Master's thesis – Technical Medicine

Blood pressure waveform analysis in cardiogenic shock & acute myocardial infarction

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Acronyms

(p)PCI	(primary) Percutaneous coronary intervention
AIx	Augmentation index
AMI	Acute myocardial infarction
AUC	Area under the curve
BMI	Body-mass index
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CI	Cardiac index
CO	Cardiac output
CPO	Cardiac power output
CS	Cardiogenic shock
HR	Heart rate
IABP	Intra-aortic balloon pump
ICU	Intensive care unit
IQR	Interquartile range
LAD	Left anterior descending artery
LM	Left main artery
LVET	Left ventricle ejection time
MAP	Mean arterial pressure
MI	Myocardial infarction
NSTEMI	Non ST-elevation myocardial infarction
OHCA	Out-of-hospital cardiac arrest
PCPW	Pulmonary capillary wedge pressure
PWV	Pulse wave velocity
PWV	Pulse wave velocity
RCA	Right coronary artery
RCx	Ramus circumflexus
RDNP	Relative dicrotic notch pressure
STEMI	ST-segment elevation myocardial Infarction
SV	Stroke volume
SVR	Systemic vascular resistance

Abstract:

Introduction**:** Cardiogenic shock (CS) is the main cause of death in patients with acute myocardial infarction and mortality of patients diagnosed with CS is around 50%. The definition of cardiogenic shock suggests an on/off phenomenon although CS is more likely a gradual disease manifesting in different forms, from mild to severe shock. The arterial pulse is globally recognized as the most fundamental sign of life and is a complex entity determined by the heart and the complete vasculature. We aim to determine an objective grading for cardiogenic shock (CS) based on the morphology of the blood pressure curve.

Method**:** For the purpose of this thesis, a custom blood pressure analysis method is developed calculating pressure, time, slope and area parameters based on the detection of 5 markers in the blood pressure curve: diastolic pressure, dp/dt max, anacrotic notch, systolic pressure and the dicrotic notch. This thesis consists of two studies. In study I, a retrospective cohort study on CS patients aims to identify parameters that differ between outcome groups defined as ‘cardiac death’, ‘no cardiac death’ and ‘survival’. Also the difference in change of blood pressure parameters between the outcome groups is determined. In study II, the change of blood pressure parameters in time and with nitroglycerin is determined in patients with acute myocardial infarction (AMI) treated with primary PCI.

Results**:** In 9 parameters a difference was detected between one of the CS outcome groups. Relative dicrotic notch pressure (RDNP), left-ventricular ejection time (LVET) and absolute systolic area under the curve are significantly different (p=0.014, p= 0.039, p=0.017 resp.) between survivors and non-survivors. The change of these parameters after revascularization is not different for the survivors and non-survivors. The blood pressure curve morphology shows limited change in time in AMI patients. With intracoronary administered nitroglycerin, noninvasively determined RDNP decreases with nearly 50 % while absolute blood pressure values decrease with 10 to 15 percent.

Conclusion**:** ‘RDNP’, ‘LVET’ and ‘absolute systolic AUC’ are identified as potential parameters in predicting outcome of patients with cardiogenic shock.

Dankwoord

Na 7 jaar studeren komt met deze thesis een einde aan mijn studententijd. Gedurende iets meer dan een jaar heb ik met veel plezier onderzoek gedaan op de afdeling cardiologie van het AMC. Het is een onderzoek geworden waarin ik een hoop vrijheid heb gekregen. Door metingen te verrichten bij spoed patiënten op de cathkamer heb ik van dichtbij ervaring op mogen doen met de procedure, de gebruikte technieken en de overwegingen en uitdagingen die een interventiecardioloog tegenkomt. Ik heb ook regelmatig contact gehad met patiënten en hun familie die de gebeurtenis van een hartinfarct vanuit hun perspectief met mij hebben willen delen. Voor hun deelname aan mijn studie wil ik deze mensen graag bedanken.

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Introduction

Cardiogenic shock (CS) is a physiological state with inadequate end-organ perfusion, which is primarily caused by a decreased pumping function of the heart. As a consequence of this reduced pumping capacity of the heart, CS is characterized by a low systolic blood pressure and defined by a systolic blood pressure lower than 90 mmHg. This definition implies that the occurrence of cardiogenic shock is an on/off phenomenon. However, CS is more likely a gradual phenomenon, manifesting in different forms, from mild to severe shock. Currently, there is no classification system to objectively grade CS. Clinical trials aiming to improve therapy have almost all failed to show an improvement in these patients. In the clinical field there is a sense that absence of such a grading in CS could at least partly explain failure of clinical trials.

Ideally, a CS grade would appropriately classify the depth of CS and it is likely that various therapies would be adjusted accordingly. A CS grade can also be the key to success in research, by identifying subgroups in various states rather than the current “one size fits all” CS category and subsequent therapy.

The arterial pulse, globally recognized as the most fundamental sign of life, is a complex phenomenon mainly determined by the heart and the arterial vasculature. In CS the decrease of cardiac performance and consequent decrease of blood pressure causes inadequate perfusion pressure. Blood pressure plays a central role in the definition of cardiogenic shock. Since arterial blood pressure is mainly determined by both heart and vasculature, its components or morphology may have a key role in the search for a cardiogenic shock grading.

The aim of this thesis is to create an objective grading for cardiogenic shock based on the morphology of the blood pressure curve. This thesis consists of two studies. The first and retrospective study aims to explore differences in morphology of the blood pressure curve in patients with cardiogenic shock on admission according to clinical outcome. In the second and prospective study, blood pressure curves of patients suffering acute myocardial infarction (AMI) were analyzed to detect changes of blood pressure parameters in time after revascularization.

The clinical entity of cardiogenic shock

Epidemiology

Patients diagnosed with CS have a mortality of around 50%[1-3]. In the past 20 years, advances in the management of acute myocardial infarction (AMI) resulted in a decrease in the reported overall mortality of AMI[3-5]. Early revascularization with primary percutaneous coronary intervention (pPCI) is one of these major advances. Despite early revascularization overall mortality in patients suffering from CS remains high. The recently reported mortality rates still range from 40 to 50%[4,6,7].

CS complicates 6 - 10% of all patients suffering from AMI[1,2] and is the main cause of death in these patients[8,9]. Standard therapy for AMI consists of pPCI. It is suggested that early revascularization decreases mortality compared to medical therapy[10-12], however evidence is still scarce. It is only shown that the 6 months mortality is improved by early revascularization, which is immediate transfer to an emergency center for emergency angioplasty in order to restore coronary blood flow, compared to initial medical stabilization[5]. Medical stabilization aims to decrease myocardial oxygen demand and/or increase myocardial oxygen supply and decrease thrombus formation through antiplatelet and anticoagulant therapy. Hochmann et al. also reported that patients aged over 75 showed significantly higher mortality with early revascularization, indicating that in this patient category, revascularization might do more harm than good[3]. Therefore, to optimize treatment effects, it is important to define patient categories.

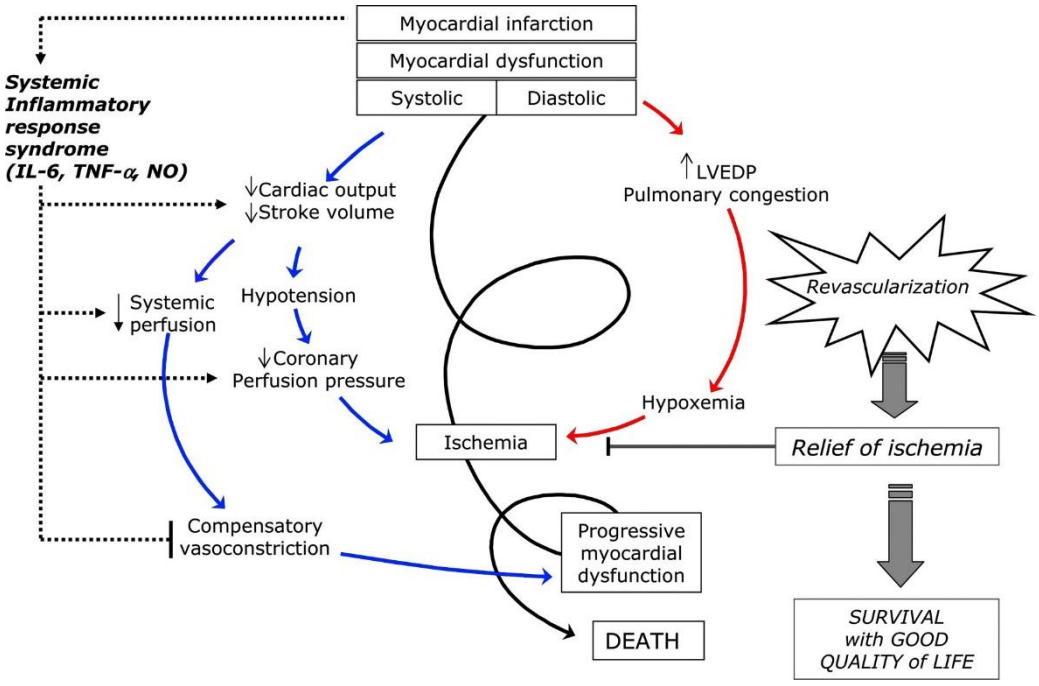


Figure 1. The current concept of cardiogenic shock pathophysiology. (Black) Myocardial injury causes systolic and diastolic dysfunction. A decrease in cardiac output (CO) leads to a decrease in systemic and coronary perfusion. This exacerbates ischemia and causes cell death in the infarct border zone and the remote zone of myocardium. (Blue) Inadequate systemic perfusion triggers reflex vasoconstriction, which is usually insufficient. Systemic inflammation (Dashed lines) may play a role in limiting the peripheral vascular compensatory response and may contribute to myocardial dysfunction. Whether inflammation plays a causal role or is only an epiphenomenon remains unclear. Revascularization leads to relief of ischemia. It has not been possible to demonstrate an increase in CO or LVEF as the mechanism of benefit of revascularization; however, revascularization does significantly increase the likelihood of survival with good quality of life. IL-6 indicates interleukin-6; TNF-α, tumor necrosis factor-α; and LVEDP, LV end-diastolic pressure. After Reynolds et al.[13].

Etiology

Acute myocardial infarction

In AMI, the blood flow is either diminished or fully blocked in one or more coronary arteries. The blood flow to the myocardium is often blocked by an intracoronary thrombus. The myocardium, isolated from oxygen supply, becomes ischemic and necrotic without timely revascularization. Transmural ischemia, the cause of ST-segment elevation, can cause ventricular wall movement disorders which in turn cause deterioration of both systolic and diastolic myocardial performance. This myocardial dysfunction causes a detrimental cascade of progressive myocardial dysfunction as depicted in the black in figure 1, which is the widespread paradigm of CS. Many of the cardiovascular contributions to CS are partly or completely reversible, which may explain the good functional outcome in most survivors[14].

Left ventricular failure

Inadequate end-organ perfusion is the hallmark of CS, which is caused by a decreased pumping function of the heart. Since the heart as a pump is responsible for its own blood supply, a functional impairment can put it in a downward spiral, as depicted in figure 1. In case of myocardial dysfunction caused by myocardial infarction (MI), cardiac output (CO) decreases (figure 1, blue arrows) and the blood pressure drops which causes a decrease in coronary blood flow. Due to this decrease, myocardial ischemia increases, which in turn increases myocardial dysfunction when no intervention is applied that can interrupt this downward spiral.

Vasoconstriction

The decrease in CO caused by ongoing ischemia and systemic hypoperfusion trigger the release of catecholamines, which cause vasoconstriction of the peripheral arterioles. The hallmark of CS, hypoperfusion of the extremities and vital organs is caused by vasoconstriction. Although an increase of peripheral vascular resistance improves coronary blood flow by increasing mean arterial pressure (MAP). This also increases left ventricular afterload, which raises the myocardial workload and oxygen demand, and also the ischemia may increase.

Systemic inflammation

In addition to the myocardial components also other factors may contribute to the manifestation of CS, shown in figure 1. A cascade of factors is released during systemic inflammation. These factors induce vasodilatation, a decrease in diastolic pressure and coronary blood flow. Cytokine level are increased directly after revascularization[15] and tumor necrosis factor-α induces coronary endothelial dysfunction. This can further diminish myocardial oxygen supply[16].

Management of cardiogenic shock

Management of patients with CS consists of early revascularization with pPCI or emergency coronary artery bypass grafting (CABG), and intensive care. Although there is little evidence proving the benefit of early revascularization, it is a widely applied therapy and a class I recommendation in both European and American guidelines[17,18]. Short term mechanical support may be considered, for example the use of the Impella, which actively generates continuous flow (2-5 L/min, dependent on device type) from the left ventricle to the aorta, or extracorporeal membrane oxygenation (ECMO), in which blood from the vena cava or right atrium is oxygenated and pumped into the aorta at flows up to 5 L/min. The use of intra-aortic balloon counterpulsation by means of an intra-aortic balloon pump (IABP), was recently shown to not reduce 30 day mortality, has no long term benefits[19], and is therefore not routinely recommended by the European guidelines on myocardial revascularization. The IABP consists of a cylindrical balloon, placed in the aorta, which is deflated during systole, providing afterload reduction through a vacuum effect, and is inflated during diastole, providing increased coronary flow by creating retrograde flow with inflation of the balloon.

After revascularization, patients are mostly admitted to the intensive care unit (ICU). Treatment on the ICU consists of mechanical ventilation and pharmacological hemodynamic support to maintain a mean arterial pressure (MAP) of >65 mmHg. Until recently, induced hypothermia was applied in these patients, although no large studies assessed therapeutic hypothermia in cardiogenic shock. It was hypothesized that induced hypothermia would improve outcome[20]. Recently a multicenter randomized control trial showed no benefit of induced hypothermia with a target temperature of 33 °C over hypothermia with a target temperature of 33 °C in patients after cardiac arrest[21].

Outcome

As mentioned earlier, mortality of cardiogenic shock is around 50%. The functional outcome of patients surviving CS is very good. Sleeper et al. demonstrated that at one year after hospitalization for cardiogenic shock 83% of the patients discharged alive were in NYHA class I or II[14]. This means that early interventions, if successful, may offer good clinical results in fair clinical condition.

Hemodynamic parameters in cardiogenic shock

Most studies with a focus on hemodynamic parameters in cardiogenic shock use parameters determined during admission on the ICU. In 2004 Finke et al. demonstrated that cardiac power output (CPO) was an independent hemodynamic predictor of in-hospital mortality[22] using data from the SHOCK trial registry. CPO, which is the combination of flow and pressure is calculated as *(MAP * CO) / 451*. In 2007, Jeger et al. investigated differences in hemodynamic parameters between patients with early revascularization and patients with initial medical stabilization in cardiogenic shock, in a secondary analysis with data from the SHOCK trial, as described by Hochmann et al.[5] Stroke volume index (SVI, calculated as *stroke volume / body surface area*) and stroke work index (SWI, calculated as *(MAP – PCWP) * SV * 0.0136 / BSA*) were the most powerful predictors of 30-day mortality[23]. In 2009 Torgesen et al. showed significantly lower cardiac index and cardiac power index (substituting CI for CO in the CPO calculation) in the first 24 hours after ICU admission in non-survivors[24], however this was a retrospective cohort study and is thus considered hypothesis generating. In contrast, in 2003 Lim et al. showed that 45% of all non-survivors in CS died with a normal CI[25]. In 2010, Sleeper et al. determined a cardiogenic shock grading with hemodynamic and non-hemodynamic parameters using data from 872 patients in the SHOCK-study and registry. Anoxic brain damage, end organ hypoperfusion and age were shown to be the most important non-hemodynamic predictors of cardiogenic shock. SWI was identified as the best individual predictor of mortality. In the univariate analysis of this study among others, diastolic and systolic pressure, cardiac index and systemic vascular resistance (SVR) were identified as

significantly different between 30-day survivors and non-survivors. The results were not validated using an independent validation set. In 2013 Rigamonti investigated hemodynamic parameters in the first 24 h after ICU admission and showed that minimum diastolic arterial pressure was independently associated with 28 day-mortality[26].

None of these studies explicitly determines hemodynamic parameters before or during pPCI. Also, hemodynamic parameters, like stroke volume and cardiac output, are not regularly determined during catheterization and therefore not applicable for this study. From all parameters in the blood pressure curve, only systolic & diastolic pressure, MAP and heart rate are currently used in clinical evaluation of the patient. In patients suffering from CS, these are parameters not consistently proven useful in predicting outcome on the ICU.

The limited amount of studies on hemodynamic parameters in CS almost all focus on parameters related to stroke volume and CO determined on the ICU. With this approach a major clinical decision moment is ignored: reperfusion in the catheterization theatre. This is the moment at which the ability to accurately assess the extensiveness or intensity of cardiogenic shock creates the opportunity to adjust and personalize medical care accordingly.

The blood pressure waveform

The arterial pulse is globally recognized as the most fundamental sign of life. 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.

The heart is responsible for the circulation of blood and is thereby the main generator of pressure. The arterial tree with its arteries, arterioles and capillaries is responsible for maintaining the pressure generated by the heart. If the vasomotor tone of these vessels would decrease, vasodilatation will cause a decrease in blood pressure. Also duration of systole, MAP, pulse wave velocity, pulse wave reflection, and stiffness of the arterial vessels influence blood pressure[27]. Blood pressure also depends on the measurement location, with peripherally measured systolic- and pulse pressure exceeding pressure measured at the aortic root. Since all these factors influence blood pressure, do systolic and diastolic pressure provide for enough hemodynamic information about a patient? It is therefore unlikely that a dichotomous definition with a cut-off of 90 mmHg would be a physiological appropriately representation for the complexity of cardiogenic shock. For general purposes these values do, but for more detailed hemodynamic information about a patient, the continuously recorded blood pressure should be analyzed. An example of a continuous measurement is shown in figure 2. This recording can be visually assessed and already provides some hemodynamic information of the patient.

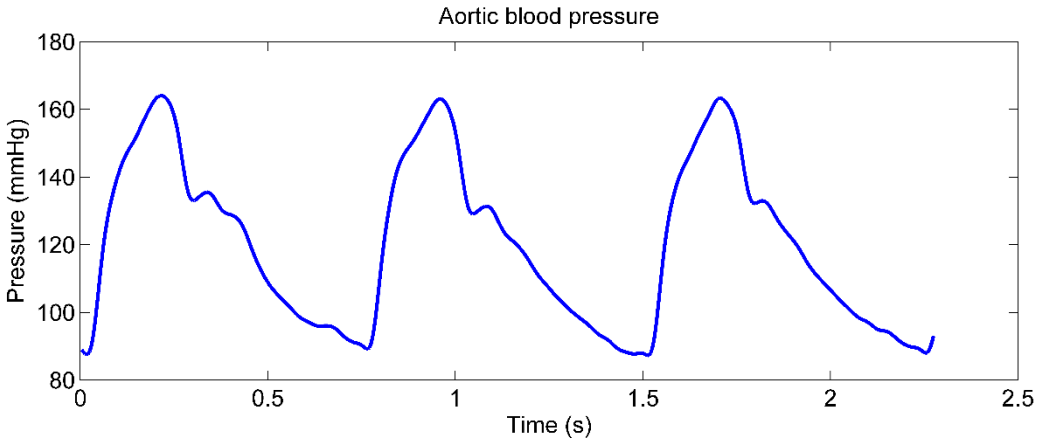


Figure 2. Continuous blood pressure recording measured in the ascending aorta through a cardiac catheter inserted through the radial artery with the proximal opening of the catheter in the ascending aorta, in or near one of the coronary ostia. On visual assessment systolic and diastolic pressure can be determined, just as pulse pressure and heart rate.

The cyclic movement is caused by the regular heart rhythm. The left ventricle (LV) as a pump 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 an increase of arterial pressure, this is seen as a steep rise in pressure in the pressure signal. The point of maximal slope (dp/dt max) is somewhat correlated to left ventricular contractility[28]. The point at which maximal pressure is achieved is the systolic maximum, or systolic pressure. At this point, pressure inside the ventricle still exceeds pressure in the aorta and the ventricle still ejects blood. When pressure inside the ventricle equals the pressure of the aorta, the aortic valve closes, this is seen as a characteristic dip after the systolic maximum[29] (see figure 2) called the dicrotic notch. 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 increase 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[30]. 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[31], which is called the augmentation of pressure. The position and amplitude of the systolic 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 travels through the arterial system, called pulse wave velocity (PWV). PWV is mainly determined by the stiffness of the vessel. So, stiffness of the vessels influences the timing of arrival of the backward running wave at the measurement location, which for this study is the ascending aorta. Besides wave reflection, also the duration of systole influences systolic pressure. With a short duration of systole, the reflected wave will appears 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).

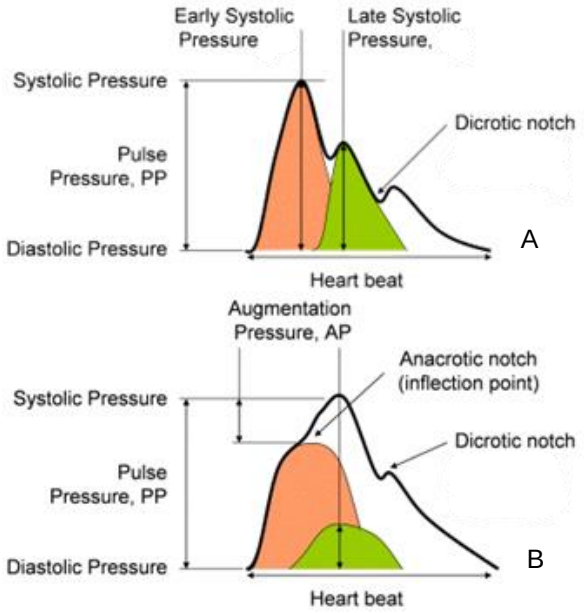


Figure 3. Visualization of augmentation of the aortic pressure waveform. In orange: the forward running pressure wave, in green the backward running pressure wave. In the resulting pressure waveform the backward running wave is superimposed on the forward running wave. In figure A the reflected wave 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.

