Cardiac hemodynamics in PCI: effects of ischemia, reperfusion and mechanical support
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Citation for published version (APA):
Remmelink, M. (2009). Cardiac hemodynamics in PCI: effects of ischemia, reperfusion and mechanical support
CHAPTER 1

Introduction and outline
Introduction

Coronary revascularization therapy by means of percutaneous coronary intervention (PCI) has become the treatment of first choice in patients with stable anginal complaints despite optimal medical therapy and in patients with acute coronary syndromes. Technical advances in equipment, devices, and developments in adjuvant pharmacotherapy have improved safety, short and long-term outcomes in patients, and extended the indications for PCI to patients with complex and multiple coronary artery lesions. Moreover, left ventricular (LV) assist devices have been developed to allow protected percutaneous treatment in patients who are poor candidates for surgery. Therapeutic interventions in the catheterization laboratory may have direct effects on LV function. It is known that LV function directly responds to myocardial ischemia. Early reperfusion in primary PCI may reduce LV dysfunction, which is the most important determinant of early and long-term survival. Direct LV intracavitary pressure and volume (PV) measurements by pressure-conductance catheter provide the opportunity to obtain these instantaneous diastolic and systolic LV function responses. Moreover, the use of the PV-loop analysis allows evaluation of reperfusion after ST-segment elevation myocardial infarction (STEMI) and of LV unloading e.g. by the intra-aortic balloon pump (IABP) or the Impella LP2.5 (Impella).

In this thesis various aspects of current daily practice in the setting of PCI are reported. We assessed the effects of acute ischemia, both acute and long-term effects on LV recovery of primary PCI, phenomena such as repeated ischemia-induced preconditioning and primary PCI-induced arrhythmias (i.e. accelerated idioventricular rhythm). In addition, we investigated whether intracoronary pressure, flow and resistance are influenced by LV dysfunction (e.g. remodeling). Therefore, the aim of this thesis is to assess the cardiac hemodynamic effects in the current era of PCI.

Myocardial ischemia

Myocardial ischemia caused by occlusion of a coronary artery leads to a cascade of LV dynamic effects, electrocardiographic changes, and subsequent anginal complaints and cellular injury. Early experimental studies that showed reduced infarct size in dogs that were preconditioned with multiple ischemic bouts, suggested that the multiple anginal episodes that often precede myocardial infarction in man may reduce cell death after coronary occlusion, and thereby allow for greater salvage of myocardium by reperfusion therapy. Clinical data on LV function responses to acute ischemia are available from studies during angioplasty, whereas the magnitude and timing of LV dynamic responses to acute ischemia induced by repeated and prolonged ischemic periods is limitedly documented. Therefore, the main objective of the first part of this thesis is to evaluate acute responses of LV dynamic parameters to ischemia and repeated ischemic periods throughout elective PCI procedures by direct and continuous assessment of LV pressure and volume.
Myocardial reperfusion

In acute myocardial infarction LV compliance decreases, which correlates directly with prognosis. The goal of reperfusion therapy is to restore coronary flow in the obstructed infarct-related artery to reduce infarct size and improve clinical outcome. It is known that infarct size is a critical determinant of LV function, which in turn, is the most important determinant of early and long-term survival. Currently, primary PCI has evolved to be the best reperfusion modality. Data on the direct changes in LV dynamics by primary PCI are limitedly available. Recent studies have shown that STEMI patients have elevated filling pressures directly after primary PCI, reflecting LV dysfunction and implicating that primary PCI may not have beneficial acute effects on LV compliance. For the evaluation of treatment by primary PCI, it is valuable to have information on the acute LV dynamic responses during the procedure.

A conventionally considered sign of coronary artery reperfusion, is the arrhythmia accelerated idioventricular rhythm (AIVR). AIVR as a reperfusion arrhythmia is often observed immediately after primary PCI. In general, AIVR is considered as a relatively benign form of ventricular tachycardia, though some authors suggest that AIVR may be a manifestation of cellular injury. Also, its effect on the systemic circulation has not been systematically investigated. Hence, there is little and conflicting evidence of the clinical relevance of reperfusion-related AIVR in primary PCI. The aim of the second part of the thesis is to evaluate direct hemodynamic and LV dynamic responses to reperfusion in primary PCI.

Coronary revascularization

The introduction of PCI, percutaneous revascularization therapy has evolved to be the treatment of first choice in patients with progressive anginal complaints despite optimal medical therapy. The number of PCIs in the Netherlands is expected to increase from 32 000 in 2005 to 40 000 in 2010. The increase is mainly due to the application of PCI in STEMI and acute coronary syndrome patients, and the shift of surgical treatment, i.e. coronary artery bypass grafting (CABG), to percutaneous treatment for patients with 1 and 2 vessel disease.

