adjusted shock index are shown to have predictive value in determining outcome, especially prior to revascularization. Classic clinical pressure derived parameters such as systolic, diastolic and mean arterial pressure are of limited value in determining outcome. Pulse pressure and stroke volume variability related parameters could be of interest for determining change in filling-status and preload in CS patients to guide treatment during PCI. Though when regarding PPV, SVV and HRV, no significant differences in relation to outcome is seen in this research. This research also provides insight in cut-off values that are important for these parameters in determining the probability of 30-day mortality.

The combination of the studies in the STEMI patients that have been admitted to the ICU and STEMI patients that were not, shows how different the blood pressure morphology between these groups is. This underlines the importance of the blood pressure morphology in CS. Another important finding of this research is the limited effect of revascularization in the acute phase. In the STEMI patients of study III, which are in relatively good clinical condition, only some small changes were seen in diastolic and mean arterial pressures. In ICU population of study II, standard deviations for parameter differences with revascularization were larger and no significant differences have been found at all. This shows that in patients that are in a bad condition, revascularization has a very limited or very unpredictable effect on haemodynamics in the acute phase. Some patients collaps after revascularization or receive high amounts of introtropics, resulting in the higher standard deviations of changes with revascularization and making interpretation difficult. Also, comparison of the results of both patient groups should be done with caution, since both are measured with different blood pressure measurement techniques.

Dicrotic -and anacrotic notch related parameters were regarded unreliable because of the results of study I. This large variation is thought to result from poor detection with the automatic algorithm. The dicrotic notch could be of additive value when analyzing the predictive value of the blood pressure curve morphology in cardiogenic shock patients.

Assessment of sympathovagal balance did not show a clear relation with TIMI flow before pPCI. This parameter is interesting to investigate with respect to the behavior of the vasculature. Though, it is a difficult parameter to assess in critical and acute situations, where quick assessment of haemodynamic stability is important. Sympathovagal balance would be interesting to assess during treatment in the ICU and for example effects of administered medication.

# General conclusion

The morphology of the blood pressure curve of cardiogenic shock patients not surviving hospital admission, measured before revascularization, differs from survivors. Even a larger difference is seen between patient groups that show cardiac recovery and no-cardiac recovery. Shock index, LVET, cardiac (power) output, stroke volume, diastolic AUC, cardiac (power) index and age adjusted shock index are shown to have predictive value in determining outcome in CS.

## Future recommendations

To improve the findings of this thesis, more patients should be included as well as in the cardiogenic shock cohort as in the stable STEMI patient cohort. The strength and reliability of multivariate analysis will be improved as well with a bigger cohort. Since all investigated parameters come from the same measured blood pressure curve, they are somehow related to each other. Though, this research has shown that the correlation between parameter does differ, making some parameters more appropriate to be combined in multivariate analysis than others.

A complete and proper cardiogenic shock grading will not only consist of parameters derived from the blood pressure curve, but also other clinical parameters that provide information about hemodynamic function, such as blood lactate levels, peripheral resistance and brain perfusion. During treatment of AMI with pPCI, quick assessment of cardiac function is important to make decisions on treatment with i.e. mechanical circulatory support on time. This will be a challenge and the blood pressure curve is easy and quick to assess.

Some more research is done before on some of the parameters that were identified as useful for assessment of outcome and cardiac function, such as LVET, shock index and CPO. More research on with greater clinical trials should be done on these parameters. Some of these parameters should be used in real-time in cardiac catheterization labs to assess (changes in) hemodynamic function, in addition to systolic and diastolic pressure, since multiple studies indicate that parameters such as shock index and LVET are of greater predictive value than the classic pressure derived parameters.

Also, more non-invasive blood pressure measurements should be done on CS patients to evaluate the value of blood pressure measurements measured peripherally. Also, a transfer function could be made to compare and use results from invasive blood pressure measurements with non-invasive blood pressure measurements. It would be of interest to not only measure during PCI, but also have continuous blood pressure measurements in the ICU.

As depicted before, the dicrotic notch is regarded unreliable with the detection method that is currently used. With a proper and validated detection method for the dicrotic notch, the dicrotic notch related parameters could be investigated in future for the assessment of outcome in CS patients.

Pulse pressure -and stroke volume variation and heart rate variability seem to show some differences between patients groups, though not significant. For proper assessment of these parameters, the respiratory cycle should be measured simultaneously. These parameters have already shown to be of value in assessment of volume responsiveness and could be of interest to track changes in hemodynamics during treatment and recovery of AMI. More research with more patients and decent respiratory measurements should be performed to investigate the predictive value of these parameters.

Another method that would be very interesting to use for the characterization of the morphology of the blood pressure curve is machine learning. Machine learning is a statistical method that is capable of recognizing patterns in signals.

# References


1. Michard F, Lopes MR, Auler J-OC. Pulse pressure variation: beyond the fluid management of patients with shock. *Critical Care.* 2007;11(3):131.
2. Shock C. Current Concepts and Improving Outcomes. Hochman. *Harmony R Reynolds and Judith S sl: Circulation, Vols.* 2008;117:686-697.
3. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *The Lancet.* 2003;361(9351):13-20.
4. Keeley EC, Grines CL. Primary coronary intervention for acute myocardial infarction. *Jama.* 2004;291(6):736-739.
5. Babaev A, Frederick PD, Pasta DJ, et al. Trends in management and outcomes of patients with acute myocardial infarction complicated by cardiogenic shock. *Jama.* 2005;294(4):448-454.
6. Goldberg RJ, Gore JM, Alpert JS, et al. Cardiogenic shock after acute myocardial infarction: incidence and mortality from a community-wide perspective, 1975 to 1988. *New England Journal of Medicine.* 1991;325(16):1117-1122.
7. Holmes DR, Bates ER, Kleiman NS, et al. Contemporary reperfusion therapy for cardiogenic shock: the GUSTO-I trial experience. *Journal of the American College of Cardiology.* 1995;26(3):668-674.
8. Jacobs AK, French JK, Col J, et al. Cardiogenic shock with non-ST-segment elevation myocardial infarction: a report from the SHOCK Trial Registry. *Journal of the American College of Cardiology.* 2000;36(3):1091-1096.
9. Kohsaka S, Menon V, Lowe AM, et al. Systemic inflammatory response syndrome after acute myocardial infarction complicated by cardiogenic shock. *Archives of internal medicine.* 2005;165(14):1643-1650.
10. Menon V, Fincke R. Cardiogenic shock: a summary of the randomized SHOCK trial. *Congestive Heart Failure.* 2003;9(1):35-39.
11. Hollenberg SM, Kavinsky CJ, Parrillo JE. Cardiogenic shock. *Annals of internal medicine.* 1999;131(1):47-59.
12. De Hert SG, Robert D, Cromheecke S, Michard F, Nijs J, Rodrigus IE. Evaluation of left ventricular function in anesthetized patients using femoral artery dP/dt(max). *J Cardiothorac Vasc Anesth.* 2006;20(3):325-330.
13. Gibbs N, Gardner R. Dynamics of invasive pressure monitoring systems: clinical and laboratory evaluation. *Heart & lung: the journal of critical care.* 1988;17(1):43-51.
14. Henneman EA, Henneman PL. Intricacies of blood pressure measurement: reexamining the rituals. *Heart & lung: the journal of critical care.* 1989;18(3):263-271.
15. Hirschfeld S, Liebman J, Borkat G, Bormuth C. Intracardiac pressure-sound correlates of echographic aortic valve closure. *Circulation.* 1977;55(4):602-604.
16. Westerhof BE, Westerhof N. Magnitude and return time of the reflected wave: the effects of large artery stiffness and aortic geometry. *J Hypertens.* 2012;30(5):932-939.
17. Murgo JP, Westerhof N, Giolma JP, Altobelli SA. Aortic input impedance in normal man: relationship to pressure wave forms. *Circulation.* 1980;62(1):105-116.
18. Bogert L, Wesseling K, Schraa O, et al. Pulse contour cardiac output derived from non-invasive arterial pressure in cardiovascular disease. *Anaesthesia.* 2010;65(11):1119-1125.
19. Wesseling K. Finapres, continuous noninvasive finger arterial pressure based on the method of Penaz. In: *Blood pressure measurements.* Springer; 1990:161-172.