Blood pressure waveform analysis

Introduction

As mentioned earlier, this thesis consists of two studies. In both studies the same exploratory blood pressure waveform analysis is used. An automatic blood pressure waveform analysis method was developed for these studies. In this chapter, the automated analysis is described.

The waveform analysis is conducted off line using MATLAB (MATLAB R2013 A, The MathWorks Inc., Natick, MA, 2000). A custom, semi-automatic blood pressure analysis is performed on selected parts of the pressure signal. The analysis is performed in 4 steps, which will be described in detail. First, a section of blood pressure signal is (manually) selected. Then, all individual beats are determined, and in each beat, 5 landmarks are determined. Finally, all other parameters are calculating using the 5 landmark points in each beat.

Step 1: Data selection and Preprocessing

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 the it was chosen to select data to a maximum of 30-40 seconds.

Preprocessing of the selected data only consists of low-pass filtering of the signal. A non-causal 25 Hz low pass filter was used to decrease high frequency noise originating from artifacts and from the low spatial resolution of the acquisition system, which is 0.2 mmHg.

Step 2: Beat identification

Individual beats are defined by first detecting systolic pressure, defined as the maximal pressure during one heart-cycle. The 80th percentile is used as a flexible threshold for detection of systole. A local maximum ($f'(x) = 0$) not located in the 80th 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 80th 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 80th 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 80th 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 3: 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 4, 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 4), 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 4 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.

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.[32] 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 3. 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

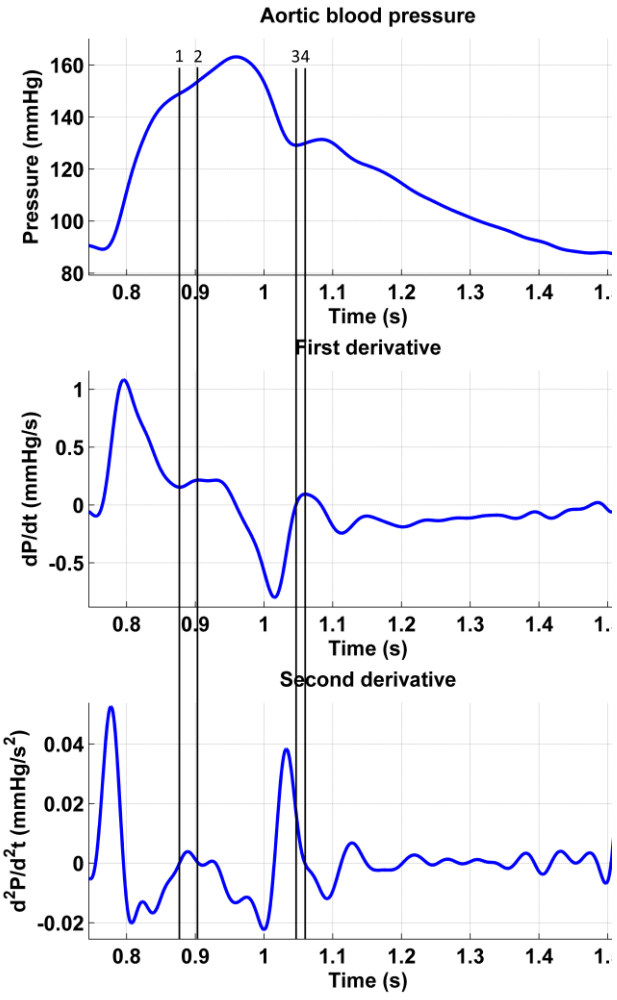


Figure 4: Determination of anacrotic notch and dicrotic notch using the first and second derivative of the blood pressure signal. Vertical black lines 1 and 2 indicate bending points (f''(x)=0). The anacrotic notch is determined in the middle of these lines. Line 3 indicates the dicrotic notch (f'(x)=0)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

anacrotic notch 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 5. 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.

In order 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.

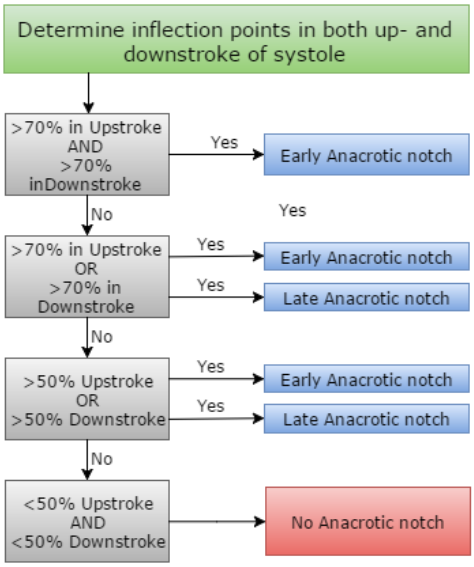


Figure 5: Algorithm used for determining the early or late anacrotic notch in case both are detected.

Step 4: Calculation of parameters

With the 5 markers placed as shown in figure 6 all other parameters can be calculated.

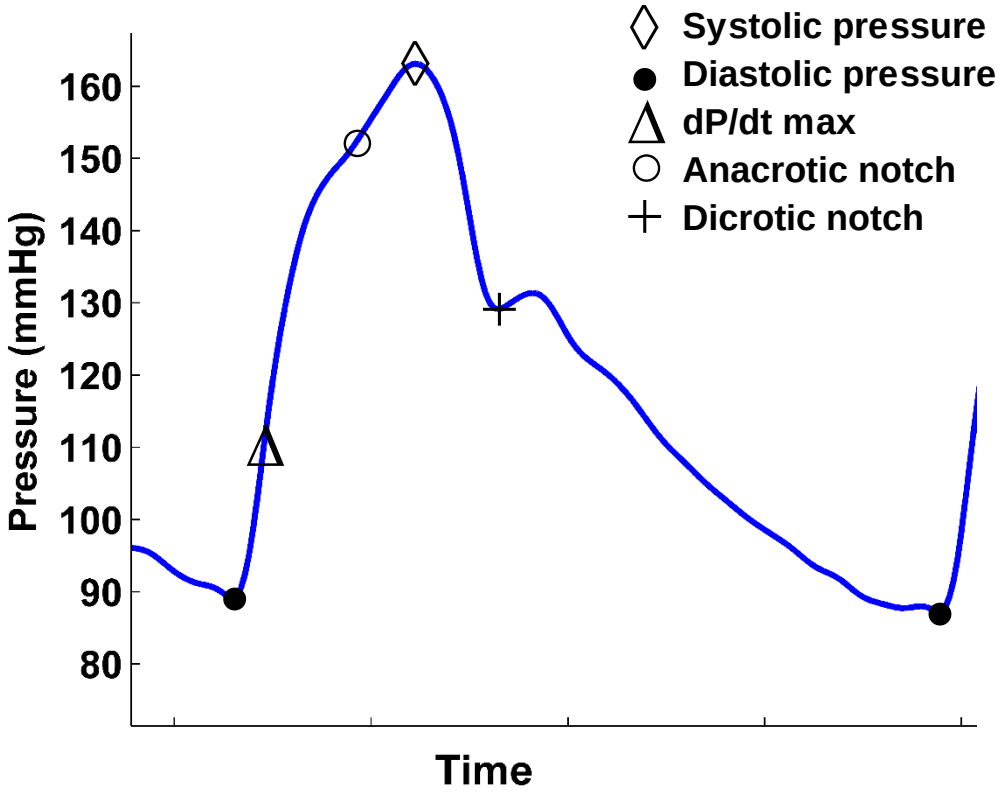


Figure 6: Blood pressure curve with 5 markers for each beat. From left to right: Diastolic pressure. dp/dt max, anacrotic notch, systolic pressure, dicrotic notch.

Table 1: Pressure, time, slope and area parameters
Calculation of pressure, time, slope and area parameters.

Pressure derived parameters (shown in figure 7)	
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
Relative dicrotic notch pressure (RDNP)	$Dicrotic\ notch\ pressure - \ diastolic\ pressure$
Dicrotic notch index	$\frac{Relative\ dicrotic\ notch\ pressure}{Pulse\ pressure} * 100$
Augmentation index	$\frac{Relative\ anacrotic\ notch\ pressure}{Pulse\ pressure} * 100$
Time derived parameters (shown in figure 7)	
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 8 A)	
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 8 A & B)	
Relative AUC	Relative systolic + diastolic AUC
Relative systolic AUC	Shown in figure 8 B
Relative diastolic AUC	Shown in figure 8 B
Absolute AUC	Absolute systolic + diastolic AUC
Absolute systolic AUC	Shown in figure 8 B
Absolute diastolic AUC	Shown in figure 8 B
Relative myocardial oxygen/demand ratio	$\frac{Relative\ diastolic\ AUC}{Relative\ systolic\ AUC}$
Absolute myocardial oxygen/demand ratio	$\frac{Absolute\ diastolic\ AUC}{Absolute\ systolic\ AUC}$

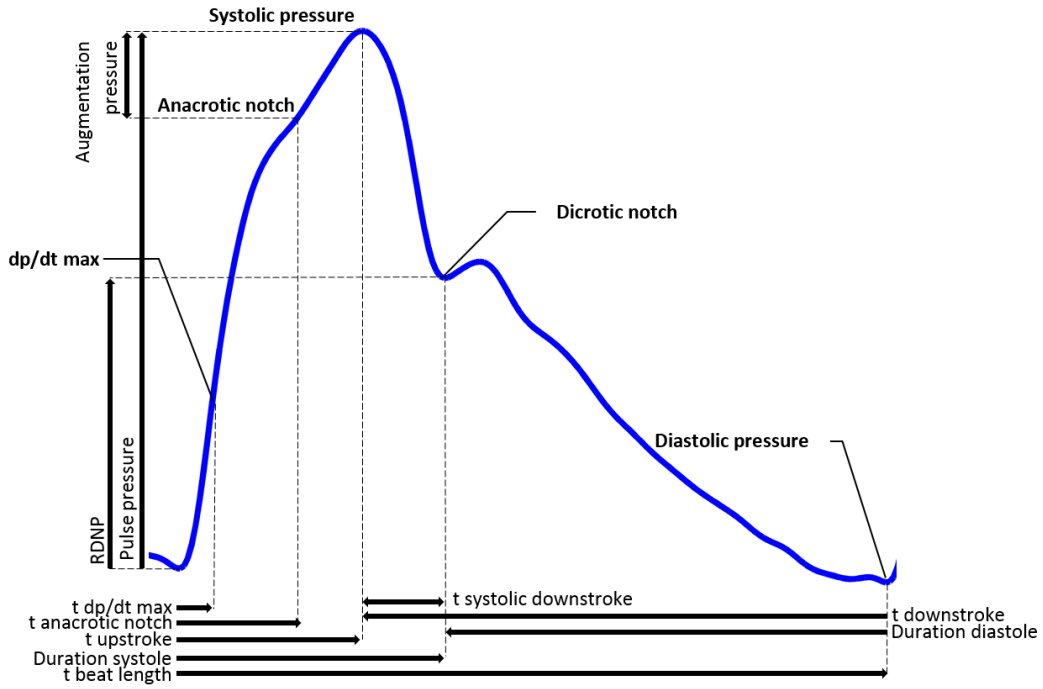


Figure 7: Pressure and time derived parameters

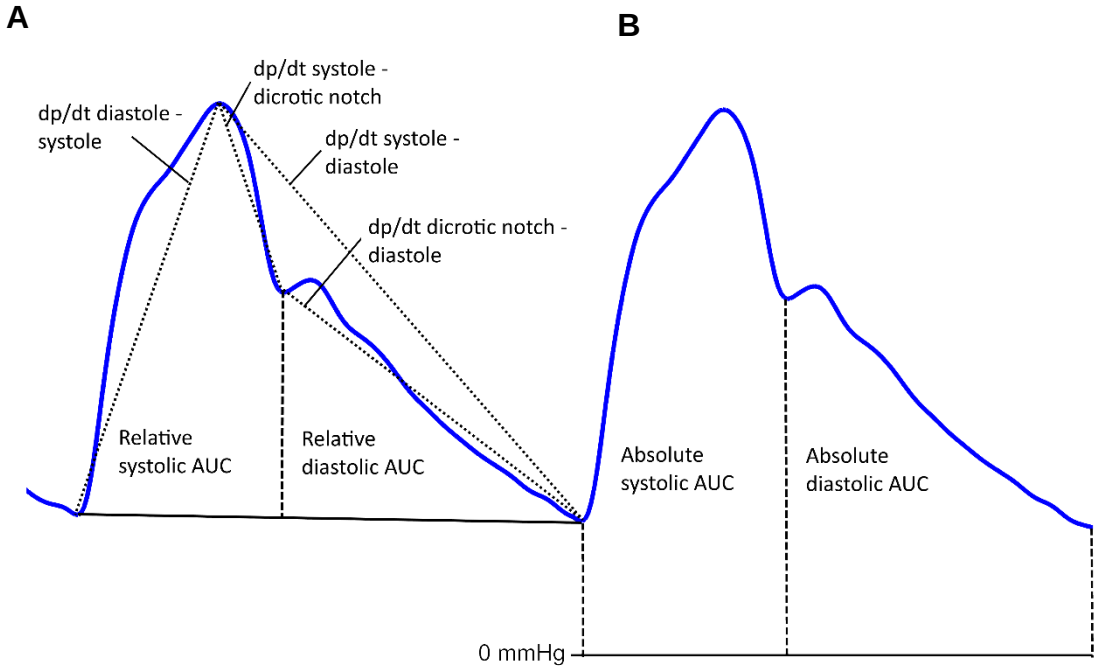


Figure 8: Slopes and areas.
A: Slopes and relative area under the curve. The linear interpolation between both diastoles acts as the lower limit of calculation of AUC. B: Absolute AUC-parameters..
AUC = area under the curve

Beatscope parameters

Hemodynamic parameters are determined using pulse contour analysis provided by Beatscope 1.1a (TNO), which essentially is a software-version of the pulse contour analysis as conducted by the Nexfin (Edwards Lifesciences BMEYE, Amsterdam)[33]. 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, in 'Study II', the algorithm is used to analyze the noninvasively measured blood pressure curve. 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.

Calculation of mean values

Of every blood pressure waveform parameter, the mean value was calculated after discarding 5% of the values of each parameter in order to normalize the data and 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.

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':* $CPO = \frac{MAP*CO}{451}$

Study 1: Aortic blood pressure waveform analysis of cardiogenic shock patients

Introduction

The aim of this retrospective cohort study in patients with cardiogenic shock is to determine if parameters describing the morphology of the blood pressure curve at the beginning of pPCI differ for patients with a different clinical outcome, defined as cardiac death (CD), non-cardiac death (NCD) or survival. Secondly, we determine if the change of parameters from pre,- to post revascularization differs for patients with a different outcome.

Method

Patient selection

In order to select patients suffering from cardiogenic shock, patients were included that were treated for AMI by pPCI and subsequently admitted to the intensive care unit (ICU).

For this retrospective cohort study 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 1 January 2012 to 1 June 2015 were reviewed. Patients were included when successful pPCI was performed for the treatment of AMI with subsequent admission to the ICU. Exclusion criteria consist of: complications during or after pPCI (tamponade, ventricle-septum rupture, severe hemorrhage, papillary muscle rupture), severe comorbidities (sepsis with clear focus, intoxications, transfusion acquired lung injury), the inability to determine cardiac outcome (transfer to another hospital or death within 24 hours) and trauma.

Of the selected patients, blood pressure recordings, procedure logs and intensive care electronical records were collected. ICU data consists of hemodynamic support (vasoactive medication infusion rates, mechanical support), the type of cooling protocol, mechanical ventilation and the need for renal replacement therapy.

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). This signal acquisition system applies no filtering to the blood pressure signal.

Cardiac outcome definition

From a clinical perspective it seems straightforward to compare patients that survive to the patients that do not survive their hospital admission. However, as this is a very complex patient category, it is possible that a patient experiences cardiac recovery but does not survive due to other comorbidities. We aimed to differentiate between patients suffering from severe cardiac impairment with no recovery, and patients showering cardiac recovery that do not survive due to other comorbidities.

Vasoactive medication, such as positive inotropes, which mainly increase myocardial contractility, and catecholamines, which among others influence blood pressure, are used to support the cardiovascular system and maintain adequate cerebral perfusion. This medication is titrated to a patient and situation specific target MAP. As therapy with catecholamines and vasoconstrictors may impair microcirculation and decrease tissue perfusion, its use is restricted to the lowest possible dose and shortest possible duration. For this reason, patients with a relatively good cardiac performance are likely to receive less vasoactive medication compared to patients with greater cardiac impairment. Besides the clinical endpoint of survival, the amount of vasoactive medication is used as a definition of cardiac recovery to distinguish two subgroups in the non-survivor group

Since the goal of this study is determine differences of blood pressure parameters in the three outcome groups, CD, NCD and survival, a definition of cardiac outcome was created. The first group consists of patients surviving hospital admission. These patients are labelled ‘survivors’, which by definition have a good cardiac outcome. The non-survivor group is then divided into two subgroups based on the use of vasoactive medication on the ICU. The first group of non-survivors consists of patients that show cardiac recovery. These patients receive low (< 0.5 mg/h), or decrescendo infusion rates of noradrenalin before the moment of death. These patients are labeled **‘**No cardiac death’ (NCD). Most of these patients suffer from severe post-anoxic encephalopathy with a very bad neurological prognosis, for which treatment ultimately is not continued. The second group of non-survivors consists of patients receiving high (> 0.5 mg/h) and/or crescendo infusion rates of noradrenalin before the moment of death, and are labeled **‘**Cardiac death**’** (CD).

To support the choice of good or bad outcome, infusion rates of vasoactive drugs are determined at 3, 48 and 72 hours after admission to the ICU. Infusion rates at 24 hours are not taken into account due to the 24-hour induced hypothermia-protocol that is used in some patients, which causes hemodynamic instability and therefore higher infusion rates of vasoactive medication.

Negative cardiac outcome was defined as a high, or increasing need for vasoactive support. Rate of administration of vasoactive medication at 3 hours, 48 and 72 hours was registered. During the first 24 hours after out-of-hospital cardiac arrest (OHCA), body temperature was controlled in most patients. Either a therapeutic hypothermia (target core temperature 33 °C) or prevention of hyperthermia (target core temperature 36 °C) protocol was applied in most patients. Since hypothermia induces cardiovascular instability and potentially increases the need for pharmacological vasoactive support, this time point was not taken into account.

Aortic blood pressure data selection

After collection of blood pressure data, the signals were visually inspected to select a part of the signal that could be analyzed. Sections of at least 15 seconds of pressure signal without artifacts were selected from the invasive aortic blood pressure registration both before and after revascularization. The selected data contains the least amount of artifacts and no contrast injections. During these injections, used for fluoroscopic imaging of the coronary arteries, the catheter-system is subjected to pressures of >300 mmHg which causes a major artifact. The heart rhythm needs to be regular and segments with no, or a low level of irregularities (for example ventricular ectopy, heart blocks) and artifacts are preferred. The moment of revascularization was defined as the first balloon inflation or thrombosuction as registered in the catheterization laboratory’s log file. A section before revascularization and a section after revascularization were selected for analysis.

Statistical analysis

For both baseline values and the change of parameters from pre- to post-revascularization the following statistical methods are used:

For all parameters, normality is determined with use of the Shapiro-Wilk-test. To test if the three groups significantly differ for each parameter, an ANOVA analysis is performed for the normal distributed parameters and a Kruskal-Wallis test is performed for not normal distributed parameters. The two subgroups ‘survival vs no survival’ and ‘cardiac recovery vs no cardiac recovery’ are tested using an independent samples T-test for normal distributed parameters and the Mann Whitney U test for not normal distributed parameters. A p-value <0.05 was considered significant.

We expect blood pressure curve morphology to differ between pre- and post-revascularization in these patients. During pPCI many factors can influence the blood pressure curve morphology, for example vasoactive medication, administration of fluids, anesthesia and mechanical ventilation. Therefore we do not test if parameters are different, we test if the change in blood pressure curve morphology parameters is different for the described outcome groups and subgroups.