Currently, CABG is the treatment of choice in patients with multiple or complex lesions, whereas PCI is only recommended for patients who are considered poor candidates for surgery. Nowadays more advanced techniques give the opportunity for more difficult PCI procedures (e.g. left main coronary artery, multiple, complex, long, calcified, bifurcated lesions, and chronic total occlusions) in more complex patient categories (e.g. patients with renal dysfunction, higher age, diabetes mellitus, chronic lung disease, peripheral vascular disease, and heart failure) with concomitant increased risk of complications. Part three of this thesis concerns the performance of PCI: patients with severely compromised LV function with a LV ejection fraction <30%, a left main coronary artery stenosis or a last remaining vessel, the so-called ‘high-risk’ PCI procedures.
An important development is the expanded collaboration between the interventional cardiologist and the cardiac surgeon, which forms the basis for the opportunity to perform these high-risk PCI procedures in the catheterization laboratory, and hybrid procedures in patients with pathologic complexity to reduce perioperative morbidity and/or mortality.

Mechanical cardiac support

In order to safely perform the aforementioned high-risk procedures, several devices have been developed to provide temporary cardiac support. IABP therapy has been introduced more than 40 years ago. Technical refinements in catheter development have led to the introduction of new LV assist devices in the catheterization laboratory, that are potentially superior to the IABP.

The IABP is widely used in situations when the LV cardiac output is insufficient to meet the organs oxygenation demands. The primary goals of IABP treatment are to increase myocardial oxygen supply and decrease myocardial oxygen demand. The intra-aortic balloon is positioned in the descending aorta with its tip at the distal aortic arch (below the origin of the left subclavian artery). Inflation and deflation are synchronized to the patients’ cardiac cycle. Inflation at the onset of diastole results in proximal and distal displacement of blood volume in the aorta. Deflation occurs just before the onset of systole. Therefore, the IABP operates only in a heart with electrical activity and on top of a ‘functioning’ LV.

In the clinical setting, IABP therapy results in afterload reduction and limited LV unloading, increase in coronary flow, while there are conflicting data on its effect on pulmonary capillary wedge pressure and cardiac index. The most important indication for IABP is temporary support in cardiogenic shock. However, the class IB recommendation according to the ACC/AHA guidelines is being challenged in a recently reported meta-analysis showing that there is insufficient evidence endorsing the current guideline recommendation for the use of IABP therapy in the setting of STEMI complicated by cardiogenic shock. Other indications for LV support may be bridge to recovery (e.g. post cardiothoracic surgery) or therapy in LV failure and bridge to transplantation. Furthermore, IABP may facilitate the performance of complex PCI procedures in the catheterization laboratory as more high-risk PCI procedures are performed nowadays in patients who are poor candidates for surgery. Moreover, IABP therapy may improve myocardial salvage, as reported in experimental studies. Therefore, LV support and unloading may be beneficial for patients with compromised LV function undergoing high-risk PCI, and for patients treated by primary PCI for STEMI. The Impella LP2.5 (Abiomed Europe GmbH, Aachen, Germany), as easy to handle as the IABP, is a novel percutaneous microaxial blood pump that directly unloads the LV by continuously aspirating blood from the LV cavity and expelling it into the ascending aorta, which is in contrast to the non-pulsatile nature of the generated blood pressure.
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by the myocardium itself. It has 9 support levels, producing a flow of up to 2.5 L/min. The differential pressure sensor at the tip of the cannula allows proper positioning of the pump and continuously registers the intracavitary and aortic pressure to derive pump flow and control its rotational speed. The unloading mechanism is essentially different than that of the IABP.\textsuperscript{26, 34, 24} While IABP therapy has failed to shown an improved clinical outcome or a reduction in infarct size,\textsuperscript{31} stronger support devices like the Impella have the potential to be beneficial in the previously mentioned indications for LV support.\textsuperscript{22} In order to allow proper clinical application of the new Impella device, safety and feasibility studies are warranted before studies on clinical outcome can be initiated. Moreover, the physiologic effects, i.e. the effects on coronary and LV dynamics, during direct and profound LV unloading as effected by this true LV assist device needs to be assessed in patients. Therefore, the third part of this thesis addresses these issues.

Recovery of left ventricular function after primary PCI

LV remodeling and residual systolic function are important markers of clinical outcome, which have been the focus of research for several decades.\textsuperscript{5, 35} Several studies showed that LV remodeling, defined as at least 20% increase in LV end-diastolic volume from baseline up to one year, is still frequently observed after STEMI, despite successful coronary reperfusion.\textsuperscript{36, 37} Systolic as well as diastolic LV function after STEMI have shown to be strongly related to LV remodeling and prognosis.\textsuperscript{38, 39, 40, 41, 35} The LV function parameters assessed in these studies have been obtained non-invasively by means of echocardiography or cardiac magnetic resonance imaging, techniques that are importantly influenced by changes in loading conditions.