20. Spyridopoulos I, Noman A, Ahmed JM, et al. Shock-index as a novel predictor of long-term outcome following primary percutaneous coronary intervention. *European Heart Journal: Acute Cardiovascular Care.* 2015;4(3):270-277.
21. Jeger RV, Lowe AM, Buller CE, et al. Hemodynamic parameters are prognostically important in cardiogenic shock but similar following early revascularization or initial medical stabilization: a report from the SHOCK Trial. *Chest.* 2007;132(6):1794-1803.
22. Fincke R, Hochman JS, Lowe AM, et al. Cardiac power is the strongest hemodynamic correlate of mortality in cardiogenic shock: a report from the SHOCK trial registry. *Journal of the American College of Cardiology.* 2004;44(2):340-348.
23. Levin M, Fischer G, Lin H-M, McCormick P, Krol M, Reich D. Intraoperative arterial blood pressure lability is associated with improved 30 day survival. *British journal of anaesthesia.* 2015;115(5):716-726.
24. Filipovic M, Jeger R, Probst C, et al. Heart rate variability and cardiac troponin I are incremental and independent predictors of one-year all-cause mortality after major noncardiac surgery in patients at risk of coronary artery disease. *Journal of the American College of Cardiology.* 2003;42(10):1767-1776.
25. Ryan ML, Ogilvie MP, Pereira BM, et al. Heart rate variability is an independent predictor of morbidity and mortality in hemodynamically stable trauma patients. *Journal of Trauma and Acute Care Surgery.* 2011;70(6):1371-1380.
26. Kleiger RE, Miller JP, Bigger JT, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *The American journal of cardiology.* 1987;59(4):256-262.
27. Michard F. Changes in arterial pressure during mechanical ventilation. *The Journal of the American Society of Anesthesiologists.* 2005;103(2):419-428.
28. Michard F, BOUSSAT S, CHEMLA D, et al. Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. *American journal of respiratory and critical care medicine.* 2000;162(1):134-138.
29. Keyl C, Stockinger J, Laule S, Staier K, Schiebeling-Römer J, Wiesenack C. Changes in pulse pressure variability during cardiac resynchronization therapy in mechanically ventilated patients. *Critical Care.* 2007;11(2):R46.
30. Marik PE. Techniques for assessment of intravascular volume in critically ill patients. *Journal of intensive care medicine.* 2009;24(5):329-337.
31. Yang X, Du B. Does pulse pressure variation predict fluid responsiveness in critically ill patients? A systematic review and meta-analysis. *Critical care.* 2014;18(6):650.
32. Marik PE, Cavallazzi R, Vasu T, Hirani A. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. *Critical care medicine.* 2009;37(9):2642-2647.
33. Scully CG, Kramer GC, Strauss DG. Evaluation of heart rate and blood pressure variability as indicators of physiological compensation to hemorrhage before shock. *Shock.* 2015;43(5):463-469.
34. Jiménez RF, Günther B, Torres P. Time-frequency analysis of arterial pressure oscillations in anesthetized dogs: effects of standardized hemorrhages. *Shock.* 2001;15(2):143-150.
35. Stauss HM. Identification of blood pressure control mechanisms by power spectral analysis. *Clinical and experimental pharmacology and physiology.* 2007;34(4):362-368.
36. Palazzolo JA, Estafanous FG, Murray PA. Entropy measures of heart rate variation in conscious dogs. *American Journal of Physiology-Heart and Circulatory Physiology.* 1998;274(4):H1099-H1105.
37. Günther B, Jimenez R, Picarte C. Wavelet analysis of arterial pressure and blood velocity pulsations in the aorta of anesthetized dogs. *Biological research.* 1993;26:391-391.
38. Boudou N, Despas F, Van Rothem J, et al. Direct evidence of sympathetic hyperactivity in patients with vasospastic angina. *American Journal of Cardiovascular Disease.* 2017;7(3):83.

39. de Vecchi A, Clough RE, Gaddum NR, et al. Catheter-induced errors in pressure measurements in vessels: an in-vitro and numerical study. *IEEE Transactions on Biomedical Engineering.* 2014;61(6):1844-1850.
40. Wesselink R. Master's thesis: Blood pressure waveform analysis in cardiogenic shock & acute myocardial infarction. 2016.
41. Esper SA, Pinsky MR. Arterial waveform analysis. *Best Practice & Research Clinical Anaesthesiology.* 2014;28(4):363-380.
42. Gardner RM. Direct blood pressure measurement—dynamic response requirements. *The Journal of the American Society of Anesthesiologists.* 1981;54(3):227-236.
43. Meinsma G, Heida, C, van Putten, MJAM. Advanced Techniques for Signal Analysis. 2015.
44. Grassi P, Nigro LL, Battaglia K, Barone M, Testa F, Berlot G. Pulse pressure variation as a predictor of fluid responsiveness in mechanically ventilated patients with spontaneous breathing activity: a pragmatic observational study. *HSR proceedings in intensive care & cardiovascular anesthesia.* 2013;5(2):98.
45. Weissler AM, Peeler RG, Roehll WH. Relationships between left ventricular ejection time, stroke volume, and heart rate in normal individuals and patients with cardiovascular disease. *American heart journal.* 1961;62(3):367-378.
46. Weissler AM, Harris WS, Schoenfeld CD. Bedside technics for the evaluation of ventricular function in man. *The American journal of cardiology.* 1969;23(4):577-583.
47. Weissler AM, Harris WS, Schoenfeld CD. Systolic time intervals in heart failure in man. *Circulation.* 1968;37(2):149-159.
48. Altman PL, Dittmer DS. *Respiration and circulation.* Federation of American Societies for Experimental Biology Bethesda MD;1971.
49. Hochman JS, Boland J, Sleeper LA, et al. Current spectrum of cardiogenic shock and effect of early revascularization on mortality. *Circulation.* 1995;91(3):873-881.
50. Hasdai D, Holmes DR, Califf RM, et al. Cardiogenic shock complicating acute myocardial infarction: predictors of death. *American heart journal.* 1999;138(1):21-31.
51. Hoffman JI, Buckberg GD. The myocardial oxygen supply: demand index revisited. *Journal of the American Heart Association.* 2014;3(1):e000285.
52. Ross J, Frahm CJ, Braunwald E. Influence of carotid baroreceptors and vasoactive drugs on systemic vascular volume and venous distensibility. *Circulation Research.* 1961;9(1):75-82.
53. Myat A, Patel N, Tehrani S, Banning AP, Redwood SR, Bhatt DL. Percutaneous circulatory assist devices for high-risk coronary intervention. *JACC: Cardiovascular Interventions.* 2015;8(2):229-244.
54. Bonow RO, Mann DL, Zipes DP, Libby P. *Braunwald's Heart Disease E-Book: A Textbook of Cardiovascular Medicine.* Elsevier Health Sciences; 2011.
55. Sanders AB, Ewy GA, Taft TV. Prognostic and therapeutic importance of the aortic diastolic pressure in resuscitation from cardiac arrest. *Critical care medicine.* 1984;12(10):871-873.
56. Segers P, Rietzschel ER, De Buyzere ML, et al. Assessment of pressure wave reflection: getting the timing right! *Physiol Meas.* 2007;28(9):1045-1056.