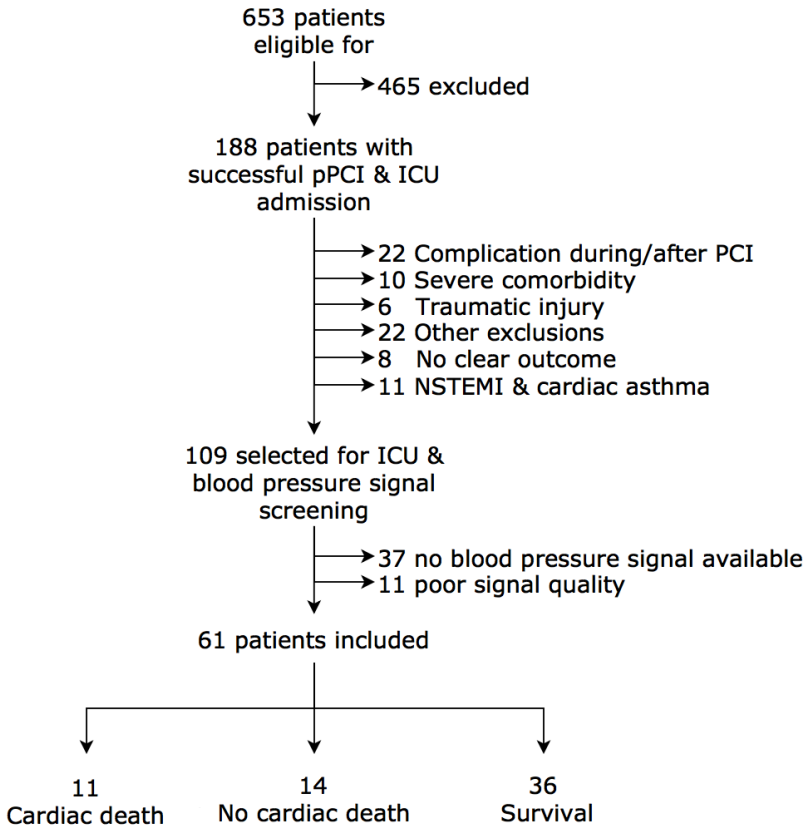
Results

A flow chart showing the exclusions per category is showed in figure 9. A total of 653 patients were identified as eligible for inclusion. Of these 653 patients, 188 patients underwent successful pPCI and were directly transferred to the ICU. Of these 188 patients with successful pPCI and subsequent ICU admission, 22 patients were excluded based on severe complications during or after PCI. These patients suffered of traumatic bleeding, tamponade, ventricular wall rupture, hemorrhagic shock or transfusion acquired lung injury. In the category 'other exclusions' patients were excluded through a variety of reasons. For example, a patient intoxicated with benzodiazepines, one with hemodynamic instability after pericardectomy, ventricular fibrillation after cocaine use with in stent thrombosis and congenital heart disease. A total of 10 patients were excluded due to severe comorbidities. These included pre-existent dilated cardiomyopathy, Brugada-syndrome, pre-existent cardiac failure and sepsis with a clear focus, mainly.

Of the 8 patients with 'no clear outcome', four patients were transferred to another hospital within 24 hours. Of the other four patients, one suffered from recurrent ventricular tachycardia, one from combined septic & cardiogenic shock, one patient did not survive the first 24 hours after pPCI and of one patient cardiac recovery was not clear.

Figure 9: Flow chart of inclusion.

Flow chart demonstrating the selection of cardiogenic shock patients for the retrospective cohort study. 11 patients categorized with 'non ST-elevation myocardial infarction' (NSTEMI) and 'cardiac asthma' were wrongly excluded from analysis. These categories do not fulfill the exclusion criteria, but the 11 patients were nonetheless excluded. PCI: Percutaneous coronary intervention, ICU: intensive care unit, AMI: acute myocardial infarction.



109 patients were included based on the medical files. Of these patients, blood pressure data was screened. Of 37 patients the blood pressure signal was not available. These patients were treated in the catheterization theatre in 2012. Currently, blood pressure records were only available from 2013. Of 11 patients the blood pressure recording was of very poor quality. Most of these patients underwent manual or mechanical resuscitation during PCI, or intra-aortic balloon counter pulsation was used, which severely deteriorates the blood pressure curve.

Baseline, procedural and treatment characteristics for these patients are shown in table 4. Mortality for this cohort was 41%. 82% of the patients are males.

Nearly all patients received vasoactive medication. 28 patients received mechanical support. 52 of the 61 included patients had an OHCA with ventricular fibrillation (VF).

The median time to death in the CD group is 2.8 days, while in the NCD group the time to death is 7.0 days. The corresponding p-value (Fischer's exact test) is <0.001.

Table 3: Performance of blood pressure analysis.

Assessment of the performance of the blood pressure analysis. 2 observers determined the amount of correctly placed markers in the sections of blood pressure used for retrospective analysis in three categories; >90% correct, >75% correct and <75% correct placement of the markers. In this table, the results are shown in % of the total amount of analyzed recordings.. For example, diastole is correctly identified (>90% correct placement) in 95% of the recordings, and not correctly identified (<75% correct placement) in 5% of the recordings. Missing markers were not taken into account.

	Correct placement of markers		
	>90%	**>75%**	**<75%**
Diastole	95 (58/61)	95 (58/61)	5 (3/61)
Systole	100 (61/61)	100 (61/61)	0 (0/61)
Anacrotic notch	62 (28/45)	69 (31/45)	31 (14/45)
Dicrotic notch	67 (41/61)	75 (46/61)	25 (15/61)

Values are presented as % of the total amount of analyzed recordings (n/N)

Table 4: Baseline, PCI and treatment characteristics for the retrospective cohort study.

						Subgroups	
		Cardiac death	No cardiac death	Survival		No survival	Cardiac recovery
		n=11	n=14	n=36	P-value	n=25	n=50
Baseline characteristics							
Male sex		82 (9/11)	71 (10/14)	86 (31/36)	0.479	76 (19/25)	82 (41/50)
Age (years)		62 ± 9	59 ± 7	57 ± 10	0.202	60,9 ± 8	59 ± 10
BMI (kg/m^2)		27 ± 3	26 ± 3	26 ± 4	0.714	27 ± 3	26 ± 4
Diabetes		14 (1/7)	45 (5/11)	17 (5/30)	0.127	33 (6/18)	24 (10/41)
Dyslipidemia		0 (0/5)	25 (2/8)	21 (6/29)	0.494	15 (2/13)	22 (8/37)
Hypertension		33 (2/6)	58 (7/12)	26 (8/31)	0.132	50 (9/18)	27 (10/37)
Smoking	never	0 (0/11)	14 (2/14)	11 (4/36)	0.454	8 (2/25)	12 (6/50)
	current	45 (5/11)	7 (1/14)	50 (18/36)	• 0.019	24 (6/25)	38 (19/50)
	previous	0 (0/11)	14 (2/14)	17 (6/36)	0.354	8 (2/25)	16 (8/50)
Family history of CAD		33 (1/3)	67 (2/10)	48 (12/25)	0.919	50 (3/6)	50 (14/28)
Stroke		0 (0/7)	20 (2/10)	6 (2/33)	0.255	12 (2/17)	9 (4/43)
Peripheral artery disease		0 (0/5)	25 (2/8)	6 (1/16)	0.257	15 (2/13)	13 (3/24)
MI		13 (1/8)	15 (2/13)	15 (5/34)	0.983	14 (3/21)	15 (7/47)
PCI		10 (1/10)	23 (3/13)	11 (4/35)	0.541	17 (4/23)	15 (7/48)
CABG		0 (0/10)	0 (0/13)	0 (0/35)	N.A.	0 (0/23)	0 (0/48)
OHCA with VF		64 (7/11)	93 (13/14)	89 (32/36)	0.136	80 (20/25)	90 (45/50)
PCI characteristics							
Culprit vessel	LM	18 (2/11)	7 (1/14)	6 (2/36)	0.297	12 (3/25)	6 (3/50)
	LAD	55 (6/11)	50 (7/14)	50 (18/36)	0.749	52 (13/25)	50 (25/50)
	RCx	18 (2/11)	29 (4/14)	19 (7/36)	0.591	24 (6/25)	22 (11/50)
	RCA	9 (1/11)	14 (2/14)	25 (9/36)	0.431	12 (3/25)	22 (11/50)
Multivessel Disease		56 (5/9)	27 (3/11)	45 (14/31)	0.418	40 (8/20)	40 (17/42)
Vasoactive medication		100 (9/9)	100 (11/11)	73 (24/33)	• 0.037	100 (20/20)	80 (35/44)
Mechanical ventilation		91 (10/11)	93 (13/14)	92 (33/36)	0.433	92 (23/25)	92 (46/50)
Mechanical support	IABP	36 (4/11)	21 (3/14)	11 (4/36)	0.523	28 (7/25)	39 (7/50)
	Impella	55 (6/11)	14 (2/14)	25 (9/36)	0.523	32 (8/25)	61 (11/50)
Treatment: ICU							
Mechanical ventilation		91 (10/11)	100 (14/14)	97 (35/36)	0.336	96 (24/25)	98 (49/50)
Dialysis		36 (4/11)	29 (4/14)	11 (4/36)	0.116	32 (8/25)	16 (8/50)
Cooling protocol	32 degrees	18 (2/11)	57 (8/14)	42 (15/36)	0.143	40 (10/25)	46 (23/50)
	36 degrees	27 (3/11)	43 (6/14)	50 (18/36)	0.411	36 (9/25)	48 (24/50)
Outcome							
Time to death (days)		2.8 [1.0 - 3.0]	7.0 [6.0 - 13.0]		• <0.001		

Values are presented as % (n / N) or mean ± stdandard deviation

P-value was determined between the three outcome groups

- indicates p<0.05

BMI indicates body mass index; CAD: coronary artery disease; MI: myocardial infarction; PCI: primary percutaneous infarction; 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

Results pre-revascularization

Pressure variables

In table 5 the results of classic clinical parameters and parameters with $p<0.05$ are shown. Systolic, diastolic mean arterial pressure and pulse pressure are not significantly different between the three groups, however, all mean and median pressure values of the 'classic clinical parameters' are higher in the 'survival' group compared to the 'CD' group. 'RDNP' is the only parameter that is significantly different between in at least one of the three outcome groups, with a median of 8 mmHg in the 'CD' group, to 14 mmHg in the 'survival' group. 'RDNP' is higher in survivors compared to the non-survivors. 'Dicrotic notch index' ('RDNP' as a percentage of 'pulse pressure') is 41% in both non-survivor groups and is significantly different from the survival group, which has a mean dicrotic notch index of 50%. In figure 10 it is shown that 'RDNP' is not directly related to LVET, but that 'pulse pressure' and 'absolute systolic AUC' are significantly related to 'RDNP'.

Time derived parameters

Of the time derived parameters, none of the parameters show significant differences between the three outcome groups. Heart rate is 10% higher (97 bpm) in the 'CD' group compared to the other subgroups (88 bpm). This result is not significant, but it can be of influence on the absolute time variables. In the subgroup analysis, mean 't upstroke' is decreased in the survival group compared to the 'no survival' group (0.16 and 0.19 s respectively). The duration of systole has a $p<0.05$ in both subgroups analyses and is longer in the survival subgroup and the 'cardiac recovery' subgroup. In figure 11 the relationship between 'LVET' compared to 'heart rate' of this cohort is shown. Patients with a high heart rate show a relatively long 'duration of systole compared to the duration of diastole. However, 'relative LVET' is equal in the three outcome groups and in both subgroup analyses.

Slopes and areas

The slope from dicrotic notch to diastole (which equals 'RDNP' / 'duration of diastole') and 'RDNP / LVET' both are lower in the 'no survival' subgroup compared to the 'survival' subgroup.

Of the 'area' parameters, 'relative systolic AUC' and 'absolute systolic AUC' are the only significant parameters. 'Relative systolic AUC' is lower in the 'no cardiac recovery' subgroup compared to the 'cardiac recovery' subgroup. In the 'survival versus no survival' subgroup analysis, 'relative systolic AUC' is not significant with a p value of 0.051. For 'absolute AUC' the 'survival versus no survival' subgroup analysis has a $p<0.05$, with the non-survivors showing a lower area (23 mmHg.s) compared to the survivors (27 mmHg.s).

Beatscope derived parameters

Of the parameters calculated by Beatscope, 'LVET' is the only parameter with $p<0.05$, which is also seen in 'LVET' calculated by the custom analysis. 'SV', 'CO' and 'CPO' show a trend, with low values for the 'CD' group, and higher values in the survival group, but these differences are not significant. Systemic vascular resistance shows no difference between the two groups or the subgroups.

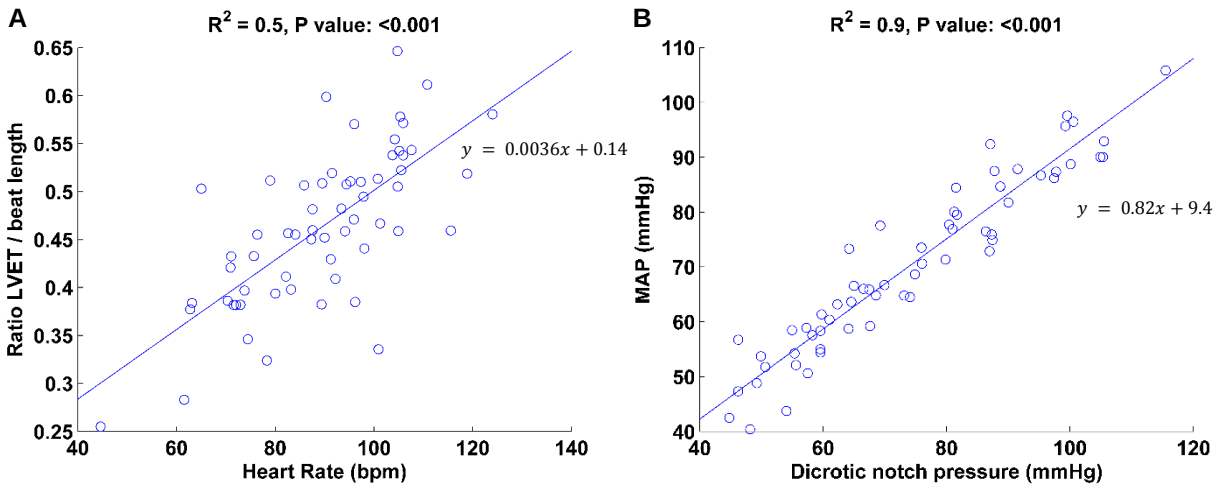


Figure 11. A: Ratio of LVET / beat length versus heart rate. This plot shows the principle of diastolic shortening with increasing heart rate. At higher heart rates, the duration of diastole decreases relative to the duration of systole (LVET). B: MAP versus dicrotic notch pressure. MAP and dicrotic notch pressure are highly correlated.

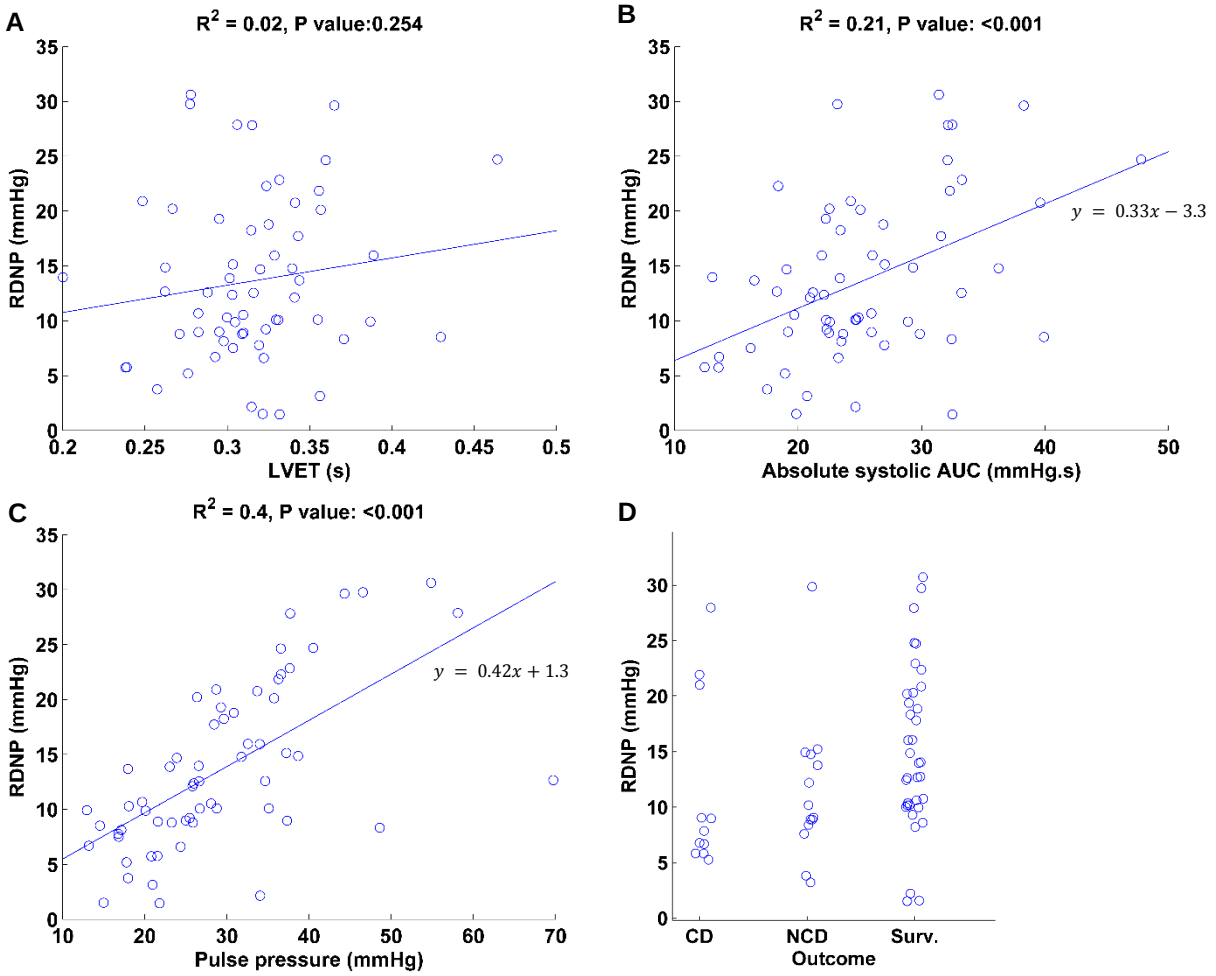


Figure 10: Relationship between RDNP and LVET, absolute AUC and pulse pressure.

A: RDNP and LVET are not related. B: RDNP and absolute systolic AUC are significantly related in this cohort although the plot shows that the parameters have no strong linear relationship.. C: RDNP and pulse pressure show a significant, linear relationship. D: The values of RDNP scattered in three columns of outcome. In the CD group 3 patients have very high RDNP, and in the survival group, three patients have a very low (<5 mmHg) RDNP

RDNP = relative dicrotic notch pressure, LVET = left-ventricular ejection time, AUC = area under the curve.

Table 5. Retrospective results pre-revascularization.

Classic clinical parameters and parameters with p<0.05. Blood pressure measured in the proximal aorta using a fluid filled cardiac catheter connected to an external pressure transducer. The full table of results is added in appendix

	Cardiac death		No cardiac death		Survival		p-values		
	n	value	n	value	n	value	Between groups	Survival vs non-survival	Cardiac recovery vs no cardiac recovery
Classic clinical parameters									
Systolic pressure (mmHg)	11	86 ± 23	14	85 ± 22	36	93 ± 17	0.326	0.136	0.502
Diastolic pressure (mmHg)	11	59 ± 14	14	57 ± 15	36	63 ± 16	0.428	0.224	0.777
MAP (mmHg)	11	68 ± 16	14	66 ± 17	36	73 ± 15	0.359	0.167	0.651
Pulse pressure (mmHg)	11	22 [18 - 36]	14	25 [21 - 37]	36	29 [24 - 35]	0.354	0.187	0.223
Heart rate (bpm)	11	97 ± 15	14	88 ± 18	36	88 ± 15	0.231	0.329	0.085
Pressure derived variables									
RDNP (mmHg)	11	8 [6 - 21]	14	10 [8 - 15]	36	14 [10 - 20]	0.045	0.014	0.088
Dicrotic notch index (%)	11	41 ± 16	14	41 ± 18	36	50 ± 18	0.145	0.049	0.306
Time derived variables									
t upstroke (s)	11	0.16 ± 0.04	14	0.16 ± 0.04	36	0.19 ± 0.05	0.107	0.034	0.267
Duration systole(LVET) (s)	11	0.29 ± 0.04	14	0.31 ± 0.04	36	0.32 ± 0.05	0.063	0.039	0.036
Slopes									
dp/dt dicrotic notch - diastole (mmHg / s)	11	-24 [-40 - -19]	14	-31 [-42 - -16]	36	-39 [-52 - -29]	0.064	0.019	0.189
RDNP / LVET (mmHg/s)	11	25.6 [23.9 - 62.5]	14	31.7 [25.7 - 45.8]	36	47.4 [31.9 - 63.2]	0.095	0.031	0.159
Areas									
Relative systolic AUC (mmHg.s)	11	4.1 [2.7 - 4.9]	14	5.0 [3.9 - 6.4]	36	5.7 [4.2 - 7.4]	0.086	0.051	0.049
Absolute systolic AUC (mmHg.s)	11	22.4 ± 7.1	14	22.9 ± 5.2	36	27.0 ± 7.3	0.060	0.017	0.145

Values are presented as mean ± standard deviation or as median [IQR]. MAP: mean arterial pressure; RDNP: relative dicrotic notch pressure; LVET: left ventricular ejection time; AUC: area under the curve;

Results pre-post revascularization

Of 53 patients pre- and post-revascularization blood pressure data could be selected. For each parameter the difference in the change of parameters between the outcome groups from pre- to post-revascularization was tested. In table 6 the values are shown for pre- and post-revascularization per outcome group.