Together with the LV function markers of outcome, intracoronary functional markers (i.e. coronary flow velocity reserve (CFVR), have demonstrated to predict recovery of systolic LV function after STEMI.\textsuperscript{42, 43, 44} Bax et al. showed that CFVR and variable microvascular resistance are decreased during the acute phase of STEMI, probably due to microembolization and/or disturbed microvascular autoregulatory function.\textsuperscript{42, 45} CFVR reflects microvascular integrity and may also be influenced by LV dynamics.\textsuperscript{46} Clinical reports on this subject are scarce. Recent reports suggest that an increased end-diastolic pressure contributes to coronary microvascular dysfunction in myocardial infarction patients,\textsuperscript{45, 12} but direct measurements of the influence of LV dynamics on the coronary microcirculation have not been performed in STEMI patients.

In addition to reperfusion therapy, mechanical LV unloading after STEMI may reduce infarct size and facilitates recuperation from ischemic stunning.\textsuperscript{2} This may be particularly relevant in STEMI patients presenting with cardiogenic shock. However, the results of a recent meta-analysis indicate the limited value of IABP on infarct size, LV function and remodeling, and mortality in the setting of STEMI.\textsuperscript{31} In the fourth part of this thesis, these issues concerning recovery of LV function are addressed.
Assessment of left ventricular function

Insight in the effect of acute ischemia on LV function has been studied during PCI procedures using pressure recordings from high-fidelity micromanometer-tipped catheters complemented with volume information obtained from LV diameter tracings on LV angiograms or complemented with volume recordings from the conductance catheter technique by positioning a second catheter in the LV apex. The development of the combined pressure-conductance catheter provides the opportunity to safely, swiftly, and reliably assess continuous information on systolic and diastolic LV function from PV-loops in the catheterization laboratory. Continuous data from this single catheter enables more accurate assessment of the timing and magnitude of the effects of myocardial ischemia and reperfusion, and allows assessment of the effects of LV support, even in combination with the Impella, which is also positioned over the aortic valve. This method has an advantage over hemodynamic assessment from right heart catheterization using the Swan-Ganz catheter, which indirectly provides information about the status of LV function by deriving right atrial pressure, pulmonary capillary wedge pressure, and cardiac output. Furthermore, methods such as echocardiography are impractical to continuously monitor a patient during a procedure in the catheterization laboratory. Moreover, in contrast to PV-loops, interpretation of data from echocardiography, nuclear imaging, and magnetic resonance imaging, may be difficult due to their dependency on heart rate or loading conditions. In the catheterization laboratory, noninvasive data is valuable in complementing invasive PV-loop measurements, e.g. for anatomical information, and the assessment of LV mass. LV function parameters in this thesis were mainly obtained by use of PV-loops derived by the pressure-conductance catheter, and occasionally complemented with non-invasive measurements.

Instrumentation for using the conductance catheter. The 7F pigtail equipped combined pressure-conductance catheter (CD Leycom, Zoetermeer, The Netherlands) should be placed in the LV via the femoral artery. In order to calibrate the volume signals of the conductance catheter, a 5 mL blood sample is used to measure rho (blood resistivity), and a Swan-Ganz catheter, as placed in the pulmonary artery via the femoral vein, can be used to determine cardiac output by thermodilution and parallel conductance by hypertonic saline injections. Online LV dynamic data which are recorded on the CFL-512 (CD Leycom, Zoetermeer, The Netherlands), can be analyzed offline.

LV dynamic data from PV-loops. Continuously recorded pressure and volume data during a cardiac cycle are displayed as a PV-loop (Figure 1A), which represents a working diagram of the LV, describing LV function during all four phases of the cardiac cycle (i.e. isovolumetric contraction, ejection phase, isovolumetric relaxation, and filling phase). The PV-loop is an extrapolation of the force-length relationships of the cardiac muscle, which are referred to as the Frank-Starling law of the heart, and is based on the ventricular function curves of Sarnoff and the force-velocity relations described by Sonnenblick. According to Suga and coworkers, the time-varying elastance model was
considered optimal to characterize LV performance. PV-loops and PV-relations have shown to be a useful tool for basic physiologic understanding of LV function. The following parameters of LV function may be obtained from PV-loops:

1. Systolic function: end-systolic pressure (ESP) and volume (ESV), ejection fraction, peak positive derivative of LV pressure (dP/dt\text{max})\text{,} and the end-systolic elastance (E_{ES}) as the slope of the end-systolic pressure-volume relation (ESPVR). A change in the slope as well as a left- or rightward shift of the ESPVR has shown to indicate a change in contractility (Figure 1B).\text{54}\n
2. Diastolic function: end-diastolic pressure (EDP) and volume (EDV), peak negative derivative of LV pressure change (dP/dt\text{min})\text{,} the relaxation time constant Tau defined as the time required for the cavity pressure at dP/dt\text{min} to be reduced by half, and
the end-diastolic stiffness as the slope of the end-diastolic pressure-volume relation (EDPVR), which is preload dependent. An up- or downward shift of the EDPVR indicates a change in LV distensibility, which is a preload independent change in the intrinsic LV properties (Figure 1B).