# Appendix

## Detection method of landmark points from the blood pressure curve

Detection method of landmark points in the blood pressure curve, developed by Wesselink[40]

### Step 1: Beat identification

Individual beats are defined by first detecting systolic pressure, defined as the maximal pressure during one heart-cycle. The 80$^{th}$ percentile is used as a flexible threshold for detection of systole. A local maximum ( $f'(x) = 0$ ) not located in the 80$^{th}$ percentile, calculated over a window of 3.3 s, qualifies for a potential systolic maximum. The window length is chosen so that it contains at least three beats, for which the repetitive variation of the 80$^{th}$ percentile in time does not affect systole detection. If the window length is increased, relatively fast variations in the pressure signal can cause the pressure signal to completely fall under the threshold of the 80$^{th}$ percentile and then systolic maxima are not detected. If the window length is set too short, irregularities and low frequency variations in the signal will influence the 80$^{th}$ percentile too much, potentially exceeding the value of systolic maxima, causing it to not detect a systolic maximum.

If the local maximum is preceded by an upstroke with a high gradient, defined as exceeding the mean of all positive local maxima in the first derivative of the signal, minus 0.2 mmHg/sample, and no other local maxima follow within 0.2 s it is selected as the systolic maximum. However, if other local maxima are present within 0.2 s, the local maximum with the highest pressure value is selected as the systolic maximum.

Next, the diastolic pressure corresponding to each systolic pressure is determined. Diastolic pressure was defined as the lowest point of one heart cycle, preceding a quick increase of pressure. In 1/3 of the systole-systole interval, preceding a systolic maximum, the absolute minimum pressure value is determined. However, if the fist derivative does not exceed a value of 24 mmHg/s within 0.033 s of the location of the absolute minimum, the location of the diastolic pressure is set at the point where the first derivative of the pressure signal exceeds a value of 24 mmHg/s.

In the last step all beats with a beat length that is very different than the mean beat length in the selected section of data are excluded. Therefore all beats shorter than ½ of the mean beat length, and all beats longer than 1.5 times the mean beat length are excluded from analysis.

### Step 2: Determination of landmark points

In the beat identification process, systolic and diastolic markers pressure are identified. Three other landmark points remain, namely the maximal positive systolic pressure (dp/dt max), the dicrotic notch and the anacrotic notch.

***Maximal positive systolic pressure gradient (dp/dt max):***

The point during systolic upstroke where the slope of the pressure signal is maximal. This corresponds to the absolute maximum of the first derivative of the pressure signal (dp/dt) in the interval 'diastole to systole' of one beat. This point is shown in figure , the middle diagram, at t=0.8 s.

***Dicrotic notch:***

The dicrotic notch is determined as the fastest change of direction of the blood pressure signal in the down sloping part of the curve, after the maximal negative slope and before 0.5 times the systolic maximum – diastolic minimum interval. If a local minimum occurs in this interval (f'(x)=0, depicted with the third vertical black line in figure 23), this point is selected as the dicrotic notch. When no local minimum occurs, the first point at which the second derivative is zero, corresponding to a local maximum in the first derivative will be selected as the dicrotic notch, depicted in figure 23 with the fourth vertical black line. If this point is not found, a local minimum in the second derivative is determined and selected as the dicrotic notch.

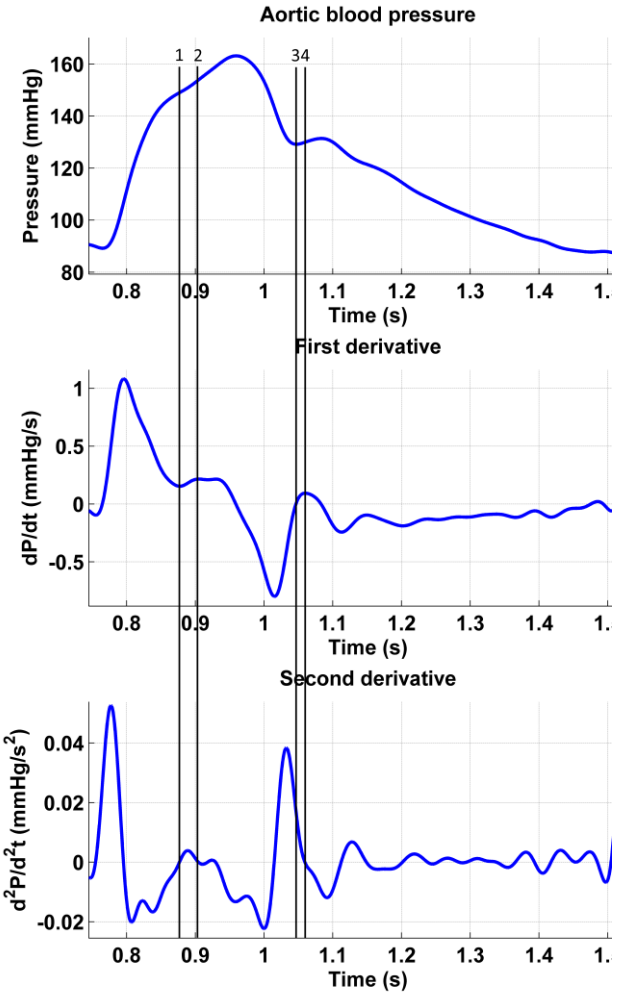



*Figure 23: Determination of anacrotic notch and dicrotic notch using the first and second derivative of the blood pressure signal. Vertical black lines 1 and 2 indicate bending points (f''(x)=0). The anacrotic notch is determined in the middle of these lines. Line 3 indicates the dicrotic notch (f'(x)=0) and line 4 indicates the point of dicrotic notch if no local minimum would have occurred (f''(x)=0)*

***Anacrotic notch:***

The anacrotic notch is defined as an inflection point during systole. An inflection point can only exist between two successive bending points. The inflection point was located in the middle of two second derivative zero crossings as described by Segers et al.[56] Inflection points are determined both before and after the systolic maximum. These two different forms of the anacrotic notch are called an early or a late anacrotic notch, as described in figure . For an early anacrotic notch, the second derivative in between these zero crossings has to reach a threshold of 0.02 mmHg/s$^2$ to be labeled an early anacrotic notch to reduce the false detection of inflection points due to noise or small artifacts. In the downsloping part of the curve no threshold was used due to the more low-frequency characteristics of the late anacrotic notch. If more than one inflection point is detected, the one with the highest gradient in the zero crossing of the second derivative is selected.

Both early and late inflection points are detected. Selection of an early- or late anacrotic notch is based on the amount of detected early and late inflection points compared to the total amount of beats used for analysis. The algorithm used for this selection is depicted in figure . If both early and late inflection points are detected in over 70% of the beats, the anacrotic notch is set at the early inflection point. If inflection points are determined >70% at one side only, this side is chosen. If inflection points are determined in between 70% and 50% at one side of the systolic maximum only, the anacrotic notch is set to that side. If inflection points are determined less than 50% at both sides, the anacrotic notch is marked as not determinable.

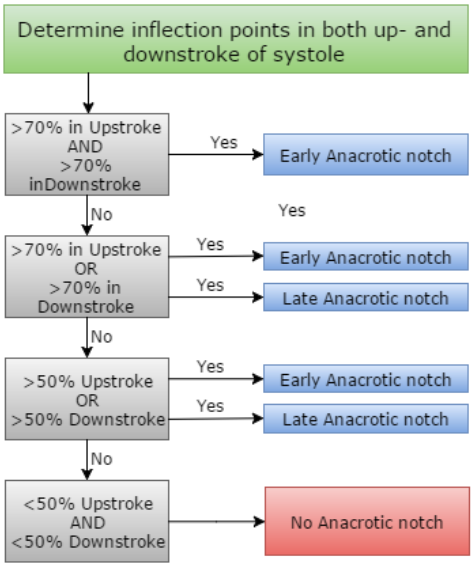



*Figure 24: Algorithm used for determining the early or late anacrotic notch in case both are detected.*

To decrease temporal errors in the determination of points on the second derivative, the pressure signal is linearly interpolated to increase the sampling frequency with a factor 4, for the aortic pressure signals this increases the signal frequency from 240 Hz to 960 Hz. Linear interpolation is chosen to prevent spatial shifting of the signal.

### Step 3: Calculation of parameters

With the 5 markers placed as shown in 2 all other parameters can be calculated.

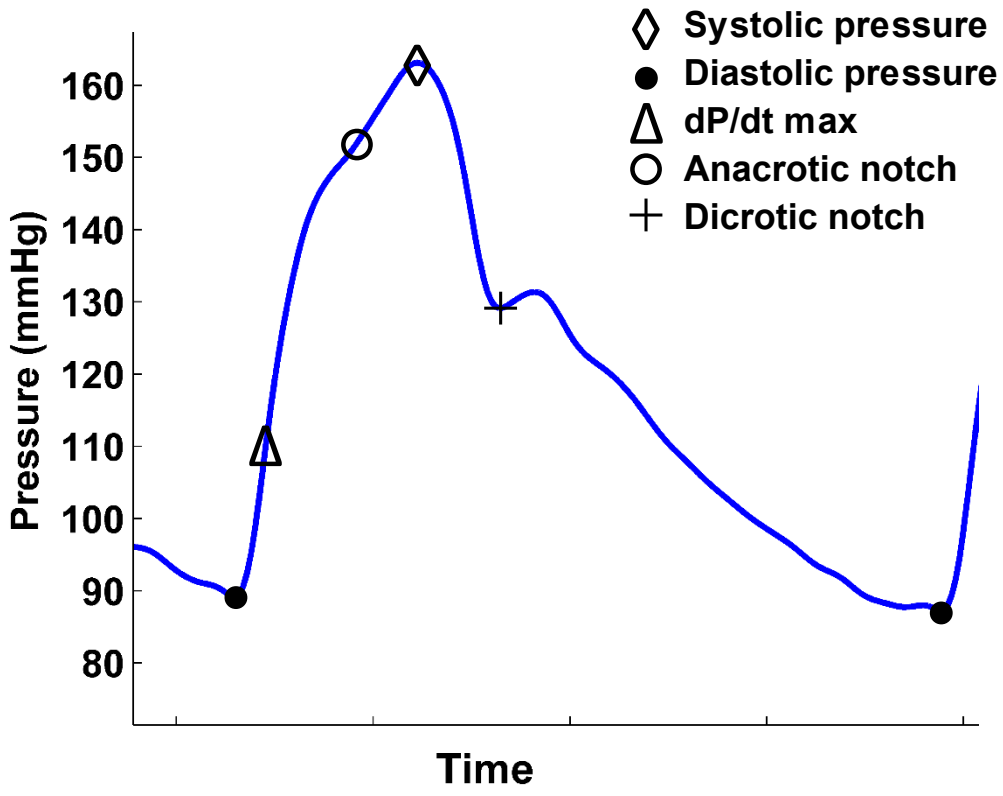



*Figure 25: Blood pressure curve with 5 markers for each beat. From left to right: Diastolic pressure. dp/dt max, anacrotic notch, systolic pressure, dicrotic notch.*

# Results from factor analysis

*Table 13: **Component matrix** for factor analysis based on Principal Component Analysis. All parameters can be reduced and combined to 3 subgroups. Correlation values [-1 , 1] with each subgroup are shown for each parameter. 1 = perfect correlation, -1 = no correlation. Parameters that show strongest correlation with each subgroup are bold.*

| **Blood pressure curve parameter (pre revascularization)** | **Component** | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| ***Shock index*** | **0,884** | 0,131 | -0,507 |
| ***AUC*** | **0,969** | 0,000 | -0,462 |
| ***Systolic AUC*** | **0,670** | 0,341 | -0,635 |
| ***Diastolic AUC*** | **0,930** | -0,247 | -0,208 |
| ***LVET beatscope*** | 0,162 | 0,113 | -0,927 |
| ***LVET custom analysis*** | 0,256 | 0,237 | -0,928 |
| ***Age Adusted shock index*** | -0,783 | -0,370 | **0,404** |
| ***CPO*** | 0,085 | **0,942** | -0,016 |
| ***CO*** | -0,275 | **0,938** | -0,040 |
| ***SV*** | 0,100 | **0,753** | -0,525 |
| ***Downstroke time*** | 0,289 | -0,151 | 0,079 |
| ***Upstroke time*** | **0,532** | 0,057 | -0,818 |
| ***Heart rate*** | -0,531 | 0,381 | **0,681** |
| ***% of total variance explained by component*** | 44% | 22% | 13% |

Extraction Method: Principal Component Analysis. Correlations [-1,1] are shown. Parameters with a correlation > 0.4 are shown in bold.

*Table 14: Correlations[-1,1] and significance values between all parameters with P<0.05 on the univariate analysis in study II. A correlation of 1 represents 100%positive correlation whereas a correlation of 0 represents no correlation. A correlation of -1 repsents 100% negative correlation*

| | | Shock index | AUC | Systolic AUC | Diastolic AUC | LVET custom | LVET Beatscope | AASI | CPO | CO | SV | Downstroke time | Upstroke time | HR | Age | 30 day mortality | Cardiac Recovery |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Shock index | Pearson Correlation | 1 | ,899** | ,725** | ,756** | ,368** | ,509** | -,721** | 0,192 | -0,062 | ,403** | 0,047 | ,620** | -,583** | ,229* | -,210* | ,252* |
| | Sig. (2-tailed) | | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,052 | 0,537 | 0,000 | 0,635 | 0,000 | 0,000 | 0,026 | 0,033 | 0,010 |
| AUC | Pearson Correlation | ,899** | 1 | ,787** | ,859** | ,387** | ,427** | -,781** | 0,170 | -,211* | 0,166 | 0,099 | ,658** | -,569** | 0,131 | -,245* | ,267** |
| | Sig. (2-tailed) | 0,000 | | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,087 | 0,032 | 0,094 | 0,318 | 0,000 | 0,000 | 0,207 | 0,012 | 0,006 |
| Systolic AUC | Pearson Correlation | ,725** | ,787** | 1 | ,360** | ,597** | ,697** | -,700** | ,448** | 0,063 | ,307** | -0,007 | ,667** | -,322** | 0,027 | -,196* | ,310** |
| | Sig. (2-tailed) | 0,000 | 0,000 | | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,524 | 0,002 | 0,947 | 0,000 | 0,001 | 0,795 | 0,047 | 0,001 |
| Diastolic AUC | Pearson Correlation | ,756** | ,859** | ,360** | 1 | 0,086 | 0,064 | -,630** | -0,113 | -,371** | -0,006 | 0,167 | ,439** | -,588** | 0,173 | -,208* | 0,145 |
| | Sig. (2-tailed) | 0,000 | 0,000 | 0,000 | | 0,386 | 0,521 | 0,000 | 0,255 | 0,000 | 0,954 | 0,091 | 0,000 | 0,000 | 0,095 | 0,035 | 0,143 |
| LVET custom | Pearson Correlation | ,368** | ,387** | ,597** | 0,086 | 1 | ,830** | -,313** | 0,059 | 0,054 | ,436** | -0,172 | ,720** | -,612** | 0,051 | -,253** | ,346** |
| | Sig. (2-tailed) | 0,000 | 0,000 | 0,000 | 0,386 | | 0,000 | 0,002 | 0,557 | 0,588 | 0,000 | 0,082 | 0,000 | 0,000 | 0,625 | 0,010 | 0,000 |
| LVET Beatscope | Pearson Correlation | ,509** | ,427** | ,697** | 0,064 | ,830** | 1 | -,386** | 0,123 | 0,118 | ,536** | -0,160 | ,726** | -,567** | 0,081 | -,235* | ,363** |
| | Sig. (2-tailed) | 0,000 | 0,000 | 0,000 | 0,521 | 0,000 | | 0,000 | 0,217 | 0,234 | 0,000 | 0,106 | 0,000 | 0,000 | 0,436 | 0,017 | 0,000 |
| AASI | Pearson Correlation | -,721** | -,781** | -,700** | -,630** | -,313** | -,386** | 1 | -,416** | -0,137 | -,401** | -0,033 | -,458** | ,370** | ,386** | ,393** | -,369** |
| | Sig. (2-tailed) | 0,000 | 0,000 | 0,000 | 0,000 | 0,002 | 0,000 | | 0,000 | 0,189 | 0,000 | 0,756 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 |
| CPO | Pearson Correlation | 0,192 | 0,170 | ,448** | -0,113 | 0,059 | 0,123 | -,416** | 1 | ,824** | ,572** | -0,103 | 0,071 | ,382** | -,358** | -0,111 | ,204* |
| | Sig. (2-tailed) | 0,052 | 0,087 | 0,000 | 0,255 | 0,557 | 0,217 | 0,000 | | 0,000 | 0,000 | 0,303 | 0,478 | 0,000 | 0,000 | 0,266 | 0,039 |
| CO | Pearson Correlation | -0,062 | -,211* | 0,063 | -,371** | 0,054 | 0,118 | -0,137 | ,824** | 1 | ,756** | -0,181 | -0,051 | ,357** | -,342** | -0,124 | ,198* |
| | Sig. (2-tailed) | 0,537 | 0,032 | 0,524 | 0,000 | 0,588 | 0,234 | 0,189 | 0,000 | | 0,000 | 0,067 | 0,610 | 0,000 | 0,001 | 0,212 | 0,045 |
| SV | Pearson Correlation | ,403** | 0,166 | ,307** | -0,006 | ,436** | ,536** | -,401** | ,572** | ,756** | 1 | -,224* | ,357** | -,251* | -0,159 | -,217* | ,283** |
| | Sig. (2-tailed) | 0,000 | 0,094 | 0,002 | 0,954 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | | 0,023 | 0,000 | 0,011 | 0,125 | 0,028 | 0,004 |
| Downstroke time | Pearson Correlation | 0,047 | 0,099 | -0,007 | 0,167 | -0,172 | -0,160 | -0,033 | -0,103 | -0,181 | -,224* | 1 | -0,028 | 0,022 | 0,186 | -0,052 | 0,128 |
| | Sig. (2-tailed) | 0,635 | 0,318 | 0,947 | 0,091 | 0,082 | 0,106 | 0,756 | 0,303 | 0,067 | 0,023 | | 0,782 | 0,829 | 0,073 | 0,599 | 0,196 |
| Upstroke time | Pearson Correlation | ,620** | ,658** | ,667** | ,439** | ,720** | ,726** | -,458** | 0,071 | -0,051 | ,357** | -0,028 | 1 | -,631** | ,225* | -,285** | ,292** |
| | Sig. (2-tailed) | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,478 | 0,610 | 0,000 | 0,782 | | 0,000 | 0,029 | 0,004 | 0,003 |
| HR | Pearson Correlation | -,583** | -,569** | -,322** | -,588** | -,612** | -,567** | ,370** | ,382** | ,357** | -,251* | 0,022 | -,631** | 1 | -,266** | ,215* | -,225* |
| | Sig. (2-tailed) | 0,000 | 0,000 | 0,001 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,011 | 0,829 | 0,000 | | 0,010 | 0,029 | 0,022 |
| Age | Pearson Correlation | ,229* | 0,131 | 0,027 | 0,173 | 0,051 | 0,081 | ,386** | -,358** | -,342** | -0,159 | 0,186 | ,225* | -,266** | 1 | 0,171 | -0,085 |
| | Sig. (2-tailed) | 0,026 | 0,207 | 0,795 | 0,095 | 0,625 | 0,436 | 0,000 | 0,000 | 0,001 | 0,125 | 0,073 | 0,029 | 0,010 | | 0,099 | 0,417 |
| 30 day mortality | Pearson Correlation | -,210* | -,245* | -,196* | -,208* | -,253** | -,235* | ,393** | -0,111 | -0,124 | -,217* | -0,052 | -,285** | ,215* | 0,171 | 1 | -,654** |
| | Sig. (2-tailed) | 0,033 | 0,012 | 0,047 | 0,035 | 0,010 | 0,017 | 0,000 | 0,266 | 0,212 | 0,028 | 0,599 | 0,004 | 0,029 | 0,099 | | 0,000 |
| Cardiac recovery | Pearson Correlation | ,252* | ,267** | ,310** | 0,145 | ,346** | ,363** | -,369** | ,204* | ,198* | ,283** | 0,128 | ,292** | -,225* | -0,085 | -,654** | 1 |
| | Sig. (2-tailed) | 0,010 | 0,006 | 0,001 | 0,143 | 0,000 | 0,000 | 0,000 | 0,039 | 0,045 | 0,004 | 0,196 | 0,003 | 0,022 | 0,417 | 0,000 | |

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

*Table 15: Results for difference between prior -and post revascularization*

| | No survival no cardiac recovery | | No survival cardiac recovery | | Survival | | p-values | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | value | n | value | n | value | Between groups | Survival vs non-survival | Cardiac recovery vs no cardiac recovery |
| **Pressure derived variables** | | | | | | | | | |
| Systolic pressure (mmHg) | 15 | -1 ± 29 | 17 | 3 ± 30 | 59 | 4 ± 20 | ns | ns | ns |
| Diastolic pressure (mmHg) | 15 | 0 ± 20 | 17 | 3 ± 13 | 59 | 3 ± 14 | ns | ns | ns |
| MAP (mmHg) | 15 | 0 ± 22 | 17 | 3 ± 19 | 59 | 3 ± 15 | ns | ns | ns |
| Pulse pressure (mmHg) | 15 | -1 ± 15 | 17 | 0 ± 18 | 59 | 1 ± 12 | ns | ns | ns |
| **Time derived variables** | | | | | | | | | |
| t dp/dt max (s) | 15 | -1.3 ± 3.4 | 17 | 0.0 ± 1.1 | 59 | -0.4 ± 2.3 | ns | ns | ns |
| t upstroke (s) | 15 | 0.006 ± 0.056 | 17 | 0.016 ± 0.039 | 59 | 0.007 ± 0.054 | ns | ns | ns |
| t downstroke (s) | 15 | 0.124 [0.093 - 0.163] | 17 | 0.149 [0.100 - 0.176] | 59 | 0.136 [0.096 -0.185] | ns | ns | ns |
| Heart rate (bpm) | 15 | -1 [-7 - 14] | 17 | -1 [-17 - 5] | 59 | -6 [-13 - 3] | ns | 0.046 | ns |
| Duration systole(LVET) (s) | 15 | 0.025 ± 0.053 | 17 | 0.008 ± 0.065 | 59 | 0.005 ± 0.052 | ns | ns | ns |
| relative t upstroke | 15 | -0.001 ± 0.083 | 17 | 0.023 ± 0.058 | 59 | 0.007 ± 0.079 | ns | ns | ns |
| relative t dp/dt max | 15 | -0.008 [-0.103 - 0.021] | 17 | 0.003 [-0.160 - 0.027] | 59 | 0.001 [-0.020 - 0.023] | ns | ns | ns |
| relative LVET | 15 | 0.017 ± 0.096 | 17 | -0.025 ± 0.096 | 59 | -0.026 ± 0.084 | ns | ns | ns |
| **Slopes** | | | | | | | | | |
| dp/dt max (mmHg / s) | 15 | -19 [-235 - 92] | 17 | 8 [-59 - 102] | 59 | 9 [-114 - 140] | ns | ns | ns |
| dp/dt diastole - systolic max (mmHg / s) | 15 | 4 [-9 - 20] | 17 | -2 [-12 - 9] | 59 | 2 [-8 - 12] | ns | ns | ns |
| dp/dt systolic max - diastole (mmHg / s) | 15 | 4 [9 - 20] | 17 | -2 [-12 - 9] | 59 | 2 [-8 - 12] | ns | ns | ns |
| **Areas** | | | | | | | | | |
| Absolute AUC (mmHg.s) | 15 | 883 ± 2572 | 17 | 1351 ± 3724 | 63 | 1247 ± 2874 | ns | ns | ns |
| Absolute systolic AUC (mmHg.s) | 15 | 429 ± 1309 | 17 | 308 ± 2331 | 63 | 289 ± 1646 | ns | ns | ns |
| Absolute diastolic AUC (mmHg.s) | 15 | 428 ± 2093 | 17 | 1030 ± 2443 | 63 | 946 ± 2108 | ns | ns | ns |
| **Indexes** | | | | | | | | | |
| Absolute Myocardial oxygen supply/demand ratio | 15 | 0.007 ± 0.520 | 17 | 0.052 ± 0.454 | 63 | 0.094 ± 0.389 | ns | ns | ns |
| Shock index | 15 | 0.05 ± 0.29 | 17 | 0.11 ± 0.37 | 63 | 0.11 ± 0.28 | ns | ns | ns |
| Age adjusted shock index | 15 | 0 ± 21 | 17 | -5 ± 15 | 63 | -13 ± 15 | ns | ns | ns |
| **Variability parameters** | | | | | | | | | |
| Pulse pressure variation | 8 | 2.9 [-2.6 - 21.5] | 16 | 0.1 [-4.7 - 11.0] | 57 | -2.5 [-10.0 - 4.7] | ns | ns | ns |
| Stroke volume variation | 8 | 6.3 [-1.0 - 19.7] | 16 | -0.3 [-5.3 - 8.3] | 57 | -3.5 [-15.3 - 3.6] | 0.083 | 0.053 | 0.053 |
| Heart rate variability | 8 | 3.0 [-0.8 - 17.8] | 16 | -0.5 [-2.8 - 2.5] | 57 | -0.6 [-5.2 - 1.3] | ns | ns | ns |
| **Beatscope derived parameters** | | | | | | | | | |
| BS systolic pressure (mmHg) | 15 | 87 ± 32 | 17 | 3 ± 30 | 63 | 4± 20 | ns | ns | ns |
| BS diastolic pressure (mmHg) | 15 | 0 ± 20 | 17 | 3 ± 13 | 63 | 3 ± 14 | ns | ns | ns |
| BS MAP (mmHg) | 15 | 0 ± 25 | 17 | 3 ± 21 | 63 | 3 ± 16 | ns | ns | ns |
| BS Heart rate (bpm) | 15 | -0.7 [-5.8 - 13.9] | 17 | -0.8 [-5.4 - 6.2] | 63 | -5.6 [-14.6 - 0.2] | ns | 0.049 | ns |
| BS LVET (s) | 15 | 0.006 ± 0.071 | 17 | -0.001 ± 0.059 | 63 | 0.002 ± 0.063 | ns | ns | ns |
| BS Stroke Volume (ml) | 15 | -5.0 ± 18.0 | 17 | -2.0 ± 15.0 | 63 | -3.0 ± 18.0 | ns | ns | ns |
| BS Cardiac output (L/min) | 15 | -0.32 ± 1.64 | 17 | 0.12 ± 1.13 | 63 | 0.60 ± 1.74 | ns | ns | ns |
| BS Systemic vascular resistance (dynes.s/cm5) | 15 | 0 [-1 - 169] | 17 | 0 [-1 - 176] | 63 | 0 [-1 - 246] | ns | ns | ns |
| Cardiac Power Output (mmHg.L/min) | 15 | 0.01 ± 0.40 | 17 | 0.02 ± 0.41 | 63 | 0.02 ± 39 | ns | ns | ns |

Values are presented as mean ± standard deviation or as median [IQR].

# Informed consent letters

**Study I**

**Patiënten informatie brief:**

---

**Bloeddruk analyse tijdens procedure op hartkatheterisatiekamer**

---

Geachte mevrouw, meneer,

U zal in het AMC op de afdeling cardiologie een onderzoek of behandeling krijgen op de hart-katheterisatiekamer. Tijdens dit onderzoek wordt uw bloeddruk gemeten in uw hart en met een bloeddrukmanchet om de vinger. Wij willen u vragen om deel te nemen aan een medisch-wetenschappelijk onderzoek wat zich richt op het vergelijken van de bloeddruk die in het hart wordt gemeten en de bloeddruk die aan de vinger wordt gemeten.

Informatie over het onderzoek kunt u rustig nalezen in deze patiënten informatie brief. Mocht u na het onderzoek of de behandeling nog vragen hebben dan kunt u altijd contact opnemen met een van de onderzoekers of onderzoeksartsen. Aan het eind van deze informatie brief vind u de namen en telefoonnummers van deze personen. Meer informatie over medisch wetenschappelijk onderzoek kunt u vinden in de Algemene Brochure Medisch-wetenschappelijk onderzoek van het ministerie van Volksgezondheid, Welzijn en Sport.

**Verslaglegging**
Uw privacy zal altijd gewaarborgd blijven. De bij het onderzoek verkregen meetgegevens zullen onder een codenummer worden opgeslagen, slechts met behulp van een codesleutel kan de identiteit van de deelnemende patiënten worden achterhaald. Die codesleutel is alleen toegankelijk voor de onderzoekers en, als controle van het onderzoek, voor vertegenwoordigers van de Inspectie voor de Gezondheidszorg en door vertegenwoordigers die door het AMC, in haar rol als opdrachtgever, zijn aangewezen om de studie te controleren. Uw gegevens worden na afloop van het onderzoek nog 20 jaar in het AMC bewaard. De resultaten van de studie zullen worden gepubliceerd in wetenschappelijke vakbladen, maar uw identiteit zal daaruit niet te herleiden zijn. Indien bij het onderzoek voor u relevante bevindingen worden gedaan zullen wij u daarover informeren. In dat geval, en alleen wanneer u daartegen geen bezwaar heeft, ontvangt uw huisarts van ons een brief met deze informatie.

**Vrijwilligheid van deelname**
U bent geheel vrij om al of niet aan dit onderzoek mee te doen. Daarnaast hebt u altijd het recht om zonder opgave van redenen af te zien van verdere deelname aan het onderzoek. Een beslissing om uw medewerking te beëindigen zal geen nadelige gevolgen hebben op de zorg en aandacht waarop u in ons ziekenhuis recht hebt.

**Wat zijn de voor- en nadelen van deelname aan dit onderzoek**
Het meedoen aan dit onderzoek is zonder risico. Tijdens de bloeddrukmeting kan er een kloppend gevoel in de vinger optreden, dit kan als onprettig worden ervaren.

**Verzekering**
Aangezien aan deelname aan deze studie geen risico's verbonden zijn, heeft de Medisch Ethische Commissie ontheffing verleend van de verplichting voor de deelnemers een speciale schadeverzekering af te sluiten.

**Nadere informatie**
Voor nadere informatie kunt u altijd contact opnemen met de initiatiefnemers van dit onderzoek: S. Dulger, stagiair onderzoeker (tel. 020-56 62 893) of D.M. Ouweneel, onderzoeker (tel. 020-56 66 603).

**Uw handtekening**
Als u besluit mee te werken, dan willen wij u vragen dit formulier te ondertekenen.
Hiermee bevestigt u uw voornemen om aan het onderzoek mee te werken.

**Toestemmingsformulier voor het onderzoek: 'Bloeddruk tijdens procedure op hartkatheterisatiekamer'**

- Ik heb de informatiebrief voor de proefpersoon gelezen en begrepen. Ik kon aanvullende vragen stellen en mijn vragen zijn naar tevredenheid beantwoord.

- Ik heb genoeg bedenktijd gehad om te beslissen over mijn deelname aan de studie.

- Ik weet dat mijn deelname helemaal vrijwillig is. Ik weet dat ik op ieder moment mijn toestemming, zonder opgaaf van reden, kan intrekken.

- Ik geef toestemming om mijn medische gegevens op te vragen bij mijn huisarts of cardioloog indien dit voor het onderzoek noodzakelijk is.

- Ik ga akkoord met het anoniem opslaan van de verkregen gegevens en ben me bewust van het feit dat mijn identiteit enkel te achterhalen is door de onderzoekers en, als controle van het onderzoek, door vertegenwoordigers van de Inspectie voor de Gezondheidszorg en door vertegenwoordigers die door het AMC, in haar rol als opdrachtgever, zijn aangewezen om de studie te controleren.

- Ik geef toestemming om mijn gegevens nog maximaal 20 jaar na afloop van dit onderzoek te bewaren.

- Hierbij verklaar ik dat ik bereid ben deel te nemen aan bovengenoemd onderzoek.

| Naam van de patiënt: | |
|---|---|
| Handtekening: | Datum: |

----------(in te vullen door de onderzoeker) ----------

Ik verklaar hierbij dat ik deze proefpersoon volledig heb geïnformeerd over het genoemde onderzoek.
Als er tijdens het onderzoek informatie bekend wordt die de toestemming van de proefpersoon zou kunnen beïnvloeden, dan breng ik hem/haar daarvan tijdig op de hoogte.

| Naam van de onderzoeker: | |
|---|---|
| Handtekening: | Datum: |

**Study III**

## Patiënten informatie brief:

# Bloeddruk tijdens en na een hartinfarct

Geachte mevrouw, meneer,

U hebt in het AMC op de afdeling cardiologie een dotterbehandeling ondergaan na een acuut hartinfarct. Tijdens deze dotterbehandeling is uw bloeddruk gemeten met een bloeddrukmanchet om de vinger. Wij willen u vragen om deel te nemen aan een medisch-wetenschappelijk onderzoek wat zich richt op veranderingen in de bloeddruk tijdens en na deze dotterbehandeling. Wij zullen u uitgebreid informeren over dit onderzoek. U kunt deze informatie ook nog rustig nalezen in deze patiënten informatie brief. Mocht u daarna nog vragen hebben dan kunt u altijd contact opnemen met een van de onderzoekers of onderzoeksartsen. Aan het eind van deze informatie brief vind u de namen en telefoonnummers van deze personen. Meer informatie over medisch wetenschappelijk onderzoek kunt u vinden in de Algemene Brochure Medisch-wetenschappelijk onderzoek van het ministerie van Volksgezondheid, Welzijn en Sport.

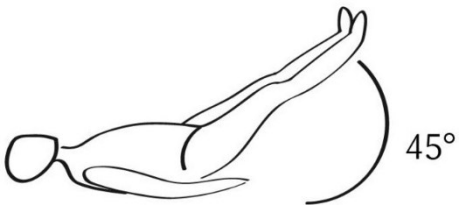
**Onderzoek**
Het doel van dit onderzoek is om veranderingen in de bloeddruk waar te nemen tijdens de dotterbehandeling. Hierbij zullen we onderzoeken of veranderingen in de vorm van het bloeddruk signaal iets zeggen over de pompfunctie van het hart. Met behulp van dit bloeddruk signaal kan in de toekomst mogelijk een betere inschatting gemaakt worden over de acute conditie van het hart. Tijdens uw dotterbehandeling is de bloeddruk gemeten met een bloeddrukmeter om de vinger. Om veranderingen van de bloeddruk na deze dotterbehandeling te kunnen onderzoeken willen we regelmatig uw bloeddruk meten in de dagen na uw behandeling.

**Hoe wordt het onderzoek uitgevoerd?**
Voor dit onderzoek willen we twee maal per dag uw bloeddruk meten. Deze bloeddrukmeting zal telkens ongeveer een half uur in beslag nemen en hiervoor moet u plat op uw rug liggen. Vanaf het moment dat u plat gaat liggen duurt het ongeveer 10 minuten tot uw lichaam is gewend aan de liggende houding. Daarna zullen we gedurende 10-15 minuten uw bloeddruk meten.

Tijdens een dotterbehandeling wordt de bloeddruk gemeten in de lichaamsslagader. Deze bloeddrukgegevens willen wij gebruiken om ze te vergelijken met de bloeddruk gemeten aan uw vinger.

**Wat betekent meedoen voor u**

Tijdens uw verblijf in het AMC zal tweemaal per dag uw bloeddruk worden gemeten. Een bloeddrukmeting duurt in totaal ongeveer 30 minuten en veroorzaakt geen pijn. Wel kunt u een kloppend gevoel in de vinger krijgen. Dit gevoel verdwijnt direct zodra het bandje wordt losgemaakt. Aan het eind van elke meting tillen wij uw benen op tot uw benen een hoek maken van 45 graden(zie figuur 1). Hierdoor stroomt er kortdurend extra bloed naar het hart, wat zorgt voor verandering in de bloeddruk.




**Figuur 1**

De eerste meting zal plaatsvinden tussen 2 en 4 uur na uw dotterbehandeling. Gedurende de rest van uw verblijf in het AMC zal de bloeddruk elke dag twee keer worden gemeten: een keer in de ochtend en een keer in de middag. Deze metingen zullen worden herhaald tot u uit het ziekenhuis wordt ontslagen.

De laatste bloeddrukmeting zal gepland worden op dezelfde dag dat u een afspraak heeft met uw cardioloog in het AMC. Hiervoor hoeft u dus niet extra naar het ziekenhuis te komen. Voor het maken van een afspraak zal een van de onderzoekers te zijner tijd telefonisch contact met u opnemen.

**Verslaglegging**

Uw privacy zal altijd gewaarborgd blijven. De bij het onderzoek verkregen meetgegevens zullen onder een codenummer worden opgeslagen, slechts met behulp van een codesleutel kan de identiteit van de deelnemende patiënten worden achterhaald. Die codesleutel is alleen toegankelijk voor de onderzoekers en, als controle van het onderzoek, voor vertegenwoordigers van de Inspectie voor de Gezondheidszorg en door vertegenwoordigers die door het AMC, in haar rol als opdrachtgever, zijn aangewezen om de studie te controleren. Uw gegevens worden na afloop van het onderzoek nog 20 jaar in het AMC bewaard. De resultaten van de studie zullen worden gepubliceerd in wetenschappelijke vakbladen, maar uw identiteit zal daaruit niet te herleiden zijn. Indien bij het onderzoek voor u relevante bevindingen worden gedaan zullen wij u daarover informeren. In dat geval, en alleen wanneer u daartegen geen bezwaar heeft, ontvangt uw huisarts van ons een brief met deze informatie.

**Vrijwilligheid van deelname**

U bent geheel vrij om al of niet aan dit onderzoek mee te doen. Daarnaast hebt u altijd het recht om zonder opgave van redenen af te zien van verdere deelname aan het onderzoek. Een beslissing om uw medewerking te beëindigen zal geen nadelige gevolgen hebben op de zorg en aandacht waarop u in ons ziekenhuis recht hebt.

**Wat zijn de voor- en nadelen van deelname aan dit onderzoek**

Het meedoen aan dit onderzoek is zonder risico. Tijdens de bloeddrukmeting kan er een kloppend gevoel in de vinger optreden, dit kan als onprettig worden ervaren.

**Bedenktijd**

Wij adviseren u voldoende tijd te nemen om erover na te denken of u aan dit onderzoek wilt meewerken.

**Verzekering**
Aangezien aan deelname aan deze studie geen risico's verbonden zijn, heeft de Medisch Ethische Commissie ontheffing verleend van de verplichting voor de deelnemers een speciale schadeverzekering af te sluiten.

**Nadere informatie**
Voor nadere informatie kunt u altijd contact opnemen met de initiatiefnemers van dit onderzoek: S. Dulger, stagiair onderzoeker (tel. 020-56 62 893) of D.M. Ouweneel, onderzoeker (tel. 020-56 66 603).

**Uw handtekening**
Als u besluit mee te werken, dan willen wij u vragen dit formulier te ondertekenen.
Hiermee bevestigt u uw voornemen om aan het onderzoek mee te werken.

**Toestemmingsformulier voor het onderzoek: 'Bloeddruk tijdens en na een hartinfarct'**

- Ik heb de informatiebrief voor de proefpersoon gelezen en begrepen. Ik kon aanvullende vragen stellen en mijn vragen zijn naar tevredenheid beantwoord.

- Ik heb genoeg bedenktijd gehad om te beslissen over mijn deelname aan de studie.

- Ik weet dat mijn deelname helemaal vrijwillig is. Ik weet dat ik op ieder moment mijn toestemming, zonder opgaaf van reden, kan intrekken.

- Ik geef toestemming om mijn medische gegevens op te vragen bij mijn huisarts of cardioloog indien dit voor het onderzoek noodzakelijk is.

- Ik ga akkoord met het anoniem opslaan van de verkregen gegevens en ben me bewust van het feit dat mijn identiteit enkel te achterhalen is door de onderzoekers en, als controle van het onderzoek, door vertegenwoordigers van de Inspectie voor de Gezondheidszorg en door vertegenwoordigers die door het AMC, in haar rol als opdrachtgever, zijn aangewezen om de studie te controleren.

- Ik geef toestemming om mijn gegevens nog maximaal 20 jaar na afloop van dit onderzoek te bewaren.

- Hierbij verklaar ik dat ik bereid ben deel te nemen aan bovengenoemd onderzoek.

- Ik geef toestemming om in de toekomst eventueel benaderd te worden (telefonisch of per brief) met het verzoek om aan een vervolgonderzoek deel te nemen.

| Naam van de patiënt: | |
|---|---|
| Handtekening: | Datum: |

----------(in te vullen door de onderzoeker) ----------

Ik verklaar hierbij dat ik deze proefpersoon volledig heb geïnformeerd over het genoemde onderzoek. Als er tijdens het onderzoek informatie bekend wordt die de toestemming van de proefpersoon zou kunnen beïnvloeden, dan breng ik hem/haar daarvan tijdig op de hoogte.

| Naam van de onderzoeker: | |
|---|---|
| Handtekening: | Datum: |