The classic clinical parameters, systolic, diastolic, mean arterial, and pulse pressure all show a positive, but not significant trend after revascularization.

Augmentation index decreases from 33% to 15% in the 'CD'-group and increases with 2 and 3 % for the 'NCD' and 'survival' group respectively. The 'anacrotic notch' could only be determined in both pre- and post-revascularization data in 3 out of 7 patients in the 'CD' group.

Heart rate has decreased post revascularization with 6 bpm in the survival group and increased with 2 bpm in the 'NCD' group. In the 'CD' group, heart rate increases with 5 bpm.

'T systolic downstroke', the time between systolic maximum and dicrotic notch is different for survivors and non-survivors. From the values in the table, this difference cannot be determined. The proportional change of the sum of the survival groups should be calculated. $(0.04 * 7 - 0.001 * 13) / 20 = 0.0075$. Thus, 't systolic downstroke' increases with 0.0075 s in the 'non-survivors' subgroup, compared to an increase of 0.004 s in the 'survivors' group.

'Relative t upstroke' decreases in both the 'CD' group and the 'survival' group with 0.04 and 0.02 respectively. This means that 't upstroke' increased with 4% and 2% compared to the complete beat length. 'Relative t upstroke' increases with 0.03 (3%) in the 'NCD' group and does not change in the 'CD' group.

'Relative LVET' decreases with 0.03 (3%) in the survival group and increases with 0.04 (4%) and 0.02 (2%) in the 'CD' and 'NCD' groups. This could be the effect of diastolic shortening, since heart rate increases in both 'non-survival' groups and decreases in the 'survival' group. Since the change of 'relative LVET' is significantly different it is straightforward that 'duration of systole / duration of diastole' also has $p<0.05$ for the 'cardiac recovery versus no cardiac recovery' analysis.

The relative time of maximal upstroke, 'relative t dp/dt max', increases with 0.01 (1%) in the no cardiac recovery group compared to the cardiac recovery subgroup.

The change of 'CPO' has no $p<0.05$, but the CPO shows an increase of 0.2 and 0.17 for the 'CD' and 'NCD' groups, while 'CPO' does not change in the 'survival' group.

Table 6: Results pre-post revascularization

Blood pressure parameters before and after revascularization. Classic parameters and parameters with p<0.05 are shown. Blood pressure measured in the proximal aorta using a fluid filled cardiac catheter connected to an external pressure transducer. The full table of results is added in appendix

	Cardiac death		No cardiac death		Survival		p-values		
	n	value	n	value	n	value	Between groups	Survival vs. no survival	Cardiac recovery vs. no cardiac recovery
		Pre revasc. | Post revasc.		Pre revasc. | Post revasc.		Pre revasc. | Post revasc.			
Classic clinical parameters									
Systolic pressure (mmHg)	7	88 ± 24 | 104 ± 33	13	83 ± 21 | 99 ± 14	33	93 ± 17 | 102 ± 19	0.481	0.574	0.225
Diastolic pressure (mmHg)	7	59 ± 13 | 68 ± 14	13	56 ± 15 | 66 ± 11	33	63 ± 15 | 69 ± 12	0.424	0.674	0.199
MAP (mmHg)	7	69 ± 16 | 80 ± 20	13	65 ± 17 | 77 ± 12	33	73 ± 15 | 80 ± 14	0.371	0.599	0.163
Pulse pressure (mmHg)	7	22 [21 - 36] | 33 [18 - 53]	13	25 [21 - 29] | 34 [30 - 35]	33	29 [23 - 36] | 30 [24 - 37]	0.657	0.660	0.357
Heart rate (bpm)	7	93 ± 15 | 97 ± 13	13	87 ± 18 | 89 ± 14	33	88 ± 15 | 82 ± 18	0.046	0.128	0.014
Pressure derived parameters									
Augmentation index (%)	3	33 ± 16 | 15 ± 10	8	21 ± 12 | 23 ± 18	21	27 ± 13 | 30 ± 16	0.039	0.012	0.144
Time derived variables									
t systolic downstroke (s)	7	0.11 ± 0.03 | 0.16 ± 0.04	13	0.15 ± 0.04 | 0.14 ± 0.04	33	0.14 ± 0.04 | 0.14 ± 0.04	0.052	0.023	0.707
t downstroke (s)	7	0.47 [0.42 - 0.58] | 0.48 [0.40 - 0.58]	13	0.50 [0.47 - 0.59] | 0.51 [0.47 - 0.56]	33	0.52 [0.45 - 0.59] | 0.58 [0.49 - 0.66]	0.067	0.415	0.022
Duration diastole (s)	7	0.38 [0.29 - 0.49] | 0.33 [0.27 - 0.39]	13	0.34 [0.31 - 0.48] | 0.36 [0.30 - 0.41]	33	0.38 [0.31 - 0.45] | 0.45 [0.35 - 0.51]	0.061	0.088	0.023
relative t upstroke	7	0.25 ± 0.05 | 0.21 ± 0.05	13	0.22 ± 0.05 | 0.25 ± 0.05	33	0.27 ± 0.06 | 0.25 ± 0.05	0.049	0.308	0.166
relative t dp/dt max	7	0.09 [0.05 - 0.11] | 0.09 [0.05 - 0.13]	13	0.07 [0.07 - 0.09] | 0.08 [0.07 - 0.10]	33	0.08 [0.06 - 0.11] | 0.07 [0.06 - 0.09]	0.055	0.074	0.022
relative LVET	7	0.43 ± 0.06 | 0.47 ± 0.06	13	0.44 ± 0.10 | 0.46 ± 0.06	33	0.47 ± 0.07 | 0.44 ± 0.07	0.082	0.112	0.031
duration systole / duration diastole	7	0.82 [0.63 - 0.88] | 0.82 [0.78 - 1.00]	13	0.79 [0.62 - 1.09] | 0.87 [0.70 - 1.05]	33	0.88 [0.70 - 1.05] | 0.78 [0.63 - 0.93]	0.091	0.080	0.044

Values are presented as mean ± standard deviation or as median [IQR]. Pre revasc.: Pre revascularization; Post revasc.: post revascularization. MAP: mean arterial pressure; LVET: left ventricular ejection time.

Discussion

This first of its kind exploratory study resulted in several findings.

First, to our knowledge no one has yet analyzed the blood pressure curve of cardiogenic shock patients in such a manner. We have tried to scrutinize the various pressures, times, slopes, and areas and tried to relate these known and unknown parameters to clinical outcome. Also, clinical outcome may sometimes be a complex issue as these patients not only decease from cardiac failure. This is the reason why we tried to include a group of patients that were deemed to have recovered from cardiac failure but died nonetheless.

In our studies, we found that 'classic clinical parameters' used in clinical assessment of cardiogenic shock, heart rate, systolic,- diastolic,- mean arterial,- and pulse pressure were not significantly different between the (two or) three subgroups. This confirms our hypothesis that systolic pressure is not an appropriate and only predictor of cardiac outcome in these patients.

Cardiac output is a classic marker derived from the multiplication of heartrate (frequency of cardiac ejection) and stroke volume (marker of volume and contractility) and in case of CPO this is also multiplied with MAP. Both SV and MAP show no significant differences in either group or subgroup. CO is relatively high, the 'CD' group has a median CO of 4,4 L/min and a median cardiac index of 2.2 L/min/m^2. This supports our hypothesis that 'cardiac output' and 'MAP' do not provide enough information to accurately predict outcome of cardiogenic shock patients. In the large cohort analyzed by Fincke et al.[22] CPO has proven to contain prognostic value, but this parameter is not the ideal parameter to predict outcome in the individual patient as demonstrated by this study, CPO is not significantly different between the survivors and non-survivors. From the results of our analysis cardiac (power) output seems of limited value in categorizing cardiogenic shock before revascularization. CPO could provide for an important factor in the categorization of cardiogenic shock although the relationship with mortality is not very strong. The patients in the 'CD' group have a mean CPO of 0.78 W, which according to Fincke et al. should correspond to an estimated in hospital mortality of 20 to 40 % (95% confidence interval) although none of these patients survived. The survivors have a CPO of 0.87 W which corresponds to 15 to 25 % in hospital mortality. From the results of this study the importance of CPO in predicting outcome in the individual patient seems limited. Sleeper et al. also conducted a study on patients from the SHOCK-study with the goal of determining cardiogenic shock severity score and successively predicting outcome. Part of these patients were also used by Fincke et al. Sleeper identified CI, pulmonary capillary wedge pressure (PCPW), stroke work, stroke work index and cardiac power index as different between survivors and non-survivors, with stroke work as the most promising parameter in categorizing cardiogenic shock. Stroke work is calculated using MAP, PCPW, and stroke volume. Since PCPW is not available in this study, this parameter could not be evaluated. From the before mentioned studies it seems that CO, CI, CPO and/or stroke work could provide for valuable support in a model or parameter in which different variables are combined to provide for a specific and sensitive cardiogenic shock marker or grading. However, as CI and CPO in our study are not significantly different between subgroups, the results of our study differs from both the study of Fincke et al. and Sleeper et al. These studies were both conducted using data from the ICU while we determined blood pressure parameters in the ongoing myocardial infarction.

Heart rate is known to have profound effects on the blood pressure waveform. Although heart rate is not significantly different between the outcome groups in this study, it could be of value in discriminating the cardiac recovery from the no cardiac recovery subgroup ($p=0.085$). Heart rate has a major effect on the calculated parameters, which is of course inherent to analysis of the blood pressure curve in the time domain. For example, at high heart rates, the systole/diastole ratio is higher compared to low heart rates. With increasing heart rate, the total duration of each heart beat shortens, during which the duration of diastole decreases more rapidly compared to duration of systole. This effect is shown in figure 11. This decrease of diastolic time could increase myocardial ischemia, which will be discussed later on. The parameters describing the morphology of the blood pressure curve are influenced by heart rate, in particular the absolute time-parameters are directly or indirectly influenced by heart rate, which is inherent to an analysis in the time domain. Since we expected heart rate to be an important parameter

in categorizing CS, not all time derived parameters are corrected for heart rate. The 'relative' time parameters are corrected for heart rate and thereby provide insight in the influence of heart rate on the blood pressure curve. 'Duration of systole' ('LVET') is significantly different in both subgroup analyses. This absolute time parameter is strongly correlated to heart rate, although heart rate itself is not significantly different. When the duration of systole is corrected for heart rate, the difference between the groups diminishes, suggesting that heart rate is in fact of major influence on the significant difference of this parameter between the outcome groups. Also, no parameters corrected for heart rate, such as relative duration of systole, were significantly different between the groups, emphasizing that heart rate is a factor that should be taken into account.

We studied other parameters subdivided in pressure, time, slope, area and Beatscope parameters which will now be discussed per category.

The absolute duration of systole differs between survivors and non-survivors, however when duration of systole is divided by the total beat length, which gives the relative location of the dicrotic notch, the resulting values are equal between the groups. This suggests that heart rate is of importance in discriminating between survivors and non-survivors although heart rate itself shows no significant differences between either of the subgroups. The trend of heart rate does suggests a higher heart rate in the no survival no cardiac recovery group compared to the survival group. Heart rate has a strong influence, not only on time parameters, but on the morphology of the blood pressure curve as an entity. Correction of parameters for heart rate should therefore be applied with caution. Heart rate dependent phenomena, such as diastolic shortening, should not directly be attributed to, in this case, depth of cardiogenic shock.

Relative dicrotic notch pressure is the only parameter significantly different in at least one of the three outcome groups. This parameter is significantly different between subgroups survival and no survival, making it a potentially important clinical parameter in predicting outcome. RDNP is significantly related to pulse pressure, as shown in figure 10 C. However, the dicrotic notch index, which is the ratio between RDNP and pulse pressure, is also significantly different between the survival and non-survival groups while pulse pressure is not significantly different between those groups. This suggests that RDNP is not only influenced by pulse pressure, but determined by other, currently unknown factors which apparently are different for survivors and non-survivors. The underlying mechanism of a low dicrotic notch in these patients is currently unknown. In study II of this thesis, intracoronary injection of 0.2 mg NTG causes RDNP to decrease with nearly 50 percent, an effect most likely caused by vasodilatation. Since pressure is measured peripherally the comparison with results from study II should be made with caution. Vasodilatation is not an obvious cause for a low RDNP in the non-survivors of this study since cardiogenic shock typically causes peripheral vasoconstriction. Ewy et al. studied the dicrotic pulse, which is a prominent pressure peak during diastole. This includes a low relative dicrotic notch pressure, in young patients with elevated SVR and a low stroke volume[34]. Although mean stroke volume in all three of our outcome groups is low, 50 – 60 ml, SVR in the shock patients is lower compared to the patients of study II, but equal between the outcome groups. Low RDNP compared to pulse pressure as calculated with the 'dicrotic notch index' could also be a sign of low intravascular volume although we assume adequate vascular filling in these patients.

The dicrotic notch is a blood pressure landmark that, if measured in the proximal aorta, reflects closure of the aortic valves[29]. A low RDNP therefore implies that the aortic valves close at a lower pressure relative to diastole, and a low dicrotic notch index implies that the aortic valves close at a lower pressure relative to pulse pressure. Absolute dicrotic notch pressure, which is strongly correlated to MAP, is not significantly different between the groups but shows a trend between survivors and non-survivors, with non-survivors having a lower absolute dicrotic notch pressure compared to survivors. This implies that mean arterial pressure in non-survivors is lower, although mean arterial pressure itself is not significantly different between the outcome groups or subgroups, the trend equals that of absolute dicrotic notch. The association of MAP an dicrotic notch is shown in figure 11. The relationship between MAP and dicrotic notch pressure was demonstrated by Hébert et al. in 1995. In a group of seventeen male patients, referred to the catheterization laboratory for cardiac catheterization, dicrotic notch and mean arterial pressure were compared at rest and during Valsalva maneuver. End diastolic pressure (dicrotic

notch pressure) was strongly related to MAP, calculated as 'total AUC / beat length'. Comparable results are found in our study, as shown in figure 11, although we used a different calculation of MAP.

The height of the dicrotic notch is the result of a complex coupling between the left ventricle and arterial vasculature in which cause and effect are difficult to distinguish with the current data. It is clear that MAP strongly correlates with dicrotic notch pressure. It is however RDNP, the difference between dicrotic notch and diastolic pressure, that is different between the groups. To determine which factors influence 'RDNP' more specific research should be conducted to determinants of this parameter.

The results related to the anacrotic notch should be interpreted with caution. The anacrotic notch was the most difficult parameter to automatically determine due to its low frequency nature, which makes it difficult to distinguish from noise and other features of the blood pressure curve. It is the marker with the lowest number of correct identifications and is not determined in 16 patients. The anacrotic notch can be early or late in respect to systolic maximum which further complicates automatic detection. The values of the anacrotic notch are equal in the three groups and the interquartile range or standard deviation is large, approximately equal to the median or mean value.

The slope variables, 'RDNP / LVET' and 'dp/dt dicrotic notch – diastole' are significantly different between survivors and non survivors. These parameters are both calculated using 'RDNP', which on itself is significantly different between survivors and non-survivors. In case of 'RDNP/LVET', both 'RDNP' and 'LVET' are significantly different between survivors and non-survivors. It is most likely that the significance of the composite slope parameters originates from the pressure and time derived parameters used to calculate the slope.

Since dp/dt max is somewhat correlated to cardiac contractility[28], we expected this to be an important parameter in this analysis, but it is not significantly different between the outcome groups. Arterial dp/dt max is mainly determined by left ventricular contractility and left ventricular preload[35], but also influenced by arterial compliance, fluid status and pulse wave reflection. According to Morimont et al., arterial dp/dt max accurately reflects left ventricular contractility in endotoxin-induced shock if adequate vascular filling is achieved[36]. Without adequate vascular filling dp/dt max and left ventricle dp/dt max were correlated but had a bad agreement. With adequate vascular filling pulse pressure variation <11%) arterial dp/dt max had good agreement and correlation with both left ventricular dp/dt max and end systolic elastance, which is the gold standard for assessing left ventricular contractility. The fact that dP/dt max is not significantly different in any group in our study underlines the complexity of cardiogenic shock. Left ventricular contractility is impaired although the extent of impairment is not different for survivors and non-survivors.

The only 'area' parameter that significantly differs between survivors and non-survivors is 'absolute systolic AUC'. This parameter can be described as the combination of relative area under the systolic curve, which is related to stroke volume[37], 'diastolic pressure' and 'LVET'. All relative area parameters, 'absolute AUC' and 'absolute systolic AUC' are potentially important parameters for categorizing cardiogenic shock since these parameters all have p-values <0.08 in the 'survival versus no survival' subgroup. In the absolute area parameters it has to be noted that differences in diastolic blood pressure and heart rate have more influence on the resulting area compared to the relative area parameters itself. The absolute AUC values are 5 to 10 times increased compared to the corresponding relative AUC parameters. Absolute AUC values are therefore mainly determined by the sum of diastolic pressure and the duration of 1 beat.

Blood flow to the myocardium of the left ventricle mainly occurs during diastole[38]. Therefore diastolic pressure and duration of systole are the main mechanical determinants of coronary oxygen supply. This is described by Buckberg et al. as the 'diastolic pressure time index', which is calculated as the AUC of aortic blood pressure during diastole, minus the AUC of left ventricular pressure in the same time interval[39]. In this article, Buckberg et al. already discussed that the effect of shortened diastole should be related to the 'myocardial oxygen supply – demand ratio' to determine the adequacy of subendocardial perfusion. In this study, left ventricular pressure was not available, so the diastolic AUC is used as the best available alternative. 'Absolute diastolic AUC' slightly overestimates myocardial oxygen supply compared to the definition of Buckberg since the AUC of left ventricular pressure is not substracted from absolute diastolic AUC. The 'absolute myocardial oxygen supply / demand ratio' is 1.0

in both non-survival groups and 1.1 in the ‘survival’ group. This indicates a marginal balance between oxygen supply and demand, and if oxygen supply is slightly underestimated an oxygen supply/demand mismatch could be present, which implicates potential subendocardial ischemia. If in this situation heart rate would further increase, assuming equal diastolic pressure, diastolic time shortening could cause an increase of myocardial ischemia in an already impaired ventricle.

All 9 parameters with $p<0.05$ in one of the two subgroup analyses are significantly related to LVET and/or RDNP. Either ‘RDNP’ or ‘LVET’ is fundamentally part of the parameter, or a positive correlation between the parameters is found. Both LVET and RDNP are statistically significant in the ‘survival versus no survival’ subgroup. ‘Absolute systolic AUC’ is related to RDNP, as shown in figure 10 B. ‘RDNP’ and ‘t upstroke’ are also significantly related, this is shown in figure a 1 in the appendix. This shows that parameters determined from the blood pressure curve morphology are strongly correlated, which should be expected in the regulated human hemodynamic system.

The effect of revascularization on the blood pressure waveform:

Between pre- and post-revascularization none of the pressure parameters show significant changes between the groups with different outcome. Nearly all pressure variables show an increase after revascularization. The effect of revascularization is thought to not to instantly affect systolic myocardial function. The increase of absolute pressure could be the effect of pharmacologic compensation of blood pressure through vasoactive medication administered during pPCI. This hypothesis is supported by the fact that 44 out of 53 patients have received vasoactive medication during pPCI.

The change of RDNP from pre- to post-revascularization is not significantly different between either group or subgroup. However, some trends could support RDNP as a potential parameter for predicting outcome. Absolute pressures in the ‘CD’ group show the most striking increase. MAP, systolic and diastolic pressure increase with 12, 15 and 7 mmHg respectively. However, RDNP decreases with 2 mmHg, and the dicrotic notch index decreases with 11 % in the ‘CD’ group. The increase of absolute pressure in the ‘survival’ group is less, 5 mmHg for both MAP and diastolic pressure and 9 mmHg for systolic pressure compared to a small increase in both cardiac recovery groups. RDNP increases with 1 mmHg and the dicrotic notch index decreases with 1%. From these results we hypothesize that RDNP is a stable indicator for cardiogenic shock. While in the ‘CD’ group absolute pressure parameters increase, RDNP does not increase, it rather shows a decrease. If RDNP proves to be a sensitively and specifically predictor of outcome, determinants of this parameter should be evaluated. What influences cause RDNP to increase and decrease. How does RDNP change over time during and after cardiogenic shock? To provide answers on these questions RDNP should be determined in a variety of different situations, preferably within the same patient. If multiple measurements are conducted in one patient, the patient can act as its own control, which makes the determination of changes in measured parameters like RDNP easily relatable to an applied perturbation.

The change of absolute time parameters is strongly influenced by a different change in heart rate of the three groups, of which the ‘CD’ group shows an increase of 4 bpm, and the survival group a decrease of 6 bpm. This difference in the change of heart rate causes a different change in absolute time parameters and a different change in relative LVET, most likely caused by different diastolic time shortening. Although heart rate increases, the relative time of maximal pressure increase, ‘relative t dp/dt max’ slightly increases in the cardiac recovery group. It is not known if the timing of dp/dt max in an arterial pressure recording correlates to the moment of dp/dt max of the left ventricle.

RDNP could be an important parameter in evaluating and guiding therapy on the ICU when continuous blood pressure monitoring is applied. If this parameter accurately reflects depth of cardiogenic shock it could be used as a real time reflection of effectiveness of therapy on the ICU. For this reason the change of this parameter should be evaluated in time, as described in study II.