3. global LV function: heart rate, cardiac output, cardiac index, stroke volume (SV), and stroke work as the area of the PV-loop. The effective arterial elastance (Ea) as calculated by ESP/SV, is an index of LV afterload, and the ventricular-arterial coupling ratio as calculated by ES/EA, describes the interaction between LV performance and the systemic arterial system.55

Functional assessment of coronary hemodynamics

In the catheterization laboratory, physiological assessment of coronary artery narrowings has become increasingly important for diagnosis and treatment and research applications. After achievement of maximal blood flow in response to a hyperemic stimulation (e.g. an intracoronary bolus of adenosine), the fractional flow reserve and/or coronary flow velocity reserve (CFVR) may be calculated, respectively. CFVR is a combined measure of the capacity of the major resistance components (the epicardial coronary artery and microvascular bed) to achieve maximal blood flow in response to hyperemic stimulation. A normal CFVR implies that both the epicardial and minimally achievable microvascular resistances are low and normal. However, in patients with essential hypertension and normal coronary arteries or in patients with aortic stenosis and normal coronary arteries, CFVR may be reduced, in part because of LV hypertrophy and an abnormal microvasculature.57

By combining pressure and flow velocity measurements, the status of coronary microvascular function can be determined by calculation of the coronary microvascular resistance index as distal coronary pressure divided by average peak flow velocity. The role of the combination of flow velocity and pressure is being explored to reveal their contributions to important clinical syndromes involving vulnerable plaques, microvascular disease, and endothelial dysfunction.58

Recent technologic advances led to the introduction of the Combowire® (Volcano Corporation, Rancho Cordova, CA). This guidewire (diameter of 0.014 inch) with a dual-sensor (pressure and Doppler) at the tip, provides hemodynamic information about the physiological condition of the entire coronary circulation. In order to evaluate coronary microvascular function, previous studies in our center (Academic Medical Center, Amsterdam, the Netherlands) combined measurements from 2 sensor-equipped wires in elective PCI or used Doppler measurements complemented with pressure measurements from the guiding catheter in primary PCI. The advanced single wire technique allows more easily and accurate (i.e. it measures on exactly the same location) assessment of coronary microvascular function, and its response to treatment.61, 62
Outline of the thesis

This thesis focuses on left ventricular and coronary hemodynamic effects in the setting of current PCI, i.e. elective PCI for progressive anginal complaints, primary PCI for STEMI, and mechanical cardiac support during and after high-risk and primary PCI.

Part I (Chapter 2)
Part I focuses on the effects of acute myocardial ischemia on LV function. Chapter 2 describes how a temporary coronary balloon occlusion during an elective PCI procedure influences LV function. In addition, LV dynamics were assessed during repeated coronary balloon occlusions, which was a previously reported measure to precondition the myocardium against an ischemic event.

Part II (Chapters 3-6)
Part II describes the instantaneous effects of reperfusion by primary PCI on LV function. In Chapter 3, the acute effects of reperfusion are shown by means of PV-loop assessment. In Chapter 4, the effect of reperfusion is compared in patients with and without the occurrence of reperfusion-induced AIVR in order to assess the trigger for this phenomenon. In Chapter 5, the consequences of AIVR for the systemic circulation are described. Chapter 6 illustrates the effect of AIVR on PV-loops, and of LV unloading on AIVR by elimination of the trigger for the arrhythmia.

Part III (Chapters 7-10)
Part III demonstrates the use of the new percutaneously inserted LV unloading device Impella LP2.5 for cardiac support in the setting of elective high-risk PCI. Chapter 7 illustrates the safety and feasibility of the Impella. In Chapter 8, direct flow effects of the Impella are demonstrated using echocardiography. Chapter 9 shows the effect of support by the Impella on the coronary circulatory, and Chapter 10 shows its effect on LV function.

Part IV (Chapters 11-13)
Part IV presents the long-term hemodynamic effects of primary PCI. In Chapter 11, recovery of LV function is described by means of PV-loop analysis. Chapter 12 shows the relation of the coronary microcirculatory function with LV function after 4 months. In Chapter 13, the use of the LV unloading device Impella LP2.5 after primary PCI on short-term and long-term recovery is shown.
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