Performance of the analysis

The performance of the custom analysis method was determined by two observers through assessment of the amount of correctly placed markers. Systole and diastole were correctly detected in nearly all records, respectively 100% and 95% of these markers were correctly placed in >90% of the beats. Dicrotic notch performed reasonable, with correct identification in 67% of the recordings, and in 75% of the recordings the dicrotic notch was correctly identified in >75% of the beats. In 25% of the recordings. The anacrotic notch was correctly identified in 62% of the recordings, although this parameter was more difficult to detect. In 16 of 61 recordings no anacrotic notch was determined. This is due to the algorithm for the detection of the anacrotic notch, which states that if the anacrotic notch is detected in <50% of the beats, the determination of the anacrotic notch is probably unreliable and no anacrotic notch value is calculated. The dicrotic notch is determined correctly (>75% correct placement) in 75% of the recordings. Of the 12 recordings in which the dicrotic notch was not correctly determined, 2 belong to patients in the ‘CD’ group, 1 to the ‘NCD’ group and 9 to the ‘Survival’ group. The results of this study could be improved by either improving the algorithm, or excluding the recordings with insufficient correct placement of markers.

Limitations

In this study 58 of 61 patients were mechanically ventilated during pPCI. Since mechanical ventilation causes hemodynamic changes by elevation of intrathoracic pressures during inspiration, the results of this thesis can be best compared to mechanically ventilated patients. In ‘Study 2’ the same parameters were determined in 14 non-ventilated patients, however, these patients are not in cardiogenic shock and therefore the effect of mechanical ventilation on the blood pressure curve cannot be derived from comparing the results of both studies.

44 patients received vasoactive medication (for example noradrenalin, adrenalin or dobutamin) at some point during pPCI. Since administration of medication in time could not accurately be related to the time in blood pressure recordings due a lack of accurate registration and synchronization in time it is not possible to assess the influence of vasoactive medication on the blood pressure curve for these patients.

In this study, patients not surviving pPCI and patients not surviving the first 24 hours after pPCI were not included because cardiac recovery, which is based on the administration of vasoactive medication, could not be assessed properly. Use of vasoactive medication in the catheterization laboratory is not accurately registered in time, in particular for the older records. Vasoactive medication in the first 24 hours after admission on the ICU is influenced by the ‘induced hypothermia’ protocol, in which body temperature of resuscitated patients was lowered to 32 degrees during 24 hours. During induced hypothermia, increased vasoactive medication is used due to an increased hemodynamic instability caused by hypothermia. Especially in the first hours after pPCI it is difficult to determine the cause of high vasoactive medication use. However, one could argue that patients not surviving the first 24 hours of ICU admission provide for a an even worse category of cardiogenic shock. Since these patients do not survive, they show no cardiac recovery and medical therapy is insufficient for stabilization of these patients. With the current results in mind, we hypothesize that RDNP is lower in patients not surviving the first 24 hours compared to the ‘CD’ group.

Only very limited information is available of non-survivors compared to survivors of cardiogenic shock. Patient status reports are less detailed by which comorbidities are less reported. The magnitude of this limitation is unknown. The impact of this limitation is expected to be minor since survival was used as a primary endpoint. However, if this study will be expanded to include more detailed patient characteristics, or secondary, functional outcome parameters are used, this could pose a serious limitation.

The variability in blood pressure parameters in this study, as reflected by the large standard deviations, underlines both the variability of blood pressure as a measurement value, but also the complexity of

cardiogenic shock. This variability of parameters could potentially be used in new parameters, describing the stability of hemodynamics by means of variability in blood pressure parameters. Pulse pressure variation is an example of the qualitative use of the variability of a blood pressure parameter. Pulse pressure variation should be calculated using maximal and minimal pulse pressure during one respiratory cycle. Respiratory data was not available, however in ventilated patients, if the pressure signal is stable and regular, the respiratory cycle can be identified from the blood pressure signal. This parameter was not taken into account in this study. The results of this study and other studies on hemodynamic parameters in cardiogenic shock are not able to identify a single sensitive and specific parameter to determine outcome, which also underlines the complexity of cardiogenic shock.

Absolute blood pressure recorded during pPCI could be influenced by partial opening of the y-connector at which catheterization materials are inserted into the catheter sheath, which offers access to the arterial system and ultimately the coronary arteries. This y-connector connects the fluid column to the pressure transducer and enables the cardiologist to introduce materials, such as wires, balloons and stents into the inner lumen of the catheter. A rubber closure valve prevents blood from leaking out of the y-piece, but closure of this valve also fixes materials inside the valve. During maneuvering of the materials this valve is therefore not fully closed. If this y-piece is not fully closed, the catheter system is open to the outside, inducing an error in the pressure measurement. Since maneuvering of the materials causes movement of the fluid column, it is thought that this activity can be recognized by artifacts in the signal. In retrospect, a temporary blood pressure drop is not distinguishable from inadequate closure of the y-connector.

In this study, no sub analysis is performed on right- versus left sided myocardial infarction. The etiology of right versus left sided infarction is different from that of left sided MI. For example, when blood supply to the sinoatrial node is limited due to a proximal RCA lesion, heart rate can decrease causing a sudden and severe decrease of blood pressure. For categorizing CS, differentiating between left and right ventricle infarction could provide for a more accurate assessment of depth of cardiogenic shock. If analysis of the blood pressure curve would be specified on ventricle involvement, a future cardiogenic shock grading could potentially be improved. In this analysis it was decided not to discriminate between these two since functional impairment and ventricle involvement were not assessed.

Since IABP-support completely deteriorates the blood pressure curve these patients are not included due to an unusable blood pressure curve. IABP is only used in severely impaired patients, which leads to a potential inclusion bias for this study since the most severely impaired patients are potentially excluded.

Signal quality was not objectively quantified in this analysis. This is an obvious limitation to the study and this should be assessed in order to further develop both analysis and conclusions about blood pressure parameters in cardiogenic shock patients. In the second study of this thesis signal quality is assessed prospectively using a fast-flush test.

If measures are taken in quantifying and improving signal quality in a prospective fashion, future studies should be able to more accurately analyze hemodynamic parameters. In this study 13 out of 74 blood pressure recordings were of insufficient quality due to artifacts, long periods of absence of signal and excessive damping. In particular the pressure recordings of critical patients are of low quality. It is thought that this is caused by the medical team focusing on keeping the patient alive. The quality of the blood pressure signal in those critical moments simply has less priority. The blood pressure signal currently has the limited purpose of providing the ‘classic clinical parameters’. If analysis of the blood pressure curve as described in this thesis will be involved in clinical decision-making, quality of the pressure signal is required to increase and should therefore be regularly and systematically assessed. This will be described in the section ‘future perspectives & recommendations’.

Strengths

The amount of parameters calculated in this study enables assessment of the blood pressure curve from various points of perspective. Since most of these parameters are never used in clinical context and individual parameters are difficult to interpret, the combination of different parameters provides a useful context. Calculation of an absolute time, a relative pressure and the resulting dp/dt provides insight in which parameters actually differ between groups and which parameters should and should not be combined to ultimately determine an integral parameter for determining the depth of CS.

The wide spectrum of CS patients provides a reference for the variety that exists in these patients. Both extremely impaired patients in need of maximal pharmacological support, and patients without any need of vasoactive medication are included. Only patients not surviving the first 24 hours are excluded, which probably is the only group of patients suffering from CS that is excluded. This group could provide for the worst category of CS. For categorizing CS based on the morphology of the blood pressure curve patients suffering from AMI without cardiogenic shock should also be analyzed to provide for perspective and 'normal' values to the determined parameters.

The use of death as an endpoint in this study provides for a strong outcome parameter. Cardiac recovery based on the use of vasoactive medication on the ICU is somewhat more difficult to interpret, but this category provides for a very useful discrimination in the different pathophysiology that ultimately causes death.

Conclusion

With the results of this study, cardiogenic shock cannot yet be categorized based on the blood pressure curve. New and known parameters were identified as being associated with mortality. 'Left-ventricular ejection time', 'relative dicrotic notch pressure' and 'absolute systolic AUC' are parameters with potential value in objectively grading cardiogenic shock.

Study 2: Change of blood pressure parameters over time in patients with acute myocardial infarction

The aim of this prospective observational cohort study is to determine changes over time of parameters describing the blood pressure curve morphology in patients suffering from AMI treated with primary PCI.

Patient selection

We aimed to include 15 patients suffering from ST-segment elevation myocardial infarction (STEMI), referred to the catheterization laboratory of the Academic Medical Centre (AMC) for treatment with primary PCI. STEMI is defined as: new ST-segment elevation in at least 2 contiguous leads of ≥ 2 mm (0.2 mV) in men or ≥ 1.5 mm (0.15 mV) in women in leads V_2-V_3 and/or of ≥ 1 mm (0.1 mV) in other contiguous chest leads or the limb leads. New or presumably new left bundle branch block (LBBB) is considered the equivalent of STEMI. Exclusion criteria consist of: 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.

This study was approved by the Institutional Review Board. Written informed consent was obtained from every patient.

Measurement protocol & Materials

Primary PCI

Continuous noninvasive blood pressure was measured during pPCI using the Nexfin (Edwards Lifesciences BMEYE). The Nexfin monitor is a CE-marked (European Union cleared) device which uses the volume clamp method as first described by Penaz and later developed by Wesseling et al.[40] to measure blood pressure noninvasively at the finger. With the use of a dedicated finger cuff, digital blood pressure was measured between the distal and proximal interphalangeal joints of the middle finger at a sampling frequency of 200 Hz. The continuous blood pressure measured from the finger is transformed by the Nexfin to a brachial pressure signal. During the measurements, the hand was positioned at the level of the mattress of the operating table. The finger cuff should ideally be placed at the same level as the heart, but since we aim to detect changes of blood pressure over time we accept a small but structural error in absolute blood pressure.

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, through a coaxial cable to the analog input channel of the Nexfin.

During pPCI, several events were registered in time. The moment of first wire passage of the culprit lesion, all balloon inflations and deflations and administration of medication were saved by placing markers in the Nexfin pressure measurement.

Before the end of pPCI, 0.2 mg nitroglycerin (NTG) was administered intracoronary, provided that the interventional cardiologist approved the administration.

During a selection of the primary PCIs, fast flush tests were conducted to determine the aortic pressure signal quality. A fast flush test consists of quick closing of a valve which introduces pressurized saline(>200 mmHg) to the catheter system. This quick closing provides an excitation after which the pressure signal will oscillate before returning to the ‘baseline’, in this case the actual blood pressure.

The oscillations can be used to determine the damping coefficient and natural frequency of the catheter system.

Follow-up measurements

The first follow up measurement was conducted within 4 hours of primary PCI. After the first day, measurements were conducted twice a day until hospital discharge. These follow-up measurements were conducted within 4 hours of the coronary intervention and twice each day until hospital discharge.

Follow-up measurements were conducted with the patient in complete horizontal position and the left hand resting on the mattress. After a 5 minute calibration-period, 10 minutes of blood pressure measurement were conducted in rest. Follow-up measurements were conducted twice a day until discharge from the hospital. If patients had an appointment in the AMC hospital one month after pPCI, a follow-up measurement was conducted at the same day.

Patients with a one-month follow-up appointment in the AMC hospital were invited to attend a follow-up measurement for this study.

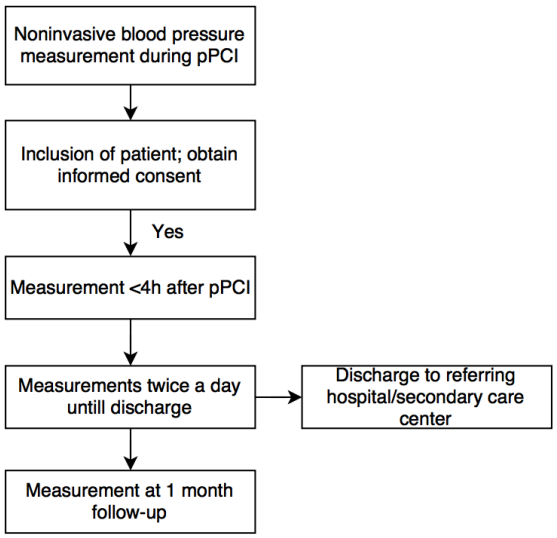


Figure 12: Flow diagram of study design of study II

Endpoint definition

In this prospective study, the change of parameters describing the blood pressure curve in time will be analyzed. Also, the change of parameters under the influence of NTG will be analyzed.

The method for analyzing the blood pressure curve is described in section *'Blood pressure waveform analysis'.*

For measurements where simultaneous recording of noninvasive and invasive was not possible, data was retrospectively synchronized through visual inspection and manual shifting of one of the two signals. The aortic blood pressure signal was downsampled from 240 to 200 Hz. Irregularities present in both signals (for example extrasystoles) were synchronized and synchronization was verified through irregularities elsewhere in the signal. Since the blood pressure signal is analyzed per beat, synchronization mismatch of up to 0.2 s is considered acceptable.

Natural frequency and damping coefficient are determined from the step response of the signal, generated by the fast-flush test. The natural frequency of the catheter system was calculated as $\frac{1}{\lambda}$ with λ the time between the first two local minima of the oscillations. For calculation of damping of the step response, the difference in amplitude of two oscillations should be determined. However, the baseline to which the pressure signal returns is not a static value, but the varying, underlying blood pressure. For this reason, an extrapolation of the blood pressure signal was made in order to determine the amplitude of the oscillations to the estimated aortic blood pressure. This extrapolation is performed by comparing a section of blood pressure to the section of pressure signal directly after the oscillations of the step response have vanished. Suppose the fast flush test is performed at t=0. The correlation between the blood pressure signal from t=1 s to t=1.5 s is calculated to the blood pressure signal between t=1.5 s and t=6.5 s. The signal is fitted to the point with the highest correlation. The height of the extrapolated signal is corrected so that the sum of the difference between the two sections of signal is minimal. Now,

the extrapolated signal is used as the baseline from which the amplitude of the oscillations is determined. The damping coefficient is calculated using equation 1. Determination of amplitudes a_1, a_2, and a_3 is shown in figure 13.

$$\zeta = -ln \frac{(\frac{A_2}{A_1})}{\sqrt{\pi^2 + (ln\frac{A_2}{A_1})^2}} \qquad \text{(Equation 1)}$$

A_1 & A_2: amplitude of oscillations. $A_1 = |a_1|+|a_2|$, $A_2 = |a_2|+|a_3|$

Data selection

For the pPCI analysis, a section of +- 15-30 s of noninvasively determined blood pressure signal was selected at the start and at the end of the procedure. Pressure signal was selected in which both signals contain very few or no visible artifacts. The moment of revascularization was determined from the integrated markers of the Nexfin which were placed during pPCI. For follow-up measurements, 15-30 s noninvasive blood pressure signal was selected from the middle of the recording, provided that the signal contains no or very few artifacts

For analysis of the change of parameters under the influence of 0.2 mg intracoronary administered nitroglycerin, sections of +- 15-30 s noninvasive blood pressure were selected just prior to administration of NTG, and at the moment of minimal MAP during two minutes after administration.

For the analysis of the fast flushes, the full recording of aortic pressure is used.

Statistical analysis

The change of blood pressure parameters over time is determined through analysis of variance between the time points. Differences between parameters at the time points is tested though analysis of variance with two factors, the fixed factor ‘patient’ and the variable factor ‘time’. This test is robust for the assumption of normality, but less robust for difference in variance between the groups. Residual plots are checked for patterns, parameters with a visual relationship between predicted and residual values are logarithmically transformed. For parameters with $p<0.05$ post hoc testing is applied to determine which time points are significantly different from each other. For these post-hoc tests, Hukey’s post-hoc analysis is used. To test significant differences of timepoint 4, Hochberg’s GT2 test is used, which is robust for different sample sizes. A p-value of < 0.05 is considered significant.

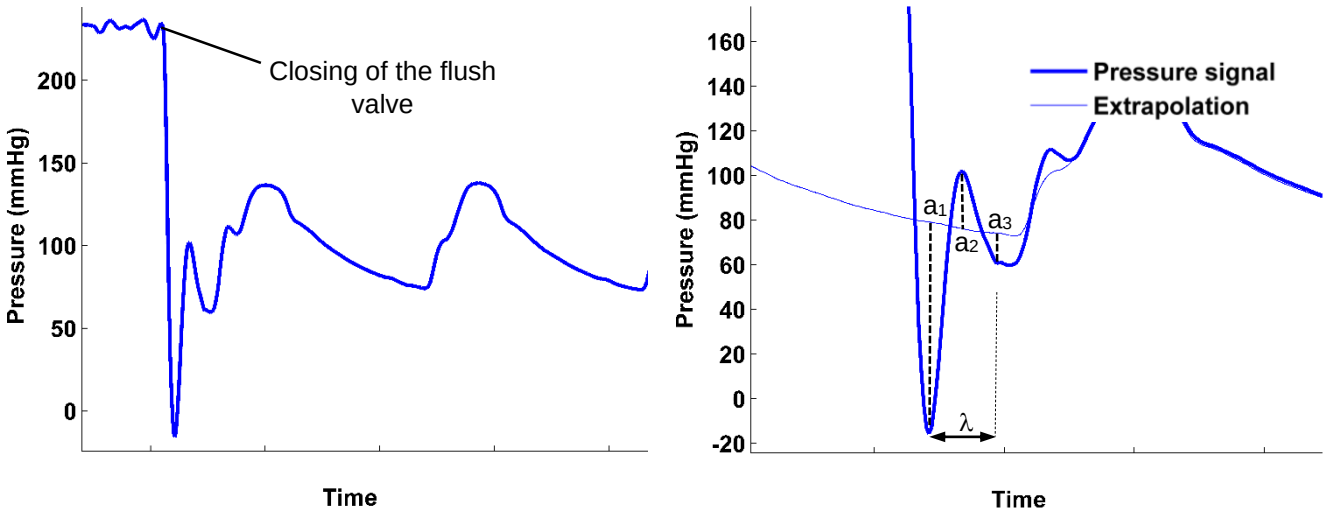


Figure 13: Fast-flush analysis. A: After closing the valve, pressure rapidly declines from ± 230 mmHg. This causes the signal to oscillate before returning the 'baseline', in this case the blood pressure signal. B: Enlarged version of A, focused on the oscillations and the extrapolation as an estimation of the baseline blood pressure. Amplitudes a_1-a_3 are determined with the use of the extrapolated baseline. λ is the time between the first two local minima of the oscillation. The natural frequency of the catheter system is $1/\lambda$.

Results

For this prospective study, blood pressure measurements were initiated for 33 patients. Of 19 patients, at least one of the inclusion criteria was not fulfilled. Two patients did not fulfill the STEMI criteria. In 5 patients no culprit lesion was found. With 2 patients, technical difficulties with the Nexfin prevented inclusion, and of 9 patients no informed consent was signed. The main reason for no informed consent was transfer to the ICU while the patients were unconscious. In this period the ICU of the AMC hospital was very busy and most of the patients were transferred to a different hospital.

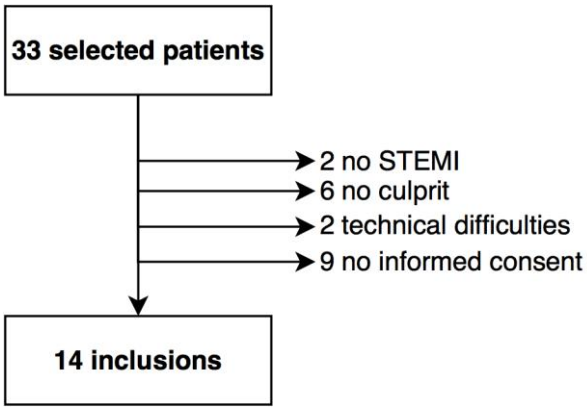


Figure 14: In- and exclusions of the prospective study

Baseline & treatment characteristics

Table 7 Baseline, PCI and treatment characteristics of patients included in this prospective study.

		n=14
Baseline characteristics		
Sex (male)		71 (10/14)
BMI (kg/m^2)		27 ± 4
Age (years)		63 ± 14.8
Hypertension		50 (7/14)
Diabetes		14 (2/14)
Dyslipidemia		38 (5/13)
Current smoker		43 (6/14)
Family history of CAD		36 (5/14)
Stroke		7 (1/14)
Peripheral artery disease		15 (2/13)
MI		7 (1/14)
PCI		14 (2/14)
CABG		0 (0/14)
PCI characteristics		
Culprit Vessel	LM	0 (0/14)
	LAD	57 (8/14)
	RCx	29 (4/14)
	RCA	14 (2/14)
Multivessel disease		14 (2/14)
Treatment		
Vasoactive medication		0 (0/14)
Mechanical ventilation		0 (0/14)

Values are presented as percentage of total(n/N) or mean ± standard deviation. BMI indicates body mass index; CAD: coronary artery disease; MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; LM: left main artery; LAD: left anterior descending artery; RXc: ramus circumflexus; RCA: right coronary artery;

Change of blood pressure parameters in time

Of the pressure parameters, a decreasing trend is seen in systolic, diastolic, dicrotic notch pressure and MAP. These four pressure parameters all decrease during follow-up. However, this change is only significant for diastolic pressure. The mean diastolic pressure decreases 11 mmHg between timepoint 1 and 4.

Four time derived parameters changed between one of the four timepoints. ‘t upstroke’ and ‘t anacrotic notch’ increase after PCI, ‘relative t upstroke’ only differs between timepoint 2 and 3. ‘t systolic downstroke’ decreases after PCI. Heart rate is not significantly different between the timepoints.

The parameters ‘t anacrotic notch’ and ‘t upstroke’ both increase from timepoint 1 to timepoint 3. Both parameters also increase from post-revascularization to the <4 hours measurement. Both parameters

have a lower mean value post-revascularization compared to pre-revascularization, but this difference is not significant.

5 parameters are significantly different in at least one of the groups, however the significance of these parameters was not strong enough to result in significant results in the post-hoc analysis. In the discussion the underlying principle will be discussed.

Change of parameters with NTG

In table 8 the blood pressure parameters are shown under the influence of 0.2 mg intracoronary administered NTG. 23 parameters changed significantly after administration of NTG.

Absolute pressure values decreased with 10 to 15%. Pulse pressure is not significantly different, but the relative dicrotic notch pressure is. It decreases from 27 to 15 mmHg. Heart rate increases with almost 10%, but of the absolute times only t downstroke is significantly shorter. Of the relative times however duration of diastole decreases with 14%, which agrees to the trend seen in figure 11.

Of the slopes only dp/dt max decreases significantly, with 25%. Of the area's, only the myocardial oxygen demand/supply ratios are not significantly different. All area's decrease with 15-30%, with relative diastolic area decreasing with 36%.

A significant decrease in systemic vascular resistance is seen, a decrease of 20%. Cardiac output and stroke volume did not significantly change under the influence of intracoronary NTG.

Table 8: Change of blood pressure parameters with 2 cc intracoronary administered nitroglycerine(0.1 mg/ml)

	Before NTG		With NTG		
	n	value	n	value	p
Classic clinical parameters					
Systolic pressure (mmHg)	8	147 ± 28	8	126 ± 23	0.052
Diastolic pressure (mmHg)	8	82 ± 12	8	71 ± 8	0.023
MAP (mmHg)	8	104 ± 17	8	90 ± 13	0.035
Pulse pressure (mmHg)	8	65 ± 18	8	55 ± 15	0.103
Heart rate (bpm)	8	77 ± 16	8	84 ± 15	0.022
Pressure derived variables					
Dicrotic notch pressure (mmHg)	8	108 ± 16	8	87 ± 13	0.006
RDNP (mmHg)	8	27 ± 8	8	15 ± 9	0.005
Dicrotic notch index (%)	8	42 ± 9	8	29 ± 18	0.010
Time derived variables					
t downstroke (s)	8	0.698 ± 0.146	8	0.616 ± 0.118	0.004
Duration diastole (s)	8	0.485 ± 0.133	8	0.418 ± 0.077	0.022
relative t upstroke	8	0.142 ± 0.043	8	0.166 ± 0.038	0.025
Slopes					
dp/dt max (mmHg / s)	8	1.159.6 ± 425.6	8	845.3 ± 313.1	0.046
RDNP / LVET (mmHg/s)	8	82.1 ± 23.4	8	46.9 ± 24.6	0.018
RDNP / t upstroke (mmHg/s)	8	254.7 ± 85.6	8	129.2 ± 77.5	0.013
Areas					
Relative AUC (mmHg.s)	8	18.2 ± 5.3	8	12.9 ± 5.3	0.011
Relative systolic AUC (mmHg.s)	8	13.2 ± 3.6	8	9.8 ± 4.2	0.028
Relative diastolic AUC (mmHg.s)	8	5.0 ± 1.8	8	3.2 ± 1.2	0.003
Absolute AUC (mmHg.s)	8	84.9 ± 17.2	8	66.9 ± 17.3	0.000
Absolute systolic AUC (mmHg.s)	8	40.0 ± 5.6	8	33.0 ± 8.9	0.016
Absolute diastolic AUC (mmHg.s)	8	45.0 ± 12.3	8	34.0 ± 8.9	0.000
Beatscope derived parameters					
BS diastolic pressure (mmHg)	7	83 ± 12	7	73 ± 9	0.047
BS MAP (mmHg)	7	107 ± 18	7	91 ± 13	0.046
BS Heart rate (bpm)	7	65 ± 14	7	72 ± 12	0.024
BS Systemic vascular resistance (dynes.s/cm5)	7	1.524 [1.245 - 2.246]	7	1.156 [1.110 - 1.882]	0.018

Values are presented as mean ± standard deviation or as median [IQR].NTG = nitroglycerin; MAP: mean arterial pressure; RDNP = relative dicrotic notch pressure; LVET: left ventricular ejection time; AUC: area under the curve;

Table 9: Change of blood pressure parameters in time

Change of brachial artery blood pressure parameters over time. Classic clinical parameters and parameters with p<0.05

	Timepoint 1		Timepoint 2		Timepoint 3		Timepoint 4		p-values						
	n	value	n	value	n	value	n	value	Between groups	Between 1 and 2	Between 1 and 3	Between 1 and 4	Between 2 and 3	Between 2 and 4	Between 3 and 4
Classic clinical parameters															
Systolic pressure (mmHg)	14	144 ± 19	14	139 ± 23	14	137 ± 23	7	126 ± 23	0.497	-	-	-	-	-	-
Diastolic pressure (mmHg)	14	81 ± 7	14	78 ± 7	14	75 ± 10	7	68 ± 6	0.047	-	-	0.009	-	-	-
MAP (mmHg)	14	102 ± 10	14	99 ± 12	14	96 ± 14	7	87 ± 10	0.171	-	-	-	-	-	-
Pulse pressure (mmHg)	14	63 ± 16	14	61 ± 18	14	62 ± 14	7	58 ± 20	0.778	-	-	-	-	-	-
Heart rate (bpm)	14	85 ± 21	14	82 ± 17	14	84 ± 16	7	83 ± 15	0.283	-	-	-	-	-	-
Time derived variables															
t systolic downstroke (s)	14	0.205 ± 0.037	14	0.213 ± 0.029	14	0.187 ± 0.025	7	0.176 ± 0.033	0.030	-	-	0.048	0.014	0.06	-
t upstroke (s)	14	0.123 ± 0.035	14	0.115 ± 0.019	14	0.141 ± 0.025	7	0.131 ± 0.018	0.002	-	0.026	-	0.002	-	-
relative t upstroke	14	0.172 ± 0.052	14	0.159 ± 0.048	14	0.194 ± 0.028	7	0.181 ± 0.041	0.003	-	-	-	0.001	-	-
relative LVET	14	0.453 ± 0.073	14	0.441 ± 0.081	14	0.456 ± 0.063	7	0.419 ± 0.051	0.020	-	-	-	-	-	-
duration systole / duration diastole	14	0.869 ± 0.277	14	0.831 ± 0.293	14	0.864 ± 0.227	7	0.740 ± 0.153	0.017	-	-	-	-	-	-
Slopes															
dp/dt max (mmHg / s)	14	1.011.9 ± 381.4	14	999.6 ± 388.5	14	843.1 ± 290.4	7	784.8 ± 320.5	0.038	-	-	0.061	-	-	-
Areas															
Relative Myocardial oxygen supply/demand ratio	14	3.7 ± 1.4	14	3.4 ± 1.4	14	3.6 ± 1.1	7	3.1 ± 1.0	0.035	-	-	-	-	-	-
Absolute Myocardial oxygen supply/demand ratio	14	1.1 ± 0.3	14	1.1 ± 0.3	14	1.1 ± 0.3	7	1.0 ± 0.2	0.035	-	-	-	-	-	-

Values are presented as mean ± standard deviation or as median [IQR]. MAP: mean arterial pressure; LVET: left ventricular ejection time; AUC: area under the curve;

Assessment of signal quality

The fast flush test was used to determine signal quality of the aortic blood pressure signal. In table 10 the results of the fast flush tests of one patient are shown as an example. Flushes 3 & 4 and 5 & 6 are conducted consecutively, with the second flush following the first within 10 s. The results show a large variation in both damping coefficient and natural frequency during the catheterization. Also small variation exists between the consecutively executed flushes 5 & 6. According to the minimal dynamic response criteria of Gardner et al. only flush 5 and 6 provide an adequate dynamic response. The other results are categorized as underdamped.

Table 10: Results of fast-flush analysis of the cardiac catheter.

The damping coefficient (zeta) and natural frequency f_n were determined. Flushes 3 & 4 and 5 & 6 were conducted 5 seconds after each other. Flushes 1 to 4 were performed before revascularization, flushes 5 to 7 were performed after revascularization.

Flush no:	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Damping coefficient ζ	0.43	0.20	0.31	0.29	0.51	0.43	0,15
Fn (Hz)	7.7	14.3	12.5	11.8	10.0	14.3	15,4
	Pre-revascularization				*Post-revascularization*		

Discussion

This study shows that only 7 parameters change during the first 24 hours after MI. None of the parameters have significantly changed between pre- and post-revascularization, suggesting pPCI causes no immediate hemodynamic changes. This could imply that PCI has no effect on hemodynamics during AMI, or it implies that these patients are hemodynamically not very impaired by the event and are able to adequately compensate for the decreased ventricular performance. Heart rate and pressure variables show a decreasing trend between pre- and post-revascularization although this change is not significant. This most likely is the effect of a decrease in stress. A 'heart attack' causes a severe stress situation for the patient. Most patients suffer from chest pains and pain is known to increases blood pressure and heart rate. When the patient is (partially) relieved from the pain and comforted by the fact that their medical problem is solved it seems very straightforward that the stress and thus blood pressure and heart rate decrease.

The 'classic' clinical parameters, systolic, diastolic, mean arterial and pulse pressure all show a slight, non-significant downward trend over time. Heart rate is equal for the first 3 time points which provides the opportunity to compare absolute time variables.

In this study, absolute dicrotic notch pressure shows a downward trend in time. This trend equals the trend of systolic and diastolic pressure in time since the dicrotic notch index does not change. The Relative dicrotic notch pressure does not change in time. From these results we conclude that RDNP is a stable parameter that is not influenced by revascularization in AMI patients. Further research should determine what factors influence the value of RDNP and if RDNP changes over time in both shock and non-shock patients.

'Absolute systolic AUC' shows a small negative trend in time, from 40 mmHg to 37.5 mmHg.s at timepoint 3 and 32.5 mmHg.s at timepoint 4. Relative systolic AUC does not change over time, which makes it likely that the change in absolute systolic AUC is caused by the decrease of diastolic pressure and heart rate.

Comparing the results of this study with the results of study I should be done with caution since blood pressure is measured at a different location, using a different measurement technique and measuring a different patient category. In this study blood pressure was measured noninvasively at the middle finger, from which brachial artery blood pressure curve was calculated using an unknown transfer function. Despite the major differences, qualitative comparison of the change in parameters from pre- to post-revascularization is possible since these measurements were repeated within the same patient, in which the patient acts as its own control.

The absolute blood pressures in this study decreases, where shock patients show an increase in absolute blood pressures. The decrease in this study is thought to reflect a decrease in stress, where the increase of blood pressure parameters in study I is thought to be the result of vasoactive medication. This alone already underlines the difference in the selected patient categories for the two studies.

In table 9 several parameters are listed with $p<0.05$, with no p values <0.05 for the post-hoc tests. This is the result of a more conservative post-hoc test compared to the F-test, which is used for testing if at the values at all timepoints are equal. This more conservative approach increases the chance of false negative results, which is seen in this study.

Nitroglycerin is a very effective drug in relieving angina but its exact, dose dependent mechanism is still not fully understood. NTG causes venous vasodilatation and in lesser amount vasodilatation of larger arteries and arterioles. This causes a decrease of central venous and arterial pressure, resulting in a reduced pre- and afterload. The change of blood pressure parameters with NTG provides insight in the change of parameters compared to each other. In absolute blood pressure parameters there is significant decrease of diastolic but not systolic pressure, no significant change of pulse pressure but significant change of relative dicrotic notch pressure. Relative dicrotic notch pressure decreases with nearly 50%. The absolute decrease of RDNP is about equal of the decrease in MAP. All area parameters significantly decrease with NTG. The systolic and diastolic area's decrease proportionally to each other

since relative and absolute myocardial oxygen supply/demand ratios are not significantly different. Also cardiac output and stroke volume are not significantly different with NTG. Stroke volume decreases with less than 5% and cardiac output does not change. This suggests that the hemodynamic changes induced by NTG are accurately compensated for.

The measurement protocol was aimed at conducting multiple measurements per patient. After AMI, patients are hospitalized for approximately one week. We aimed at continuing measurements for several days after pPCI and during the regular 1 month follow-up at the outpatient clinic in the AMC-hospital. Since the AMC is an emergency care center, patients are transferred to secondary care hospitals mostly after 4 hours after pPCI if possible. Most of these patients are followed up by a cardiologist at the regional hospital or local cardiologist. For this reason only few patients were measured for more than 24 hours after pPCI and only one patient was successfully measured at 1 month follow-up. For this lack of follow-up measurements only acute and very short term changes of the blood pressure curve could be determined.

We expected to detect more differences in the blood pressure curve morphology after pPCI. Mainly time related parameters have $p<0.05$ which can largely be explained by the change of heart rate in time. Absolute pressure parameters only show limited change, with a large standard deviation. The high standard deviation, combined with (or caused by) a low number of included patients results in high p-values.

The results of the fast-flush analysis indicate a substantial variability in both damping and natural frequency during PCI. It can be concluded that the damping and natural frequency are susceptible to change during PCI and that signal quality should be regularly assessed, or at least be determined, in order to formulate hard conclusions on the results of these measurements. Gardner et al. provide minimum requirements for damping coefficient and natural frequency of the catheter system[41]. Only flush 5 and 6 show adequate dynamic response, the other flushes are in the ‘underdamped’ part of the diagram. The diagram of Gardner et al. is added in the appendix, figure a 2. In study I of this thesis 11 out of 72 blood pressure recordings were of insufficient quality based on visual assessment and had to be excluded. The simple and easy to execute fast-flush test could provide the key to improving signal quality and reduce the aforementioned exclusions in a prospective study. For implementation, a real time flush-analysis tool should be available, and more research should be conducted on which factors can and cannot be influenced/improved during catheterization. Optimal dynamic response is required if systolic and diastolic are to be measured accurately. De Vecchi et al. demonstrated an overestimation of up to 24 % in peak systolic pressure of measurements conducted with a fluid column and external pressure transducer[42] compared to measurements using a pressure wire, which has a small pressure transducer at the tip and is therefore not subjective to the dynamic response of the catheter system. This underlines the need for quantification of the dynamic response of the catheter system.

Conclusion

Noninvasively determined blood pressure morphology, measured with the Nexfin at the middle finger and analyzed using the method as described earlier, shows limited change in the first 24 hours after pPCI for the treatment of STEMI. We were not able to detect immediate effects of revascularization on the blood pressure curve morphology in these patients. Administration of nitroglycerin causes a decrease in noninvasive RDNP of nearly 50 % while classic clinical pressure parameters decrease with 15%.

General discussion

The combination of both studies provides a new perspective on the assessment of cardiogenic shock patients. With only 61 CS patients, three parameters are identified that are different for survivors and non-survivors, namely ‘duration of systole’, ‘relative dicrotic notch pressure’ and ‘absolute systolic area under the curve’. These parameters have potential to contribute to an integrated cardiogenic shock severity parameter. Results of study I show that survivors and non-survivors present with different blood pressure morphology at the start of pPCI. We are not able to determine a cardiogenic shock grading yet, further research should increase patient numbers, determine cut-off values and determine the combination of parameters that optimally distinguishes survivors from non-survivors, before increasing the number of shock categories.

‘Classic clinical parameters’ such as systolic and diastolic pressure, MAP, but also parameters used to evaluate CS such as stroke volume, cardiac output, cardiac index and cardiac power output are individually of very limited value in determining outcome, these parameters were equal among the different CS outcome groups. It has to be noted that the cardiac output-related parameters were determined with a suboptimal technique although this was the best technique readily available for retrospective analysis.

Patients with cardiogenic shock show a different change of blood pressure parameters after revascularization compared to AMI patients without shock. In CS patients, absolute pressure variables show an increasing trend while the opposite trend is seen in patients not suffering from CS. Dp/dt max increases in CS patients post-revascularization while it decreases post-revascularization in non-CS patients. One explanation could be the relieve of chest-pain and stress in non-CS patients while CS patients are provided with vasoactive medication to support the marginal hemodynamic situation. Despite these influences

The aim of this thesis was to create an objective grading for cardiogenic shock based on the morphology of the blood pressure curve. We intended to create a multivariate model based on significant parameters from the univariate analysis. In the current state of this research, with a relatively low amount of included patients, determining a multivariate model would be of very limited value since only 2 or 3 parameters could be used in respect to the rule of thumb to use one parameter per 10 events. Also, no validation cohort is currently available to evaluate the performance of the model.

Noninvasively determined RDNP decreases with nearly 50% after administration of NTG, while absolute pressure parameters, systolic, diastolic, mean and pulse pressure decrease with 10 to 15%. If noninvasive RDNP reflects the value of aortic RDNP, RDNP with NTG approaches the value of the ‘survival’ group from study I, while absolute blood pressure parameters are well within the normal range. The change of aortic RDNP with NTG should be determined, as this could provide useful information about the dynamic behavior of ‘RDNP’. With the current data this is not possible as directly after the administration of NTG the cardiac catheter was removed from the patient.

General conclusion

The morphology of the blood pressure curve of cardiogenic shock patients not surviving hospital admission, measured before revascularization, differs from survivors. RDNP and LVET are identified as new potential markers for assessment of the depth of cardiogenic shock as an addition to the already known cardiac (power) output and area parameters.

Future perspectives & recommendations

This thesis provided new parameters for assessment of cardiogenic shock. To improve the value of these findings, more patients should be included. Both cardiogenic shock and non-cardiogenic shock patients should be analyzed to be able to assess the complete 'spectrum' of values for the different parameters, in order to determine cut-off values for the prediction of outcome with the identified parameters from study I.

Continuous blood pressure signal from the ICU should be used to evaluate parameters in time. Aortic blood pressure is not available, but more importantly not safe to continuously monitor invasively since coagulation of blood and embolization of blood clots in the proximal aorta could cause severe complications. However, peripheral arterial pressure is mostly available in these patients both during PCI and on the ICU. If these were to be recorded simultaneously on the same acquisition system, a personalized transfer function could be determined. This enables calculation of the aortic blood pressure using the peripheral blood pressure measurement. For evaluation of the dynamic response of the blood pressure measurements, fast flushes are recommended. Minimizing factors known to reduce the natural frequency of a measurement system are reduction of air bubbles throughout the measurement system, use of low compliant tubing. The system should be as short and simple as possible.

The continuous measurement of blood pressure on the ICU can provide for real time parameters to evaluate the effectiveness of therapy. Techniques for continuous monitoring of invasive or noninvasive blood pressure on the ICU are readily available. When parameters are identified as predictors of outcome, these should be continuously determined to evaluate the depth of cardiogenic shock. Consequently the effectiveness of the applied therapy can be evaluated with this method.

The influence of used materials on the quality of the blood pressure curve should be evaluated if a prospective study will be conducted using aortic blood pressure signals measured during pPCI. The main purpose of the fluid column in the inner lumen of the cardiac catheter is to guide materials such as guide wires, balloon dilators and stents to the coronary arteries. With multiple instruments inside this catheter, the quality of the blood pressure measurement could be influenced.

The presented method provides an intuitive and straightforward method for the analysis of the morphology of the blood pressure curve in time. Various other methods could be applied in the time or frequency domain with the current analysis 'platform' as fundament. Analysis in the frequency domain was not conducted since damping and natural frequency of the signals is subject to change during PCI, and therefore signal and noise are difficult to distinguish. With adequate filtering or transformation of the signals, analysis in the frequency domain could provide for additional parameters.

We recommend development of a standardized test to assess blood pressure signal quality. The fast-flush test could provide for this purpose since it is easy to execute, fast and inexpensive. A real time analysis method should be developed for real-time calculation of signal characteristics.

The analysis method should be validated. The assessment of correct placement of markers in study I is a subjective and imprecise method. Although it was sufficient for the purpose of this thesis, for determination of a cardiogenic shock grading more accuracy is desirable.

If the patient cohort is expanded, a multivariate regression model should be determined based on different combinations of significant parameters in the univariate model

The measurements from study II should be transformed to aortic pressure signals using Beatscope. In the current study design, brachial pressure was used for analysis, which was sufficient for determining changes of blood pressure parameters. However, for comparison of these signals with results from study I, transformation to an aortic blood pressure signal is desirable.

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Appendix

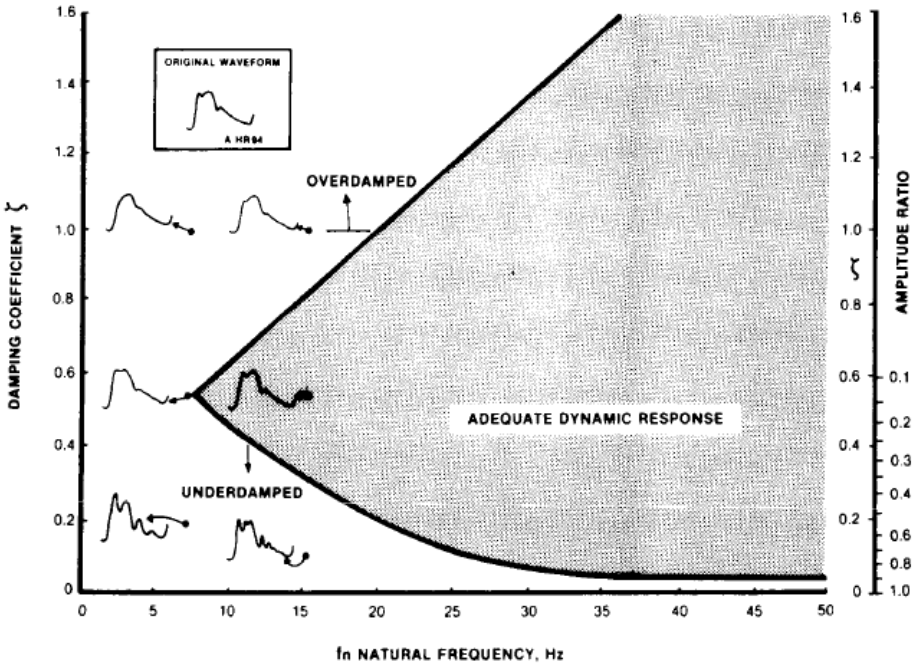

Figure A 2. Dynamic response criteria as described by Gardner et al.. Combinations of damping coefficient and natural frequency inside the marked area have an adequate dynamic response. Figure after Gardner et al.[41]

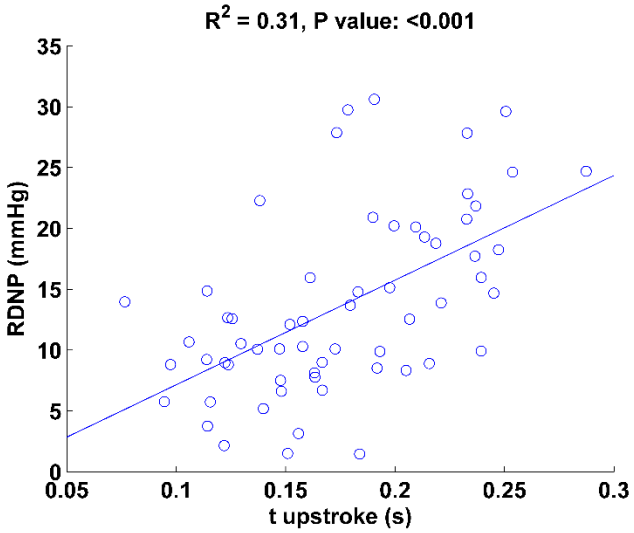

Figure A 1. Relationship between RDNP and t upstroke. Equation of fitted line: $y = 86x - 1.5$

Table A 1: Study I: Results pre-revascularization. Blood pressure measured in the proximal aorta (Part 1)

	Cardiac death		No cardiac death		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)	11	86 ± 23	14	85 ± 22	36	93 ± 17		0.326	0.136	0.502
Diastolic pressure (mmHg)	11	59 ± 14	14	57 ± 15	36	63 ± 16		0.428	0.224	0.777
MAP (mmHg)	11	68 ± 16	14	66 ± 17	36	73 ± 15		0.359	0.167	0.651
Pulse pressure (mmHg)	11	22 [18 - 36]	14	25 [21 - 37]	36	29 [24 - 35]		0.354	0.187	0.223
Anacrotic notch pressure (mmHg)	7	6 [4 - 14]	13	7 [4 - 8]	24	8 [4 - 12]		0.503	0.383	0.785
Dicrotic notch pressure (mmHg)	11	71 ± 19	14	68 ± 17	36	78 ± 18		0.181	0.071	0.516
RDNP (mmHg)	11	8 [6 - 21]	14	10 [8 - 15]	36	14 [10 - 20]	•	0.045	0.014	0.088
Dicrotic notch index (%)	11	41 ± 16	14	41 ± 0.18	36	50 ± 18	•	0.145	0.049	0.306
Augmentation index (%)	7	31 ± 12	13	22 ± 0.11	24	27 ± 14		0.300	0.576	0.316
Time derived variables										
t systolic downstroke (s)	11	0.13 ± 0.03	14	0.15 ± 0.04	36	0.14 ± 0.04		0.415	0.827	0.338
t dp/dt max (s)	11	0.06 [0.04 - 0.07]	14	0.05 [0.04 - 0.07]	36	0.06 [0.04 - 0.07]		0.887	0.639	0.881
t anacrotic notch (s)	7	0.12 [0.08 - 0.18]	13	0.13 [0.12 - 0.21]	24	0.13 [0.10 - 0.15]		0.458	0.689	0.395
t upstroke (s)	11	0.16 ± 0.04	14	0.16 ± 0.04	36	0.19 ± 0.05	•	0.107	0.034	0.267
t downstroke (s)	11	0.47 [0.41 - 0.53]	14	0.50 [0.46 - 0.59]	36	0.52 [0.45 - 0.59]		0.269	0.428	0.107
Heart rate (bpm)	11	97 ± 15	14	88 ± 18	36	88 ± 15		0.231	0.329	0.085
Duration systole(LVET) (s)	11	0.29 ± 0.04	14	0.31 ± 0.04	36	0.32 ± 0.05	•	0.063	0.039	0.036
Duration diastole (s)	11	0.32 [0.28 - 0.38]	14	0.33 [0.27 - 0.48]	36	0.37 [0.31 - 0.45]		0.496	0.319	0.277
relative t upstroke	11	0.25 ± 0.04	14	0.23 ± 0.06	36	0.27 ± 0.06		0.123	0.077	0.859
relative t dp/dt max	11	0.10 [0.06 - 0.11]	14	0.07 [0.07 - 0.09]	36	0.08 [0.06 - 0.11]		0.640	0.660	0.348
relative LVET	11	0.47 ± 0.07	14	0.45 ± 0.11	36	0.47 ± 0.07		0.884	0.720	0.933
relative t anacrotic notch	7	0.20 [0.11 - 0.31]	13	0.20 [0.15 - 0.32]	24	0.19 [0.14 - 0.23]		0.757	0.671	0.736
duration systole / duration diastole	11	0.87 [0.73 - 1.06]	14	0.82 [0.62 - 1.19]	36	0.89 [0.68 - 1.05]		0.925	0.792	0.925

Values are presented as mean ± standard deviation or as median [IQR]. MAP: mean arterial pressure; RDNP: relative dicrotic notch pressure LVET: left ventricular ejection time; ; AUC: area under the curve;

• indicates parameters with p<0.05

Table A 2 Study I: Results pre-revascularization Blood pressure measured in the proximal aorta (part 2)

	Cardiac death		No cardiac death		Survival			p-values		
	n	value	n	value	n	value		Between groups	Survival vs non-survival	Cardiac recovery vs no cardiac recovery
Slopes										
dp/dt max (mmHg / s)	11	341 [320 - 612]	14	383 [292 - 469]	36	412 [304 - 505]		0.910	0.681	0.910
dp/dt diastole - systolic max (mmHg / s)	11	153 [102 - 227]	14	179 [135 - 237]	36	154 [120 - 213]		0.779	0.681	0.807
dp/dt systolic max - diastole (mmHg / s)	11	-50 [-60 - -40]	14	-49 [-68 - -40]	36	-58 [-66 - -50]		0.318	0.135	0.302
dp/dt systolic max - dicrotic notch (mmHg / s)	11	-123 [-138 - -94]	14	-101 [-163 - -81]	36	-112 [-129 - -88]		0.796	0.681	0.499
dp/dt dicrotic notch - diastole (mmHg / s)	11	-24 [-40 - -19]	14	-31 [-42 - -16]	36	-39 [-52 - -29]	•	0.064	0.019	0.189
RDNP / LVET (mmHg/s)	11	25.6 [23.9 - 62.5]	14	31.7 [25.7 - 45.8]	36	47.4 [31.9 - 63.2]	•	0.095	0.031	0.159
RDNP / t upstroke (mmHg/s)	11	50.1 [42.0 - 92.4]	14	69.9 [52.8 - 79.6]	36	81.7 [62.1 - 100.1]		0.157	0.063	0.149
Areas										
Relative AUC (mmHg.s)	11	4.7 [3.4 - 9.1]	14	7.2 [5.2 - 8.9]	36	7.4 [5.7 - 10.4]		0.110	0.069	0.058
Relative systolic AUC (mmHg.s)	11	4.1 [2.7 - 4.9]	14	5.0 [3.9 - 6.4]	36	5.7 [4.2 - 7.4]	•	0.086	0.051	0.049
Relative diastolic AUC (mmHg.s)	11	0.8 [0.6 - 3.2]	14	1.5 [1.0 - 2.4]	36	2.1 [1.2 - 3.3]		0.159	0.065	0.143
Absolute AUC (mmHg.s)	11	42.4 [29.3 - 55.4]	14	45.7 [39.3 - 51.8]	36	49.8 [42.4 - 67.7]		0.178	0.078	0.138
Absolute systolic AUC (mmHg.s)	11	22.4 ± 7.1	14	22.9 ± 5.2	36	27.0 ± 7.3		0.060	0.017	0.145
Absolute diastolic AUC (mmHg.s)	11	19.5 [16.1 - 24.3]	14	23.9 [15.5 - 26.7]	36	25.7 [19.2 - 34.3]		0.210	0.110	0.129
Relative Myocardial oxygen supply/demand ratio	11	2.4 [2.1 - 4.1]	14	2.9 [1.6 - 4.9]	36	2.6 [1.7 - 3.9]		0.971	0.826	0.970
Absolute Myocardial oxygen supply/demand ratio	11	1.0 [0.9 - 1.4]	14	1.0 [0.7 - 1.4]	36	1.1 [0.8 - 1.3]		0.918	0.814	0.881
Beatscope derived parameters										
BS systolic pressure (mmHg)	11	86 ± 23	14	85 ± 22	36	93 ± 17		0.344	0.147	0.530
BS diastolic pressure (mmHg)	11	59 ± 14	14	56 ± 15	36	62 ± 15		0.434	0.236	0.817
BS MAP (mmHg)	11	70 ± 18	14	68 ± 17	36	76 ± 16		0.297	0.127	0.569
BS Heart rate (bpm)	11	97 ± 15	14	88 ± 18	36	87 ± 18		0.304	0.335	0.122
BS LVET (s)	11	0.28 ± 0.05	14	0.30 ± 0.04	36	0.32 ± 0.04	•	0.058	0.035	0.036
BS Stroke Volume (ml)	11	51 [40 - 55]	14	54 [48 - 63]	36	59 [46 - 68]		0.189	0.107	0.107
BS Cardiac output (L/min)	11	4.4 [3.9 - 5.5]	14	4.7 [3.5 - 6.3]	36	5.0 [4.3 - 6.0]		0.625	0.333	0.561
BS Systemic vascular resistance (dynes.s/cm5)	11	1.187 [1.008 - 1.343]	14	1.156 [941 - 1.424]	36	1.191 [884 - 1.661]		0.519	0.725	0.955
BS Cardiac index (L/min/m2)	11	2.2 [1.9 - 2.5]	14	2.3 [1.7 - 3.1]	36	2.4 [2.1 - 2.9]		0.869	0.284	0.348
Cardiac power output (W)	11	0.78 ± 0.37	14	0.75 ± 0.36	36	0.87 ± 0.29		0.455	0.212	0.582

Values are presented as mean ± standard deviation or as median [IQR]. MAP: mean arterial pressure; RDNP: relative dicrotic notch pressure LVET: left ventricular ejection time; ; AUC: area under the curve;

• indicates parameters with $p<0.05$

Table A 3 Study I: Results pre-post revascularization. Blood pressure measured in the proximal aorta. (Part 1)

	Cardiac death		No cardiac death		Survival			p-values		
	n	value	n	value	n	value		Between groups	Survival vs. no survival	Cardiac recovery vs. no cardiac recovery
		Pre revasc. | Post revasc.		Pre revasc. | Post revasc.		Pre revasc. | Post revasc.				
Pressure derived variables										
Systolic pressure (mmHg)	7	88 ± 24 | 104 ± 33	13	83 ± 21 | 99 ± 14	33	93 ± 17 | 102 ± 19		0.481	0.574	0.225
Diastolic pressure (mmHg)	7	59 ± 13 | 68 ± 14	13	56 ± 15 | 66 ± 11	33	63 ± 15 | 69 ± 12		0.424	0.674	0.199
MAP (mmHg)	7	69 ± 16 | 80 ± 20	13	65 ± 17 | 77 ± 12	33	73 ± 15 | 80 ± 14		0.371	0.599	0.163
Pulse pressure (mmHg)	7	22 [21 - 36] | 33 [18 - 53]	13	25 [21 - 29] | 34 [30 - 35]	33	29 [23 - 36] | 30 [24 - 37]		0.657	0.660	0.357
Anacrotic notch pressure (mmHg)	3	13 [3 - 14] | 4 [1 - 19]	8	6 [2 - 8] | 5 [4 - 9]	21	8 [4 - 12] | 7 [5 - 15]		0.731	0.425	0.746
Dicrotic notch pressure (mmHg)	7	73 ± 21 | 81 ± 24	13	68 ± 17 | 81 ± 12	33	78 ± 18 | 86 ± 16		0.528	0.885	0.368
RDNP (mmHg)	7	9 [6 - 22] | 7 [3 - 21]	13	10 [9 - 15] | 13 [12 - 21]	33	14 [10 - 20] | 16 [10 - 22]		0.358	0.345	0.648
Dicrotic notch index (%)	7	44 ± 18 | 33 ± 13	13	42 ± 17 | 46 ± 17	33	51 ± 19 | 50 ± 17		0.280	0.186	0.912
Augmentation index (%)	3	33 ± 16 | 15 ± 10	8	21 ± 12 | 23 ± 18	21	27 ± 13 | 30 ± 16	•	0.039	0.012	0.144
Time derived variables										
t systolic downstroke (s)	7	0.11 ± 0.03 | 0.16 ± 0.04	13	0.15 ± 0.04 | 0.14 ± 0.04	33	0.14 ± 0.04 | 0.14 ± 0.04	•	0.052	0.023	0.707
t dp/dt max (s)	7	0.05 [0.04 - 0.07] | 0.06 [0.04 - 0.07]	13	0.05 [0.04 - 0.06] | 0.05 [0.05 - 0.06]	33	0.06 [0.05 - 0.07] | 0.05 [0.05 - 0.06]		0.223	0.318	0.085
t anacrotic notch (s)	3	0.08 [0.07 - 0.18] | 0.14 [0.06 - 0.14]	8	0.13 [0.12 - 0.21] | 0.13 [0.12 - 0.17]	21	0.13 [0.11 - 0.16] | 0.12 [0.10 - 0.17]		0.920	0.707	0.765
t upstroke (s)	7	0.17 ± 0.05 | 0.13 ± 0.02	13	0.16 ± 0.04 | 0.17 ± 0.05	33	0.19 ± 0.05 | 0.19 ± 0.05		0.106	0.063	0.959
t downstroke (s)	7	0.47 [0.42 - 0.58] | 0.48 [0.40 - 0.58]	13	0.50 [0.47 - 0.59] | 0.51 [0.47 - 0.56]	33	0.52 [0.45 - 0.59] | 0.58 [0.49 - 0.66]	•	0.067	0.415	0.022
Heart rate (bpm)	7	93 ± 15 | 97 ± 13	13	87 ± 18 | 89 ± 14	33	88 ± 15 | 82 ± 18	•	0.046	0.128	0.014
Duration systole(LVET) (s)	7	0.28 ± 0.04 | 0.30 ± 0.04	13	0.31 ± 0.03 | 0.31 ± 0.06	33	0.32 ± 0.05 | 0.33 ± 0.05		0.933	0.895	0.714
Duration diastole (s)	7	0.38 [0.29 - 0.49] | 0.33 [0.27 - 0.39]	13	0.34 [0.31 - 0.48] | 0.36 [0.30 - 0.41]	33	0.38 [0.31 - 0.45] | 0.45 [0.35 - 0.51]	•	0.061	0.088	0.023
relative t upstroke	7	0.25 ± 0.05 | 0.21 ± 0.05	13	0.22 ± 0.05 | 0.25 ± 0.05	33	0.27 ± 0.06 | 0.25 ± 0.05	•	0.049	0.308	0.166
relative t dp/dt max	7	0.09 [0.05 - 0.11] | 0.09 [0.05 - 0.13]	13	0.07 [0.07 - 0.09] | 0.08 [0.07 - 0.10]	33	0.08 [0.06 - 0.11] | 0.07 [0.06 - 0.09]	•	0.055	0.074	0.022
relative LVET	7	0.43 ± 0.06 | 0.47 ± 0.06	13	0.44 ± 0.10 | 0.46 ± 0.06	33	0.47 ± 0.07 | 0.44 ± 0.07	•	0.082	0.112	0.031
relative t anacrotic notch	3	0.11 [0.08 - 0.31] | 0.24 [0.09 - 0.28]	8	0.16 [0.15 - 0.26] | 0.22 [0.18 - 0.25]	21	0.19 [0.15 - 0.24] | 0.18 [0.13 - 0.23]		0.606	0.635	0.314
duration systole / duration diastole	7	0.82 [0.63 - 0.88] | 0.82 [0.78 - 1.00]	13	0.79 [0.62 - 1.09] | 0.87 [0.70 - 1.05]	33	0.88 [0.70 - 1.05] | 0.78 [0.63 - 0.93]	•	0.091	0.080	0.044

Values are presented as mean ± standard deviation or as median [IQR]. Pre revasc.: Pre revascularization; Post revasc.: post revascularization. MAP: mean arterial pressure; RDNP: relative dicrotic notch pressure; LVET: left ventricular ejection time; AUC: area under the curve;

• indicates parameters with p<0.05

Table A 4: Study I: results pre-post revascularization. Blood pressure measured in the proximal aorta. (Part 2)

	Cardiac death		No cardiac death		Survival		p-values		
	n	value	n	value	n	value	Between groups	Survival vs. no survival	Cardiac recovery vs. no cardiac recovery
		Pre revasc. | Post revasc.		Pre revasc. | Post revasc.		Pre revasc. | Post revasc.			
Slopes									
dp/dt max (mmHg / s)	7	382 [330 - 612] | 418 [257 - 1.209]	13	368 [292 - 469] | 490 [333 - 618]	33	384 [301 - 497] | 432 [362 - 539]	0.486	0.228	0.573
dp/dt diastole - systolic max (mmHg / s)	7	153 [129 - 227] | 225 [119 - 518]	13	170 [135 - 195] | 184 [150 - 252]	33	145 [120 - 198] | 170 [122 - 221]	0.289	0.115	0.441
dp/dt systolic max - diastole (mmHg / s)	7	-50 [-60 - -40] | -68 [-93 - -37]	13	-47 [-59 - -40] | -65 [-73 - -55]	33	-58 [-65 - -51] | -54 [-61 - -44]	0.194	0.854	0.099
dp/dt systolic max - dicrotic notch (mmHg / s)	7	-125 [-138 - -109] | -124 [-205 - -76]	13	-100 [-125 - -81] | -133 [-150 - -101]	33	-112 [-130 - -86] | -111 [-146 - -91]	0.742	0.478	0.927
dp/dt dicrotic notch - diastole (mmHg / s)	7	-24 [-44 - -16] | -27 [-48 - -9]	13	-28 [-42 - -16] | -43 [-51 - -28]	33	-39 [-51 - -29] | -34 [-45 - -26]	0.152	0.497	0.223
RDNP / LVET (mmHg/s)	7	28.8 [24.0 - 84.2] | 30.4 [13.2 - 62.3]	13	32.6 [28.5 - 45.8] | 46.7 [34.2 - 66.4]	33	46.1 [30.7 - 65.4] | 47.4 [31.0 - 68.1]	0.390	0.380	0.639
RDNP / t upstroke (mmHg/s)	7	60.8 [42.0 - 110.2] | 64.0 [24.1 - 200.7]	13	71.1 [54.3 - 79.6] | 79.4 [72.9 - 95.2]	33	81.0 [61.3 - 100.8] | 81.6 [60.0 - 103.7]	0.102	0.733	0.582
Areas									
Relative AUC (mmHg.s)	7	6.0 [3.4 - 13.4] | 5.0 [3.7 - 15.0]	13	6.9 [5.2 - 8.6] | 7.9 [6.3 - 10.5]	33	7.4 [5.9 - 10.5] | 9.5 [6.1 - 12.1]	0.737	0.511	0.971
Relative systolic AUC (mmHg.s)	7	4.1 [2.7 - 9.2] | 4.3 [2.7 - 11.7]	13	4.9 [3.9 - 5.9] | 6.0 [4.5 - 7.2]	33	5.8 [4.0 - 7.6] | 6.4 [4.8 - 8.2]	0.835	0.726	0.548
Relative diastolic AUC (mmHg.s)	7	1.9 [0.8 - 4.3] | 0.8 [0.2 - 3.3]	13	1.6 [1.0 - 2.4] | 1.8 [1.4 - 2.3]	33	2.1 [1.2 - 3.4] | 2.7 [1.7 - 4.4]	0.186	0.079	0.177
Absolute AUC (mmHg.s)	7	46.8 [29.3 - 68.4] | 44.5 [36.4 - 67.7]	13	45.3 [39.3 - 51.8] | 52.9 [49.1 - 55.4]	33	50.7 [42.5 - 68.1] | 62.8 [52.3 - 73.8]	0.895	0.713	0.660
Absolute systolic AUC (mmHg.s)	7	22.3 ± 8.1 | 27.1 ± 10.1	13	22.1 ± 4.6 | 26.9 ± 4.8	33	27.1 ± 7.3 | 30.0 ± 5.8	0.394	0.655	0.180
Absolute diastolic AUC (mmHg.s)	7	23.0 [16.8 - 36.4] | 25.4 [17.2 - 33.0]	13	25.2 [21.6 - 26.7] | 27.4 [23.2 - 30.2]	33	25.6 [19.5 - 34.8] | 35.3 [24.6 - 38.2]	0.468	0.356	0.240
Relative Myocardial oxygen supply/demand ratio	7	2.2 [2.1 - 3.7] | 3.5 [1.8 - 3.8]	13	2.9 [1.6 - 4.0] | 2.7 [2.2 - 3.5]	33	2.5 [1.7 - 3.9] | 2.2 [1.7 - 2.9]	0.165	0.198	0.064
Absolute Myocardial oxygen supply/demand ratio	7	0.9 [0.7 - 1.0] | 1.1 [1.0 - 1.2]	13	0.9 [0.7 - 1.4] | 1.0 [0.8 - 1.2]	33	1.1 [0.8 - 1.3] | 0.9 [0.8 - 1.1]	0.104	0.074	0.059
Beatscope derived parameters									
BS systolic pressure (mmHg)	7	88 ± 24 | 103 ± 33	13	83 ± 21 | 99 ± 14	33	93 ± 17 | 102 ± 19	0.494	0.594	0.233
BS diastolic pressure (mmHg)	7	59 ± 13 | 68 ± 14	13	56 ± 15 | 66 ± 11	33	63 ± 15 | 69 ± 12	0.424	0.674	0.199
BS MAP (mmHg)	7	71 ± 18 | 82 ± 22	13	67 ± 18 | 79 ± 12	33	76 ± 15 | 83 ± 15	0.549	0.697	0.278
BS Heart rate (bpm)	7	93 ± 15 | 97 ± 13	13	87 ± 19 | 89 ± 14	33	87 ± 18 | 82 ± 19	• 0.042	0.128	0.013
BS LVET (s)	7	0.28 ± 0.06 | 0.27 ± 0.05	13	0.29 ± 0.04 | 0.30 ± 0.05	33	0.32 ± 0.05 | 0.32 ± 0.05	0.736	0.537	0.911
BS Stroke Volume (ml)	7	51 [40 - 73] | 48 [35 - 73]	13	53 [48 - 63] | 54 [49 - 67]	33	58 [46 - 68] | 59 [48 - 66]	0.600	0.528	0.714
BS Cardiac output (L/min)	7	4.4 [3.9 - 5.5] | 5.0 [4.1 - 7.3]	13	4.6 [3.5 - 6.0] | 4.5 [4.1 - 6.4]	33	4.9 [4.3 - 5.8] | 4.6 [3.8 - 5.6]	0.225	0.599	0.091
BS Systemic vascular resistance (dynes.s/cm5)	7	1.187 [985 - 1.261] | 1.345 [1.093 - 1.706]	13	1.166 [941 - 1.424] | 1.266 [1.065 - 1.622]	33	1.207 [966 - 1.684] | 1.472 [1.122 - 1.957]	0.736	0.793	0.441
BS Cardiac index (L/min/m2)	7	2.2 [1.9 - 2.5] | 2.5 [1.9 - 3.3]	13	2.3 [1.7 - 3.1] | 2.2 [2.1 - 3.3]	33	2.4 [2.1 - 2.6] | 2.3 [1.9 - 2.8]	0.263	0.674	0.115
Cardiac power output (W)	7	0.78 ± 0.38 | 0.97 ± 0.55	13	0.72 ± 0.36 | 0.89 ± 0.25	33	0.85 ± 0.28 | 0.85 ± 0.24	0.216	0.351	0.079

Values are presented as mean ± standard deviation or as median [IQR]. Pre revasc.: Pre revascularization; Post revasc.: post revascularization. MAP: mean arterial pressure; RDNP: relative dicrotic notch pressure; LVET: left ventricular ejection time; AUC: area und

• indicates parameters with p<0.05

Table A 5: Study II: Results: Change of blood pressure parameters in time. Noninvasively measured digital blood pressure (Nexfin), transformed to brachial blood pressure. (Part 1)

	Timepoint 1		Timepoint 2		Timepoint 3		Timepoint 4		p-values						
	n	value	n	value	n	value	n	value	Between groups	Between 1 and 2	Between 1 and 3	Between 1 and 4	Between 2 and 3	Between 2 and 4	Between 3 and 4
Pressure derived variables															
Systolic pressure (mmHg)	14	144 ± 19	14	139 ± 23	14	137 ± 23	7	126 ± 23	0.497	-	-	-	-	-	-
Diastolic pressure (mmHg)	14	81 ± 7	14	78 ± 7	14	75 ± 10	7	68 ± 6	0.047 •	-	-	0.009	-	-	-
MAP (mmHg)	14	102 ± 10	14	99 ± 12	14	96 ± 14	7	87 ± 10	0.171	-	-	-	-	-	-
Pulse pressure (mmHg)	14	63 ± 16	14	61 ± 18	14	62 ± 14	7	58 ± 20	0.778	-	-	-	-	-	-
Anacrotic notch pressure (mmHg)	14	14 ± 13	14	9 ± 6	14	23 ± 14	7	13 ± 9	0.302	-	-	-	-	-	-
Dicrotic notch pressure (mmHg)	14	104 ± 13	14	101 ± 16	14	97 ± 16	7	90 ± 11	0.414	-	-	-	-	-	-
RDNP (mmHg)	14	23 ± 8	14	23 ± 9	14	22 ± 8	7	22 ± 9	0.450	-	-	-	-	-	-
Dicrotic notch index (%)	14	37 ± 11	14	37 ± 10	14	36 ± 11	7	38 ± 11	0.396	-	-	-	-	-	-
Augmentation index (%)	14	22 ± 20	14	15 ± 11	14	35 ± 18	7	21 ± 14	0.615	-	-	-	-	-	-
Time derived variables															
t systolic downstroke (s)	14	0.205 ± 0.037	14	0.213 ± 0.029	14	0.187 ± 0.025	7	0.176 ± 0.033	0.030 •	-	-	0.048	0.014	0.06	-
t dp/dt max (s)	14	0.051 ± 0.008	14	0.050 ± 0.006	14	0.055 ± 0.011	7	0.056 ± 0.011	0.128	-	-	-	-	-	-
t anacrotic notch (s)	14	0.156 ± 0.083	14	0.139 ± 0.053	14	0.225 ± 0.079	7	0.147 ± 0.085	0.785	-	-	-	-	-	-
t upstroke (s)	14	0.123 ± 0.035	14	0.115 ± 0.019	14	0.141 ± 0.025	7	0.131 ± 0.018	0.002 •	-	0.026	-	0.002	-	-
t downstroke (s)	14	0.622 ± 0.148	14	0.651 ± 0.144	14	0.595 ± 0.113	7	0.613 ± 0.131	0.110	-	-	-	-	-	-
Heart rate (bpm)	14	85 ± 21	14	82 ± 17	14	84 ± 16	7	83 ± 15	0.283	-	-	-	-	-	-
Duration systole(LVET) (s)	14	0.329 ± 0.043	14	0.328 ± 0.028	14	0.329 ± 0.034	7	0.307 ± 0.039	0.483	-	-	-	-	-	-
Duration diastole (s)	14	0.418 ± 0.129	14	0.439 ± 0.132	14	0.408 ± 0.111	7	0.437 ± 0.108	0.084 •	-	-	-	-	-	-
relative t upstroke	14	0.172 ± 0.052	14	0.159 ± 0.048	14	0.194 ± 0.028	7	0.181 ± 0.041	0.003 •	-	-	-	0.001	-	-
relative t dp/dt max	14	0.072 ± 0.023	14	0.068 ± 0.017	14	0.076 ± 0.016	7	0.078 ± 0.024	0.572	-	-	-	-	-	-
relative LVET	14	0.453 ± 0.073	14	0.441 ± 0.081	14	0.456 ± 0.063	7	0.419 ± 0.051	0.020 •	-	-	-	-	-	-
relative t anacrotic notch	14	0.216 ± 0.135	14	0.183 ± 0.088	14	0.295 ± 0.105	7	0.201 ± 0.112	0.967	-	-	-	-	-	-
duration systole / duration diastole	14	0.869 ± 0.277	14	0.831 ± 0.293	14	0.864 ± 0.227	7	0.740 ± 0.153	0.017 •	-	-	-	-	-	-

Values are presented as mean ± standard deviation or as median [IQR]. Pre revasc.: Pre revascularization; Post revasc.: post revascularization, MAP: mean arterial pressure; RDNP: relative dicrotic notch pressure; LVET: left ventricular ejection time; AUC: area under the curve;

- indicates $p<0.05$

Timepoint 1: pre revascularization, Timepoint 2: post revascularization, Timepoint 3: <4 hours after pPCI, Timepoint 4: <24 hours after pPCI

Table A 6 Study II: Results: Change of blood pressure parameters in time. Noninvasively measured digital blood pressure (Nexfin), transformed to brachial blood pressure. (Part 2)

	Timepoint 1		Timepoint 2		Timepoint 3		Timepoint 4		p-values							
	n	value	n	value	n	value	n	value	Between groups		Between 1 and 2	Between 1 and 3	Between 1 and 4	Between 2 and 3	Between 2 and 4	Between 3 and 4
Slopes																
dp/dt max (mmHg / s)	14	1.011.9 ± 381.4	14	999.6 ± 388.5	14	843.1 ± 290.4	7	784.8 ± 320.5	0.038	•	-	-	0.061	-	-	-
dp/dt diastole - systolic max (mmHg / s)	14	549.8 ± 192.7	14	556.4 ± 206.8	14	451.8 ± 123.6	7	447.9 ± 130.6	0.055		-	-	-	-	-	-
dp/dt systolic max - diastole (mmHg / s)	14	-105.2 ± 29.7	14	-95.0 ± 27.2	14	-108.9 ± 32.9	7	-95.5 ± 25.1	0.214		-	-	-	-	-	-
dp/dt systolic max - dicrotic notch (mmHg / s)	14	-201.9 ± 71.9	14	-180.5 ± 56.4	14	-216.1 ± 67.8	7	-205.0 ± 55.0	0.088		-	-	-	-	-	-
dp/dt dicrotic notch - diastole (mmHg / s)	14	-56.3 ± 11.9	14	-52.0 ± 14.3	14	-56.2 ± 20.7	7	-50.5 ± 18.5	0.851		-	-	-	-	-	-
RDNP / LVET (mmHg/s)	14	70.9 ± 21.9	14	70.5 ± 28.2	14	67.5 ± 24.2	7	70.3 ± 21.3	0.332		-	-	-	-	-	-
RDNP / t upstroke (mmHg/s)	14	194.9 ± 70.8	14	205.8 ± 84.1	14	156.5 ± 51.1	7	165.3 ± 55.7	0.060		-	-	-	-	-	-
Areas																
Relative AUC (mmHg.s)	14	17.0 ± 6.4	14	16.9 ± 6.6	14	16.2 ± 5.2	7	15.0 ± 7.1	0.677		-	-	-	-	-	-
Relative systolic AUC (mmHg.s)	14	12.9 ± 4.5	14	12.5 ± 4.8	14	12.5 ± 4.2	7	11.1 ± 5.9	0.890		-	-	-	-	-	-
Relative diastolic AUC (mmHg.s)	14	4.2 ± 2.2	14	4.5 ± 2.2	14	3.8 ± 1.5	7	3.9 ± 1.6	0.218		-	-	-	-	-	-
Absolute AUC (mmHg.s)	14	78.3 ± 19.7	14	78.2 ± 20.1	14	71.6 ± 13.9	7	66.4 ± 15.6	0.255		-	-	-	-	-	-
Absolute systolic AUC (mmHg.s)	14	39.9 ± 7.9	14	38.5 ± 7.5	14	37.5 ± 7.8	7	32.5 ± 9.5	0.422		-	-	-	-	-	-
Absolute diastolic AUC (mmHg.s)	14	38.5 ± 13.0	14	39.7 ± 14.4	14	34.2 ± 8.5	7	33.9 ± 8.1	0.185		-	-	-	-	-	-
Relative Myocardial oxygen supply/demand ratio	14	3.7 ± 1.4	14	3.4 ± 1.4	14	3.6 ± 1.1	7	3.1 ± 1.0	0.035	•	-	-	-	-	-	-
Absolute Myocardial oxygen supply/demand ratio	14	1.1 ± 0.3	14	1.1 ± 0.3	14	1.1 ± 0.3	7	1.0 ± 0.2	0.035	•	-	-	-	-	-	-
Beatscope derived parameters																
BS systolic pressure (mmHg)	13	145 ± 20	13	139 ± 24	13	138 ± 24	6	128 ± 25	0.681		-	-	-	-	-	-
BS diastolic pressure (mmHg)	13	82 ± 8	13	79 ± 8	13	76 ± 11	6	70 ± 4	0.167		-	-	-	-	-	-
BS MAP (mmHg)	13	105 ± 11	13	101 ± 13	13	99 ± 16	6	91 ± 11	0.496		-	-	-	-	-	-
BS Heart rate (bpm)	13	72 ± 17	13	69 ± 15	13	71 ± 13	6	71 ± 13	0.240		-	-	-	-	-	-
BS LVET (s)	13	0.327 ± 0.034	13	0.329 ± 0.025	13	0.315 ± 0.025	6	0.306 ± 0.032	0.028	•	-	-	-	-	0.027	-
BS Stroke Volume (ml)	13	74.9 ± 16.5	13	75.1 ± 19.2	13	80.6 ± 19.3	6	83.2 ± 13.0	0.082		-	-	-	-	-	-
BS Cardiac output (L/min)	13	5.4 ± 1.5	13	5.1 ± 1.5	13	5.7 ± 1.8	6	5.8 ± 0.5	0.218		-	-	-	-	-	-
BS Systemic vascular resistance (dynes.s/cm5)	13	1.762 ± 932	13	1.736 ± 703	13	1.537 ± 608	6	1.264 ± 202	0.287		-	-	-	-	-	-
BS Cardiac index (L/min/m2)	13	2.7 ± 0.8	13	2.6 ± 0.8	13	2.9 ± 0.8	6	3.0 ± 0.7	0.279		-	-	-	-	-	-
Cardiac power output (W)	13	1.3 ± 0.4	13	1.1 ± 0.3	13	1.3 ± 0.5	6	1.2 ± 0.2	0.323		-	-	-	-	-	-

Values are presented as mean ± standard deviation or as median [IQR]. Pre revasc.: Pre revascularization; Post revasc.: post revascularization, MAP: mean arterial pressure; RDNP: relative dicrotic notch pressure; LVET: left ventricular ejection time; AUC: area under the curve;

- indicates $p<0.05$

Timepoint 1: pre revascularization, Timepoint 2: post revascularization, Timepoint 3: <4 hours after pPCI, Timepoint 4: <24 hours after pPCI

Table A 7: Study II: Results: Change of blood pressure parameters with NTG. Noninvasively measured digital blood pressure transformed to brachial blood pressure (Nexfin).

	Before NTG		With NTG		
	n	value	n	value	p
Pressure derived variables					
Systolic pressure (mmHg)	8	147 ± 28	8	126 ± 23	0.052
Diastolic pressure (mmHg)	8	82 ± 12	8	71 ± 8	• 0.023
MAP (mmHg)	8	104 ± 17	8	90 ± 13	• 0.035
Pulse pressure (mmHg)	8	65 ± 18	8	55 ± 15	0.103
Anacrotic notch pressure (mmHg)	8	7 ± 4	8	11 ± 5	0.107
Dicrotic notch pressure (mmHg)	8	108 ± 16	8	87 ± 13	• 0.006
RDNP (mmHg)	8	27 ± 8	8	15 ± 9	• 0.005
Dicrotic notch index (%)	8	42 ± 0.09	8	29 ± 0.18	• 0.010
Augmentation index (%)	8	12 ± 0.09	8	23 ± 0.14	0.059
Time derived variables					
t systolic downstroke (s)	8	0.213 ± 0.016	8	0.198 ± 0.045	0.316
t dp/dt max (s)	8	0.052 ± 0.005	8	0.054 ± 0.010	0.652
t anacrotic notch (s)	8	0.122 ± 0.061	8	0.134 ± 0.051	0.732
t upstroke (s)	8	0.111 ± 0.025	8	0.118 ± 0.014	0.443
t downstroke (s)	8	0.698 ± 0.146	8	0.616 ± 0.118	• 0.004
Heart rate (bpm)	8	77 ± 16	8	84 ± 15	• 0.022
Duration systole(LVET) (s)	8	0.325 ± 0.026	8	0.316 ± 0.045	0.605
Duration diastole (s)	8	0.485 ± 0.133	8	0.418 ± 0.077	• 0.022
relative t upstroke	8	0.142 ± 0.043	8	0.166 ± 0.038	• 0.025
relative t dp/dt max	8	0.067 ± 0.018	8	0.074 ± 0.012	0.348
relative LVET	8	0.411 ± 0.069	8	0.436 ± 0.028	0.282
relative t anacrotic notch	8	0.118 [0.101 - 0.172]	8	0.180 [0.116 - 0.240]	0.161
duration systole / duration diastole	8	0.726 ± 0.242	8	0.781 ± 0.088	0.488
Slopes					
dp/dt max (mmHg / s)	8	1.159.6 ± 425.6	8	845.3 ± 313.1	• 0.046
dp/dt diastole - systolic max (mmHg / s)	8	649.1 ± 275.5	8	481.0 ± 174.7	0.096
dp/dt systolic max - diastole (mmHg / s)	8	-89.6 ± -96.2	8	-88.4 ± -96.7	0.575
dp/dt systolic max - dicrotic notch (mmHg / s)	8	-184.4 ± 72.9	8	-196.5 ± 57.9	0.500
dp/dt dicrotic notch - diastole (mmHg / s)	8	-56.6 ± 16.0	8	-35.0 ± 18.1	0.056
RDNP / LVET (mmHg/s)	8	82.1 ± 23.4	8	46.9 ± 24.6	• 0.018
RDNP / t upstroke (mmHg/s)	8	254.7 ± 85.6	8	129.2 ± 77.5	• 0.013
Areas					
Relative AUC (mmHg.s)	8	18.2 ± 5.3	8	12.9 ± 5.3	• 0.011
Relative systolic AUC (mmHg.s)	8	13.2 ± 3.6	8	9.8 ± 4.2	• 0.028
Relative diastolic AUC (mmHg.s)	8	5.0 ± 1.8	8	3.2 ± 1.2	• 0.003
Absolute AUC (mmHg.s)	8	84.9 ± 17.2	8	66.9 ± 17.3	• 0.000
Absolute systolic AUC (mmHg.s)	8	40.0 ± 5.6	8	33.0 ± 8.9	• 0.016
Absolute diastolic AUC (mmHg.s)	8	45.0 ± 12.3	8	34.0 ± 8.9	• 0.000
Relative myocardial oxygen supply/demand ratio	8	2.6 [2.5 - 3.1]	8	3.2 [2.6 - 4.1]	0.161
Absolute myocardial oxygen supply/demand ratio	8	0.9 ± 0.2	8	1.0 ± 0.1	0.648
Beatscope derived parameters					
BS systolic pressure (mmHg)	7	149 ± 30	7	127 ± 24	0.075
BS diastolic pressure (mmHg)	7	83 ± 12	7	73 ± 9	• 0.047
BS MAP (mmHg)	7	107 ± 18	7	91 ± 13	• 0.046
BS Heart rate (bpm)	7	65 ± 14	7	72 ± 12	• 0.024
BS LVET (s)	7	0.325 ± 0.022	7	0.326 ± 0.021	0.928
BS Stroke Volume (ml)	7	80.3 ± 22.7	7	75.8 ± 19.3	0.117
BS Cardiac output (L/min)	7	5.3 ± 1.9	7	5.4 ± 1.4	0.624
BS Systemic vascular resistance (dynes.s/cm5)	7	1.524 [1.245 - 2.246]	7	1.156 [1.110 - 1.882]	• 0.018
BS Cardiac index (L/min/m2)	7	2.5 ± 0.8	7	2.6 ± 0.8	0.423
Cardiac power output (W)	7	1.3 ± 0.6	7	1.1 ± 0.3	0.294

Values are presented as mean ± standard deviation or as median [IQR]. NTG = nitroglycerin. MAP: mean arterial pressure; RDNP = relative dicrotic notch pressure; LVET: left ventricular ejection time; AUC: area under the curve;

• indicates parameters with $p<0.05$

Informed consent letter

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 en na de dotterbehandeling. Tijdens uw dotterbehandeling is de bloeddruk gemeten in de lichaamsslagader en met een bloeddrukmeter om de vinger. Deze bloeddrukgegevens willen wij gebruiken om te 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. Om veranderingen van de bloeddruk na deze dotterbehandeling te kunnen onderzoeken willen we regelmatig uw bloeddruk aan de vinger meten in de dagen na uw behandeling.

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. Gedurende de 30 minuten moet u plat op uw rug liggen. Vanaf het moment dat u plat gaat liggen duurt het ongeveer 10-15 minuten tot uw lichaam is gewend aan de liggende houding. Daarna zullen we gedurende 10-15 minuten uw bloeddruk meten. 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: R. Wesselink, stagiair onderzoeker (tel. 020-56 66 409) of D.M. Ouweneel, onderzoeker (tel. 020-56 65 204). Indien u er prijs op stelt uw deelname te bespreken met een arts die verder niet bij het onderzoek betrokken is, dan kunt u contact opnemen met dr. W.E.M. Kok, cardioloog in het AMC (tel. 020-56 66 952)

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: