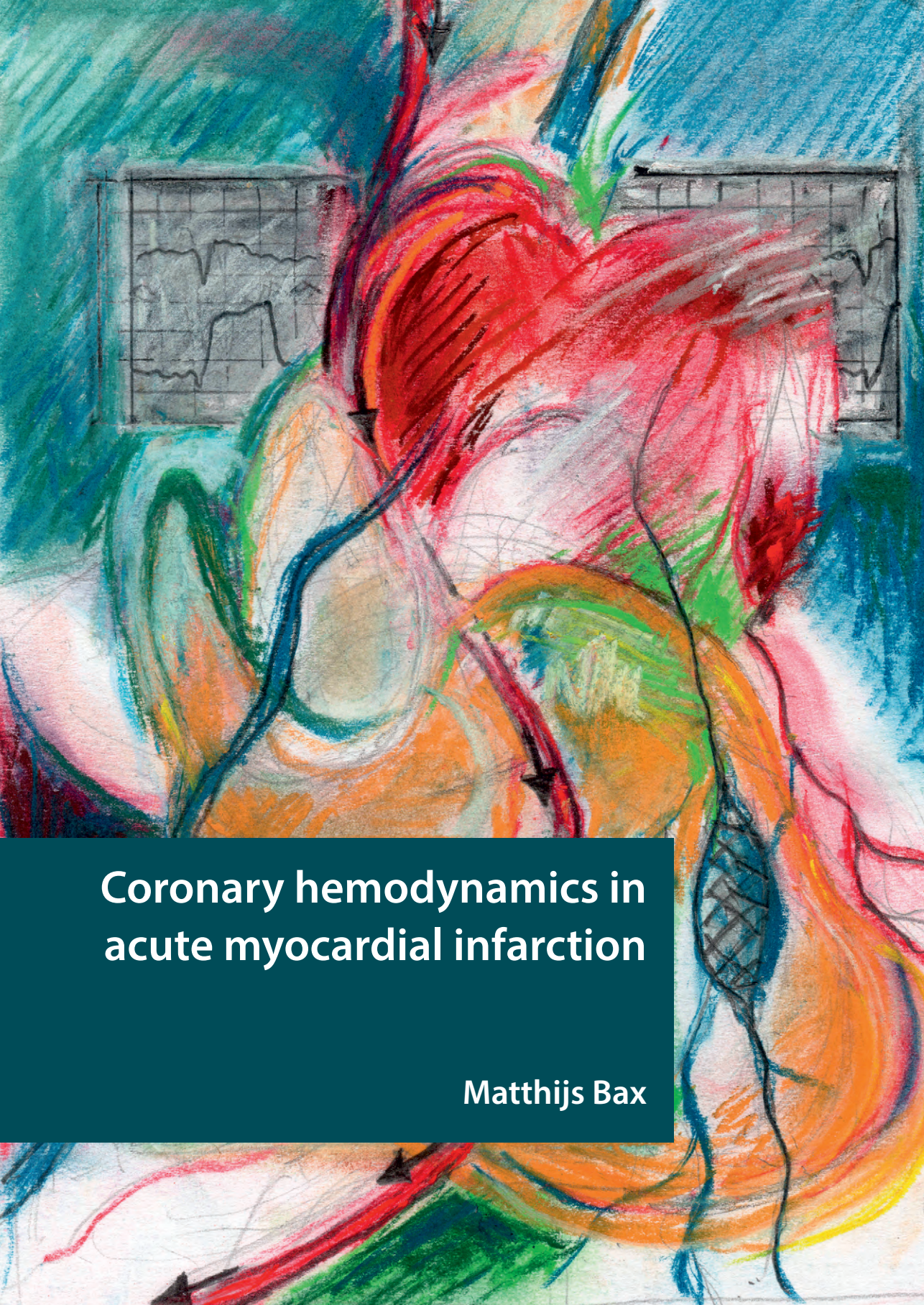

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Editor	Matthijs Bax, m.bax@hagaziekenhuis.nl
Cover illustration	Marianne van Veldhuizen
Lay-out	Ferdinand van Nispen tot Pannerden, *my*-thesis.nl
Printing	GVO drukkers & vormgevers B.V.
ISBN/EAN	978-94-6332-751-0

Financial support by Stichting Percutane Hart Interventies for the publication of this thesis is gratefully acknowledged.

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ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. ir. K.I.J. Maex
ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel
op woensdag 2 juni 2021, te 10.00 uur

door

Matthijs Bax

geboren te Amsterdam

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Ter nagedachtenis aan mijn vader Gerrit Marten Bax
Voor mijn moeder Nora Bax-Loeber
Voor Jannine, Vera, Isabelle en Brenda

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Chapter 1

General introduction and outline of the thesis

General introduction

Irreversible damage to the heart muscle cell occurs due to a lack of delivery of oxygenated blood within 20 minutes after the blockage of a coronary artery. The wavefront phenomenon describes how ischemic cell death due to coronary occlusion in dogs develops over time from the subendocardium to the epicardium leading to an increase in infarct size and a decrease in left ventricular function.[1] After the first myocardial infarction, the risk of re-infarction or another cardiovascular event is considerably enhanced even above 50% in the next ten years in high-risk patients,[2, 3] This patients face an annual death rate of six times that in people of the same age who do not have coronary heart disease.[4, 5]
The purpose of the initial treatment of the acute myocardial infarction is to limit the infarct size, maintain the left ventricle function and to reduce the associated risk of mortality.

In the sixties of the previous century the risk of dying in the acute phase of the myocardial infarction was reduced by almost 30% by installment of acute Coronary Care Units with ECG monitoring and the possibility of direct defibrillation.[6] The in-hospital mortality could be further reduced in the 80s and 90s from around 20% to 10% through early treatment with aspirin, thrombolysis and other medication interfering with coagulation.[7, 8]

In the following years, mechanical reperfusion by percutaneous transluminal coronary angioplasty (PTCA) or percutaneous coronary intervention (PCI), initially with balloon only and later on with stent implantation, was the therapy of first choice due to its effectiveness and sustainable result.[9, 10] With current treatment methods, the in-hospital mortality is now below 4%.

The duration between coronary blockage and definite reperfusion is of great importance to maintain left ventricular function and improve clinical outcome. [11]

ST-elevation myocardial infarction

The myocardial infarction with ST segment elevation on the ECG generally occurs on the basis of (sub) acute thrombosis on a destabilized, ruptured or eroded atherosclerotic plaque.[12, 13] The endothelium of the coronary vessels

plays an extremely important role in the control process of the vasomotor tone and in influencing the thrombotic risk by, among other things, releasing nitric oxide, endothelin-1, prostacyclin etc. Endothelial dysfunction is part of the increased risk of the reoccurrence of a cardiovascular event.[14, 15]

The plaque rupture leads to a thrombotic response which is dynamic in nature. Both local thrombosis and thrombolysis and vasospasm can cause intermittent flow obstruction and distal embolization.[16] The microvascular obstruction, including distal embolization, can in turn lead to insufficient reperfusion during the treatment of the infarction, resulting in poorer outcomes. It is demonstrated that although the epicardial occlusion is successful treated, the microvascular injury precludes adequate tissue perfusion. This suggests that there is room for improving of our current standard treatment.

Infarct size

The final infarct size is a function of the area-at-risk as result of the location of the epicardial coronary occlusion, ischemic time (time between vessel occlusion and reperfusion) and collateral flow from non-infarct related arteries. The final extend of the infarct might be increased as result of additional damage know as reperfusion injury. The concept of reperfusion injury is believed to be related to tissue damage from oxygen radicals generated at the time of reperfusion.

Cardiac dysfunction due to myocardial reperfusion injury

Timely PCI treatment in ST-elevation myocardial infarction (STEMI) is critical for myocardial reperfusion in order to limit infarct size and to preserve left ventricular function. However, the reperfusion of acutely ischemic myocardium may itself induce cardiomyocyte death. This, so called myocardial reperfusion injury was postulated by Jennings et al. in the sixties of the previous century. [17] It was postulated that reperfusion acutely induced explosive myocardial cell swelling,[18] and capillary disruption inducing hemorrhagic necrosis.[19]
Although the underlying mechanisms leading to reperfusion injury have still not been fully elucidated, potential myocardial reperfusion damage is generally classified into four forms.

Stunned myocardium indicating postischemic (regional) ventricular dysfunction of vital myocytes.[20, 21] This phenomenon is probably reversible

in days tot weeks. Secondly, reperfusion arrhythmias including ventricular tachycardia and ventricular fibrillation occurring within seconds to minutes after reflow are self-limiting or treatable and hence, reversible phenomena.[22, 23] Lethal reperfusion injury as a controversial concept of myocyte cell death due to reperfusion itself rather than ongoing ischemia.[24, 25] Observations suggest that this irreversible and lethal reperfusion injury may explain up to 50% of the ultimate infarct size. Among important contributory factors are oxidative stress, calcium overload, mitochondrial permeability transition pore opening and hypercontraction of myocytes, rapid wash-out of lactic acid.[26]

The last form is vascular reperfusion injury or microvascular obstruction and refers to progressive damage to the vasculature during reperfusion phase.[27, 28] It is recognized as expanding zone of no-reflow despite the open epicardial artery and as deterioration of coronary flow reserve.[29] Post ischemic irreversibly injured myocardial cells may demonstrate an acceleration of the necrotic process when exposed to reperfusion including massive swelling probably aggravating obstruction of the smaller vessels.[27] This microcirculatory disorder has also been demonstrated in post ischemic brain, kidney, small intestine and skeletal muscle. Various factors seem to contribute to no-reflow. Endothelial cells play a pivotal role in this process through regulation of vascular permeability, hemostasis, recruitment and homing of neutrophils and control of the vascular tone. Furthermore, capillary damage contributes significantly to this process. Besides gaps in the endothelium and neutrophil infiltration, the capillaries in the no-reflow areas show large protrusions of endothelial cytoplasm into the vascular lumen probably acting to occlusion of capillary lumens.[27] The observed marked myocardial cell swelling is a manifestation of the loss of the capacity of the damaged cells to regulate cell volume.[18] Tissue edema influencing reflow was due primarily to the accumulation of intracellular fluid consequently compressing capillaries.[30] Oxidative stress elicited by reperfusion influence leucocyte to endothelial cell adhesion and alters Na^+-H^+ exchange affecting endothelial cell swelling. Reactive oxygen metabolites promote the formation of inflammatory agents that recruit and activate polymorphonuclear leukocytes.[31] Besides physical leucocytes impaction in the capillary lumen partly due to their amount, the interaction with endothelial cells, the increased stiffness of the neutrophils in an ischemic, acid environment, the lower perfusion pressures based on macrovascular and

microvascular changes in the infarcted area might influence reflow. Red blood cell packing in the capillary lumens indicate downstream obstruction to flow. These localized areas of increased hematocrit can increase blood viscosity and stimulate hemostasis and flow obstruction.

Furthermore, hemorrhages are not-uncommon in infarcted areas, and are determined as a potential consequence of microvascular injury.[32] In cardiovascular magnetic resonance (CMR) studies, infarcts of substantial size show core necrosis and erythrocyte extravasation without intact vasculature and hence, no microvascular obstruction.[33]

In some studies platelet and fibrin thrombi were infrequently seen by electron microscopy in areas of no reflow, making it questionable that capillary thrombosis is the primary cause of no reflow. Peripheral embolization of thrombus caused by mechanical actions of PCI equipment might play a role in suboptimal reperfusion. In patients treated with primary PCI (PPCI) in whom angiographically blood flow in the infarct related artery appears to be normal, 30-40% of them have evidence of microvascular obstruction as detected by contrast echocardiography[34, 35] or CMR[36]

Severe downstream localized microvascular obstruction after PPCI is related to the duration of myocardial ischemia, [37] the extent of transmural necrosis and age.[38, 39] It is striking that the maximum extent of the microvascular obstruction does not occur immediately during ischemia but after reperfusion. In a rat model, Hollander et al. showed that ischemia for 90 minutes effected limited morphological changes to the coronary microcirculation, but that 30 minutes of ischemia followed by 60 minutes of reperfusion caused massive microvascular injury.[40] This illustrates the potentially adverse effect of reperfusion on the integrity of the microvasculature.

Interventions in reperfusion injury

Despite many attempts to improve the reperfusion injury, such as targeting coagulation with IIb/IIIa receptor blockers or targeting metabolic modulation via glucose-insulin-potassium (GIK) infusion, no adequate additional treatments have been successfully implemented to date in clinical practice.[41, 42] In some countries intracoronary infused Nicorandil, a potassium channel opener, is

advocated to be administered at the time of PPCI to ameliorate myocardial reperfusion where it can significantly improve myocardial microcirculation. However, a recent meta-analysis failed to demonstrate clinically significant benefits in this form of therapy.[43] A meta-analysis showed adenosine therapy to be promising in some subgroups in patients undergoing PPCI as it was associated with a lower incidence of no-reflow, improved left ventricular ejection fraction and less heart failure. However, it failed to show reduction of hard endpoints such as mortality or re-infarction.[44] Beside adenosine and nicorandil, other agents such as diltiazem, verapamil, urapidil, nitroprusside and anisodamine were evaluated for the purpose of optimization of reperfusion therapy. In a meta-analysis evaluating these seven pharmacological agents, administered in the setting of PPCI, demonstrated improved coronary flow but no corresponding benefits regarding cardiac function and clinical outcomes for adenosine, nicorandil and verapamil compared to standard care.[45] Only intracoronary administered anisodamine appeared to improve reperfusion, cardiac function and clinical outcomes in small sized studies. Given the complexity of the cardioprotective signal transduction,[46] combined treatment of several targets maybe needed.[47]

In summary, many experimental studies have been performed in which both pharmacological interventions and mechanical interventions, such as pre- and post-conditioning, remote or not, demonstrated a significant reduction in the infarct size. However, as we know now from studies performed in de last two decades, none of these agents have shown a relevant effect in larger sized clinical studies.[48, 49]

Coronary blood flow regulation and microvascular function

The control of coronary blood flow is determined by the metabolic demand of the heart muscle and has both long-term adaptation as well as acute regulation mechanisms. The acute regulation aims to meet the metabolic need. The intrinsic tendency of an organ to maintain blood flow despite changes in arterial perfusion pressure is named autoregulation.[50] Coronary pressure-flow autoregulation maintains the relatively constant coronary blood flow through adaptive changes in microvascular resistance.[51] The coronary blood flow can mathematically be described as a correlate to Ohm's Law (Flow = Δ Pressure / Resistance). Bayliss described in 1902 that the vascular myogenic response is

defined as the ability of vascular smooth muscle cells to constrict as response to an increase in transmural force, such as perfusion pressure.[52] This myogenic response, as behavior of small arteries and arterioles is believed to represent efforts of the vessel to minimize wall stress, supported mathematically by Laplace's law (wall stress = pressure x radius / wall thickness). Recently Goodwill et al. published a comprehensive review about the quite complex regulation of coronary blood flow describing multiple mechanisms including extravascular compressive forces (tissue pressure), coronary perfusion pressure, myogenic, local metabolic, endothelial as well as neural and hormonal influences.[53]

The coronary autoregulation aims to ensure that the blood and thus oxygen supply matches the myocardial oxygen demand. Coronary venous pO2 is maintained constant even in exercise.[54] Several control mechanisms regulate coronary blood flow to maintain this stable venous pO2. Various regulatory mechanisms play a role at different locations in the coronary microvascular tree. Regulation of the intravascular pressure in the microcirculation necessary to prevent myocardial ischemia reflects the regulation of the microvascular resistance. This coronary autoregulation is triggered by several stimuli such as flow generating shear stress which triggers endothelium-dependent vasodilatation;[55] distension pressure affecting stretch receptors on vascular smooth muscle cells (VSMC) leading to chemical reactions influencing VSMC tone and hence, intravascular pressure and resistance to flow; metabolic factors as carbon dioxide, reactive oxygen species and other metabolic messengers as well as the modulating influence of the autonomic nervous system and adrenergic effects contribute to the continuously adapting microvascular resistance.[56]

The discovery of the cardiac microvascular pericyte and adventitial pericyte-like progenitor cell and their functions is of great importance to understand their control in physiological processes as blood flow, regulation of the coagulatory process and vessel permeability. [57-59] Dysfunction of pericytes influences the pathogenesis of cardiovascular disease e.g., myocardial edema, vascular remodeling and post-ischemic no-reflow. [60, 61]

The microvascular status is a strong prognostic marker of event-free survival.[36] In clinical practice this marker is not readily available at the time of PPCI for risk stratification.

Wang et al. suggested a clinical risk score to predict no-reflow in PPCI treated STEMI patients comprising 6 items: age, plasma glucose on admission, neutrophil count, Killip class, β-blocker administration and time-to-hospital admission.[62] Although no procedural variables were included and the measure of no-reflow was derivative, namely TIMI flow grade and myocardial blush grade, a risk score for clinical use is valuable. Notwithstanding being a practical and simple score for risk stratification, the clinical relevance has to be determined yet in prospective studies.

At the end of last century when we prepared our studies, it was unclear what was the best timing to interrogate the coronary microvasculature, for example at the time of PPCI or a day or a week after reperfusion, as well as by what means, e.g., intracoronary Doppler-derived flow velocity measurements, CMR, contrast echocardiography, angiographically or ECG-derived measurements. Furthermore, in the late 1990s it was unclear when microvascular autoregulation, disturbed by the myocardial infarction, would recover and whether the severity and duration of this dysregulation would affect the recovery of left ventricular function.

Besides changes in flow in the infarct related artery (IRA) during acute myocardial infarction also the non-infarct related arteries (non-IRA) show changes in blood flow and in vasodilator capacity. After patients with single vessel disease had received thrombolytic therapy for myocardial infarction Uren et al. demonstrated in 1994 severe vasodilator abnormalities by PET scans in basal and hyperemic status at 1 week and 6 months after the infarction.[63] This disturbed vasodilation function was not only measured in the IRA but also in the non-IRA. Of relevance was the finding that at 6-months follow-up the value in remote myocardium remained lower than that in similar regions in control patients. Thus, myocardial infarction affects vasomotor regulation in the whole cardiac microvascular tree for at least 6 months.

With our studies, we wanted to assess the degree of deviation of microvascular dysfunction at the time of reperfusion of the acute myocardial infarction. Furthermore, we wanted to clarify the time course of recovery of microvascular dysfunction and the predictive value of acutely disturbed microvascular function in relation to left ventricular function recovery.

In conclusion, insufficient restoration of blood flow, both at the epicardial level and based on reperfusion injury and no-reflow in the microcirculation, leads to a larger myocardial infarction and poorer prognosis. Even after correction for the size of the myocardial infarction, no-reflow entails suboptimal recovery of the left ventricular function. For the risk stratification of patients with acute myocardial infarction, it is important to know the extent of microvasculature dysfunction at the time of reperfusion. This knowledge might help to identify high risk patients, to identify timing and effect of adjunctive interventions and gaining more insight into the process of reperfusion injury.

Doppler derived flow velocity signal information

When starting our studies described in this thesis, PPCI as mechanical reperfusion therapy had just become the treatment of choice in STEMI patients as it still is today. After complete restoration of the epicardial coronary blood flow, no- or slow reflow was recognized as a suboptimal treatment outcome in the acute phase of myocardial infarction resulting in poor long-term clinical outcomes. Restoration of blood flow was evaluated on the basis of the eyeballing technique determining TIMI angiographic flow grades (flow grades based on results of the Thrombolysis In Myocardial Infarction trial). Semi quantitative measurements as (corrected) TIMI-frame count using the film frame rate as measure of speed was used for the same purposes. Using Doppler tipped guide wires to determine flow velocity after reperfusion absolute blood flow velocity could directly be measured. Profound heterogeneity was observed between the TIMI techniques and the blood flow velocity in reperfused infarct arteries.[64] Furthermore, TIMI flow assessment had a low sensitivity for detecting microvascular obstruction.[65] It was unclear what the best parameters were at the time of acute myocardial infarction, to predict the recovery of left ventricular function. In the timeframe of our studies, it was possible to determine coronary flow reserve (CFR) as a measure of microvascular integrity and microvascular autoregulatory function by means of quantification of the coronary blood

flow velocity with an intracoronary wire mounted with a Doppler crystal. Dysfunctional microvasculature might among others be reflected by reversed early systolic coronary flow, a steep deceleration slope of the diastolic flow velocity, higher microvascular resistance and impaired CFR as quotient of hyperemic blood flow velocity and baseline blood flow velocity as indicator of recruitable functional microvascular capacity.[66, 67]

On the basis of the Doppler flow velocity studies of Kern et al. concluding that determination of flow velocity after reperfusion might enhance patient characterization and provide the physiological rationale for clinical variations after reperfusion therapy,[64] we started our research in order to determine the post reperfusion microvascular changes over time as well as the relationship between microvascular dysfunction and the potential effects on left ventricular function recovery.

Aim of this thesis

The main aim of the studies presented in this thesis is to investigate the characteristics of coronary blood flow velocity rates reflecting coronary microvascular function during reperfusion of acute myocardial infarction and how these characteristics change over time in the post infarction phase. In addition, it was investigated whether patient characteristics, intervention or specific coronary microvasculature factors, insofar as they can be determined by intracoronary Doppler studies, may be predictive of left ventricular function recovery and long-term survival.

Thesis outline

Chapter 2 reports a prospective clinical study of a homogenous group of 100 consecutive patients with monovascular coronary artery disease suffering a first anterior STEMI, treated with PPCI. Standard methods to determine treatment efficacy as TIMI flow grade, corrected TIMI frame count and myocardial blush grade, being surrogates for tissue reperfusion are compared to Doppler derived flow velocity values. These Doppler determinants, together with patient and procedure characteristics are related to potential recovery of the left ventricle during follow-up. Left ventricular function is evaluated by means of echocardiography in the course of the infarction until 6-months of follow-up. Early determinants of recovery of left ventricular function are identified in the acute phase of the myocardial infarction.

Thus far, the post infarct changes over time of microvascular function and autoregulation in terms of flow velocity reserve and resistances in infarcted and remote areas were unclear. *Chapter 3* details unique data of Doppler derived flow velocity characteristics obtained directly after reperfusion in patients with an acute anterior myocardial infarction and at follow-up at 1-week and 6-months. This concerns the first published data reporting the intracoronary measured flow rates and microvascular resistances in the course of myocardial infarction and follow-up, not only in the infarct-related vessel but also in the non-infarct-related artery.

Chapter 4 presents a review regarding the value of using the Doppler flow-wire in the setting of acute myocardial infarction. This treatise not only describes the value of performing CFR measurements at the time of PPCI but also the typical properties of Doppler signals in microvascular dysfunction due to obstruction or injury and how it can be used to predict recovery of left ventricular function. Finally, this Doppler technique is compared to other invasive and non-invasive techniques to assess microvascular function.

Chapter 5 describes the importance of knowledge of the microvascular function, especially in the coronary arteries remote from the infarcted artery, and its relation to long-term (10 years) mortality. Furthermore, the relation between CFR in the reference vessel at 6-months following the de index procedure and also long-term mortality is evaluated.

Chapter 6 is the only chapter in this thesis not reporting about patients with acute myocardial infarction. As in Chapter 5 the usefulness of measuring CFR in angiographical normal arteries is evaluated during elective PCI. However, evaluation in this chapter deals with stable patients with chronic coronary syndromes. Again, the relationship between abnormal microvascular function and long-term mortality is researched.

Chapter 7 reports the prognostic value of microvascular dysfunction, assessed by CFR, in the subacute phase of STEMI in relation to CMR derived left ventricular function in a subgroup analysis of the HEBE trial (designed to assess the effect of bone marrow mononuclear cell therapy on cardiac improvement in STEMI patients).

In several non-diabetic patients presenting with STEMI, high levels of serum glucose are measured. *Chapter 8* evaluates the relation between high blood glucose levels during STEMI and the microvascular function in infarct related and remote arteries.

Several limitations may apply to the use of CFR in assessing ischemic heart disease and microvascular function, such as factors influencing resting or hyperemic flow. The concept of the coronary flow capacity (CFC) was recently developed, based on the assumption that myocardial ischemia originates when both maximal coronary flow and the reserve capacity of the coronary circulation are below ischemic thresholds and that myocardial ischemia is unlikely once CFR or maximal flow is among normal values.[68, 69] Since CFC should be less prone to alterations in hemodynamics than CFR, in *Chapter 9* is CFC used to document the time course of microvascular function in the setting of anterior wall STEMI in both the infarct as well as the remote regions.

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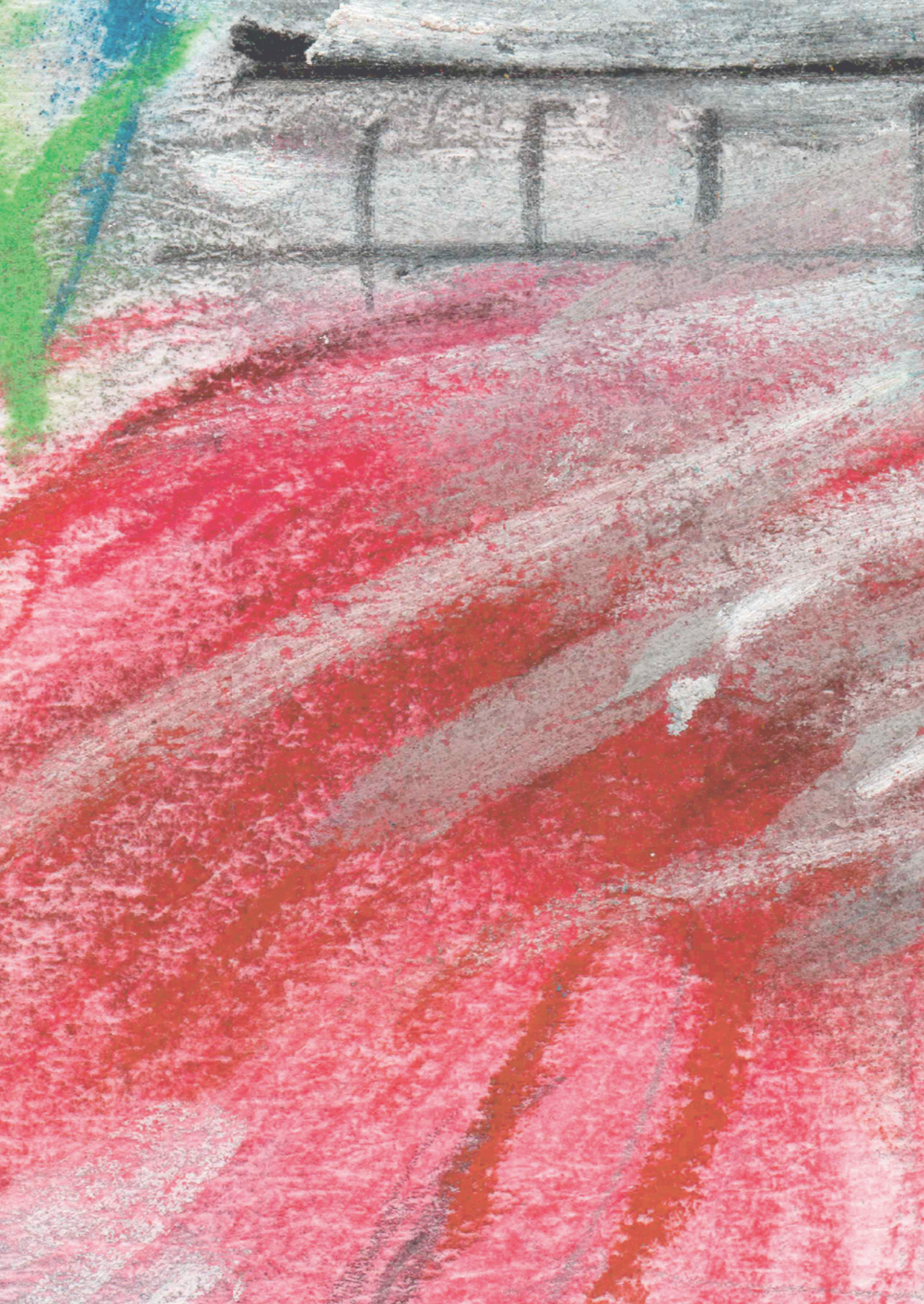

Chapter 2

Short- and long-term recovery of left ventricular function predicted at the time of primary percutaneous coronary intervention in anterior myocardial infarction

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J Am Coll Cardiol. 2004;43:534-41.
https://doi.org/10.1016/j.jacc.2003.08.055

Abstract

Objectives

The aim of this study was to determine predictors of left ventricular (LV) function recovery at the time of primary percutaneous coronary intervention (PCI).

Background

Angiographic, intracoronary Doppler flow, and electrocardiographic variables have been reported to be predictors of recovery of LV function after acute myocardial infarction (MI). We directly compared the predictive value of Thrombolysis In Myocardial Infarction (TIMI) flow grade, corrected TIMI frame count (cTfc), myocardial blush grade, coronary Doppler flow velocity analysis, and resolution of ST-segment elevation for recovery of LV function in patients undergoing primary PCI for acute MI.

Methods

We prospectively studied 73 patients who underwent PCI for an acute anterior MI. Recovery of global and regional LV function was measured using an echocardiographic 16-segment wall motion index (WMI) before PCI, at 24 h, at one week, and at six months. Directly after successful PCI, coronary flow velocity reserve (CFR), cTfc, TIMI flow grade, and myocardial blush grade were assessed.

Results

Mean global and regional WMI improved gradually over time from 1.86 ± 0.23 before PCI to 1.54 ± 0.34 at six-month follow-up ($p < 0.0001$) and from 2.39 ± 0.30 before PCI to 1.87 ± 0.48 at six-month follow-up ($p < 0.0001$), respectively. Multivariate analysis revealed CFR as the only independent predictor for global and regional recovery of LV function at six months.

Conclusions

Doppler-derived CFR is a better prognostic marker for LV function recovery after anterior MI than other currently used parameters of myocardial reperfusion.

Introduction

Early restoration of perfusion after myocardial infarction (MI) reduces mortality, limits infarct size, and preserves left ventricular (LV) function.[1-3] The primary objective of reperfusion therapy is not only to restore epicardial vessel patency but also to reperfuse tissue in order to maintain myocyte integrity and function and, thus, LV function. At present, it is unclear which diagnostic method in the acute phase of MI accurately predicts the recovery of LV function. Electrocardiographic (ECG) determinants such as ST-segment deviation resolution[4] and (in)direct measurements of microvascular function after reperfusion therapy may indicate recovery of LV function).[5,6] Angiographic predictors include Thrombolysis In Myocardial Infarction (TIMI) flow grade,[2,7,8] corrected TIMI frame count (cTfc),[9] and myocardial blush grade as surrogates for tissue reperfusion.[10] Coronary flow velocity reserve (CFR) obtained by digital subtraction cine-angiography significantly correlated with regional myocardial function at follow-up in the setting of acute MI.[5] Both Doppler derived CFR and blood flow velocity pattern may indicate LV function recovery.[11-13] The purpose of this study was to identify early determinants (at the time of reperfusion) of recovery of LV function by a direct comparison of the aforementioned parameters in patients with acute MI treated with primary percutaneous coronary intervention (PCI).

Methods

Patient selection

We studied 100 consecutive patients presenting with a first, acute, anterior MI treated with primary PCI. Acute MI was defined as chest pain lasting more than 30 min in conjunction with persistent ST-segment elevation in the precordial leads. Exclusion criteria were cardiogenic shock defined as systolic blood pressure below 90 mm Hg despite conservative measurements, previous anterior MI, previous coronary artery bypass grafting, prior LV ejection fraction <40%, LV hypertrophy (interventricular septum or posterior wall >12 mm), absence of thoracic windows for echocardiography, three-vessel coronary artery disease, TIMI grade 2 or 3 flow at time of initial angiography, or unsuccessful PCI defined as no antegrade flow and/or >50% residual stenosis in the infarct-related artery

(IRA). All patients gave informed consent to the study before the procedure. The institutional review board had approved the study protocol.

Primary angioplasty and Doppler flow measurements

Primary PCI was performed within 6 h after the onset of symptoms via 6F sheath in the femoral artery, according to standard clinical practice with provisional stent implantation. Coronary angiography was performed at the end of PCI for off-line flow analyses. Five to 10 min after successful PCI, blood flow velocity was measured with a 0.014 inch Doppler wire (FloWire, Jomed, Ulestraten, The Netherlands) distal to the lesion. Coronary flow velocity reserve was determined as the ratio of adenosine (20 μg intracoronary), induced hyperemic average peak flow velocity (APV), and baseline APV. Flow velocities were recorded continuously on videotape (FloMap, Jomed). Coronary flow velocity reserve was also measured in an angiographically normal (diameter stenosis <30%) reference artery at the end of the procedure. A 12-lead ECG was performed before and at the end of PCI to evaluate ST-segment deviation.

Concomitant medical therapy

All patients were treated with aspirin 300 mg orally and heparin 5,000 IU intravenously before the procedure. An additional 2,500 IU heparin intravenously was administered if the procedure lasted more than 90 min. According to the protocol, patients subsequently received unfractionated heparin for 48 h, aspirin 100 mg daily, and ticlopidine 250 mg or clopidogrel 75 mg once daily after stent placement. Captopril was administered within 24 h after PCI and uptitrated if possible to 25 mg three times a day, metoprolol 50 mg twice a day, uptitrated if possible. Statin treatment was started the day after admission irrespective of serum cholesterol values.

LV function evaluation and follow-up

Two-dimensional echocardiography was performed immediately before primary PCI with a commercially available imaging system (Philips SONOS 2500, 2.0/2.5 MHz transducer). Data was stored on videotape. Echocardiographic evaluation of the LV function was repeated at day one, at one week, and at six months follow-up. After five weeks, a gated radionuclide ventriculography was performed. At six months follow-up, coronary angiography was repeated to assess vessel patency and/or restenosis. At six months, all patients were

evaluated for major events, defined as death from all causes, non-fatal reinfarction, repeat PCI, or coronary artery bypass grafting.

Data extraction

The sum of ST-segment elevations was measured manually 80 ms after the end of the QRS complex (J-point) in leads I, aVL, and V1 through V6. Resolution of ST-segment elevation was expressed as a percentage of the initial ST-segment elevation. Resolution of 70% was defined as indicative for good myocardial reperfusion.[14] Collateral flow to the IRA was graded before PCI, according to Rentrop's classification.[15] The TIMI flow and myocardial blush were graded,[7,10] and cTfc was measured off-line.[9] The rate–pressure product was defined as the product of heart rate and systolic blood pressure at the end of the procedure. Doppler flow velocity spectra were analyzed off-line to determine the following parameters: diastolic APV, diastolic deceleration time with a cutoff value of 600 ms,[11] average antegrade systolic flow velocity with a cutoff value of 6.5 cm/s,[11] the calculated ratio of mean diastolic-to-systolic flow velocity and early systolic retrograde flow velocity defined as retrograde peak velocity ≥10 cm/s, and duration ≥60 ms as previously described.[16]

A 16-segment model was used to determine systolic LV function.[17] All segments with a good delineation of the endocardium were scored: 1 = normal, 2 = hypokinesis, 3 = akinesis, 4 = dyskinesis. Global wall motion score index (WMI) was calculated by summation of the scores divided by the number of analyzed segments. Nine segments were used to calculate regional WMI: basal and mid-anteroseptal; mid-septal; apico-septal; apico-lateral; basal-, mid-, and apico-anterior; and apico-inferior—usually representing the perfusion territory of the left anterior descending [LAD] artery. Recovery of global and regional LV function was defined as the difference in global and, respectively, regional WMI before PCI and that at specific time points at follow-up.

Statistical analysis

The study cohort consisted of patients who had an uneventful follow-up with an analyzable six-month follow-up echocardiography. The primary end point was recovery of LV function at six months, as defined above. Variables are presented as percentage of number of patients. Continuous variables are expressed as mean ± SD. Normally distributed variables were tested by two-

tailed Student t test for paired or unpaired data, as appropriate, or by one-way analysis of variance (ANOVA) for more than two independent groups of data. The categorical variables were compared by chi-square or Fisher exact test where appropriate. Changes in global and regional WMI were tested by ANOVA for repeated measures. A p value <0.05 was considered statistically significant. Regression lines were obtained by least squares regression method. After determining univariate predictors of recovery of LV function and ejection fraction, multivariate stepwise linear regression analysis was applied to univariate variables with a significance level lower than 0.15. Qualitative variables were coded as 1 when the property was present and as 0 when absent. Statistical analysis was performed with SPSS version 10.0.7 (SPSS Inc., Chicago, Illinois).

Results

Clinical events

One patient died of a hemorrhagic stroke three days after primary PCI, and one patient of end-stage kidney failure with progressive heart failure at 147 days' follow-up. One patient underwent coronary artery bypass grafting at day 89. Eight patients underwent repeat PCI (4 patients showed target lesion restenosis, 1 acute stent closure at day 14, and 3 patients underwent non-LAD coronary artery repeat PCI). Six patients with significant restenosis at six months' follow-up were excluded from the analysis because of possible influences on LV function recovery. Ten patients with an uncomplicated clinical course at follow-up refused a reangiography. The remaining 73 of the initial 100 patients constitute the study cohort and were analyzed in the present study.

Baseline characteristics

Baseline clinical characteristics are shown in Table 1. Angiographic, Doppler, and procedural characteristics are shown in Table 2. Mean age of the analyzed patients was 54 ± 12 years. Mean summated ST-segment elevation before PCI was 26.5 ± 14.8 mV and after the procedure 7.9 ± 6.1 mV resulting in 18.6 ± 12.2 mV absolute ST-segment resolution. The relative resolution was 70.2 ± 23.0%. Mean time between reperfusion and second ECG was 106 ± 30 min. Mean cTfc in the LAD coronary artery after PCI was 44 ± 21 and in the reference

vessel 29 ± 12. A significant association existed between TIMI flow grade and cTfc (r = -0.72, p < 0.0001), TIMI flow grade and myocardial blush grade (r = 0.45, p < 0.0001), and cTfc and myocardial blush grade (r = -0.53, p < 0.0001). At the end of the PCI procedure, mean CFR in the LAD coronary artery was 1.62 ± 0.37 (range, 1.0 to 2.6), with a mean baseline APV of 20.1 ± 8.5 cm/s and a mean hyperemic APV of 32.0 ± 14.1 cm/s. The mean reference vessel CFR was 2.43 ± 0.53. In the LAD coronary artery, mean diastolic deceleration time was 635 ± 382 ms, mean average systolic flow velocity 9.9 ± 8.4 cm/s, mean diastolic-to-systolic flow velocity 4.2 ± 6.2, and mean early systolic retrograde flow velocity 6.3 ± 11 cm/s. Baseline APV in the LAD coronary artery showed fair correlations with TIMI flow grade (r = 0.31, p < 0.007) and cTfc (r = -0.54, p < 0.0001). No association was found between baseline APV and myocardial blush grade. A fair correlation existed between baseline APV and ST-segment resolution (r = -0.40, p < 0.003). Hyperemic APV in the LAD coronary artery was associated with TIMI flow grade (r = 0.35, p < 0.003), cTfc (r = -0.50, p < 0.0001), myocardial blush grade (r = 0.25, p = 0.04), and with ST-segment resolution (r = 0.29, p = 0.04). There was no significant correlation between CFR and any of the angiographic parameters or between CFR and ST-segment resolution. Mean peak CK-MB was 486 ± 255 µg/l.

Table 1. Baseline and Clinical Characteristics and Univariate Predictors for Regional LV function Recovery

		Regional LV Function Recovery					
	n = 73 %	1 Day Mean (±SD)	p Value	1 Week Mean (±SD)	p Value	6 Months Mean (±+SD)	p Value
Age≥ 55 yr			NS		NS		NS
Yes	45	0.11(0.28)		0.32(0.35)		0.54(0.55)	
No	55	0.06(0.23)		0.34(0.38)		0.49(0.42)	
Male gender			0.13		0.06		NS
Yes	84	0.06(0.24)		0.29(0.35)		0.49(0.46)	
No	16	0.19(0.30)		0.51(0.39)		0.63(0.54)	
Hypertension			NS		NS		NS
Yes	26	0.02(0.29)		0.28(0.33)		0.36(0.41)	
No	74	0.09(0.24)		0.36(0.37)		0.53(0.47)	
Smoking			NS		NS		NS
Yes	60	0.09(0.24)		0.33(0.37)		0.42(0.45)	
No	40	0.04(0.27)		0.33(0.34)		0.55(0.48)	
Hypercholesterolemia			NS		0.15		NS
Yes	29	0.05(0.22)		0.44(0.41)		0.52(0.52)	
No	71	0.09(0.26)		0.30(0.31)		0.48(0.43)	

Table 1. continued

		Regional LV Function Recovery					
	n = 73 %	1 Day Mean (±SD)	p Value	1 Week Mean (±SD)	p Value	6 Months Mean (±+SD)	p Value
Diabetes mellitus			NS		NS		NS
Yes	8	-0.07(0.19)		0.11(0.24)		0.40(0.73)	
No	92	0.09(0.26)		0.35(0.36)		0.49(0.44)	
Positive family history			NS		NS		NS
Yes	49	0.09(0.28)		0.39(0.43)		0.51(0.46)	
No	51	0.06(0.24)		0.28(0.27)		0.43(0.45)	
Beta blocker			NS		NS		NS
Yes	14	0.09(0.26)		0.30(0.38)		0.37(0.36)	
No	86	0.08(0.25)		0.34(0.37)		0.52(0.49)	
Calcium antagonist			NS		NS		NS
Yes	9	0.09(0.18)		0.30(0.35)		0.65(0.56)	
No	91	0.08(0.26)		0.33(0.38)		0.48(0.46)	
Aspirin			NS		0.02		NS
Yes	10	0.19(0.15)		0.71(0.17)		0.70(0.45)	
No	90	0.06(0.26)		0.30(0.37)		0.48(0.47)	
ACE inhibitor			0.12		NS		NS
Yes	6	-0.11(0.34)		0.21(0.58)		0.41(0.58)	
No	94	0.09(0.24)		0.34(0.36)		0.50(0.47)	
Statin			NS		0.08		NS
Yes	10	0.03(0.31)		0.59(0.35)		0.68(0.61)	
No	90	0.08(0.25)		0.31(0.37)		0.49(0.45)	
Preinfarct angina			NS		0.14		NS
Yes	63	0.11(0.26)		0.39(0.40)		0.54(0.47)	
No	37	0.03(0.23)		0.25(0.23)		0.44(0.48)	
Time to arrival <2.0 hr			NS		NS		NS
Yes	54	0.07(0.27)		0.28(0.42)		0.47(0.43)	
No	46	0.10(0.24)		0.39(0.30)		0.57(0.53)	
Time to reperfusion <3.0 hr			NS		0.1		0.08
Yes	55	0.10(0.24)		0.39(0.33)		0.60(0.53)	
No	45	0.06(0.27)		0.25(0.40)		0.41(0.38)	
Global WMI before PCI < 1.9			NS		NS		NS
Yes	56	0.07(0.30)		0.30(0.39)		0.51(0.50)	
No	44	0.11(0.18)		0.37(0.34)		0.51(0.45)	
Regional WMI before PCI <2.4			0.11		0.02		NS
Yes	45	0.000(0.29)		0.21(0.34)		0.46(0.45)	
No	55	0.16(0.20)		0.42(0.36)		0.56(0.50)	

Table 2. Angiographic, Doppler and Procedural Characteristics and Univariate Predictors for Regional LV function Recovery

		Regional LV Function Recovery					
	N=73	1 Day	p Value	1 Week	p Value	6 Months	p Value
	%	Mean (±SD)		Mean (±SD)		Mean (±SD)	
Single vessel disease			0.07		0.06		0.12
Yes	78	0.11(0.26)		0.37(0.39)		0.56(0.46)	
No	22	-0.02(0.19)		0.16(0.23)		0.35(0.51)	
Location of occlusion			NS		NS		NS
Before septal	15	0.11(0.20)		0.28(0.20)		0.57(0.43)	
Between septal and diagonal	43	0.03(0.21)		0.30(0.27)		0.44(0.49)	
Distal to first diagonal	42	0.11(0.30)		0.38(0.50)		0.58(0.51)	
Collaterals			NS		NS		NS
No collaterals	40	0.07(0.24)		0.26(0.33)		0.51(0.48)	
Rentrop grade 1	47	0.09(0.25)		0.39(0.42)		0.54(0.51)	
Rentrop grade 2	13	0.08(0.30)		0.26(0.21)		0.44(0.41)	
Rentrop grade 3	0						
Stent implantation			NS		NS		NS
Yes	62	0.09(0.26)		0.31(0.39)		0.45(0.52)	
No	38	0.09(0.25)		0.35(0.35)		0.56(0.45)	
Abciximab			NS		NS		NS
Yes	18	0.09(0.23)		0.20(0.21)		0.52(0.46)	
No	82	0.09(0.26)		0.35(0.38)		0.52(0.48)	
TIMI flow after PCI			0.06		0.07		NS
Grade 1	1	-0.5		-0.5		0.06	
Grade 2	20	0.07(0.20)		0.30(0.29)		0.45(0.44)	
Grade 3	79	0.09(0.25)		0.34(0.37)		0.54(0.49)	
cTfc after PCI			NS		NS		NS
> 40	43	0.05(0.25)		0.30(0.35)		0.52(0.47)	
30-40	31	0.10(0.25)		0.39(0.42)		0.58(0.42)	
<30	26	0.11(0.27)		0.29(0.33)		0.42(0.56)	
Myocardial blush grade after PCI			0.08		NS		NS
Grade 1	4	-0.13(0.50)		-0.08(0.59)		0.24(0.20)	
Grade 2	39	0.02(0.23)		0.30(0.33)		0.43(0.47)	
Grade 3	57	0.13(0.23)		0.36(0.37)		0.59(0.49)	
Rate-pressure product <10,000			0.11		NS		0.1
Yes	61	0.12(0.28)				0.59(0.49)	
No	39	0.02(0.20)				0.40(0.46)	
CFR LAD			NS		0.06		<0.0001
<1.50	33	0.04(0.28)		0.24(0.27)		0.26(0.41)	
1.50 - 1.75	41	0.11(0.25)		0.28(0.41)		0.53(0.48)	
>1.75	26	0.11(0.22)		0.50(0.37)		0.81(0.39)	

Table 2. continued

		Regional LV Function Recovery					
	N=73	1 Day	p Value	1 Week	p Value	6 Months	p Value
	%	Mean (±SD)		Mean (±SD)		Mean (±SD)	
Baseline APV LAD (cm/s)			NS		NS		NS
<15	27	0.06(0.27)		0.25(0.41)		0.55(0.51)	
15 - 20	33	0.08(0.26)		0.31(0.25)		0.45(0.40)	
>20	40	0.11(0.24)		0.40(0.41)		0.55(0.52)	
Hyperemic APV LAD (cm/s)			NS		0.13		NS
<25	34	0.04(0.28)		0.22(0.36)		0.46(0.52)	
25 - 35	32	0.07(0.25)		0.31(0.29)		0.50(0.40)	
>35	34	0.14(0.23)		0.44(0.42)		0.59(0.51)	
Diastolic deceleration time <600 ms			NS		NS		NS
Yes	55	0.08(0.28)		0.31(0.39)		0.51(0.44)	
No	45	0.09(0.25)		0.37(0.37)		0.55(0.56)	
Average systolic flow velocity <6.5 cm/s			NS		NS		NS
Yes	31	0.02(0.23)		0.26(0.35)		0.57(0.47)	
No	69	0.11(0.22)		0.39(0.36)		0.59(0.44)	
Diastolic-systolic velocity ratio <3			0.12		NS		0.03
Yes	62	0.12(0.24)		0.40(0.41)		0.67(0.47)	
No	38	0.03(0.18)		0.25(0.23)		0.42(0.36)	
Systolic retrograde flow velocity >= 10 cm/s			0.008		0.02		0.03
Yes	30	-0.03(0.30)		0.17(0.34)		0.33(0.43)	
No	70	0.14(0.21)		0.40(0.36)		0.59(0.49)	
CFR reference vessel			NS		NS		NS
<2.0	16	0.11(0.22)		0.40(0.46)		0.34(0.44)	
2.0 - 2.8	64	0.0.7(0.28)		0.31(0.37)		0.54(0.48)	
>2.8	19	0.11(0.21)		0.35(0.30)		0.57(0.50)	
ST-resolution >70%			NS		NS		NS
Yes	55	0.12(0.31)		0.30(0.36)		0.55(0.40)	
No	45	0.05(0.21)		0.38(0.44)		0.48(0.54)	

*Variables with a p value <0.15 were submitted to multivariate analysis for LV function recovery evaluation. APV = average peakflow velocity; CFR = coronary flow velocity reserve; cTfc = corrected TIMI frame count; LAD = left anterior descending coronary artery; LV = left ventricular; PCI = percutaneous coronary intervention; TIMI = Thrombolysis in Myocardial Infarction.

Table 3. Recovery of Global and Regional Left Ventricular Function

	Global WMI	p Value*	Regional WMI	p Value*
Before PCI	1.86 (0.23)	0.0001	2.39 (0.30)	0.0001
Recovery† at one day	0.03 (0.22)		0.09 (0.25)	
Recovery† at one week	0.20 (0.28)		0.33 (0.37)	
Recovery† at six months	0.32 (0.34)		0.52 (0.48)	

*p value obtained in analysis of variance for repeated measurements; †Recovery defined as WMI before PCI minus WMI at specific time points. Values are given as means ± SD. PCI = percutaneous coronary intervention; WMI = Wall Motion Index.

Recovery of global and regional LV function

A progressive improvement of short-term and long-term global and regional LV function was documented (Table 3). All baseline variables were used to identify univariate predictors for short-term and long-term global (data not shown) and regional (Tables 1 and 2) LV function recovery. The relation between CFR and LV function recovery is plotted in Figure 1. All patients with a CFR ≥2.0 immediately after primary PCI showed improvement of LV function (Fig. 1A). No relation existed between angiographic parameters and recovery of LV function (Fig. 1B,1C, and 1D). Coronary flow velocity reserve of the LAD coronary artery directly after primary PCI was the only independent predictor in multivariate analysis of global (Table 4) and regional (Table 5) LV function recovery at six months. Global and regional LV function recovery at one week were predicted by clinical, echocardiographic, angiographic, and Doppler-derived variables (Tables 4 and 5). Independent predictors of short-term LV function improvement were not similar to those predicting long-term improvement (Tables 4 and 5).

LV ejection fraction

Mean ejection fraction at five weeks' follow-up was 47 ± 13%. Multivariate regression analysis revealed CFR in the LAD coronary artery and early systolic retrograde flow velocity as independent predictors of ejection fraction at five weeks (coefficient of constant, 14.6; coefficient of CFR, 15.7; 95% confidence interval, 5.8 to 25.5; p = 0.003; coefficient of systolic retrograde flow, -10.0; 95% confidence interval, -18.0 to -2.1; p = 0.01).

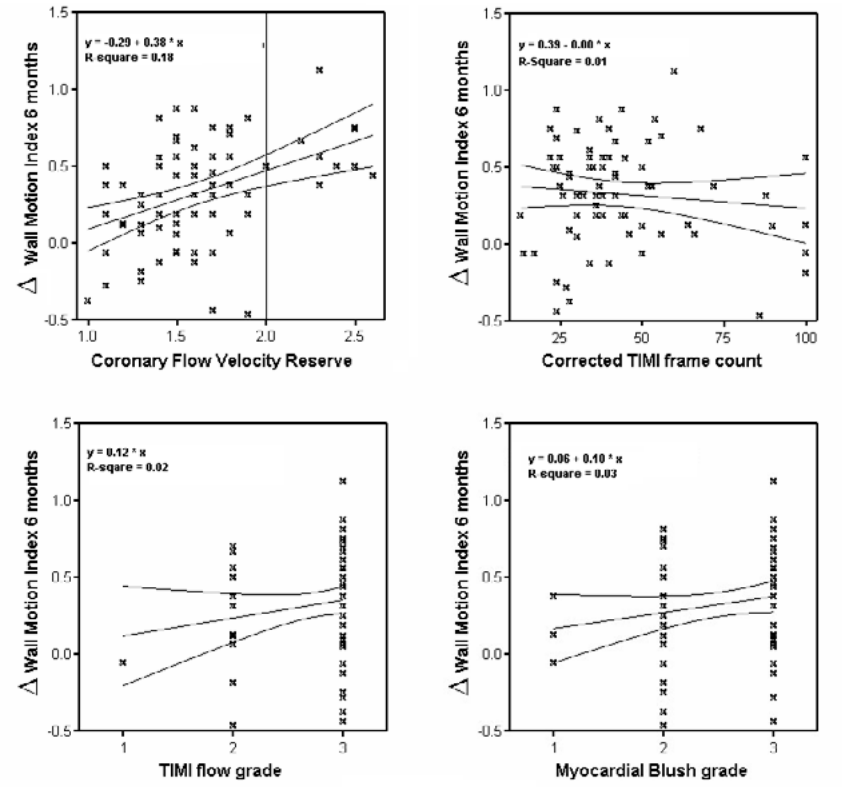

Figure 1. Relation between six-month change in global wall motion index (WMI) and coronary flow velocity reserve after percutaneous coronary intervention **(A)** and change in WMI as a function of corrected Thrombolysis In Myocardial Infarction (TIMI) frame count, **(B)** myocardial blush grade **(C)**, and TIMI flow grade **(D)**. The regression lines and 95% confidence intervals are shown. Change in WMI >0 reflects improvement of left ventricular function after six months.

Table 4. Multivariate Predictors of Recovery of Global Left Ventricular Function

	Coefficient	95% CI	p Value
Recovery at one day			
Constant	-0.076		
Early systolic retrograde flow velocity <10 cm/s	0.16	0.04-0.27	0.007
Recovery at one week			
Constant	-0.88		
Statin use	0.21	0.007-0.40	0.042
Global WMI before PCI ≥1.9	0.18	0.06-0.30	0.005
Single-vessel disease	0.19	0.04-0.34	0.012
TIMI flow grade	0.17	0.04-0.30	0.011
CFR after PCI	0.09	0.004-0.17	0.039
Recovery at six months			
Constant	-0.004		
CFR after PCI	0.17	0.06-0.27	0.002

*Recovery defined as WMI before PCI minus WMI at specific time points. CFR = coronary flow velocity reserve; CI = confidence interval; PCI = percutaneous coronary intervention; WMI = Wall Motion Index.

Table 5. Multivariate Predictors of Recovery of Regional Left Ventricular Function*

	Coefficient	95% CI	p Value
Recovery at one day			
Constant	-0.44		
Regional WMI before PCI ≥2.4	0.18	0.06-0.29	0.004
Single-vessel disease	0.17	0.03-0.31	0.016
Early systolic retrograde flow velocity <10cm/s	0.16	0.40-0.29	0.011
Recovery at one week			
Constant	-0.47		
Aspirin use	0.20	-0.07-0.47	0.148
Statin use	0.34	0.08-0.61	0.012
Regional WMI before PCI ≥2.4	0.25	0.08-0.41	0.004
Single-vessel disease	0.27	0.07-0.46	0.008
Early systolic retrograde flow velocity <10cm/s	0.22	0.04-0.39	0.015
Recovery at six months			
Constant	-0.02		
CFR after PCI	0.28	0.14-0.41	<0.0001

*Recovery defined as WMI before PCI minus WMI at specific time points. CFR = coronary flow velocity reserve; CI = confidence interval; PCI = percutaneous coronary intervention; WMI = Wall Motion Index.

Discussion

In our homogenously selected group of patients with a first anterior acute MI, Doppler-derived CFR obtained directly after primary PCI was the only independent predictor of long-term global and regional recovery of LV function. Thrombolysis In Myocardial Infarction flow grading predicted global recovery of LV function at one week, but not at other time points. No other angiographic parameter after primary PCI predicted LV function recovery. To our knowledge, this is the first study that directly compared CFR with other prognostic variables for LV function recovery at six months after primary PCI.

ST-segment resolution and LV function recovery

In contrast with earlier studies,[14,18,19] we could not demonstrate a relation between ST-segment recovery and ejection fraction nor between ST-segment recovery and improvement of LV function. Our results are in accordance with the results of Poli et al. as they found, with respect to six-month functional recovery, no additional prediction of ST-segment resolution next to myocardial blush grade.[19] ST-segment resolution is proposed as a marker of microvascular reperfusion.[20] However, in our study, no relation existed between ST- segment resolution and CFR, although it was associated with baseline and hyperemic

APV. In previous studies, ST-segment resolution was slower in patients with anterior MI than with non-anterior MI. This may explain the absence of association between ST resolution and CFR in our study in patients with only anterior MI.

Angiographic parameters in relation to LV function recovery

Our current knowledge on factors influencing LV function recovery after acute MI is based on angiographic studies. In large, multicenter studies evaluating thrombolysis, TIMI flow grading appeared to be of clinical use for risk stratification.[2,8,21] In our study, TIMI flow after PCI showed a weak correlation with LV function recovery at one week ($r = 0.30$, $p = 0.015$), and myocardial blush grade was weakly correlated with regional function recovery at one day ($r = 0.27$, $p = 0.02$). Our study consisted of non-high-risk patients (excluding shock, low ejection fraction, previous anterior MI, and excluding cardiac events on follow-up). This may be the reason for a diminished ability to detect a relationship between angiographic parameters and LV function recovery, whereas CFR is a potent predictor of LV function recovery in these patients.

Doppler-flow parameters in relation to LV function recovery

In our study, CFR was the only independent predictor of long-term global and regional LV function recovery. Coronary flow velocity reserve after PCI predicted not only the change in LV function over six months but also the ventriculographic ejection fraction at five weeks that is associated with long-term mortality. Coronary flow velocity reserve as a predictor being superior to the other parameters of myocardial perfusion may be explained by the direct way of interrogating the microvascular bed, thereby more accurately reflecting microvascular integrity and function. Iwakura et al. demonstrated altered coronary flow velocity patterns as the appearance of systolic retrograde flow, diminished systolic antegrade flow, and rapid deceleration of diastolic flow in patients with the no-reflow phenomenon after reperfusion therapy.[16] These flow velocity patterns appeared to be inversely related with in-hospital[22] and with one-month recovery of LV function.[11] This is in accordance with our findings that absence of early systolic retrograde flow immediately after primary PCI was associated with recovery of global and regional LV function at one-day follow-up and with regional LV function improvement at one week. At five weeks, systolic retrograde flow, next to CFR, independently correlated with ejection fraction. However, long-term LV function changes were not predicted by altered

coronary flow velocity patterns in contrast with CFR. Surprisingly, CFR was not assessed in the aforementioned studies. Although altered flow patterns after primary PCI could predict in-hospital complications and mortality,[23] it is unclear if these flow patterns can predict also long-term mortality.

Study limitations

This study was designed to evaluate prognostic parameters obtained during primary PCI on LV function recovery. The present study indicates that CFR is a good prognostic parameter for LV function recovery, although larger studies are needed for evaluation of Doppler-derived parameters to predict mortality. In this study we did not perform intracoronary pressure measurements with microvascular resistance calculations. Combined and repeated coronary flow and pressure assessment in the early and late phase of MI may give more insight into changes in microvascular resistance in relation to LV function recovery.

Clinical implications

Our study suggests that CFR immediately after primary PCI can predict LV function recovery. This finding is relevant for selection of patients that may benefit from adjunctive therapies aiming at improving tissue reperfusion and, hence, recovery of LV function.

Conclusions

Percutaneous coronary intervention in patients with acute MI reduces infarct size and preserves LV function. Preservation of the microvascular function, and thus, of the integrity of myocardial tissue, is the pivotal factor influencing recovery of LV function after primary PCI. This study demonstrates that Doppler derived CFR better predicts recovery of LV function than the commonly reported angiographic and clinical parameters

Acknowledgments

We thank the technical and nursing staff of our cardiac catheterization laboratory and coronary care unit for skilled assistance.

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Chapter 3

Time course of microvascular resistance of the infarct and noninfarct coronary artery following an anterior wall acute myocardial infarction.

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Am J Cardiol 2006;97:1131–1136
https://doi.org/10.1016/j.amjcard.2005.11.026

Previous studies have suggested that coronary flow velocity reserve (CFVR) in the early phase of acute myocardial infarction (AMI) is abnormal in infarcted and remote regions. This study determined the coronary microvascular resistance of infarct-related arteries (IRAs) and non-IRAs during AMI and at follow-up in patients who were treated with primary percutaneous intervention. In 73 patients with a first anterior wall AMI, baseline and minimal microvascular resistance in IRAs and non-IRAs immediately after reperfusion and at 1-week and 6-month follow-up were calculated as the ratio of mean transvascular pressure gradient to mean baseline and to adenosine-induced hyperemic blood flow velocity, respectively. CFVR in IRAs increased from 1.6 ± 0.4 after reperfusion to 1.9 ± 0.5 at 1 week and to 3.0 ± 0.8 at 6 months ($p < 0.0001$) and in non-IRAs from 2.4 ± 0.5 to 2.7 ± 0.6 at 1 week to 3.3 ± 0.6 at 6 months ($p < 0.0001$). Minimal microvascular resistance in IRAs and non-IRAs (3.2 ± 1.7 and 2.2 ± 0.6 mm Hg/second/cm, respectively) decreased significantly at follow-up (2.0 ± 0.6 and 1.7 ± 0.6 mm Hg/second/cm at 1 week and 1.8 ± 0.6 and 1.8 ± 0.7 mm Hg/second/cm at 6 months, respectively). After correction for rate–pressure product, baseline microvascular resistance after reperfusion and at 6 months did not significantly differ between IRAs and non-IRAs. In conclusion, minimal microvascular resistance is higher in infarcted and noninfarcted regions during AMI than at follow-up. The low CFVR in remote regions during AMI is probably due more to disturbed autoregulation than to increased myocardial workload.

The objective of reperfusion therapy in acute myocardial infarction (AMI) is salvage of myocardial tissue by reestablishing blood flow to the jeopardized microcirculation to preserve left ventricular function and decrease mortality.[1] Despite restoration of epicardial blood flow, microvascular integrity and function of the infarct-related artery (IRA) may be decreased,[2, 3] which represents microvascular obstruction, a phenomenon also known as the "no-reflow" phenomenon.[4] Recent studies have demonstrated that intracoronary measured coronary flow velocity reserve (CFVR) in the IRA improves during the early phase of AMI but fails to reach normal levels at long-term follow-up.[5, 6] Some clinical[7, 8] and experimental[9, 10] studies have suggested a disturbed CFVR in the non-IRA in the acute phase of AMI. It has been postulated that neurohumoral activation contributes to this phenomenon. This is of clinical relevance because of the compensatory hyperkinesis of remote vascular territories in the setting of AMI. However, the change over time of coronary

flow dynamics and resistance has not been described in a homogenous group of patients. This study examined the coronary hemodynamics of IRAs and non-IRAs in the acute phase and at short- and long-term follow-up in patients who were treated with primary percutaneous intervention for a first anterior wall AMI.

Methods

Patient selection

We studied 100 consecutive patients who presented with a first anterior wall AMI that was treated with primary angioplasty. AMI was defined as chest pain that lasted >30 minutes in conjunction with persistent ST-segment elevation ≥2 mV in 2 adjacent precordial leads. Exclusion criteria were cardiogenic shock (systolic blood pressure <90 mm Hg despite conservative measurements), previous AMI, previous coronary artery bypass surgery, previous left ventricular ejection fraction <40%, acute left-side heart failure (Killip's class >II), left ventricular hypertrophy (interventricular septum or posterior wall ≥12 mm), diffuse coronary artery disease, or 3-vessel disease. All patients gave informed consent to the study before the procedure. An institutional review board approved the study protocol. The investigation conformed with principles outlined in the Declaration of Helsinki.

Coronary angiography

Coronary angiography was performed within 6 hours after onset of symptoms through a 6Fr sheath in the femoral artery. Patients were excluded if there was 3-vessel disease with >30% diameter stenosis, Thrombolysis In Myocardial Infarction grade 2 or 3 flow in an IRA at initial angiography, or unsuccessful percutaneous coronary intervention (no anterograde flow and/or >50% residual stenosis). Systolic and diastolic blood pressures at the tip of the guiding catheter and heart rate were recorded continuously. Coronary angiography was repeated at 1-week and 6-month follow-up.

Primary angioplasty and Doppler flow measurements

Primary angioplasty was performed according to standard clinical practice. Stent implantation was at the discretion of the operator. A stent was implanted in 68% of patients. Five to 10 minutes after successful angioplasty, blood

flow velocity was measured with a 0.014-inch Doppler wire (FloWire, Jomed, Ulestraten, The Netherlands) distal to the lesion. Special attention was paid to obtain the best Doppler signal. At least 3 measurements were made each time and were accepted when the variance was lower than 10%. A bolus of 0.1 mg of nitroglycerin was administered before flow assessment and repeated every 30 minutes. CFVR was determined as the ratio of hyperemic average peak blood flow velocity induced by adenosine (20 µg intracoronary) to baseline average peak blood flow velocity. Flow velocities, heart rate, and blood pressure were recorded continuously on videotape (FloMap, Jomed). CFVR was also measured at the end of the procedure in an angiographically normal non-IRA (the largest branch of the left circumflex artery [n = 68] unless there was >30% diameter stenosis, in which case the right coronary artery was used [n = 5]). At follow-up, Doppler flow velocities were assessed at the same position as during angioplasty. Before and after angioplasty and at follow-up, Thrombolysis In Myocardial Infarction flow and myocardial blush were graded[11]and corrected. Thrombolysis In Myocardial Infarction frame count was measured[12]offline in IRAs and non-IRAs.

Concomitant medical therapy

Patients were treated with 300 mg of aspirin orally and 5,000 IU of heparin intravenously before the procedure. An additional 2,500 IU of heparin intravenously was administered if the procedure lasted >90 minutes. Treatment with abciximab, during 12 hours, was at the operator's request. According to the protocol, patients received unfractionated heparin for 48 hours and 100 mg/day of aspirin and 250 mg of ticlopidine 2 times daily or 75 mg/day of clopidogrel for 1 month after stent placement. Captopril was administered within 24 hours after angioplasty and titrated up, if possible, to 25 mg 3 times daily and 50 mg of metoprolol 2 times daily. Statin treatment was started the day after admission irrespective of serum cholesterol values.

Follow-up

At 6 months, all patients were evaluated for major events, which were defined as death from all causes, nonfatal reinfarction (>30 minutes of angina with ST-segment depression or elevation with myocardial enzyme release >2 times the upper limit of normal), repeat angioplasty, or coronary artery bypass graft surgery.

Data extraction

The ratio of mean distal coronary pressure to average peak blood flow velocity was used as an index of microvascular resistance.[13, 14] The ratio of transvascular pressure gradient (mean aortic pressure minus right atrial pressure) to baseline average peak blood flow velocity was used as an index of baseline microvascular resistance index. Because right atrial pressure was not routinely measured, it was estimated to be 10 mm Hg in all patients. Minimal microvascular resistance index was defined as microvascular resistance during hyperemia. The variable arteriolar resistance index, which represented autoregulatory function, was expressed as baseline microvascular resistance minus minimal microvascular resistance. Baseline average peak blood flow velocity, CFVR, and baseline microvascular resistance values were also noted after correction for the rate–pressure product (parameter for global cardiac workload, defined as a product of systolic blood pressure and heart rate).

Clinical events

Two patients who died at follow-up showed higher baseline and minimal microvascular resistances in IRAs compared with the study group (7.8 ± 2.5 mm Hg/s/cm, p = 0.03, and 5.8 ± 1.5 mm Hg/s/cm, p = 0.009, respectively). Other values of physiologic data (Table 1) did not differ significantly from those in the study group. One patient underwent coronary artery bypass graft surgery. Eight patients underwent repeat angioplasty (4 patients showed target lesion restenosis, 1 had a subacute stent closure, and 3 underwent non-IRA angioplasty). Six patients with asymptomatic significant restenosis at 6-month follow-up (angiographic restenosis >50% at visual assessment without angina) were excluded from analysis because of possible influences on flow velocities. Ten patients with an uncomplicated clinical course at follow-up refused repeat angiography. (Microvascular resistance values in the acute phase of MI in all excluded patients, other than those who died, did not differ from those in the study group.) The remaining 73 of the initial 100 patients constituted the study cohort and were analyzed in the present study.

Statistical analysis

Variables are presented as numbers and percentages of patients. Continuous variables are expressed as mean ± SD. Normal distributed variables were tested by 2-tailed Student's *t* test for paired or unpaired data, as appropriate.

Unrelated nonparametric variables were tested with Mann-Whitney U statistic test, and related nonparametric variables with Wilcoxon's signed-rank test. Categorical variables were compared by chi-square or Fisher's exact test, where appropriate. A p value <0.05 was considered statistically significant. Statistical analysis was performed with SPSS 11.5 (SPSS, Inc., Chicago, Illinois).

Results

Patients' baseline characteristics are listed in Table 2.

A time-dependent improvement of CFVR in IRAs and non-IRAs remained significant after correction for the rate–pressure product (Table 1). Uncorrected and corrected baseline average peak blood flow velocities in IRAs were higher than those in non-IRAs after angioplasty (p <0.01) and at 1-week follow-up (p <0.01). However, at 6-month follow-up, uncorrected and corrected baseline average peak blood flow velocities in IRAs equaled values in non-IRAs. Baseline average peak blood flow velocity in non-IRAs did not change in 6 months. However, after correction for the rate–pressure product, baseline average peak blood flow velocities at 1 week and 6 months were lower than immediately after angioplasty in IRAs and non-IRAs (Table 1; baseline average peak blood flow velocity in nonstenosed arteries in patients without infarctions was 18 cm/second, range 6 to 26).[15]

Hyperemic average peak blood flow velocity was decreased after angioplasty and significantly improved at follow-up in IRAs and non-IRAs (Table 1; hyperemic average peak blood flow velocity in nonstenosed arteries in patients without infarct was 49 cm/second, range 25 to 84).[15]

At follow-up, improvement of CFVR in IRAs and non-IRAs was primarily attributable to an increase in hyperemic average peak blood flow velocity. At the time of AMI, baseline microvascular resistance in IRAs did not differ from that in non-IRAs. Baseline microvascular resistance in the 2 artery types decreased at 1-week follow-up and increased at 6 months (in nonstenosed arteries in patients without infarct, baseline microvascular resistance is 6.5 mm Hg/cm/second, range 3.3 to 13.2).[15]

Corrected baseline microvascular resistance in IRAs and non-IRAs increased significantly from 1-week to 6-month follow-up (Table 1). Corrected baseline microvascular resistance was higher in the non-IRAs than in the IRAs only at 1-week follow-up (p = 0.001) but did not differ at other time points (acute phase, p = 0.3; 6-months follow-up, p = 0.09). The minimal (hyperemic) microvascular resistance index was increased in IRAs after primary angioplasty and decreased during 6-month follow-up (Table 1). Minimal microvascular resistance in non-IRAs was also increased, although it was lower than in IRAs and recovered faster than in IRAs (in nonstenosed arteries in patients without infarcts, minimal microvascular resistance was 1.7 mm Hg/cm/second, range 0.9 to 3.2).[15]

Table 1 Physiological data during baseline and hyperemic conditions in the infarct-related and the nonInfarct-related arteries at three time points.

	IRA					
	A	B	C		*p* Value	
				A vs B	A vs C	B vs C
Doppler flow velocity						
Baseline average peak flow velocity (cm/s)	20.4±9.1	21.2±7.1	17.8±6.6	NS	<0.05	<0.01
Corrected baseline average peak flow velocity (U)	20.6±10.4	17.8±7.3	14.9±6.6	<0.05	<0.01	NS
Hyperemic average peak flow velocity (cm/s)	31.8±15.7	39.2±12.0	50.7±16.7	<0.01	<0.0001	<0.0001
Coronary flow velocity reserve	1.6±0.4	1.9±0.5	3.0±0.8	<0.0001	<0.0001	<0.0001
Corrected coronary flow velocity reserve	1.7±0.6	2.4±0.8	3.9±1.6	<0.0001	<0.0001	<0.0001
Microvascular resistance						
Baseline microvascular resistance index ($mmHg \cdot s \cdot cm^{-1}$)	4.8±2.4	3.8±1.4	5.2±2.3	<0.01	NS	<0.0001
Corrected baseline microvascular resistance index (U)	4.9±2.8	4.7±1.9	6.8±3.9	NS	<0.01	<0.01
Hyperemic microvascular resistance index ($mmHg \cdot s \cdot cm^{-1}$)	3.2±1.7	2.0±0.6	1.8±0.6	<0.0001	<0.0001	<0.01
Variable resistance index ($mmHg \cdot s \cdot cm^{-1}$)	1.6±1.2	1.8±1.0	3.5±1.9	NS	<0.0001	<0.0001
Corrected variable resistance index (U)	1.8±1.9	2.7±1.7	5.0±3.6	<0.05	<0.0001	<0.0001
Rate-pressure product	9973±2083	8305±1669	8270±1905	<0.0001	<0.0001	NS

Values are expressed as mean ± SD.
A = acute; B = 1 week; C = 6 months.

The variable resistance index (baseline microvascular resistance minus minimal microvascular resistance) was disturbed in the acute and subacute phases of AMI in IRAs and non-IRAs but was more pronounced in IRAs (Table 1). After correction for the rate–pressure product, relative values of the variable resistance index (percent baseline resistance index) increased in IRAs from 37% after angioplasty to 57% at 1 week and to 74% at 6 months ($p < 0.0001$) and in non-IRAs from 57% to 70% and 77% ($p < 0.0001$), respectively.

Non-IRA			*p* Value		
A	B	C	A vs B	A vs C	B vs C
17.5±5.5	17.8±6.6	16.7±8.7	NS	NS	NS
17.9±7.8	14.9±6.4	14.1±9.1	<0.01	<0.05	NS
40.1±11.9	46.7±16.2	52.0±20.5	<0.05	<0.0001	<0.05
2.4±0.5	2.7±0.6	3.3±0.6	<0.0001	<0.0001	<0.0001
2.5±0.8	3.5±1.1	4.4±1.6	<0.0001	<0.0001	<0.0001
5.0±1.5	4.6±1.9	5.9±2.6	<0.05	<0.05	<0.0001
5.3±2.1	5.7±2.7	7.7±4.0	NS	<0.0001	<0.0001
2.2±0.6	1.7±0.6	1.8±0.7	<0.0001	<0.01	NS
2.8±1.2	2.9±14	4.1±2.0	NS	<0.0001	<0.0001
3.0±1.9	4.0±2.4	5.9±3.5	<0.01	<0.0001	<0.0001
9973±2083	8305±1669	8270±1905	<0.0001	<0.0001	NS

Table 2 Baseline characteristics (n = 73)

Age (yrs)	54	(33-77)
Male	64	(88%)
Smoking	43	(59%)
Hypertension	20	(27%)
Diabetes mellitus	3	(4%)
Family history	35	(48%)
Serum Cholesterol (mmol/l)	5.6	±1.0
Serum Creatinin (µmol/l)	70	±15
Aspirin	8	(11%)
ACE inhibitor	5	(6%)
Beta blocker	11	(15%)
Calcium antagonist	6	(8%)
Statin	8	(11%)
Nitrate	5	(6%)
Previous angina	46	(63%)
Singel-vessel disease	58	(80%)
2-vessel disease	15	(20%)
Left anterior descending artery occlusion		
Before septal	14	(19%)
Between first septal and first diagonal	33	(45%)
Distal from first diagonal	26	(36%)
Collateral flow	45	(62%)
Rentrop's class 1	35	(48%)
Rentrop's class 2	10	(14%)
Ischemic time to reperfusion (h)	2.8	(1.2-6.0)
Stent	49	(68%)
Abciximab	17	(23%)

Values are numbers of patients (percentages), mean ± SD, or as medians (ranges).
ACE = angiontensin-converting enzyme.

Doppler flow measurements were not significantly different between patients who were treated with or without a stent (data not shown). Thrombolysis In Myocardial Infarction flow grade, corrected Thrombolysis In Myocardial Infarction frame count, and myocardial blush grade in the 2 territories are listed in Table 3. Abnormal angiographic flow parameters (corrected Thrombolysis In Myocardial Infarction frame count >21 or myocardial blush grade <3) were found in IRAs and non-IRAs.

Table 3 Angiographic variables after reperfusion

	IRA	Non-IRA
TIMI flow grade		
1	1 (1%)	0
2	16 (22%)	1 (1%)
3	56 (77%)	72 (99%)
Corrected TIMI frame count	44 ± 22	29 ± 15
Myocardial blush grade	3 (4%)	0
1		
2	32 (44%)	12 (16%)
3	38 (52%)	61 (84%)

Values are numbers of patients (percentages) or mean ± SD.
TIMI = Thrombolysis In Myocardial Infarction.

Discussion

This study demonstrates, in a homogenous cohort of patients with a first anterior wall AMI, increased levels of minimal microvascular resistance and decreased values of CFVR in IRAs and non-IRAs. Further, this study shows that microvascular function improved during 6-month follow-up in the 2 territories. Our study confirms previous observations that CFVR in IRA is decreased after reperfusion in the early phase of AMI secondary to a low hyperemic flow velocity.[2, 3] Impairment of hyperemic flow velocity was due to increased microvascular resistance because the epicardial conduit was treated with angioplasty and stented, if necessary. Several mechanisms may contribute to a low hyperemic flow velocity in the IRA, including peripheral embolization, neurohumoral activation that leads to microvascular vasoconstriction due to vasoactive agents that are released from a thrombus, ongoing ischemia,[16, 17] and angioplasty-mediated α-receptor activation.[18] Minimal microvascular resistance in infarcted and noninfarcted territories decreased over time, resulting in similar resistances at 6-month follow-up. In accord to other studies, we demonstrated that CFVR was decreased[7, 8] and corrected Thrombolysis In Myocardial Infarction frame count was increased[19] in non-IRAs in the early phase of AMI. In our study, baseline flow velocity in non-IRAs after correction for the rate–pressure product was highest during the acute phase of AMI. In response to severe dyskinesia in the infarcted area, a compensatory increase in the thickening fraction in remote nonischemic regions was reported in the isovolumetric phase of systole, resulting in an increased baseline flow velocity and thus decreasing CFVR.[10] It is unlikely that this mechanism fully

explains the decreased CFVR in our study because no difference in baseline flow velocity was measured from 1-week to 6-month follow-up, when bulging of the nonischemic area is expected to be present at 1 week. Increased minimal microvascular resistance in non-IRAs during AMI changed over time in the same direction as minimal microvascular resistance in IRAs, suggesting an impaired vasodilation capacity in the remote microvascular bed, although obstruction (e.g., through activation of thrombocytes and leukocytes) cannot be excluded in our study. The combination of a decreased corrected baseline microvascular resistance and increased minimal microvascular resistance at the time of AMI suggests disturbed autoregulation, probably due to neurohumoral activation in areas remote from the infarction. Although minimal microvascular resistance in non-IRAs reaches a stable level at 1-week follow-up and thus sooner than in IRAs, the variable arteriolar resistance index (variable and corrected variable arteriolar resistance indexes) is lower at 1-week than at 6-month follow-up, indicating that the autoregulatory capacity in the non-IRA is not yet normalized at 1 week after MI. Although speculative, pharmacologic adjunctive measures that decrease minimal microvascular resistance might improve clinical outcome. Our observations, i.e., neurohumoral activation influences microvascular resistance, may guide therapeutic measurements for hemodynamic improvement during the acute phase of MI in remote territories.

Several potential limitations of this study should be considered when interpreting these data. Pressure in the right atrium was not measured in all patients. Therefore, the transvascular pressure gradient used for resistance calculations may have varied slightly. Left ventricular end-diastolic pressure was not measured. High end-diastolic pressure may affect subendocardial microvascular resistance. Although this may have a role in the mechanistic explanation of the study outcome, it does not influence outcome itself. The bolus of adenosine given to induce hyperemia has varied in the recent literature. Because the adenosine boluses were similar at every time point, higher dosages of adenosine likely did not affect the trend in our results. Although diabetes mellitus may alter microvascular function, diabetic patients were not excluded from the protocol and the study population included 3 patients with diabetes. Post hoc analysis showed no difference in outcome when these 3 patients were omitted. At the time of the study, ticlopidine or clopidogrel was prescribed for 1 month. It is unknown whether a longer duration of administration would affect the time course of microvascular resistance.

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Chapter 4

The Doppler flow wire in acute myocardial infarction

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Heart 2010;96:631e635.
http://dx.doi.org/10.1136/hrt.2009.186932

Abstract

Contemporary mechanical reperfusion therapy for acute myocardial infarction is aimed at early and complete restoration of myocardial perfusion. However, successful restoration of epicardial blood flow does not guarantee restoration of flow at the myocardial tissue level. The incidence of inadequate myocardial reperfusion after primary percutaneous coronary intervention (PCI) varies from 15–70%, based upon the diagnostic modality used.

The Doppler flow guidewire can be used immediately after primary PCI to identify patients with apparently restored epicardial flow but impaired reperfusion at the myocardial microcirculatory and tissue level. Characteristic findings by intracoronary Doppler flow velocity measurements such as a reduced coronary flow velocity reserve, and, in particular, systolic flow velocity reversal and a short diastolic deceleration time are associated with the presence of microvascular obstruction.

Detection of microvascular obstruction by the Doppler flow wire directly after primary PCI can identify patients who may benefit from adjunctive therapy after primary PCI.

Introduction

Contemporary mechanical reperfusion therapy in acute coronary syndromes is aimed at early and complete restoration of myocardial perfusion. However, successful restoration of epicardial blood flow does not guarantee restoration of flow at the myocardial tissue level. In about 15–30% of patients, the capillary structure becomes disorganised owing to endothelial swelling, compression by tissue, myocyte oedema and neutrophil infiltration, leading to microvascular obstruction.[1,2] This inadequate microvascular perfusion is clinically relevant, as it is associated with larger myocardial infarct size, reduced left ventricular function and a worse clinical outcome than in patients with adequate myocardial reperfusion.[3–5]

Several diagnostic modalities are currently applied to detect microvascular obstruction. A thrombolysis in myocardial infarction (TIMI) flow grade ≤2 in the absence of macrovascular obstruction is often used as a definition of microvascular obstruction.[6] However, even in patients with TIMI flow grade 3, microvascular perfusion can be impaired. The TIMI perfusion grade and the myocardial blush grade are also frequently used to assess myocardial reperfusion using coronary angiography.[7,8] Another readily available and widely used marker of tissue-level reperfusion is resolution of ST-segment elevation.[9] More accurate, non-invasive imaging modalities such as myocardial contrast echocardiography (MCE) and delayed contrast enhancement using cardiac magnetic resonance imaging (CMR) can also be used to detect microvascular obstruction.[4,5; 10,11]

Moreover, coronary blood flow can be measured invasively by an intracoronary Doppler-tipped guidewire. Since the 1970s, when catheter-based Doppler systems were first introduced by Benchimol and later Hartley and Cole, many improvements have been made to its design.[12–14] A typical contemporary Doppler guidewire transmits and receives pulsed-wave ultrasound signals generated by a piezoelectric ultrasound transmitter (figure 1). Characteristic coronary blood flow patterns in patients with coronary microvascular obstruction are systolic flow reversal, rapid deceleration of diastolic flow and a reduced coronary flow velocity reserve (CFVR).[11,15]

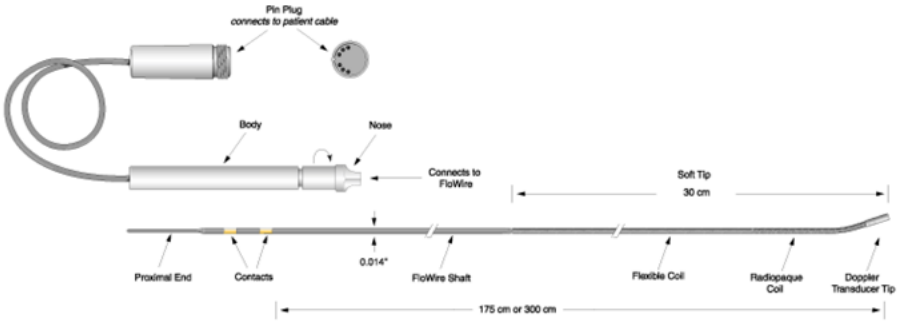

Figure 1. A typical Doppler-tipped guide wire used for instantaneous measurement of intravascular flow velocity.

Coronary flow reserve in acute myocardial infarction

In 1996, Kern *et al* were the first to study coronary blood flow directly in patients in the setting of acute myocardial infarction (MI) by using a Doppler-tipped guidewire. In 41 patients with an acute MI, coronary blood flow velocity measured in the culprit artery during primary angioplasty by Doppler guidewire was compared with TIMI flow grade.[16] In these patients, TIMI flow grades <3 were consistently associated with low baseline coronary blood flow velocity. However, among the 35 patients with post-interventional TIMI flow grade 3, 13 had a low baseline coronary blood flow velocity of <20 cm/s. In the total cohort of 42 patients, 11 patients had a clinical event during a median follow-up period of 18 months; of these events, nine occurred in patients with angiographic TIMI flow grade 3 but a low baseline blood flow velocity in the infarct-related arteries. This study shows that patients with TIMI flow grade 3 after primary percutaneous coronary intervention (PCI) have a wide range of flow velocity patterns and suggests that Doppler flow velocity measurement can further distinguish patients at increased risk for clinical events.

Ishihara *et al* measured relative CFVR in infarct-related arteries (IRAs) in a series of 14 patients with a first anterior wall acute MI directly after primary angioplasty and at 14 days and 6 months' follow-up.[17] Absolute CFVR is calculated as the ratio of hyperemic to baseline average peak flow velocity. A CFVR of <2.0 is generally considered to be abnormal. Relative CFVR is calculated as the ratio of the absolute CFVR in the IRA to the absolute CFVR in the reference artery. The CFVR measures the functional status of the distal microvascular bed and

depends on multiple factors, including myocardial resistance, metabolic demands, neurohumoral activation, filling pressures and vascular resistances of epicardial coronary arteries and distal microvascular bed. Ishihara *et al* observed an abnormal CFVR in the IRA directly after angioplasty, while CFVR gradually improved at 14 days and 6 months. However, even at 6 months, CFVR in the IRAs was still impaired (mean CFVR 2.34±0.38) in comparison with angiographically normal coronary arteries in reference patients (mean CFVR 3.13±0.48).

A similar experiment was conducted in a larger cohort by Bax *et al*, who measured CFVR in both IRAs and non-IRAs immediately after the primary angioplasty in 73 patients with a first anterior MI, at 1 week and at 6 months.[18] Figure 2 shows CFVR, and baseline and hyperemic average peak flow velocity in IRAs and non-IRAs. Immediately after primary PCI, CFVR was reduced in both IRAs and non-IRAs, although more pronounced in IRAs. At 1 week, CFVR was still impaired in IRAs, but in non-IRAs CFVR had almost returned to normal. Unlike the findings by Ishihara *et al*, CFVR was found to be normalized in IRAs at 6 months. This discrepancy can possibly be explained by the fact that all patients in the Japanese cohort were treated with balloon angioplasty alone, rather than coronary stenting. Furthermore, the Japanese study was hampered by small sample size (n=14). The reduced CFVR was mainly due to a decreased hyperemic blood flow velocity. The explanation for decreased hyperemic blood flow velocity during the acute phase of MI is multifactorial. Neurohumoral responses to ischemia lead to microvascular vasoconstriction in both IRAs and non-IRAs, and distal (micro-)embolization in IRAs. Moreover, microvascular damage and endothelium dysfunction as a result of ischemia and reperfusion lead to disturbed autoregulation. The microvascular resistance index was measured as the ratio of transvascular pressure gradient (mean aortic pressure minus right atrial pressure) to hyperemic blood flow velocity. The microvascular index was found to be increased during the acute phase of MI, and almost normalized at 1 week. Therefore, this study suggests that reduced CFVR after MI is partly explained by increased microvascular resistance, but to a greater extent by disturbed autoregulation.

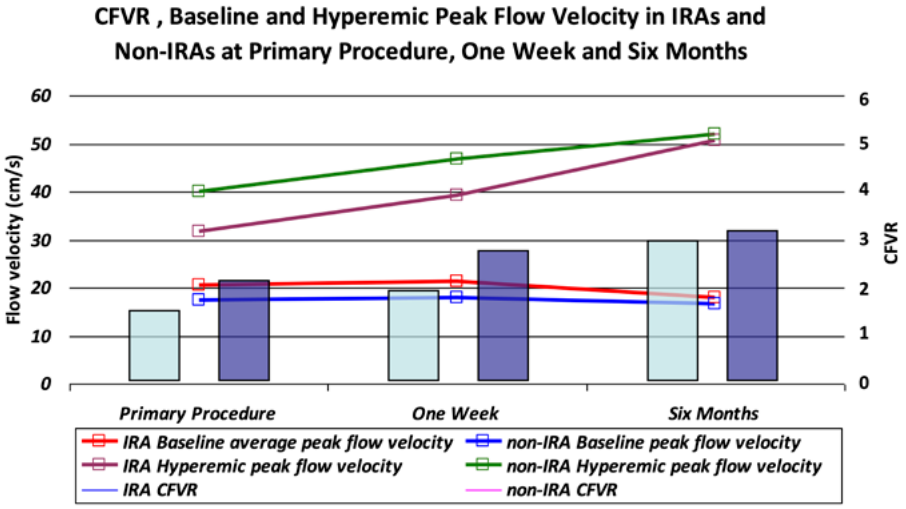

Figure 2. CFVR, Baseline and hyperaemic peak flow velocity in IRAs and non-IRAs immediately after the primary procedure, after 1 week and after 6 months. CFVR, coronary flow velocity reserve; IRA, infarct-related artery.

Systolic flow reversal and rapid deceleration of diastolic flow: characteristic Doppler flow-velocity patterns in microvascular obstruction

Iwakura *et al* were the first to report characteristic Doppler flow velocity patterns in microvascular obstruction after acute MI.[11] They examined the Doppler-flow wire derived coronary blood flow velocity pattern in 42 consecutive patients with acute MI. Additionally, MCE was performed in all patients both before and after primary angioplasty. Microvascular obstruction was detected in 11 patients (26%) by MCE. The coronary flow velocity pattern appeared to be normal in patients without microvascular obstruction on MCE (Figure 3a). However, in patients with microvascular obstruction the coronary blood flow velocity pattern was characterized by the appearance of abnormal retrograde flow in early systole, and rapid deceleration of the diastolic flow velocity (Figure 3b). Early retrograde systolic flow was seen in 10 of 11 patients with signs of no reflow compared with only one patient without signs of no reflow on MCE. The rate of decline in flow velocity in diastole was calculated as the diastolic deceleration rate (cm/s^2). Mean diastolic deceleration rate was 106.4±76.1 cm/s^2 in the no-reflow group compared with 55.9±31.2 cm/s^2 in the reflow group ($p<0.01$).

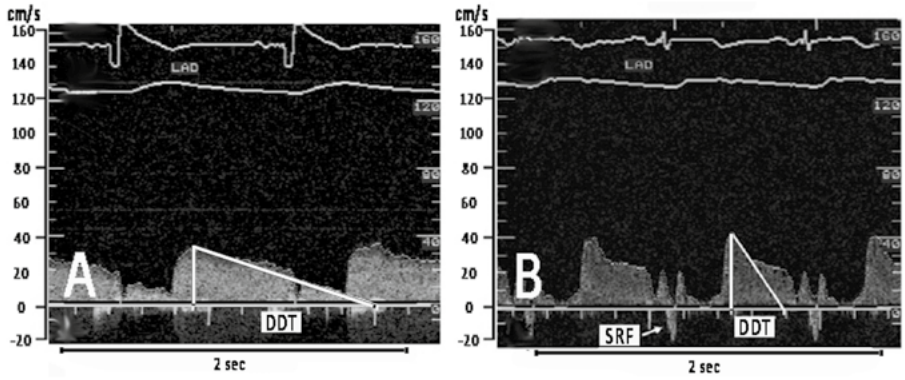

Figure 3. (A) The coronary flow velocity spectrum shows antegrade systolic flow without systolic retrograde flow (SRF) and a normal diastolic deceleration time (DDT). (B) The coronary flow velocity spectrum shows SRF and a short DDT.

A short diastolic deceleration time and systolic flow reversal were also studied by Okamura *et al* in a cohort of 72 patients with first acute anterior MI.[19] Microvascular obstruction was measured by MCE directly after primary PCI. Left ventricular ejection fraction and regional wall motion were measured by left ventriculography during the primary angioplasty procedure and again at discharge (24±2 days). Ten minutes after primary PCI, Doppler flow wire measurements were performed.

The principal finding of their study was that with advancing severity of damage in the infarcted myocardium, the diastolic deceleration time shortened first, followed by the appearance of systolic flow reversal and finally, by disappearance of systolic antegrade flow. Microvascular obstruction on MCE was not detected in patients without abnormal coronary flow characteristics on Doppler flow examination. Of the 41 patients with at least one of the aforementioned abnormal Doppler flow characteristics, 28 (68%) had evidence of microvascular obstruction on MCE. Furthermore, these characteristic flow velocity characteristics were associated with reduced recovery of regional wall motion and left ventricular ejection fraction.

It has been suggested that rapid deceleration of diastolic flow is caused by an increase in microvascular impedance and a decrease of intramyocardial blood pool volume. In normal individuals, the intramyocardial capillaries and venules are filled during diastole without an increase in intramural

pressure.[20] However, owing to capillary obstruction the capacitance of the myocardial microvasculature decreases. This has an impeding effect on diastolic flow, resulting in a rapid decrease in coronary flow velocity. Rapid deceleration of diastolic flow is associated with poorer tissue perfusion, worse functional outcome, left ventricular remodelling and an increased rate of adverse cardiac events.[21]

However, rapid deceleration of diastolic flow also occurs in patients without signs of microvascular obstruction measured by MCE or CMR. Therefore, rapid deceleration of diastolic flow alone has a high sensitivity, but a relatively low specificity for detecting microvascular obstruction.

Systolic flow reversal is another accurate marker of microvascular obstruction. The increased microvascular impedance resulting from microvascular injury hampers the heart's ability to squeeze blood forward into the venous system during systole, and consequently, blood will be squeezed back into the arterial system, resulting in systolic flow reversal. In the most severe case of microvascular obstruction, a high back pressure persists throughout systole, resulting in total disappearance of systolic antegrade flow.

Doppler flow wire as a tool to predict recovery of left ventricular recovery after acute MI

Kawamoto *et al* investigated the clinical value of the Doppler flow guidewire-derived coronary flow pattern in predicting left ventricular function in 23 patients with a first anterior acute MI.[21] The coronary flow pattern was recorded immediately after the primary angioplasty and left ventricular function was assessed before recanalisation and at 1-month follow-up by echocardiographic anterior wall motion score index. In this study, a short diastolic deceleration time (<600 ms) and low average systolic peak velocity (<6.5 cm/s) were associated with a lack of recovery of regional left ventricular function.

Bax *et al* compared the predictive value of CFVR with TIMI flow grade, corrected TIMI frame count, myocardial blush grade and resolution of ST-segment elevation for recovery of left ventricular function in the aforementioned series of 73 patients with a first anterior MI treated with primary PCI.[22] Two-dimensional echocardiography was performed immediately before the primary PCI and repeated after 1 day, 1 week and 6 months. After multivariate linear regression

analysis, CFVR as measured by the Doppler flow guidewire in comparison with the aforementioned, commonly reported angiographic and clinical parameters, was better in predicting recovery of left ventricular function. All patients with a CFVR>2.0 directly after primary PCI showed improved left ventricular function (measured as echocardiographic 16-segment wall motion index) at 6 months' follow-up. Doppler-derived CFVR was independently correlated with recovery of global and regional left ventricular function. No independent relation was found between angiographic parameters or ST-segment resolution and recovery of left ventricular function. Recovery of left ventricular function after acute MI can be accurately predicted by intracoronary Doppler flow velocity measurement during primary PCI.

Comparison of Doppler flow velocity measurement and contrast-enhanced CMR

The assessment of microvascular injury by coronary Doppler flow velocity measurement has been found to correspond well to evaluation by contrast-enhanced CMR. A series of 27 consecutive patients with a first anterior MI underwent CMR and repeat catheterisation for intracoronary flow measurement within 1 week in a study by Hirsch *et al*.[10] All patients had a postprocedural TIMI flow grade 3. However, CMR showed microvascular obstruction in 19 patients (70%). Based on the extent of microvascular obstruction detected by contrast-enhanced CMR, patients were subsequently stratified as having mild or severe microvascular obstruction. Systolic flow reversal was seen in none of eight patients without microvascular obstruction, in four of 10 (40%) patients with mild microvascular obstruction and in six of nine patients (67%) with severe microvascular obstruction. In accordance with previous studies, the diastolic deceleration time was reduced in patients with mild (mean 575 ms) and severe (mean 382 ms) microvascular obstruction in comparison with patients without microvascular obstruction (mean 708 ms). The extent of microvascular obstruction seen by CMR was independently correlated with systolic flow reversal, a short diastolic deceleration time, and low CFVR of the IRA.

Limitations of the Doppler flow wire and alternative invasive techniques to assess microvascular injury

A few limitations of the Doppler flow wire should be mentioned. Although there is fair reproducibility of CFVR, it is dependent upon a number of haemodynamic conditions such as arterial pressure and heart rate.[23–25] The haemodynamic

dependence of CFVR is mainly because resting coronary flow velocity is very sensitive to changes in myocardial oxygen consumption. Furthermore, as the extent of microvascular obstruction is known to increase within the days after primary PCI, single Doppler flow velocity measurements immediately after primary PCI might underestimate the degree of microvascular obstruction subsequently present. Another limitation is the difficulty of detecting an adequate flow signal. A novel guidewire tipped with both a Doppler flow and a pressure sensor has made signal acquisition more cumbersome. A possible explanation might be the change in display from an analogue signal to a digital signal. Based upon our own experience, reversing the tip of the guidewire to make the sensors face the proximal part of the coronary artery may improve signal quality.

The Doppler flow wire interrogates the resistance of the entire vessel and may not differentiate diffuse epicardial disease or residual epicardial stenosis from microvascular obstruction. Combined pressure–flow velocity measurements are better suited for distinguishing between epicardial and microvascular resistance. Fearon *et al* reported the index of microcirculatory resistance, measured by a pressure sensor-tipped guidewire in combination with flow using thermodilution to be an independent predictor of recovery of echocardiographic left ventricular wall motion score in 29 patients after acute MI.[26] Currently, assessment of microvascular injury by this index has not been compared with the 'gold standard' for detection of microvascular obstruction using contrast-enhanced CMR.

The introduction of the dual-sensor (Doppler velocity and pressure) tipped guidewire led to the introduction of physiological indices based upon combined pressure and flow measurements. These novel indices—most notably, hyperaemic microvascular resistance and hyperaemic stenosis resistance, have not yet been tested in the setting of acute MI.[27]

Another potential modality to assess microvascular injury is wave intensity analysis (WIA). On the basis of measurements of coronary arterial pressure and velocity, WIA allows for a better understanding of aortic, left ventricular and

microcirculatory interactions in the coronary circulation. Although promising, WIA has not yet been tested in the setting of acute MI.[28]

Summary

Microvascular obstruction after acute MI has been associated with ventricular arrhythmias, adverse ventricular remodelling and poor clinical prognosis.[4 5 10] Based upon coronary angiography, the incidence of inadequate myocardial reperfusion or a no-reflow phenomenon was approximately 15%.[8] The results of non-invasive diagnostic techniques such as MCE and contrast-enhanced CMR yielded a higher incidence rate of up to 70% with CMR.[4 5 10] Characteristic findings by intracoronary Doppler flow velocity measurements such as a reduced CFVR secondary to an impaired hyperaemic blood flow velocity, and, in particular, systolic flow velocity reversal and a short diastolic deceleration time, are associated with the presence of microvascular obstruction on MCE and contrast-enhanced CMR. An abnormal CFVR is strongly associated with reduced recovery of left ventricular function after MI.[19 22]

In primary PCI, the Doppler flow guidewire identifies patients with apparently restored epicardial flow but impaired reperfusion at the myocardial microcirculatory and tissue level. Such patients may benefit from adjunctive treatments such as intracoronary administration of streptokinase, which was recently found to have beneficial effects on infarct size, left ventricular volumes and left ventricular ejection fraction.[29]

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Chapter 5

Impact of coronary microvascular function on long-term cardiac mortality in patients with acute ST-segment-elevation myocardial infarction

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Circ Cardiovasc Interv. 2013;6:207-215.
https://doi.org/10.1161/circinterventions.112.000168

Abstract

Background

Microvascular function is increasingly being recognized as an important marker of risk in coronary artery disease, and may be accurately assessed by intracoronary Doppler flow velocity measurements. In the setting of ST-segment–elevation myocardial infarction there are limited data regarding the prognostic value of microvascular function in both infarct-related and reference coronary arteries for long-term clinical outcome. We sought to determine the prognostic value of microvascular function, as assessed by Doppler flow velocity measurements, for cardiac mortality after primary percutaneous coronary intervention for acute ST-segment–elevation myocardial infarction.

Methods and Results

Between April 1997 and August 2000, we included 100 consecutive patients with a first anterior wall ST-segment–elevation myocardial infarction. Immediately after primary percutaneous coronary intervention, intracoronary Doppler flow velocity was measured in the infarct-related artery, to determine coronary flow velocity reserve (CFVR), diastolic deceleration time, and the presence of systolic retrograde flow, as well as in a reference vessel to determine reference vessel CFVR. The primary end point was cardiac mortality at 10-year follow-up. Complete follow-up was obtained in 94 patients (94%). At 10-year follow-up, cardiac mortality amounted to 14%. Cardiac mortality amounted to 5% when reference vessel CFVR was normal (≥2.1), in contrast to 31% when abnormal (<2.1; *P*=0.001). Reference vessel CFVR <2.1 was associated with a 4.09 increase in long-term cardiac mortality hazard after multivariate adjustment for identified predictors for cardiac mortality (hazard ratio, 4.09; 95% confidence interval, 1.18–14.17; *P*=0.03)

Conclusions

Microvascular dysfunction measured by reference vessel CFVR, determined after primary percutaneous coronary intervention for acute anterior wall ST-segment–elevation myocardial infarction, is associated with a significantly increased long-term cardiac mortality.

Introduction

Timely mechanical reperfusion by means of primary percutaneous coronary intervention (PCI) is the optimal treatment strategy in ST-segment–elevation myocardial infarction (STEMI) patients.[1,2] Primary PCI aims at immediate restoration of epicardial vessel patency and subsequent reperfusion of myocardial tissue. Inadequate myocardial reperfusion at the microvascular level is known to be associated with larger infarct size, lower residual left ventricular function, and increased mortality at follow-up.[3–8] Although epicardial vessel patency is restored successfully in most primary PCI procedures, microvascular reperfusion can be inadequate even when optimal angiographic epicardial reperfusion is achieved.[9,10]

Intracoronary-derived Doppler flow velocity measurements allow sensitive assessment of microvascular function in clinical practice.[9,11] The Doppler flow velocity–derived parameters coronary flow velocity reserve (CFVR), diastolic deceleration time (DDT), and early systolic retrograde flow (SRF) in the infarct-related coronary artery were shown to correspond to the extent of microvascular dysfunction after reperfusion for STEMI.[12] Moreover, several studies have indicated that CFVR in the infarct-related artery assessed after primary PCI is the most valuable prognostic marker of recovery of left ventricular function after STEMI.[7,8,13–17]

However, although microvascular dysfunction is considered an important marker for risk, and a possible target for adjunct therapies,[11,18,19] limited interest has focused on its potential prognostic value for long-term clinical outcome. Moreover, although microvascular alterations have additionally been reported to occur at a distance from the infarcted myocardium, the prognostic value of microvascular function in a reference vessel for long-term clinical outcome after mechanical reperfusion for STEMI has not been investigated.[20]

WHAT IS KNOWN

- Microvascular function is increasingly recognized as an important marker of risk in coronary artery disease, and may be accurately assessed invasively by intracoronary Doppler flow velocity measurements.
- Microvascular function assessed by Doppler flow velocity is altered in the setting of ST-segment–elevation myocardial infarction, even in nonischemic regions remote from the infarcted myocardial tissue.
- Coronary flow velocity reserve in a reference vessel is a more selective marker of general microvascular function.

WHAT THE STUDY ADDS

- Impaired coronary flow velocity reserve in a reference vessel is independently associated with an increased risk for long-term fatal cardiac events.

We hypothesize that microvascular function, as assessed by means of Doppler flow velocity measurement, plays an important role in long-term clinical outcome after primary PCI for STEMI. Therefore, we sought to determine the prognostic value for long-term cardiac mortality of microvascular function, as assessed by Doppler flow velocity measurement, in infarct-related as well as reference coronary arteries after primary PCI for STEMI.

Methods

Data Source and Patient Selection

Between April 1997 and August 2000, 100 consecutive patients with a first anterior wall STEMI treated by primary PCI were enrolled in the study, for whom the initial results have been reported previously.[8,20] All patients were treated in the Academic Medical Center in Amsterdam, a large tertiary referral center in Amsterdam, The Netherlands.

Anterior STEMI was defined as chest pain lasting >30 minutes in the presence of persistent ST-segment elevation in ≥2 precordial leads. Primary PCI was performed within 6 hours after the onset of symptoms according to standard clinical practice, with provisional bare metal stent implantation. Major exclusion criteria comprised prior anterior wall myocardial infarction (MI), acute left-side heart failure (Killip class >II), prior coronary artery bypass grafting, known left ventricular ejection fraction of <40%, left ventricular hypertrophy, absence of thoracic windows for echocardiography, 3-vessel coronary artery

disease, Thrombolysis In Myocardial Infarction (TIMI) grade 2 or 3 flow at initial angiography before PCI, or unsuccessful PCI defined as TIMI grade 0 or 1 flow or >50% residual stenosis in the infarct-related artery after PCI. The study protocol was approved by the local ethics committee and all patients gave informed consent.

Periprocedural Measurements

Intracoronary blood flow velocity in the infarct-related coronary artery was measured 5 to 10 minutes after successful PCI using a 0.014-inch Doppler-sensor equipped guidewire (Volcano Corp., San Diego, CA). CFVR was defined as the ratio of hyperemic average peak flow velocity (APV) to baseline APV. Doppler flow velocity was additionally assessed in an angiographic normal reference coronary artery, defined as a coronary artery with <30% diameter stenosis on visual estimation. Reference vessel measurements were performed in the left circumflex coronary artery, unless a stenosis of >30% was present, in which case the right coronary artery was used. Hyperemia was induced by an intracoronary bolus of adenosine (20–40 μg). The Doppler flow velocity signal was analyzed offline to evaluate DDT and the presence of SRF in the infarct-related artery. Before and after PCI, coronary angiography suitable for quantitative coronary angiographic analysis was performed for offline analysis of TIMI flow[21] and myocardial blush grade.[6] Left ventricular function was evaluated by means of echocardiographic 16-segment Wall Motion Score Index (WMSI) performed immediately before primary PCI.[8]

At 6-month follow-up, echocardiographic evaluation of left ventricular function was repeated, and patients underwent repeat angiography with assessment of intracoronary Doppler flow velocity, the initial results of which have been reported previously.[8,20]

Long-term Follow-up

Long-term follow-up regarding the occurrence of death was collected by identifying patients in the Dutch national population registry. The cause of death was verified by evaluating hospital records or contacting the general practitioner. Death was considered cardiac unless an unequivocal noncardiac cause could be established.[22]

Statistical Analysis

To analyze the relationship between cardiac death and CFVR in the infarct-related or reference vessel, we performed 3 sequential analyses. First, we determined the optimal cut-off value for cardiac mortality of CFVR in both vessels using receiver-operator-characteristics curves. The cut-off values with the highest sum of sensitivity and specificity were used for subsequent analyses. Second, the Kaplan–Meier method was used to estimate cumulative cardiac mortality rates according to the previously identified cut-off values, which were compared by means of the log-rank test. Third, the prognostic value of CFVR in the infarct-related and in the reference vessel was evaluated in 2 sets of Cox proportional hazards models. An univariable model was used to identify variables significantly associated with cardiac mortality. Subsequent multivariable analysis was performed using a stepwise Cox proportional hazards model with adjustments for these variables ($P<0.1$), and including adjustments for age. Data are presented as mean (±SD), frequency (percentage), or median (25th–75th percentile). Student *t* test, Mann–Whitney *U* Test, χ^2, or Fisher exact test was used, when appropriate, to test for differences between groups. Event rates are reported as 10-year Kaplan–Meier estimates of cumulative cardiac mortality. A 2-sided α-level of 0.05 was considered statistically significant.

Results

Study Population Characteristics

Complete follow-up was obtained in 94 of the 100 patients (94%). Baseline characteristics of these patients are shown in Table 1.

At the end of the procedure, TIMI 3 flow was achieved in the infarct-related artery in 70 patients (75%), and myocardial blush grade 3 was achieved in 50 patients (52%). Mean CFVR in the infarct-related artery was 1.6±0.4 (median, 1.5; 25th–75th percentile 1.3–1.8) in contrast to 2.4±0.5 (median, 2.3; 25th–75th percentile 2.0–2.7) in the reference vessel (left circumflex coronary artery in 84 patients [89%]; right coronary artery in 10 patients [11%]). A rapid DDT, defined as DDT <600 ms, was found in 49 patients (52%), and SRF was present in 27 patients (29%).

Table 1. Baseline Clinical Characteristics (n=94)

Demographics	
Age	56 ± 12
Male Sex	79 (84)
Risk Factors for coronary artery disease	
Smoking	51 (54)
Hypertension	22 (23)
Family History	38 (40)
Hyperlipidemia	25 (27)
Diabetes Mellitus	6 (6)
Prior medication use	
β-Blockers	13 (14)
Calcium antagonists	7 (7)
Angiotensin-converting enzyme inhibitors	4 (4)
Nitrates	4 (4)
Lipid lowering drugs	7 (7)
Aspirin	11 (12)

Data are presented as mean±SD or frequency (%)

During a median follow-up of 11.0 years (interquartile range, 10.0–12.1 years) 18% of patients died (17 of 94), whereas 16% (15 of 94) of patients died of a cardiac cause. The 10-year Kaplan–Meier estimate of cumulative all-cause mortality was 15%, and amounted to 14% for cardiac mortality.

Flow Velocity Parameters and Long-term Cardiac Mortality

The optimal identified cut-off values were 2.1 for CFVR in the reference vessel (sensitivity 73%, specificity 71%), and 1.5 for CFVR in the infarct-related artery (sensitivity 73%, specificity 62%).

Ten-year estimates of cardiac mortality differed significantly between high and low reference vessel CFVR groups, and amounted to 5% in patients with high reference vessel CFVR values, compared with 31% in patients with low reference vessel CFVR values (*P*=0.001; Figure A). In contrast, 10-year estimates of cardiac mortality amounted to 9% and 20% in patients with high and low infarct-related artery CFVR values, respectively, which was not significantly different between groups (*P*=0.10; Figure B). In bivariate analysis, a reference vessel CFVR of <2.1 was associated with a 3.67-fold increase in long-term cardiac mortality hazard (hazard ratio [HR], 3.67; 95% confidence interval, 1.19–11.37; *P*=0.02; Table 2). Contrariwise, a target vessel CFVR of <1.5 was not associated with an increase in long-term cardiac mortality hazard (HR, 1.67; 95% confidence interval, 0.56–4.98; *P*=0.36). There was no significant difference in cardiac mortality rates

between patients with and without a rapid DDT or SRF in the infarct-related artery (log-rank *P*=0.42 and *P*=0.23, respectively).

Clinical and Procedural Characteristics According to Reference Vessel CFVR and Extent of Myocardial Infarction

Differences in clinical and procedural characteristics between the 2 reference vessel CFVR groups are shown in Table 3, which includes known prognostic factors for mortality in STEMI patients.[23–25] Notably, the impairment in reference vessel CFVR resulted primarily from a low hyperemic APV in the presence of high hyperemic microvascular resistance, in combination with a high baseline APV in the presence of a low baseline microvascular resistance in patients with an abnormal reference vessel CFVR (Table 3).

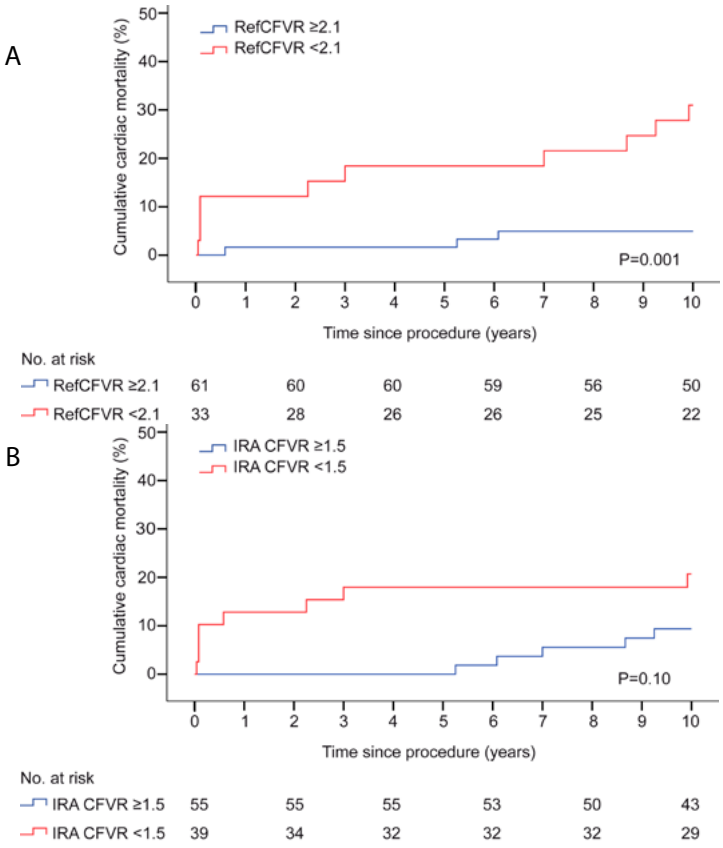

Figure. Kaplan-Meier estimates and log-rank comparison of cumulative cardiac mortality. **A,** Reference vessel coronary flow velocity reserve (refCFVR) and (**B**) Infarct-related artery (IRA) CFVR. High reference vessel CFVR values show significantly lower cardiac mortality rates as compared with low reference vessel CFVR values. No statistical difference was found between high and low infract-related artery CFVR values.

Table 2. Bivariate Analysis of the Association Between CFVR in Reference and Target Vessels, and Long-term Cardiac Mortality

Variable	Hazard Ratio	95% confidence interval	*P Value*
Reference vessel CFVR <2.1	3.67	1.19 – 11.37	0.02
Infarct-related artery CFVR <1.5	1.67	0.56 – 4.98	0.36

No significant interaction was present (*P* value for interaction=0.93). CFVR indicates coronary flow velocity reserve.

Table 3. Baseline Clinical and Hemodynamic Characteristics (n=94)

	Reference Vessel CFVR		
	≥2.1 (n=61)	<2.1 (n=33)	*P Value*
Demographics			
Age, y	53±11	61±12	0.002
Male	52 (85)	27 (82)	0.67
Risk factors			
Smoking	30 (49)	21 (64)	0.07
Hypertension	14 (23)	13 (40)	0.07
Family History	27 (44)	11 (33)	0.32
Hyperlipidemia	15 (25)	10 (30)	0.49
Diabetes Mellitus	4 (7)	2 (6)	0.97
Prior medication use			
β-Blocker	6 (10)	7 (21)	0.21
Calcium antagonist	2 (3)	5 (15)	0.09
Angiotensin-converting enzyme inhibitors	3 (5)	1 (3)	0.64
Nitrates	3 (5)	1 (3)	0.64
Lipid Lowering Drugs	4 (7)	3 (9)	0.70
Aspirin	4 (7)	7 (21)	0.05
Laboratory assessments at admission			
CRP, mg/L	1.9 (1.1–3.8)	4.5 (1.4–8.1)	0.02
Glucose, mmol/L	7.4 (6.7–9.0)	7.5 (6.8–9.8)	0.40
eGFR, mL/min	109±26	103±30	0.29
NT-proBNP after reperfusion, pg/ml	75 (44–157)	166 (69–311)	0.02
Peak CK-MB during hospitalization, µg/L	401 (231–613)	630 (410–778)	0.001
Procedural characteristics			
Heart rate, BPM	78±13	86±13	0.01
Systolic arterial pressure, mmHg	119±13	121±19	0.58
WMSI prior to reperfusion	1.8±0.2	2.0±0.2	0.03
Time to reperfusion, hours	2.8 (2.2–3.9)	3.0 (2.3–3.5)	0.51
ST-Segment resolution after reperfusion ≥70%	27 (44)	12 (36)	0.14
Angiographic and Doppler characteristics			
Final TIMI flow grade 3	50 (82)	20 (61)	0.06
Final myocardial blush grade 3	33 (54)	16 (49)	0.82
Final IRA CFVR	1.7±0.4	1.4±0.3	<0.001
Baseline APV, cm/s	20±9	21±9	0.76
Hyperemic APV, cm/s	34±16	29±13	0.12

Table 3. continuesd

	Reference Vessel CFVR		
	≥2.1 (n=61)	<2.1 (n=33)	*P* Value
IRA microvascular resistance			
Baseline MR, mmHg/cm per second	4.85±2.48	4.66±2.02	0.73
Hyperemic MR mmHg/cm per second	3.00±1.71	3.49±1.61	0.20
Final reference vessel CFVR	2.7±0.4	1.8±0.2	…
Baseline APV, cm/s	16±4	20±7	0.001
Hyperemic APV, cm/s	42±11	36±13	0.02
Reference vessel microvascular resistance			
Baseline MR, mmHg/cm per second	5.38±1.54	4.52±1.42	0.01
Hyperemic MR, mmHg/cm per second	2.05±0.56	2.49±0.73	0.002
Diastolic deceleration time ≤600 ms	28 (46)	21 (64)	0.04
Systolic retrograde flow present	13 (21)	14 (42)	0.03

Values are presented as frequency (%), mean±SD or median (25^{th}-75^{th} percentile). APV indicates average peak flow velocity; CFVR, coronary flow velocity reserve; CK-MB, creatine kinase myocardial band isoenzyme; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; IRA, infarct-related artery; MR, microvascular resistance; NT-proBNP, N-terminal probrain natriuretic peptide; TIMI, Thrombolysis In Myocardial Infarction; and WMSI, Wall Motion Score Index.

We additionally evaluated differences in clinical and procedural characteristics, as well as flow velocity parameters stratified according to the extent of infarction discriminated by the median peak creatine kinase myocardial band isoenzyme level (Appendix in the online-only Data Supplement). No clinically pertinent differences in clinical or procedural characteristics were found between patients with small (peak creatine kinase myocardial band isoenzyme <471 µg/L) or large (peak creatine kinase myocardial band isoenzyme ≥471 µg/L) MIs. Patients with large MI had a significantly higher WMSI, but no differences in infarct-related artery or reference vessel CFVR were found between groups. Although reference vessel baseline APV was significantly higher in patients with large MI (16±4 cm/s versus 18±6 cm/s, respectively; *P*=0.03), this difference was eclipsed by a numerically equivalent, but not statistically significant, difference in hyperemic APV (38±9 cm/s versus 41±14 cm/s, respectively; *P*=0.34), resulting in equal reference vessel CFVR between these groups (2.5±0.5 versus 2.3±0.6, respectively; *P*=0.09).

Association Between Impaired Reference Vessel CFVR and Long-term Cardiac Mortality

Univariable analyses of all candidate covariates as listed in Table 3 showed that reference vessel CFVR <2.1 at the end of the procedure, history of hypertension, age ≥65 years, increasing N-terminal probrain natriuretic peptide levels

assessed after reperfusion, as well as TIMI flow grade <3 at the end of the procedure as were associated with cardiac mortality at long-term follow-up (Table 4). After adjustment for these variables, a reference vessel CFVR of <2.1 was associated with a 4.09-fold increase in long-term cardiac mortality hazard (HR, 4.09; 95% confidence interval, 1.18–14.17; *P*=0.03).

Table 4. Prognostic Value for Long-term Cardiac Mortality by Univariable and Multivariable Cox Proportional Hazard Analysis

	Univariable Analysis			Multivariable Analysis		
Variable	Hazard Ratio	95% Confidence Interval	*P* value	Hazard Ratio	95% Confidence Interval	*P* value
End Procedural RefCFVR <2.1	4.33	1.48–12.68	0.01	4.09	1.18–14.17	0.03
Age≥65 y	3.10	1.12–8.56	0.03	2.27	0.62–8.28	0.22
NT-proBNP after reperfusion (per quartile increase*)	2.28	1.24–4.21	0.01	1.98	1.02–3.82	0.04
History of hypertension	3.29	1.14–9.49	0.03			
End procedural TIMI flow grade <3	4.09	1.48–11.30	0.01			

NT-proBNP incdicates N-Type probrain natriuretic peptide; RefCFVR, reference coronary flow velocity reserve; and TIMI, Thrombolysis In Myocardial Infarction.
* Quartiles represent: <47.4 ng/L, 47.4 to 87.4 ng/L, 87.5 to 207.3 ng/L, ≥207.4 ng/L.

Ventricular Function and CFVR at 6-Month Follow-up and Long-term Cardiac Mortality

Six-month follow-up WMSI and intracoronary measurements were available in 71 patients (Table 5).[20] At 6-month follow-up, there was a numerically small, but statistically significant difference in left ventricular function between both reference vessel CFVR groups, as assessed by WMSI (Table 5). Importantly, WMSI at 6-month follow-up was not associated with an increase in cardiac mortality hazard at long-term follow-up (HR, 5.49; 95% confidence interval, 0.59–50.75; *P*=0.13). CFVR in both the target, as well as the reference vessel remained lower within those patients with low reference vessel CFVR after reperfusion during the index procedure (Table 5). Notably, in contrast with the findings directly after reperfusion, the impairment of CFVR in both infarct-related, as well as reference coronary arteries at 6-month follow-up resulted from a significantly higher baseline APV in the presence of a significantly lower baseline microvascular resistance in patients with impaired CFVR. Contrariwise, hyperemic APV, in concordance with hyperemic microvascular resistance, did not differ between groups (Table 5). A persistently impaired

reference vessel CFVR at 6-month follow-up, defined as a reference vessel CFVR of ≤2.7,[26,27] was associated with a 10.7-fold increase in cardiac mortality hazard during subsequent follow-up, after adjustment for the variables previously identified as associated with cardiac mortality, and including adjustment for age at the time of 6-month follow-up (HR, 10.71; 95% confidence interval, 1.45–79.29; *P*=0.02).

Table 5. Left Ventricular Function and Intracoronary Hemodynamic Characteristics at 6-Month Follow-up

	Reference Vessel CFVR During Index Procedure		
	≥2.1 (n=53)	<2.1 (n=18)	*P* value
WMSI	1.5±0.3	1.8±0.3	0.001
IRA CFVR	3.0±0.9	2.3±0.7	0.003
Baseline APV, cm/s	16±6	20±7	0.04
Hyperemic APV, cm/s	48±19	44±19	0.49
IRA microvascular resistance			
Baseline MR, mm Hg/cm per second	5.91±2.77	4.52±1.42	0.06
Hyperemic MR, mm Hg/cm per second	2.16±1.96	2.03±0.77	0.79
Reference vessel CFVR	3.5±0.5	2.8±0.5	<0.001
Baseline APV, cm/s	15±8	21±9	0.01
Hyperemic APV, cm/s	50±21	56±17	0.29
Reference vessel microvascular resistance			
Baseline MR, mm Hg/cm per second	6.48±2.69	4.42±2.10	0.007
Hyperemic MR, mm Hg/cm per second	1.83±0.70	1.55±0.59	0.16

Values are presented as frequency (%), mean±SD or median (25^{th}-75^{th} percentile). APV indicates average peak flow velocity; CFVR, coronary flow velocity reserve; IRA, infarct-related artery; MR, microvascular resistance; and WMSI, Wall Motion Score Index.

Discussion

We have previously reported that microvascular function assessed by Doppler flow velocity is altered in the setting of STEMI, even in nonischemic regions at distance from the infarcted myocardial tissue.[20] This has also been observed in experimental studies, and studies using noninvasive imaging modalities.[28–30] The present study is the first to indicate that this altered microvascular function at regions remote from the infarct-related artery is independently associated with long-term fatal cardiac events.

We observed that an impaired CFVR in a reference coronary artery, determined after primary PCI for a first anterior wall STEMI, is associated with a 4.09-fold

increase in long-term cardiac mortality hazard. The 10-year Kaplan–Meier estimate of cardiac mortality amounted to 5% when reference CFVR was normal and to 31% when reference vessel CFVR was abnormal. Contrariwise, impaired CFVR measured in the infarct-related artery was not significantly associated with long-term cardiac mortality in the present data set. The acute impairment of reference vessel CFVR followed from a predominant decrease in hyperemic APV in the presence of an increased hyperemic microvascular resistance, in combination with a less pronounced increase in baseline APV in the presence of a decreased baseline microvascular resistance. Persistent impairment of reference vessel CFVR at 6-month follow-up resulted from a high baseline APV, in the presence of a low baseline microvascular resistance, and was associated with a 10.7-fold increase in cardiac mortality hazard during subsequent follow-up.

Previous Studies Regarding Impaired Infarct-Related Artery CFVR and Long-term Clinical Outcome

Two studies have previously reported on the prognostic value of CFVR in the infarct-related artery. Furber et al[31] described, for the first time, that Doppler flow velocity parameters in the infarct-related artery are of prognostic value for long-term cardiac events. In their study of 68 patients with a first acute MI, a short DDT in the infarct-related artery, as a parameter for impaired microvascular perfusion, was found to identify patients at high risk for cardiac events, with heart failure as the predominating cardiac event. Short DDT specifically identified those patients at risk for early occurrence of heart failure. This early differentiation in risk persisted during ≈4 years of follow-up. Additionally, a study by Takahashi et al[13] evaluated the prognostic value of CFVR in the infarct-related artery on long-term cardiac events in 118 patients after primary PCI for a first anterior acute MI. They found an impaired CFVR in the infarct-related artery to be significantly associated with increased cardiac event rates at a mean of 5.2±2.7 years of follow-up. Again, impaired CFVR in the infarct-related artery was primarily shown to identify those patients at risk for early occurrence of heart failure. These studies are therefore consistent with the earlier observation that Doppler flow velocity parameters harbor accurate prognostic information on the recovery of left ventricular function.[7,8,13–17]

Coronary Flow Velocity Reserve and Long-term Fatal Cardiac Events

In our study, in which we focused on cardiac mortality only, we found an unequivocal relationship between impaired microvascular function in a reference coronary artery and long-term fatal cardiac events, independent of left ventricular function. CFVR, the presence of SRF, or rapid DDT in the infarct-related artery did not identify individual patients at high risk for cardiac mortality at long-term follow-up. However, CFVR in the infarct-related artery was associated with a high risk for early cardiac mortality, which dissipated over time. In bivariate analysis with reference vessel CFVR, the marginal association of infarct-related artery CFVR with long-term cardiac mortality was eclipsed by the hazard inherited by impairment of reference vessel CFVR. Intuitively, the physiological alterations in the myocardium because of the acute ischemic event are more pronounced in the infarct-related artery, than in regions more remote from the infarction. The information on the microvascular status derived from CFVR in the infarct-related artery is obscured by the impact of acute and continuous ischemia, and the possible detrimental effects of reperfusion on myocardial tissue. In contrast, reference vessel CFVR provides information on the general functional status of the microvasculature after the acute ischemic event. Reference vessel CFVR may therefore be considered a more selective marker of microvascular function, which apparently plays a pivotal role in long-term outcome after STEMI.

Cause of Impaired Reference Vessel Coronary Flow Velocity Reserve After STEMI

During acute regional ischemia, several factors have been shown to impair CFVR in regions remote from the infarction. First, the regional dysfunction of the ischemic myocardium leads to a compensatory hyperkinesis of remote nonischemic myocardium.[32,33] This was reported to result in an impaired reference vessel CFVR because of a predominant increase in baseline flow velocity.[28,32,34] Second, apart from the systolic mechanical interaction between the myocardium and the coronary microvasculature, cardiac mechanics exert their effect also during diastole.[35] A restriction in myocardial capacitance, which may result from either an increase in left ventricular end-diastolic pressure (LVEDP), or stiffening of the myocardium because of hypoxic perfusion in the absence of an increased LVEDP,[36] limits coronary flow during late diastole. This is expresses as an isolated decrease in hyperemic APV in the infarct-related artery

and as an isolated increase in baseline APV in the reference vessel, resulting in a lower CFVR in both territories.[37] Third, neurohumoral activation in response to the acute ischemic event interferes with the reactivity of the coronary resistance vessels in the infarct-related as well as in remote regions. The rigorous and persistent activation of the sympathetic nervous system[38,39] results in activation of coronary vascular α-adrenoceptors by neuronal and humoral cathecholamines,[40] and induces a paradoxical vasoconstriction in times of increased myocardial oxygen demand.[41] Although metabolic vasodilation prevails in such a situation, α-adrenergic vasoconstriction competes, resulting in a decrease in hyperemic flow velocity, limiting CFVR throughout the heart.[42,43] Finally, impaired reference vessel CFVR, associated with a low baseline microvascular resistance, was shown to be of important prognostic value in patients with stable coronary artery disease, in the absence of mechanical myocardial dysfunction, and in the absence of an acute ischemic event.[44] This finding indicates that pre-existent microvascular dysfunction may play an important role in long-term clinical outcome.

Overall, mechanical factors induced by the acute ischemic event, as well as pre-existent microvascular alterations are primarily expressed as an increase in baseline flow velocity. Neurohumoral activation, however, results in an increase in reference vessel hyperemic microvascular resistance, resulting in a decrease in maximal hyperemic flow velocity. Both causes may thereby result in an impaired reference vessel CFVR.

Implications for the Present Study

We observed that an impaired reference vessel CFVR at the time of STEMI results predominantly from a low APV during the hyperemic response to an intracoronary bolus of adenosine, together with a less pronounced increase in baseline APV (Table 3).[20] Because compensatory hyperkinesis in the remote regions is associated with a predominant increase in baseline flow velocity,[28,32] compensatory hyperkinesis as the sole cause for the impaired reference vessel CFVR is unlikely. Additionally, although LVEDP was not measured in the present study, our study excluded patients with Killip class >2, and the study population consisted of patients in a hemodynamically stable state without known structural heart disease, in whom increase in LVEDP can be expected to be limited. Nonetheless, stiffening of the myocardium because

of hypoxic perfusion cannot be excluded, and may explain part of the increase in baseline flow velocity in the reference coronary artery because of a decrease in myocardial capacitance in this setting of anterior wall STEMI. Moreover, although we have no information on pre-existent microvascular dysfunction in our study population, pre-existent dysfunction would have accounted for a predominant decrease in baseline microvascular resistance. In accordance with previous reports,[29,30] the combination of observations in the present study implies that reference vessel CFVR in the setting of STEMI summarizes a complicated interrelation between neurohumoral overactivation induced by the acute ischemic event, pre-existent microvascular dysfunction, or the acute regional and global mechanical myocardial disruption, but is predominantly determined by the neurohumoral overactivation, which accounts for an immediate high risk for fatal cardiac events.

Reference Vessel CFVR at 6-Month Follow-up and Long-term Cardiac Mortality

In contrast to the findings in the acute setting, we observed that an impaired reference vessel CFVR at 6-month follow-up originated from a persistently higher baseline APV in conjunction with a lower baseline microvascular resistance, in the presence of restored minimal hyperemic microvascular resistance. This may result from pre-existent microvascular dysfunction, as was found in patients with stable coronary artery disease and after PCI,[45] or possibly from ongoing microvascular adaptation compensatory to the alterations in myocardial workload because of the loss of functioning myocardium, both of which may be responsible for a high risk for fatal cardiac events during subsequent follow-up.

Study Limitations

Assessment of intracoronary blood flow velocity is a technique that is sensitive for technical failures, and accurate evaluation of CFVR is dependent on the experience of the cardiologist. All coronary flow velocity measurements in this study were performed by operators with ample experience in intracoronary flow velocity measurements. Accurate assessment of flow velocity depends furthermore on the achievement of maximal vasodilation. Although there has been an extensive debate on the amount of adenosine needed to achieve a

maximally vasodilated state, the amount of adenosine used in this study is considered sufficient.[46]

The study protocol excluded patients with signs of acute left-sided heart failure. We felt that patients in such critical condition were not suited to undergo the extensive measurement protocol. Moreover, exclusion of these patients was motivated by the anticipated effect of a high LVEDP in the acute phase of heart failure on coronary flow velocity parameters. However, concomitantly, large MIs have been excluded from evaluation in this study; as a consequence, our observations are only valid in the context of acute anterior wall MI not complicated by acute left-sided heart failure.

In the absence of an established cut-off value, the optimal cut-off values of target vessel and reference vessel CFVR for long-term cardiac mortality were derived from the present data set. The evaluation of the relationship between CFVR at these cut-off values and long-term clinical outcome within the same data set may provide an advantageous estimate of the relationship, and should be confirmed in further studies.

Additionally, the study population was small, in particular at 6-month follow-up, and some predictors of long-term outcome may have been missed because of a lack of statistical power. Consequently, although our results are indicative for a strong prognostic value of CFVR in a reference vessel for long-term cardiac mortality, these results should be considered hypothesis generating, and should be confirmed in further studies. Moreover, in addition to the possible obscuring effect of the acute event on the association of target vessel CFVR with long-term outcome, the small sample size may in in part explain the lack of a statistically significant association between target vessel CFVR and long-term cardiac mortality.

Conclusions

We conclude that microvascular function, as assessed by the coronary vasodilator reserve in a reference vessel, plays a pivotal role in long-term cardiac mortality after primary PCI for STEMI.

Acknowledgments

The authors gratefully acknowledge the skilled assistance of the nursing staff of the cardiac catheterization laboratory (Head: M.G.H. Meesterman).

Sources of Funding

This study was funded in part by the European Community's Seventh Framework Program (FP7/2007–2013) under grant agreement no. 224495 (euHeart project), and by a grant from the Dutch Heart Foundation (2006B186).

The online-only Data Supplement is available at http://circinterventions.ahajournals.org/lookup/suppl/doi:10.1161/CIRCINTERVENTIONS.112.000168/-/DC1.

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Chapter 6

Impaired coronary autoregulation is associated with long-term fatal events in patients with stable coronary artery disease

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Circ Cardiovasc Interv. **2013;6:329–335**
https://doi.org/10.1161/CIRCINTERVENTIONS.113.000378

Abstract

Background

Abnormalities in the coronary microcirculation are increasingly recognized as an elementary component of ischemic heart disease, which can be accurately assessed by coronary flow velocity reserve in reference vessels (refCFVR). We studied the prognostic value of refCFVR for long-term mortality in patients with stable coronary artery disease.

Methods and Results

We included patients with stable coronary artery disease who underwent intracoronary physiological evaluation of ≥1 coronary lesion of intermediate severity between April 1997 and September 2006. RefCFVR was assessed if a coronary artery with <30% irregularities was present. RefCFVR >2.7 was considered normal. Patients underwent revascularization of all ischemia-causing lesions. Long-term follow-up was performed to document the occurrence of (cardiac) mortality. RefCFVR was determined in 178 patients. Kaplan–Meier estimates of 12-year all-cause mortality were 16.7% when refCFVR >2.7 and 39.6% when refCFVR ≤2.7 (P<0.001), whereas Kaplan–Meier estimates for cardiac mortality were 7.7% when refCFVR >2.7 and 31.6% when refCFVR ≤2.7 (P<0.001). After multivariable adjustment, refCFVR ≤2.7 was associated with a 2.24-fold increase in all-cause mortality hazard (hazard ratio, 2.24; 95% confidence interval, 1.13–4.44; P=0.020) and a 3.32-fold increase in cardiac mortality hazard (hazard ratio, 3.32; 95% confidence interval, 1.27–8.67; P=0.014). Impairment of refCFVR originated from significantly higher baseline flow velocity in the presence of significantly lower reference vessel baseline microvascular resistance (P<0.001), indicating impaired coronary autoregulation as its cause.

Conclusions

In patients with stable coronary artery disease, impaired refCFVR, resulting from increased baseline flow velocity indicating impaired coronary autoregulation, is associated with a significant increase in fatal events at long-term follow-up.

Introduction

Abnormalities in the function and structure of the coronary microcirculation are increasingly recognized as an elementary component in the spectrum of ischemic heart disease. Coronary microvascular alterations may represent an important marker for risk or may contribute to the pathogenesis of myocardial ischemia[1] and may arise from a wide array of pathogenetic mechanisms.[1] Such alterations may contribute to adverse outcome in patients with stable coronary artery disease (CAD) and may, potentially, offer a target for risk stratification and evaluation of preventive treatment strategies.[2]

In the absence of significant epicardial disease, the vasodilator response of coronary circulation, as measured by the coronary flow velocity reserve (CFVR), is determined by the functional status of the resistance vessels of coronary microcirculation and can, therefore, be considered a direct marker of microvascular function.[3] Defined as the ratio of hyperemic to basal average peak flow velocity,[4] impairment of reference vessel CFVR may originate from either an increased basal flow velocity or an impaired hyperemic flow velocity. Although there has been interest in the prognostic value of the vasodilatory function of coronary microcirculation,[2,5] selective evaluation of basal and hyperemic components of CFVR has not been performed in these investigations. Nonetheless, this discrimination may be particularly important to advance our understanding of processes underlying these vascular alterations and the consequent risk for adverse events.

Therefore, the aim of the present study was to evaluate the association between reference vessel CFVR and long-term fatal events in patients with stable CAD, as well as to document the relative contribution of baseline and hyperemic components in the impairment of reference vessel CFVR.

WHAT IS KNOWN

- Abnormalities in the function and structure of coronary microcirculation play an important role in the spectrum of ischemic heart disease.
- The functional status of microcirculation may accurately be evaluated by means of coronary flow (velocity) measurements.
- Impaired coronary flow velocity reserve in unobstructed coronary arteries is associated with, predominantly nonfatal, adverse cardiac events.

WHAT THE STUDY ADDS

- Impaired coronary flow velocity reserved in unobstructed coronary arteries in patients with stable coronary artery disease likely originates from disturbance of the coronary autoregulatory mechanism.
- Such disturbance is associated with an increased risk for long-term fatal (cardiac) events.

Methods

Study Population

Between April 1997 and September 2006, we evaluated patients with stable CAD whose diagnostic angiography showed ≥1 intermediate coronary artery lesion at visual assessment. These patients were enrolled in a series of study protocols,[6–9] and patient and procedural characteristics were entered into a dedicated database. We excluded patients with ostial lesions, ≥2 stenoses in the same coronary artery, severe renal function impairment (glomerular filtration rate calculated according to the Modification of Diet in Renal Disease formula <30 mL/min per 1.73 m^2), significant left main coronary artery stenosis, atrial fibrillation, recent myocardial infarction (<6 weeks before screening), prior coronary artery bypass graft surgery, or visible collateral development to the perfusion territory of interest. The institutional ethics committee approved the study procedures, and all patients gave written informed consent.

Cardiac Catheterization Procedure

Coronary angiography was performed according to standard clinical practice, and angiographic images were obtained in a manner suitable for quantitative coronary angiography analysis. Quantitative coronary angiography analysis was performed offline to determine percent diameter stenosis with the use of a validated automated contour detection algorithm (QCA-CMS version 3.32; MEDIS, Leiden, The Netherlands).

Before percutaneous coronary intervention, intracoronary pressure was measured with a 0.014" pressure sensor–equipped guidewire (Volcano Corp, San Diego, CA). Coronary blood flow velocity was subsequently measured with a 0.014" Doppler crystal–equipped guidewire (Volcano Corp, San Diego, CA). Hyperemia was induced by an intracoronary bolus of adenosine (20–40 μg). Fractional flow reserve was defined as the ratio of mean distal coronary pressure to mean aortic pressure in the target vessels during maximal hyperemia. CFVR was defined as the ratio of hyperemic to baseline average peak blood flow velocity (APV) distal to the target lesions. CFVR was additionally assessed in an angiographically normal reference coronary artery, defined as a coronary artery with <30% irregularities on visual assessment, if present. A reference vessel CFVR >2.7 was considered normal.[10] From the recorded intracoronary hemodynamic data, both the hyperemic stenosis resistance index,[9] defined as the ratio between the pressure gradient across the stenosis and distal APV during maximal hyperemia, and the microvascular resistance index,[11] defined as mean distal coronary pressure divided by distal APV, were calculated. In the absence of significant epicardial disease, microvascular resistance index in the reference vessel was calculated as the mean aortic pressure divided by distal APV. In the presence of 2-vessel CAD, the most severe coronary lesion by hyperemic stenosis resistance index was depicted as the target lesion and was used for subsequent target vessel analyses.

Patients underwent percutaneous coronary intervention of all ischemia-causing lesions at the discretion of the operator. Decisions on further treatment and medication during follow-up were entirely left to the discretion of the treating cardiologist.

Long-term Follow-up

Long-term follow-up was performed by identifying patients in the Dutch national population registry to assess the occurrence of death. In addition, the cause of death was verified by evaluating hospital records or by contacting the general practitioner. Death was considered cardiac unless an unequivocal noncardiac cause was documented.[12]

Statistical Analysis

Cumulative event rates were estimated using the Kaplan–Meier method and were compared with the log-rank test. Event rates are presented as Kaplan–Meier estimates at 12-year follow-up. The association of reference vessel CFVR with long-term fatal events was evaluated in 2 sets of Cox proportional hazards models. A univariable analysis was performed to identify variables associated with all-cause mortality ($P<0.1$). Subsequent multivariable analysis was performed with adjustments for these variables. The multivariable analysis was subsequently repeated to evaluate the association of reference vessel CFVR with cardiac mortality. Variables are presented as mean (±SD), median with first and third quartiles (Q1–Q3), or frequency (percentage), where appropriate. Comparison between groups was performed using Student *t* test or Fisher exact test, where appropriate. A 2-sided α level of 0.05 was considered statistically significant.

Results

Baseline and Procedural Characteristics

Reference vessel CFVR was measured in a total of 178 patients. Long-term follow-up was obtained in all these patients. Mean age of the study population was 59±13 years. Most patients had moderate-to-severe stable anginal complaints (15% Braunwald class I, 58% Canadian Cardiovascular Society class 3, 21% Canadian Cardiovascular Society class 2, and 6% Canadian Cardiovascular Society class 1). Two-vessel CAD was present in 69% of patients (123 of 178 patients). In 36% of patients (64 of 178 patients), the coronary lesion of interest was treated during the index procedure. All baseline clinical and procedural characteristics are presented in Table 1. The location of the reference vessel relative to the target vessel is presented in Table 2.

Clinical Characteristics of Patients With Normal Versus Abnormal Reference Vessel CFVR

Clinical and procedural characteristics stratified by normal or abnormal reference vessel CFVR (>2.7, and ≤2.7, respectively) are presented in Table 1. On average, patients with an abnormal reference vessel CFVR were older at the time of cardiac catheterization and less frequently had hyperlipidemia. All other clinical characteristics were balanced between the 2 groups. Lesion characteristics and epicardial lesion severity assessed either angiographically

or by fractional flow reserve or hyperemic stenosis resistance index were similar between groups. Accordingly, percutaneous coronary intervention of the lesion of interest was performed equivalently between groups. Nevertheless, CFVR in the target vessel was significantly lower among patients with an impaired reference vessel CFVR.

Table 1. Clinical and Procedural Characteristics of Study Population, and Stratified According to Patients with a Normal or Abnormal Reference Vessel CFVR (n=178)

		Reference CFVR		
		Normal	Abnormal	
	All	>2.7	≤ 2.7	*P* value*
No. of patients	178	101	77	
Age, y	59±13	57±9	61±16	0.04
Male Sex	128 (72)	77 (76)	51 (66)	0.18
Risk Factors				
Hypertension	70 (39)	38 (37)	32 (42)	0.64
Hyperlipidemia	102 (57)	67 (66)	35 (45)	0.01
Family History of CAD	86 (48)	50 (50)	36 (47)	0.76
Smoking	61 (34)	36 (36)	25 (32)	0.75
Diabetes Mellitus	27 (15)	14 (14)	13 (17)	0.68
Prior Myocardial Infarction	65 (37)	36 (36)	29 (38)	0.88
Prior percutaneous coronary intervention	25 (14)	14 (14)	11 (14)	1.0
Medication at hospital admission				
B-Blocker	141 (79)	80 (79)	61 (79)	1.00
Calcium antagonist	112 (63)	65 (64)	47 (61)	0.75
ACE Inhibitor	34 (19)	20 (20)	14 (18)	0.85
Nitrates	120 (67)	66 (65)	54 (70)	0.52
Lipid-lowering drugs	102 (57)	62 (61)	40 (52)	0.22
Aspirin	159 (89)	92 (91)	67 (87)	0.47
Ventricular Function				
Abnormal left ventricular function (EF <50%)	14 (8)	5 (5)	9 (12)	0.16
Left ventricular hypertrophy	9 (5)	4 (4)	5 (6)	0.73
Hemodynamics during measurements				
Baseline				
Heart rate, bpm	68±11	67±11	69±10	0.24
Mean arterial pressure, mmHg	98±13	96±11	101±14	0.03
Hyperemia				
Heart rate, bpm	68±11	67±11	70±10	0.14
Mean arterial pressure, mmHg	94±13	93±11	97±14	0.06
Functional parameters prior to PCI/deferral				
Two-vessel coronary artery disease	123 (69)	69 (68)	54 (70)	0.80
Diameter stenosis most severe lesion (%)	57±10	57±10	57±11	0.74
Reversible ischemia on MPS	61 (34)	37 (37)	24 (31)	0.52
CFVR target vessel	2.2±0.8	2.4±0.8	1.9±0.6	<0.001

Table 1. continued

		Reference CFVR		
		Normal	Abnormal	
	All	>2.7	≤ 2.7	*P* value*
Baseline APV target vessel, cm/s	17±8	15±6	20±10	<0.001
Hyperemic APV target vessel, cm/s	36±17	35±16	38±19	0.41
FFR	0.73±0.17	0.73±0.17	0.73±0.18	0.98
CFVR reference vessel	2.9±0.7	3.4±0.4	2.3±0.3	
Baseline APV reference vessel, cm/s	18±7	16±5	21±7	<0.001
Hyperemic APV reference vessel, cm/s	50±17	52±18	48±16	0.23
HSR, mmHg/cm per second	1.33±2.28	1.16±1.66	1.54±2.88	0.30
Reference vessel diameter, mm	2.9±0.6	2.9±0.6	2.9±0.7	0.72
Microvascular resistance				
Target vessel				
Baseline MR, mmHg/cm per second	6.01±3.04	6.49±2.61	5.40±3.44	0.02
Hyperemic MR, mmHg/cm per second	2.29±1.21	2.18±0.78	2.42±1.60	0.22
Reference vessel				
Baseline MR, mmHg/cm per second	6.16±2.30	6.92±2.42	5.21±1.73	<0.001
Hyperemic MR, mmHg/cm per second	2.14±1.02	2.07±1.19	2.22±0.76	0.35
PCI of target lesion	64 (36)	35 (35)	29 (38)	0.75

Values presented as n (%) or mean±SD. ACE indicates angiotensin-converting enzyme; APV, average peak flow velocity; CAD, coronary artery disease; CFVR, coronary flow velocity reserve; EF, ejection fraction; FFR, fractional flow reserve; HSR, hyperemic stenosis resistance index; MPS, myocardial perfusion scintigraphy; MR, microvascular resistance; and PCI, percutaneous coronary intervention.
**P* value for comparison between normal and abnormal reference vessel CFVR groups.

Table 2. Reference Vessel Location Relative to the Target Vessel.

	Reference vessel		
Target vessel	LAD	LCX	RCA
LAD	…	79 (44)	13 (7)
LCX	25 (14)	…	11 (6)
RCA	22 (12)	28 (16)	…

Data presented as n (%). LAD indicates left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery.

Coronary Flow Velocity Parameters

Reference vessel APV under baseline conditions was significantly higher, and microvascular resistance under baseline conditions was significantly lower among patients with an abnormal reference vessel CFVR (Table 1). Contrariwise, reference vessel hyperemic flow velocity and reference vessel hyperemic microvascular resistance were similar between both groups (Table 1).

In addition, target vessel APV under baseline conditions and baseline microvascular resistance were also significantly different between the normal and abnormal reference vessel CFVR groups, whereas hyperemic APV and microvascular resistance in the target vessel did not differ significantly (Table 1).

Reference Vessel CFVR and Long-term Fatal Events

Median follow-up amounted to 11.6 years (Q1–Q3: 10.1–13.2 years). Twelve-year Kaplan–Meier estimates of cumulative all-cause mortality amounted to 16.7% in patients with a normal reference vessel CFVR and to 39.6% in patients with an abnormal reference vessel CFVR (P<0.001; Figure A), whereas 12-year Kaplan–Meier estimates of cumulative cardiac mortality amounted to 7.7% in patients with a normal reference vessel CFVR and to 31.6% in patients with an abnormal reference vessel CFVR (P<0.001; Figure B).

Of all clinical and procedural characteristics (Table 1), reference vessel CFVR ≤2.7, age >65 years, impaired left ventricular function (left ventricular ejection fraction <50%), the presence of left ventricular hypertrophy, and history of angiotensin-converting enzyme inhibitor use were found to be associated with long-term all-cause mortality in this study population (P<0.1). After multivariable adjustment, reference vessel CFVR ≤2.7 was associated with a 2.24-fold increase in mortality hazard at long-term follow-up (hazard ratio, 2.24; 95% confidence interval, 1.13–4.44; P=0.020). Furthermore, after multivariable adjustment, reference vessel CFVR was associated with a 3.32-fold increase in cardiac mortality hazard at long-term follow-up (hazard ratio, 3.32; 95% confidence interval, 1.27–8.67; P=0.014). Additional adjustment for index procedure treatment strategy did not alter these findings (hazard ratio for all-cause mortality, 2.23; 95% confidence interval, 1.13–4.42; P=0.021 and hazard ratio for cardiac mortality, 3.34; 95% confidence interval, 1.28–8.73; P=0.014).

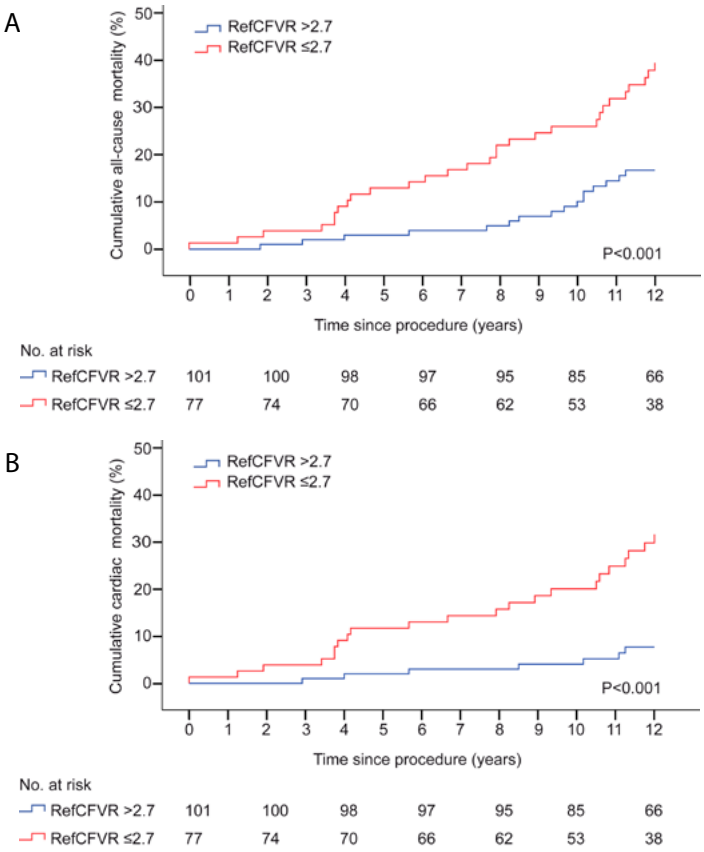

Figure. Kaplan Meier estimates and log rank comparison of cumulative fatal events. Log rank comparison of Kaplan Meier estimates resulted in a significant difference in **A)** all-cause mortality, as well as **B)** cardiac mortality, between normal and abnormal reference vessel coronary flow velocity reserve.

Discussion

In our study population, we observed that an abnormal reference vessel CFVR of ≤2.7 was associated with a 2.24-fold increase in hazard for long-term all-cause mortality after multivariable adjustment. Twelve-year Kaplan–Meier estimates of all-cause mortality amounted to 16.7% when reference vessel CFVR was normal, in contrast to 39.6% in the presence of an abnormal reference vessel CFVR. In addition, abnormal reference vessel CFVR was associated with a 3.32-fold increase in hazard for long-term cardiac mortality. The impairment in reference vessel CFVR was found to originate from a significantly higher baseline APV in the presence of a significantly lower baseline microvascular

resistance. In contrast, hyperemic microvascular resistance and hyperemic APV did not differ between abnormal and normal reference vessel CFVR groups. Furthermore, similar alterations in baseline flow velocity and microvascular resistance were also present in the target vessel.

Reference Coronary Flow Velocity and Microvascular Function

In the absence of a significant coronary stenosis, the vasodilator response of the coronary circulation is determined by the resistance vessels of the coronary microcirculation.[3] In response to a potent vasodilatory stimulus, such as adenosine, this CFVR in a reference vessel may increase >4-fold in healthy young volunteers.[10,13] In adult patients with chest pain syndromes and risk factors for CAD, reference vessel CFVR is expected to increase >2.7-fold.[10,13,14] As CFVR is determined as the ratio of hyperemic to basal coronary blood flow velocity, impairment of reference vessel CFVR may follow from either a decrease in hyperemic or an increase in basal coronary blood flow. While the former may be ascribed to impaired vasodilatory function of the coronary microvasculature and is usually associated with a high hyperemic microvascular resistance, the latter may be ascribed to disturbed coronary autoregulation and is usually associated with low microvascular resistance under baseline conditions.[15] The discrimination between these 2 entities, which can only be made by selective evaluation of the relative contributions of baseline and hyperemic components of CFVR, may provide essential insights into the pathophysiological origin of the impaired vasodilator reserve.

Interpretation of Impaired Reference Vessel CFVR in the Present Study

An increased baseline flow velocity in the presence of decreased baseline microvascular resistance has previously been described in patients with stable CAD after angioplasty and coronary stenting, contributing to the impaired flow velocity reserve frequently found in this setting.[15–17] This increase in baseline flow velocity was repeatedly ascribed to disturbed coronary autoregulation.[15,17] Under physiological circumstances, coronary autoregulation regulates vasodilation and vasoconstriction of the coronary resistance vessels to maintain stable coronary blood flow to the distal myocardium within a physiological range of perfusion pressures.[18] In response to a loss of perfusion pressure to the distal myocardium as a result of progressive epicardial coronary narrowing, autoregulation facilitates

compensatory vasodilation of the coronary resistance vessels to maintain stable resting coronary blood flow to the distal myocardium. This mechanism is capable of maintaining resting blood flow until the epicardial artery becomes narrowed by >85% of the lumen diameter, after which basal flow starts to decrease.[19] In the setting of stable CAD, prolonged compensatory vasodilation of the coronary resistance vessels because of chronic deprivation of perfusion pressure in the presence of progressive epicardial artery narrowing may impair the autoregulatory mechanism of the coronary microvasculature. An abrupt restoration of perfusion pressure by percutaneous intervention may then fail to induce appropriate adaptation of the microvasculature, resulting in an increased flow velocity at rest.[15,17] However, after percutaneous coronary intervention, this change in baseline flow velocity in response to coronary intervention was found to be transient, normalizing toward reference values at ≈6-month follow-up.[15,17]

In contrast to the previous investigations after percutaneous intervention, we assessed CFVR in vessels without flow-limiting coronary stenoses. Furthermore, we performed the intracoronary measurements at the start of the procedure before revascularization of the target lesions. The combination of an increased baseline flow velocity in the presence of decreased microvascular resistance in the present study, therefore, implies pre-existent disturbance of the coronary autoregulatory mechanism in adequately perfused myocardium. Furthermore, the same alterations were present in the target vessel, indicating that disturbance of the autoregulatory mechanism is present throughout the myocardium and implicating a systemic origin of such microvascular dysfunction. Apparently, in patients with impaired reference vessel CFVR, coronary autoregulation fails to adapt distal vascular tone appropriately to regulate coronary flow, resulting in an increase in baseline flow velocity and impairing the achievable CFVR, which apparently puts these patients at high risk for future events. In contrast, the microvascular response to a potent vasodilator remains intact and, therefore, does not provide an explanation for the adverse outcome observed in these patients.

The combination of findings in the present study allocates the cause of the impaired flow reserve to the coronary autoregulatory mechanism. Preclinical studies suggest a role of hypertension-associated left ventricular

hypertrophy,[20–22] diabetes mellitus,[23,24] and acute renal failure,[25] although the latter condition was an exclusion criterion in the present study. Disturbance of coronary autoregulation may arise from a wide variety of pathophysiological mechanisms,[1,3,26,27] and larger cohorts of patients with disturbed coronary autoregulation are necessary to elucidate the origin of such dysfunction in patients with stable CAD.

Previous Studies on the Prognostic Value of Coronary Flow Velocity Abnormalities

Two other studies reported on the prognostic value of intracoronary-derived CFVR in a reference vessel for long-term clinical outcome. Pepine et al[2] showed a similar prognostic value of CFVR in a normal reference coronary artery in women with suspected myocardial ischemia. At 5.4 years of follow-up, a reference vessel CFVR<2.32 was associated with a major adverse cardiac event rate (defined as the composite of death, myocardial infarction, stroke, and hospital stay for heart failure) of 27.0% compared with 12.2% when CFVR≥2.32 (P<0.01). Overall mortality was low at 6% (11 of 189 patients), but the mortality difference between low and high reference vessel CFVR values was not reported. The authors concluded that an impaired microvascular vasodilatory response to a potent vasodilator is associated with increased risk for major adverse cardiac event, even in the absence of significant obstructive CAD. In addition, Britten et al[5] evaluated the prognostic value of the coronary flow reserve index, an index analogous to CFVR, in a normal coronary artery in patients undergoing either diagnostic cardiac catheterization for symptoms of angina or single-vessel percutaneous coronary intervention. They found a low major adverse cardiac event rate (defined as the composite of death, myocardial infarction, stroke, unstable angina, and revascularization of a de novo coronary artery lesion) of 11% (13 of 120 patients) during 6.5 years of follow-up. Notably, cardiac mortality amounted to only 1.7% (2 of 120 patients) at long-term follow-up. Coronary flow reserve index in a normal coronary artery was found to be independently associated with cardiovascular events at long-term follow-up. The authors concluded that the coronary flow reserve index, as an integrative measure of the maximal vasodilator capacity of the microcirculation as well as epicardial resistance because of subclinical atherosclerosis, is an independent predictor of long-term adverse outcome.

Differences Between Study Results: Outcome Measures and Impaired CFVR

Interpretation

In part, our conclusions are consistent with these previous reports, because we found a similar important prognostic value of microvascular function determined by CFVR in reference vessels for long-term clinical outcome in patients with stable CAD. However, the present study is the first to indicate a significant association between reference vessel vasodilator reserve and long-term fatal events. In the previous evaluations of the prognostic value of reference vessel CFVR for long-term adverse events, nonfatal adverse events were included in the composite end points, such as stroke and revascularization of de novo coronary artery lesions, of which a direct relationship with pre-existent coronary microvascular functional alterations documented during the index procedure may be questionable.

The most important difference between our findings and the conclusions from Pepine et al[2]and Britten et al[5] is the origin of the impaired reference vessel CFVR. Both reports conclude that microvascular reactivity to a potent vasodilator was impaired in patients with an abnormal reference vessel CFVR. However, the relative influence of baseline and hyperemic flow velocity and microvascular resistance was not reported to support this conclusion, even though such discrimination seems important because an impaired vasodilator response to a potent vasodilator is most likely because of different pathophysiology than disturbed autoregulation under basal conditions. Therefore, identification of the exact origin of reference vessel CFVR impairment may alter the potential target for risk stratification or evaluation of preventive therapeutic strategies.[2]

According to the combination of observations in the present study, we postulate that impaired reference vessel CFVR does not originate from an impaired hyperemic vasodilator response of the coronary microvasculature as reported previously, but from pre-existent disturbed coronary autoregulation under baseline conditions that is present throughout the myocardium. The disturbed autoregulation results in an increased baseline flow velocity, and thereby in depletion of the vasodilator reserve throughout the myocardium. Further elucidation of factors underlying this disturbed autoregulation in patients with stable CAD may identify appropriate targets for risk stratification or evaluation of preventive treatment strategies.

Limitations

There are some limitations to this study that deserve mention. First, the present study represents a relatively small study population. Consequently, although all-cause mortality, as well as cardiac mortality, is strikingly different between patients with normal or abnormal reference vessel CFVR, these results should be considered hypothesis generating.

Second, measurement of intracoronary blood flow velocity is considered technically challenging, and accurate evaluation of CFVR is dependent on the experience of the cardiologist. However, in this study, all coronary flow velocity measurements were performed by operators with ample experience in intracoronary flow velocity measurements.

Finally, no intracoronary pressure measurements were performed in the reference coronary artery. Thereby, although reference vessels with significant epicardial narrowing were not selected for coronary flow velocity measurements, a potential role of subclinical atherosclerosis of the conduit artery in the absence of focal narrowing in the impairment of reference vessel CFVR cannot be excluded. However, (subclinical) narrowing of the reference vessel in patients with abnormal reference vessel CFVR would have resulted in a decreased hyperemic flow velocity.[4,28] Furthermore, in the absence of disturbed autoregulation, the normal physiological compensatory vasodilation by means of autoregulation in response to a decreased perfusion pressure induced by coronary narrowing is not associated with an increase in basal flow velocity.[18,19] Therefore, these findings locate the cause for an impaired reference CFVR to the coronary microvasculature, and the combination of finding implies disturbed autoregulation as the key impediment to CFVR.

Conclusions

An impaired reference vessel CFVR is associated with an increased hazard for fatal events at long-term follow-up in patients with stable CAD. Impairment of reference vessel CFVR results from disturbed coronary autoregulation, leading to an increased coronary flow velocity under baseline conditions. Further studies are warranted to elucidate the origin of dysfunction of the coronary autoregulatory mechanism, as well as its role in the unfavorable outcome of patients with stable CAD.

Acknowledgments

We gratefully acknowledge F. van der Wal, RN, J.E. Brouwer, RN, and S.H. Oortwijn, RN, for their extensive effort in collecting the follow-up data, as well as the nursing staff of the cardiac catheterization laboratory (Head: M.G.H. Meesterman) for their skilled assistance in acquiring the data.

Sources of Funding

This study was funded, in part, by the European Community's Seventh Framework Program (FP7/2007–2013) under grant agreement no. 224495 (euHeart project) and by grants from the Dutch Heart Foundation (2006B186, 2000.090, and D96.020).

Disclosures

None.

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Chapter 7

Microvascular dysfunction following ST-elevation myocardial infarction and its recovery over time

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EuroIntervention. 2017;13:e578-e584
DOI: 10.4244/EIJ-D-16-00818

Abstract

Aims

It is unclear whether microvascular dysfunction following ST-elevation myocardial infarction (STEMI) is prognostic for long-term left ventricular function (LVF), and whether recovery of the microvasculature status is associated with LVF improvement. The aim of this study was to assess whether microvascular dysfunction in the infarct-related artery (IRA), as assessed by coronary flow reserve (CFR) within one week after PPCI, was associated with LVF at both four months and two years.

Methods and results

In 62 patients, CFR and hyperaemic microvascular resistance index (HMRI) in the IRA were assessed by intracoronary Doppler flow measurements within one week and at four months. CMR was performed at the same time points and also at two years. CFR at baseline was associated with left ventricular ejection fraction (LVEF) at four months (β=4.66, SE=2.10; p=0.03) and at two-year follow-up (β=5.84, SE=2.45; p=0.02). HMRI was not associated with LVF. In large infarcts, absolute improvement of CFR in the first four months was associated with LVEF improvement (β=5.09, SE=1.86, p=0.01).

Conclusions

Microvascular dysfunction, assessed by CFR, in the subacute phase of STEMI is prognostic for LVEF at four months and two years. This underlines the pivotal role of microvascular dysfunction following STEMI.

Introduction

In 30 to 40% of ST-elevation myocardial infarction (STEMI) patients, myocardial tissue perfusion remains compromised, despite restoration of epicardial patency after primary percutaneous coronary intervention (PPCI)[1]. Microvascular dysfunction, due to reperfusion injury, endothelial dysfunction, neurohumoral activation or intramyocardial haemorrhage, has been described as a possible cause for this phenomenon[2-4]. This is, in turn, proposed as the pathophysiological mechanism in the development of adverse left ventricular (LV) remodeling and overt heart failure[1,5,6].

Microvascular function can be measured invasively with coronary flow reserve (CFR) and hyperaemic microvascular resistance index (HMRI). CFR estimates the vasodilatory capacity of the coronary microvascular bed[7]. Insights into the temporal evolution of microvascular dysfunction and its implications on long-term left ventricular function (LVF) are currently lacking. The primary objective of this study was to assess whether microvascular dysfunction in the infarct-related artery (IRA), as assessed by CFR within one week after PPCI, was associated with LVF at two years as assessed by cardiac magnetic resonance (CMR) imaging. This was compared to the prognostic value of HMRI. Secondary objectives were to assess whether an improvement in microvascular function was associated with LVF improvement.

Methods

Study population and procedures

For the current study, we included a subpopulation of the HEBE trial, designed to assess the effect of bone marrow mononuclear cell therapy on cardiac improvement in STEMI patients[8-10.] This substudy included patients who underwent paired intracoronary flow measurements in the Academic Medical Center and the VU University Medical Center, Amsterdam (n=64). Patients who experienced a reinfarction during follow-up (n=2) were excluded. The study was conducted in accordance with the Declaration of Helsinki and the study protocol was approved by the institutional review boards of both centers.

Intracoronary doppler flow measurements and data analysis

A bolus of 0.1 mg nitroglycerine was administered intracoronary prior to Doppler flow measurements. Intracoronary flow was measured with a 0.014-inch Doppler-tipped guidewire (FloWire®; Volcano Corporation, San Diego, CA, USA) that was positioned distal to the previously implanted stent in the IRA. Following optimization of the Doppler signal, the average peak flow velocity recordings were obtained before and after induction of hyperaemia by an intracoronary bolus administration of 20 to 40 µg adenosine. Also, intracoronary flow was assessed in the non-IRA (reference artery), if there was <30% stenosis. The position of the Doppler-tipped guidewire in both arteries was documented on angiography at baseline in order to obtain a similar guidewire position at four months.

Doppler flow velocity was recorded continuously and analyzed offline by an independent investigator[10]. The following parameters were assessed: systolic and diastolic mean aortic pressure and average peak flow velocity at baseline and hyperaemia. CFR was determined as the ratio of hyperaemic to baseline average peak flow velocity. An impaired CFR was defined at the cut-off value of <2.0, according to the mean of the current study population. The relative CFR was calculated as the absolute CFR in the IRA divided by the absolute CFR in the reference vessel. HMRI was calculated by dividing the mean aortic pressure by the average peak flow velocity during maximum hyperaemia. Improvement of microvascular function could be assessed by calculating the difference (Δ) between CFR and HMRI at four months and baseline. Both the absolute (Δ) and relative (%) differences of both indices were assessed.

Cardiac magnetic resonance and data analysis

CMR was performed on a clinical MRI scanner at 4±2 days following PPCI (baseline) and at four and 24 months, as previously described[8]. In short, both cine and delayed contrast-enhanced CMR was performed to measure LVF, infarct size, transmurality and the presence of microvascular obstruction. The changes (Δ) in left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) index were evaluated as the absolute and percentage increases or decreases from baseline to four months and baseline to two years. Total infarct size was determined as previously described using a predefined and standardized definition of

hyperenhancement, expressed as a percentage of LV mass8. Transmurality was determined by dividing the hyperenhanced area by the total area of the predefined segment. MVO was defined as any region of hypoenhancement within the hyperenhanced infarcted area8. CMR data were analyzed in a core lab using a dedicated software package (Mass 2008 beta; Medis, Leiden, the Netherlands), blinded to the intracoronary Doppler flow measurements.

Statistical analysis

Normally distributed data are expressed as mean(±SD) and for non-normally distributed data the median value (25th to 75th percentile) is provided. Categorical variables are presented as number (%) and compared by the chi-square test. A Student's t-test or a one-way analysis of variance was used to compare data with a normal distribution of continuous variables and a Kruskal-Wallis test for non-normally distributed continuous variables.

A univariate linear regression model was used to assess whether CFR and HMRI measured in the subacute phase were associated with global left ventricular volumes and function at baseline, four months and two years.

In a subsequent multivariate linear regression model, the prognostic value of CFR in the subacute phase was assessed with other known patient and angiographic characteristics associated with LVEF (%) at two years11,12. Based on the cut-off value of CFR <2, patients were classified into those with an impaired (CFR <2) or preserved microvascular function (CFR ≥2) at baseline. LVEF, LVEDV and LVESV index measured at baseline, four months and at two years were compared in both groups. The temporal change in LVEF, LVEDV and LVESV index was also compared between the groups.

Whether improvement in CFR and HMRI within the initial four months was concurrently associated with improvement in LVEF was investigated for two different infarct size groups stratified according to the median infarct size.

A p-value <0.05 was considered statistically significant. All statistical analysis was performed using SPSS software, Version 20.0 (IBM Corp., Armonk, NY, USA).

Results

The study population is described in Table 1. Mean age was 55±9 years and the left anterior descending artery (73%) was most frequently the IRA. Baseline characteristics of patients who underwent baseline intracoronary measurements did not differ from those who underwent paired measurements.

Table 1. Study population

Characteristic	Baseline intracoronary Doppler flow measurements (n=62)
Age (years)	55.2±9.2
Male, n (%)	49 (79)
BMI	26.2±3.4
Risk factors for coronary artery disease	
Diabetes mellitus	3 (5)
Hypertension	19 (31)
Family history of coronary heart disease	29 (47)
Hypercholesterolemia	10 (16)
Current smoking	33 (53)
Symptom onset to PCI (hrs)	3.3 (2.4-4.4)
Infarct-related artery	
Left anterior descending artery	45 (73)
Left circumflex artery	3 (5)
Right coronary artery	14 (23)
Reference artery	
Left anterior descending artery	14 (22)
Left circumflex artery	48 (74)
Right coronary artery	3 (5)
CMR infarct variables	
IS (% LV)	22.8±9.8
Extent of transmurality (% segments >75% infarcted)	21.2±14.0
Presence of MVO	41 (66)

BMI: body mass index; CMR: cardiac magnetic resonance; IS: infarct size; LV: left ventricle; MVO: microvascular obstruction; PCI: percutaneous coronary intervention

Relation between coronary microvascular function and left ventricular function

During initial coronary flow measurements, CFR in the IRA was significantly lower compared to the reference vessel (2.03±0.53 vs. 2.7±0.5; p<0.001). The observed decreased CFR in the IRA was the result of an increased baseline and decreased hyperaemic average peak velocity (Table 2).

Table 2. Intracoronary Doppler flow and CMR measurements.

Doppler flow measurements	**Baseline**	**Follow-up**	**Change**	***p*-value**
Heart rate (beats/min)	73.2±10.9	64.3±11.6	-8.9±10.2	<0.001
Systolic BP (mmHg)	111.9±22.1	121.7±20.8	9.8±19.2	<0.001
Diastolic BP (mmHg)	68.2±8.7	70.5±10	2.3±11.5	0.12
Infarct-related artery				
Baseline APV (cm/s)	23.3±9.9	17.2±9.1	-6.1±7.9	<0.001
Hyperemic APV (cm/s)	44.7±15.4	51.7±19.5	7±18.6	0.005
CFR	2.0±0.5	3.2±0.8	1.2±0.8	<0.001
BMRI (mmHg/cm per sec)	4.1±1.5	6.0±2.3	2.0±2.0	<0.001
HMRI (mmHg/cm per sec)	1.9±0.6	1.8±0.6	-0.2±0.7	0.08
Reference vessel				
Baseline APV (cm/s)	19.3±7.0	17.1±6.1	-2.2±7.2	<0.001
Hyperemic APV (cm/s)	50±14.9	54.7±17.6	4.7±20.7	0.08
CFR	2.7±0.6	3.3±0.7	0.6±0.6	<0.001
BMRI (mmHg/cm per sec)	4.8±1.6	5.6±1.9	0.9±2.1	0.002
HMRI (mmHg/cm per sec)	1.7±0.5	1.6±0.5	-0.1±0.5	0.10
Relative CFVR	0.76±0.18	0.99±0.24	0.2±0.3	<0.001
CMR measurements	**Baseline**	**Follow-up**	**Change**	**p-value**
LVEF (%)	42.9±8.7	46.2±8.7	3.3±6.2	<0.001
LVEDV index (ml/m^2)	96.2±14.4	102.3±20.7	6.2±12.3	<0.001
LVESV index (ml/m^2))	55.4±13.5	56.0±18.1	0.6±10.9	0.68
IS (% LV)	22.3±9.8	14.1±6.7	-5.0±3.7	<0.001

For the current analysis, all patient who had intracoronary flow measurements at both baseline and follow-up were included (N=61).
APV: average peak velocity; BMRI: baseline microvascular resistance index; BP: blood pressure; CFR: coronary flow reserve; CMR: cardiac magnetic resonance; HMRI: hyperemic microvascular resistance index; IS: infarct size; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume

CFR in the subacute phase was associated with LVEF at four months (β=4.66, SE=2.10; p=0.03) and at two-year follow-up (β=5.84, SE=2.45; p=0.02) and inversely associated with LVEDV and LVESV index at four months and two years (Table 3). Additionally, CFR in the subacute phase was associated with the changes in LVEDV. HMRI in the subacute phase was not associated with LVF. In a multivariate regression model, CFR was not associated with LVEF at two years (Table 4).

Table 3. Coronary flow reserve and hyperemic resistance index and their association with left ventricular function.

	CFR baseline			HMRI baseline		
Outcome	β	SE	*p*-value	β	SE	*p*-value
Global LVF						
LVEF (%)						
Baseline	6.55	2.01	0.002	-2.12	1.81	0.25
4 months	4.66	2.10	0.03	-2.57	1.8	0.16
2 years	5.84	2.45	0.02	-4.05	2.16	0.07
Δ baseline–4 month	-1.89	1.53	0.22	-1.48	1.20	0.22
Δ baseline–2 years	-1.44	2.19	0.51	-0.36	1.66	0.83
End-diastolic volume index (ml/m^2)						
Baseline	-4.86	3.53	0.17	-0.64	3.01	0.83
4 months	-11.00	4.88	0.03	4.06	4.23	0.34
2 years	-16.66	5.63	0.005	2.80	5.26	0.60
Δ baseline–4 month	-6.14	2.90	0.04	-3.05	2.37	0.20
Δ baseline–2 years	-12.18	3.86	0.003	-2.39	3.17	0.45
End-systolic volume index (ml/m^2)						
Baseline	-8.88	3.16	0.007	1.74	2.81	0.54
4 months	-11.03	4.21	0.01	5.15	3.67	0.17
2 years	-14.16	4.78	0.005	6.39	4.40	0.15
Δ baseline–4 months	-2.14	2.68	0.43	-0.20	2.13	0.93
Δ baseline–2 years	-4.96	3.33	0.14	4.25	2.88	0.15

CFR: coronary flow velocity reserve; HMRI, hyperemic microvascular resistance index; LVEF: left ventricular ejection fraction; LVF: left ventricular function.

Table 4. Multivariate model for the prediction of left ventricular ejection fraction at two years.

	Univariable analysis			Multivariate analysis		
Variable	Coefficient	SE	*p*-value	Coefficient	SE	*p*-value
Age ≥ 65 yrs	4.50	3.58	0.22			
Male gender	-1.40	3.21	0.67			
Max CKMB/ULN	-0.14	0.04	<0.001	-0.10	0.05	0.04
Number of Q-waves	-1.45	0.79	0.07	-0.58	0.80	0.47
Persistent ST-elevation	-3.28	1.50	0.03	-1.37	1.62	0.40
Myocardial blush grade	-0.19	1.15	0.87			
TIMI post PPCI	2.45	4.44	0.58			
CFR baseline IRA	5.84	2.45	0.02	2.05	3.04	0.50

CFR: coronary flow reserve; CKMB, creatine kinase-myocardial band; IRA: infarct related artery; PPCI: primary percutaneous coronary intervention; SE: standard error; TIMI: Thrombolysis in Myocardial Infarction; ULN: upper limit of normal.

Impaired microvascular function and left ventricular function

An impaired coronary microvascular function (CFR <2) in the subacute phase was observed in 36 patients (58%) with a mean CFR of 1.67±0.19. These patients had a larger infarct size than patients with a CFR >2 (25.3±7.7% LV vs. 19.5±11.3% LV; p=0.04).

As shown in Figure 1, patients with a CFR <2 had a lower LVEF at baseline (41.0±8.2% vs. 45.6±8.8%, p=0.04) and at two years (46.1±8.8% vs. 54.3±8.1%, p<0.001). Patients with a CFR <2 experienced a larger increase in LVEDV and LVESV between baseline and two years in comparison to patients with a CFR ≥2, respectively 8.5±15.1 ml/m2 vs. –1.5±13.9 ml/m2 (p=0.02) and 0.71±12.5 ml/m2 vs. –6.7±11.0 ml/m2 (p=0.03).

Change in coronary microvascular function and left ventricular function

Changes in CFR and HMRI were investigated in two groups, stratified to median infarct size (24.2% LV) at baseline. Patients with large infarct sizes (>median infarct size) had a lower CFR at baseline. However, these patients had more improvement in CFR within the initial four months compared to patients with smaller infarct sizes (Table 5). In these patients, absolute CFR improvement was concordantly associated with LVEF improvement within four months (β=5.09, SE=1.86, p=0.01) (Figure 1).

Table 5. Intracoronary flow parameters in two stratified infarct size groups.

	Small IS (n=27)	Large IS (n=28)	*p*-value
Infarct size (% LV)	14.9±6.2	30.4±5.7	<0.001
CFR Infarct-related artery			
Baseline	2.3±0.57	1.8±0.3	<0.001
Δ CFR absolute: Baseline-4 months	1.0±0.97	1.3±0.6	0.26
Δ CFR (%): Baseline-4 months	51.1±50.5	76.9±40.6	0.049
HMRI infarct-related artery			
Baseline	1.9±0.5	2.1±0.7	0.24
Δ HMRI absolute: Baseline-4 months	-0.04±0.6	-0.3±0.7	0.21
Δ HMRI (%): Baseline-4 months	2.6±43.1	-5.7±38.8	0.47

Small and large infarct size groups were stratified according to median infarct size at baseline. * DCFR and DHMRI in IRA were missing in three patients in the large infarct size group. CFR: coronary flow reserve; HMRI hyperaemic microvascular resistance index; IRA: infarct-related artery; IS: infarct size; LV: left ventricle.

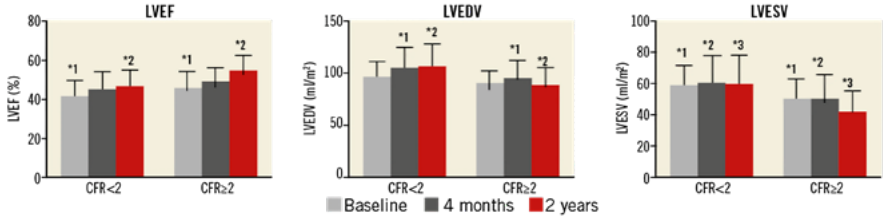

Figure 1. Left ventricular function in patients with initially impaired and normal coronary flow reserve. Bar graph on the left ventricular function parameters in patients with impaired and normal coronary flow reserve at baseline, defined according to the cut-off value CFR <2. The evolution of the left ventricular function parameters over baseline, four months and two years is visualised in both groups. The * indicates a p<0.05 and the number indicates the two matching groups corresponding to the p-value. CFR: coronary flow reserve; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume

In patients with a smaller infarct size, absolute CFR improvement was not associated with LVEF improvement between baseline and four months (β=–0.30, SE=1.24, p=0.81) (Figure 2). When considering HMRI, a trend was observed between the absolute decrease in HMRI within the initial four months and LVEF improvement (β=–3.38, SE=1.67, p=0.054). Similarly, patients with a greater decrease in microvascular resistance (<Δ median HMRI) had a significant improvement of LVEF at four months compared to baseline (42.7±6.9% vs. 37.5±7.9%, p=0.005). In the smaller infarct size group, the effects were not observed.

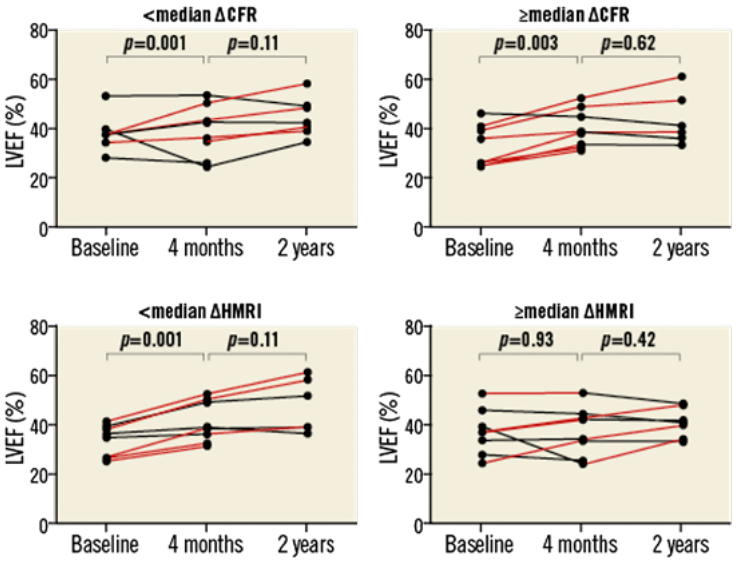

Figure 2. Change in coronary microvascular function and left ventricular function in patients with a large infarct size. Patients with a large baseline infarct size (mean infarct size 33.1±5.5% LV) were subdivided based on the mean CFR and HMRI improvement between baseline and four months. LVEF (%) between baseline and four months was compared. CFR: coronary flow reserve; HMRI: hyperaemic microvascular resistance index

Discussion

In our study, we found supporting evidence on the importance of the microvasculature status following STEMI. Microvascular dysfunction in the subacute phase, as measured with CFR, contrary to HMRI, was associated with LVEF at both four months and two years assessed with CMR. Second, an impaired CFR in the subacute phase was associated with alterations in diastolic volume. Finally, improvement in CFR was concurrently associated with improvement in LVEF between baseline and four months in patients with a large infarct size.

The added value of the current study compared to previous studies stems from the systematically obtained intracoronary Doppler flow measurements and CMR imaging at similar time points and at two years. This provides insights into the recovery of microvascular dysfunction and whether this is associated with LVF recovery. Results of previous studies support the prognostic importance of microvascular function following STEMI. These studies used different diagnostic modalities for the assessment of microvascular function, including myocardial contrast or transthoracic Doppler echocardiography[5,13-15].

Bax et al reported that CFR measured directly after PPCI in anterior STEMI was the only predictor of LV improvement at six months as assessed by echocardiography. However, the mean peak CK-MB was not included in the multivariate model since the aim of the study was to assess early determinants (at the time of reperfusion) of LVF recovery. In the current study, however, CFR in the subacute phase was not independently associated with LVEF at two years but peak CK-MB was independently associated. This observation could be the result of several factors. First, the small number of patients limits the ability to perform a reliable multivariate regression model. Second, CFR measured in the subacute phase is associated with infarct size, as measured by maximum CK-MB[16]. From a pathophysiological perspective, the ability of the coronary microvasculature to vasodilate is related to the severity of the initial myocardial injury. In our study, we also observed that patients with large infarct sizes had a significantly lower CFR. Consequently, it is difficult to determine whether CFR is a marker of larger infarcts or whether impaired microvascular function has a primary role in adverse LV remodeling. Nonetheless, CFR in the subacute phase of STEMI is associated with LVF at both four months and two years. In order

to understand these findings and implications, it is important to understand the differences between both indices. As shown in Table 2, baseline average peak velocity (APV) is probably increased due to compensatory vasodilatation, and the hyperaemic APV decreased probably secondary to microembolization. Since myocardial infarction affects both the baseline and hyperaemic coronary flow, both these effects are taken into account by the CFR, whereas the HMRI does not consider a baseline coronary flow. This observation is in accordance with previous studies. This increase in baseline peak flow velocity has been described as being a result of coronary autoregulation[17,18]. This is of importance as it facilitates the compensatory vasodilatation of the coronary resistance vessels in order to maintain stable resting coronary blood flow in the distal myocardium[19].

We also assessed the temporal evolution of microvascular dysfunction, as measured by the delta CFR and HMRI between baseline and four months. In the large infarct size group, this observed improvement of CFR and decrease in HMRI were both associated with recovery of LVEF. In the smaller infarct size group this association was not observed. Our findings are concordant with the studies by Suryapranata et al[15] and Sezer et al[20], and extend on their findings. In the first study, an increase in flow reserve documented before hospital discharge was associated with a significant improvement in global and regional LVF[15]. In the Suryapranata et al study, improvement in CFR in the total population was associated with a decreased infarct size on single-photon emission computed tomography and improved LVEF on echocardiography.

Dysfunction of the coronary microvasculature has also been associated with the occurrence of clinical endpoints, including heart failure and cardiac mortality[21-23]. Furber at al assessed whether an impaired microvascular perfusion in the IRA, as measured by a short diastolic deceleration time, is predictive of cardiac events within four years[21]. In addition to age and time to PPCI ≥6 hours, impaired microvascular perfusion was found to be an independent predictor, particularly for the occurrence of heart failure. Also, an impaired CFR in the reference vessel in STEMI patients has been independently associated with an increased cardiac mortality at 10 years[23]. These clinical implications of microvascular dysfunction following STEMI have fueled studies on therapeutic strategies aimed at protecting the microvasculature[24].

Limitations

Several limitations should be mentioned. First, intracoronary measurements were performed within one week following STEMI and the CFR may have partly recovered. Subsequently, the association between CFR in the subacute phase and LVF may have been underestimated. Second, a CFR value of 2.0 was arbitrarily chosen because of the median values of CFR in the present study.

Conclusions

Microvascular dysfunction in the subacute phase, as measured by CFR, is associated with LVF at two years in STEMI. Improvement of CFR and a decrease in HMRI within the initial months following STEMI is associated with early LVEF improvement in patients with a large infarct size, underlining the functional significance of the microvasculature after STEMI.

Impact on daily practice

The results of the current study support the growing evidence on the role of the microvasculature status following STEMI and its effect on LVF. We demonstrated that microvascular dysfunction, as measured by CFR, is associated with LV improvement in the long term. This underlines the importance of possible therapeutic strategies aimed at restoring or protecting the microvasculature following STEMI.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Chapter 8

Acute alterations in glucose homeostasis impact coronary microvascular function in patients presenting with ST-segment elevation myocardial infarction

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Neth Heart J (2020) 28:161–170
https://doi.org/10.1007/s12471-020-01366-5

Abstract

Background

Microvascular dysfunction in the setting of ST-segment myocardial infarction (STEMI) is thought to be related to stress-related metabolic changes, including acute glucose intolerance. The aim of this study was to assess the relationship between admission glucose levels and microvascular function in non-diabetic STEMI patients.

Methods

92 consecutive patients with a first anterior-wall STEMI treated with primary percutaneous coronary intervention (PPCI) were enrolled. Blood glucose levels were determined immediately prior to PPCI. After successful PPCI, at 1-week and 6-month follow-up, Doppler flow was measured in culprit and reference coronary arteries to calculate coronary flow velocity reserve (CFVR), baseline (BMR) and hyperaemic (HMR) microvascular resistance.

Results

The median admission glucose was 8.3 (7.2–9.6) mmol/l respectively 149.4 mg/dl [129.6–172.8] and was significantly associated with peak troponin T (standardised beta coefficient [std beta] = 0.281; p = 0.043). Multivariate analysis revealed that increasing glucose levels were significantly associated with a decrease in reference vessel CFVR (std beta = –0.313; p = 0.002), dictated by an increase in rest average peak velocity (APV) (std beta = 0.216; p = 0.033), due to a decreasing BMR (std beta = –0.225; p = 0.038) in the acute setting after PPCI. These associations disappeared at follow-up. These associations were not found for the infarct-related artery.

Conclusion

Elevated admission glucose levels are associated with impaired microvascular function assessed directly after PPCI in first anterior-wall STEMI. This influence of glucose levels is an acute phenomenon and contributes to microvascular dysfunction through alterations in resting flow and baseline microvascular resistance.

What's new?

- Major stress-related metabolic changes occur in the first hours after ST-segment elevation myocardial infarction (STEMI), leading to glucose intolerance in some patients
- Elevated glucose levels and glucose intolerance are associated with an increased risk of mortality, heart failure and cardiogenic shock and no-reflow phenomenon in the culprit vessel
- Elevated admission glucose levels in the setting of STEMI are associated with impaired microvascular function in non-culprit vessels at baseline
- Larger STEMI's with higher Troponin T levels are associated with higher glucose levels, which may be associated with microvascular dysfunction in non-culprit vessels

Introduction

It is well recognised that even after rapid and successful revascularisation of ST-segment elevation myocardial infarction (STEMI), myocardial tissue perfusion remains compromised in 30–40% of patients despite restored epicardial patency.[1,2] This phenomenon is attributed to microvascular dysfunction in the setting of acute STEMI,[3] which is observed in both the perfusion territory of the culprit artery, and in non-ischaemic regions remote from the infarcted myocardial tissue.[4] Whereas culprit vessel flow abnormalities have been ascribed to numerous pathophysiological mechanisms, it has partly been ascribed to metabolic consequences of the acute ischemic event.[5,6]

Major stress-related metabolic changes occur during the early hours of STEMI, which include the release of stress hormones such as noradrenaline and cortisol, increased concentration of free fatty acids, and the occurrence of glucose intolerance.[7] As a result, elevated glucose levels are frequently observed in (non-diabetic) STEMI patients, which have been associated with an increased risk of in-hospital mortality, congestive heart failure and cardiogenic shock in patients with and without diabetes.[8,9] Notably, in patients with STEMI, hyperglycaemia is associated with the no-reflow phenomenon in the culprit vessel, postulated to be a proxy of microvascular dysfunction.[10] It suggests that the acute metabolic changes in STEMI may contribute to microvascular dysfunction in this setting through alterations in glucose homeostasis.

The aim of this study was to assess the relationship between admission glucose levels and microvascular function in non-diabetic patients with first anterior-wall STEMI.

Methods

A total of 100 consecutive patients with a first anterior-wall STEMI treated by primary percutaneous coronary intervention (PPCI) were enrolled. The initial results were reported previously.[4,11] STEMI was defined as chest pain lasting >30 minutes in the presence of persistent ST-segment elevation in ≥2 precordial leads. PPCI was performed within 6 hours after onset of symptoms according

to standard clinical practice. The exclusion criteria were reported previously.[4] The study protocol was approved by the local ethics committee and all patients gave informed consent.

Cardiac catheterisation and periprocedural measurements

After successful reperfusion, intracoronary blood flow velocity was measured in the infarct-related artery (IRA) and an angiographic normal reference vessel (diameter stenosis <30% on visual estimation) using a 0.014-inch sensor equipped guide wire (Volcano Corp., San Diego, CA). Reference vessel measurements were performed in the left circumflex coronary artery, or the right coronary artery if a stenosis of >30% was present. At 1-week and 6-month follow-up, patients underwent repeat angiography with assessment of intracoronary Doppler flow velocity. Hyperaemia was induced by an intracoronary bolus of 20–40 µg adenosine. Before and after PCI, coronary angiography suitable for quantitative coronary angiographic analysis was performed for offline analysis of thrombolysis in myocardial infarction (TIMI) flow and myocardial blush grade. Left ventricular function was evaluated by means of echocardiographic 16-segment Wall Motion Score Index (WMSI) performed immediately before PPCI.

Haemodynamic data analysis

Coronary flow velocity reserve (CFVR) was calculated as the ratio of hyperaemic average peak flow velocity (hAPV) to baseline average peak velocity (bAPV). In the absence of significant epicardial disease in the reference vessels, microvascular resistance was calculated at baseline and during hyperaemia, respectively the ratio between mean aortic pressure and mean distal flow velocity at baseline (baseline microvascular resistance—BMR), and during hyperaemia (hyperaemic microvascular resistance—HMR). The delta microvascular resistance from resting to hyperaemic conditions (dMR) was determined by calculating the absolute difference between BMR and HMR.

Table 1. Baseline clinical and procedural characteristics (n=92)

Demographics	
Age, y	56±12
Male	74 (80)
Risk factors	
Smoking	49 (53)
Hypertension	23(25)
Family history	39 (42)
Hyperlipidemia	24 (26)
Prior medication use	
β-Blocker	12 (13)
Calcium antagonist	8 (9)
Angiotensin-converting enzyme inhibitors	5 (5)
Nitrates	4 (4)
Lipid-lowering drugs	7 (8)
Aspirin	11 (12)
Laboratory assessment at admission	
CRP, mg/L	1.9 (1.1-5.2)
Glucose, mmol/L	8.3 (7.2-9.6)
Creatinine, μmol/l	70 (60-79)
NT-proBNP after reperfusion, pg/mL	93 (49-242)
Peak troponin T after 24 hours, ng/mL	4.58 (2.47-6.34)
Procedural characteristics	
Heart rate, bpm	79±13
Systolic arterial pressure, mm Hg	119±15
WMSI before reperfusion	1.9±0.2
Time to reperfusion, h	2.9 (2.3-3.9)
ST-segment resolution after reperfusion ≥70%	40 (43)
Angiographic	
Final TIMI flow grade 3	56 (60)
Final myocardial blush grade 3	37 (40)

Data are presented as mean ± SD, median (25^{th}-75^{th} percentile), or frequency (%). CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; NT-proBNP: N-terminal pro-brain natriuretic peptide; TIMI: Thrombolysis In Myocardial Infarction; WMSI: Wall Motion Score Index.

Statistical analysis

Normality of the data was tested using the Shapiro-Wilk test, and homogeneity of variance was tested with Levene's test. All continuous variables are presented as mean ± standard deviation or median [25th–75th percentile] according to their normal or non-normal distribution. Categorical variables are presented as counts and percentages. Univariate regression analysis was used to identify variables associated with reference vessel CFVR at the end of the PPCI procedure ($p_{inclusion} < 0.1$), with candidate variables including all

Table 2. Haemodynamic characteristics

Infarct-related artery at admission (n=92)	
Final IRA CFVR	1.5 (1.3-1.7)
Baseline APV, cm per second	19 (14-24)
Hyperaemic APV, cm per second	29 (21-42)
Infarct-related artery at 1 week (n=62)	
Final IRA CFVR	1.9 (1.6-2.2)
Baseline APV, cm per second	21±7
Hyperaemic APV, cm per second	37 (30-44)
Infarct-related artery at 6 months (n=61)	
Final IRA CFVR	2.8±0.9
Baseline APV, cm per second	17±7
Hyperaemic APV, cm per second	48±19
Reference vessel haemodynamics at admission (n=91)	
Reference CFVR	2.3 (2.0-2.7)
Baseline APV, cm per second	16 (14-20)
Hyperemic APV, cm per second	37 (31-45)
Baseline MR, mm Hg/cm per second	7.2 (6.2-8.8)
Hyperemic MR, mm Hg/cm per second	3.1 (2.6-3.8)
Delta MR, mm Hg/cm per second	4.0 (3.3-5.4)
Reference vessel haemodynamics at 1 week (n=62)	
Reference CFVR	2.7±0.5
Baseline APV, cm per second	17 (13-20)
Hyperemic APV, cm per second	44 (35-53)
Baseline MR, mm Hg/cm per second	6.6 (5.4-8.4)
Hyperemic MR, mm Hg/cm per second	2.5 (2.1-3.0)
Delta MR, mm Hg/cm per second	4.2 (3.4-5.4)
Reference vessel haemodynamics at 6 months (n=61)	
Reference CFVR	3.4±0.6
Baseline APV, cm per second	15 (10-21)
Hyperemic APV, cm per second	47 (39-60)
Baseline MR, mm Hg/cm per second	8.9 (6.2-11.3)
Hyperemic MR, mm Hg/cm per second	2.5 (2.0-3.0)
Delta MR, mm Hg/cm per second	6.0 (4.1-8.3)

Values are presented as mean±SD or median (25th–75th percentile). APV: average peak flow velocity; CFVR: coronary flow velocity reserve; IRA: infarct-related artery; MR: microvascular resistance.

baseline, laboratory and procedural covariates as listed in Tabel 1. Subsequent multivariate analysis was performed using a multivariate linear regression model with adjustments for these variables to identify the association of glucose levels with microvascular function parameters, which are presented as standardised coefficients to facilitate comparison. A p-value below the two-sided α-level of 0.05 was considered statistically significant.

Association between admission glucose and microvascular function after PPCI

No association was found between admission glucose levels with $CFVR_{IRA}$, as well as $bAPV_{IRA}$ or $hAPV_{IRA}$ measured directly after revascularisation.

$CFVR_{reference}$ decreased significantly with increasing admission glucose levels (std beta = −0.381; $p < 0.001$). In addition, bAPVreference increased significantly with increasing admission glucose levels (std beta = 0.244; $p = 0.020$), and $BMR_{reference}$ decreased with admission glucose levels (std beta = −0.257; $p = 0.015$). Consequently, $dMR_{reference}$ decreased with increasing admission glucose levels (std beta = −0.325; $p = 0.002$) (Fig. 1). $hAPV_{reference}$ as well as $HMR_{reference}$ did not show a significant association with admission glucose levels.

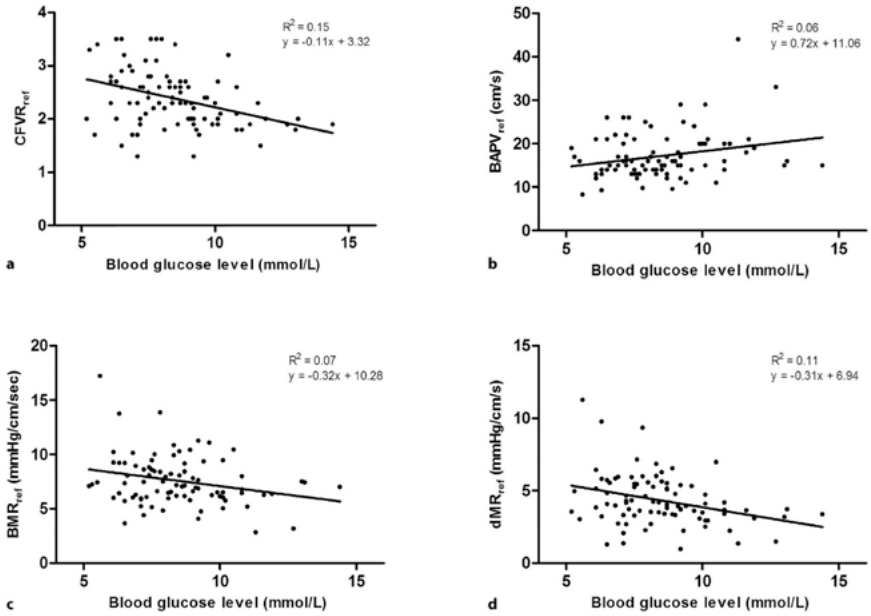

Figure1. Scatterplots of admission glucose levels with microvascular function in the reference vessel after PPCI. Admission glucose levels were significantly associated with coronary flow velocity reserve (a), bAPV (b), BMR (c) and dMR (d) in the reference vessel in the acute setting of STEMI (PPCI primary percutaneous coronary intervention, $CFVR_{ref}$ reference vessel coronary flow velocity reserve, $bAPV_{ref}$ reference vessel baseline averaged peak velocity, BMR_{ref} reference vessel baseline microvascular resistance, dMR_{ref} reference vessel delta microvascular resistance)

Univariate analysis of all candidate baseline, laboratory and procedural covariates as listed in Tab. 1. Age, heart rate, peak troponin T after 24 hours, WMSI assessed before PPCI, and the use of calcium antagonists were associated

with $CFVR_{reference}$. After adjustment for these variables, admission glucose level remained independently associated with CFVRreference (std beta = –0.313; p = 0.002), $bAPV_{reference}$ (std beta = 0.216; p = 0.033), $BMR_{reference}$ (std beta = –0.225; p = 0.038) and $dMR_{reference}$ (std beta = –0.274; p = 0.008) (Tab. 3).

Table 3. Association between reference CFVR and glucose by univariate and multi-variate analysis at admission, 1 week and 6 months follow-up

	At admission (n=92)				At 1-week follow-up (n=61)		At 6-months follow-up (n=61)	
	Univariable Analysis		Multivariable Analysis		Multivariable Analysis		Multivariable Analysis	
	Std Beta	P value	Std Beta	P value	Std Beta	P value	Std Beta	P value
CFVR in reference vessel								
Glucose	-0.381	< 0.001	-0.313	0.002	-	-	-	-
Age	-0.254	0.015	-	-	-	-	-	-
Heart rate	-0.225	0.034	-	-	-0.413	0.002	-	-
Peak troponin T (after 24h)	-0.469	< 0.001	-0.355	0.002	-	-	-	-
WMSI	-0.265	0.014	-	-	-	-	-0.278	0.042
Calcium antagonist	-0.381	< 0.001	-	-	-	-	-	-
Baseline APV in reference vessel								
Glucose	0.244	0.02	0.216	0.033	-	-	-	-
Age	-	-	-	-	-	-	-	-
Heart rate	-	-	-	-	-	-	-	-
Peak troponin T (after 24h)	0.241	0.026	-	-	-	-	-	-
WMSI	0.316	0.003	0.266	0.014	-	-	-	-
Calcium antagonist	0.349	0.001	0.385	< 0.001	-	-	-	-
Baseline MR in reference vessel								
Glucose	-0.257	0.015	-0.225	0.038	-	-	-	-
Age	-	-	-	-	-	-	-	-
Heart rate	-0.262	0.02	-0.229	0.045	-0.269	0.044	-	-
Peak troponin T (after 24h)	-0.228	0.038	-	-	-0.346	0.022	-	-
WMSI	-0.326	0.003	-0.246	0.035	-	-	-	-
Calcium antagonist	-0.295	0.006	-0.292	0.008	-	-	-	-
Delta MR in reference vessel								
Glucose	-0.325	0.002	-0.274	0.008	-	-	-	-
Age	-	-	-	-	-	-	-	-
Heart rate	-0.318	0.004	-0.244	0.023	-0.320	0.015	-	-
Peak troponin T (after 24h)	-0.376	< 0.001	-	-	-0.336	0.022	-	-
WMSI	-0.357	0.001	-0.223	0.041	-	-	-	-
Calcium antagonist	-0.299	0.005	-0.247	0.016	-	-	-	-

Std beta: standardized beta coefficient; CFVR: coronary flow velocity reserve; APV: average peak velocity: MR microvascular resistance; WMSI: Wall Motion Score Index.

Association between admission glucose and microvascular function at 1-week and 6-month follow-up

At one week follow-up, intracoronary physiology measurements in the IRA and reference vessel were repeated in 62 patients (Tab. 2). No significant association was found between admission glucose levels and CFVRIRA, bAPVIRA, as well as hAPVIRA measured at 1-week follow-up.

Univariate analysis revealed that admission glucose was significantly associated with $CFVR_{reference}$ (std beta = −0.284; p = 0.025), $BMR_{reference}$ (std beta = −0.280; p = 0.029), and $dMR_{reference}$ (std beta = −0.295; p = 0.021). However, after adjustment for the identified confounders, none of these variables retained a significant association.

At 6-month follow-up, intracoronary physiology measurements in the IRA and reference vessel were repeated in 61 patients (Tab. 2). Univariate analysis revealed that admission glucose at times of the PPCI was only associated with CFVRreference measured at 6-month follow-up, although this association was eclipsed after adjusting for the identified confounders. Univariate analysis revealed no association between admission glucose levels, BAPV, hAPV and CFVR at 6-month follow-up.

Discussion

We observed that increased admission glucose levels in the acute setting of STEMI are independently associated with alterations in microvascular function, particularly during resting, autoregulated conditions. Increasing glucose levels were associated with progressive impairment of reference vessel CFVR measured directly after PPCI, which resulted from increased bAPV secondary to decreased BMR. At 1-week and 6-month follow-up, the existing associations present in the acute setting disappeared, suggesting recovery of coronary autoregulatory function at normalisation of glucose levels.

It has been reported that age, heart rate and infarct size affect myocardial blood flow by influencing myocardial microvascular function.[12-15] Our results confirm this, and add that blood glucose, likely secondary to acute metabolic

changes in response to the infarction, plays a distinct role in the pan-myocardial microvascular dysfunction observed in the acute setting of first anterior STEMI.

We found no association between microvascular function and admission glucose levels in the IRA. The influence of admission glucose levels on the parameters of microvascular function was likely eclipsed by other physiological processes that alter microvascular function in the IRA during the acute setting of STEMI.

Microvascular function following STEMI: novelty of the present findings

Microvascular function assessed by Doppler flow velocity is known to be altered in the setting of STEMI, even in non-ischaemic regions at distance from the infarcted myocardium.[4] We previously reported that microvascular dysfunction in these regions is expressed in an impairment of reference vessel CFVR, which is independently associated with long-term fatal cardiac events.[11] We showed that the acute impairment of reference vessel CFVR in the setting of STEMI originates from a combination of decreased hAPV in the presence of increased HMR, and increased bAPV in the presence of decreased BMR. It has been hypothesised that a combination of mechanical and metabolic alterations due to the acute ischaemic event is responsible for the overall flow impairment at a distance of the infarcted myocardium. The increase in HMR leading to impairment of hyperaemic flow is generally attributed to neurohumoral overactivation.[5] A reduced BMR leading to an increased resting coronary flow may underlie a mechanical as well as a metabolic origin, which is yet to be elucidated. Our present results attribute at least part of the decrease in BMR, and the resulting increase in basal flow velocity, to metabolic changes in the setting of acute STEMI reflected in hyperglycaemia.

Glucose and insulin mediated microvascular dysfunction

Increased glucose levels are frequently observed in non-diabetic patients presenting with acute myocardial infarction. It reflects the conjoined effects of many interrelated stress mechanisms that influence glucose homeostasis secondary to the acute ischaemic event.[7,16] Relative insulin resistance is proposed as one of the contributing mechanisms, caused by antagonising effects of stress mediators that impair insulin-regulated glucose uptake.[17,18] Concomitantly, insulin plays an important role as a mediator in normal myocardial and systemic

vascular function.[19] It has been demonstrated to increase myocardial blood flow, acting as a slow vasodilator inducing vasodilation in a time and dose dependent manner.[20-22] In patients with coronary artery disease, intracoronary insulin infusion increases coronary blood flow in the absence of an increase in myocardial oxygen demand.[20] The most important physiological mechanism that contributes to insulin-induced vasodilation is the L-arginine to nitric oxide pathway in the vascular endothelium.[23] Despite the effects of insulin resistance on glucose uptake and resulting hyperglycaemia, it has been shown that the insulin-induced coronary vasodilation still occurs in obese patients with insulin resistance.[24] Therefore, the association observed between myocardial microvascular function and admission glucose levels might reflect the effect of elevated plasma levels of insulin, secondary to acute relative insulin resistance, on myocardial vascular function. Unfortunately, plasma insulin levels were not measured in the present study and the proposed mechanism of action should be considered hypothesis-generating.

Concomitant causes of increased baseline flow velocity in STEMI

In addition to the influence of alterations in glucose homeostasis on microvascular function, and in particular bAPV and BMR, other factors may have had a concomitant effect on bAPV. Due to regional myocardial dysfunction, hyperkinesia of remote non-ischaemic myocardium may occur, leading to a predominant increase in bAPV due to an increase in local myocardial oxygen demand.[25,26] In addition, an increase in left ventricular end-diastolic pressure or stiffening of the myocardium because of hypoxic perfusion, may result in a restriction in myocardial capacitance, leading to an isolated increase in reference vessel bAPV.[27,28] Nonetheless, the association between admission glucose levels and the bAPV retained significance after adjusting for the identified confounders, including infarct size WMSI which can be considered important predictors for the magnitude of hyperkinesia, left ventricular end-diastolic pressure and hypoxic perfusion.

Implications for the present study

The present study implies that admission glucose levels are associated with reference vessel microvascular function in the acute setting of STEMI, influencing resting coronary vascular tone and increasing resting flow. Importantly, increased bAPV has previously been documented to be associated

with impaired clinical outcomes in both stable coronary artery disease and STEMI.[11,29] Due to the role of insulin in establishing glucose homeostasis and altering vascular tone, we hypothesise that high insulin levels, secondary to acute insulin resistance, are the mechanism of action responsible for the increase in bAPV. Recovery of this phenomenon at follow-up likely drives recovery of normal coronary autoregulatory function. The fact that larger myocardial infarctions, as determined by troponin T levels, were associated with higher glucose levels, as well as with higher resting flow levels, suggests that the severity of the acute ischaemic event determines the magnitude of metabolic disturbance, and is thereby indirectly related to the magnitude of pan-myocardial microvascular dysfunction.

Limitations

Accurate assessment of flow velocity depends on the operator's experience, and, furthermore, on the achievement of maximal vasodilation. The measurements in this study were performed by experienced operators. The amount of adenosine used in this study is considered sufficient.[30]

We only assessed reference vessel microvascular resistance in coronary arteries without angiographically significant epicardial narrowing using aortic pressure as a substitute for distal pressure.

In this study, glucose levels were only measured at admission and were not repeated at 1-week and 6-month follow-up. This did not allow for exploration of the time course of glucose levels in the period following myocardial infarction. In addition, insulin levels were not determined at any of the time points, resulting in the fact that the hypothesised mechanism could not be further elucidated. Subjects were excluded based on known pre-existing diabetes at the time of admission, however, information on the HbA1C levels was not available to reveal unknown pre-existing impaired glucose homeostasis. Additionally, the study population was relatively small, in particular at 6-month follow-up, and some statistical analyses may lack statistical significance because of a lack of statistical power.

Conclusion

Elevated glucose levels at admission for anterior STEMI are associated with impaired microvascular function in myocardial territories remote from the infarction, as assessed by CFVR in reference coronary arteries measured after PPCI. This influence of glucose levels is an acute phenomenon dominantly affecting coronary autoregulation, affecting BMR and bAPV, and contributes to the pan-myocardial microvascular dysfunction observed in acute STEMI.

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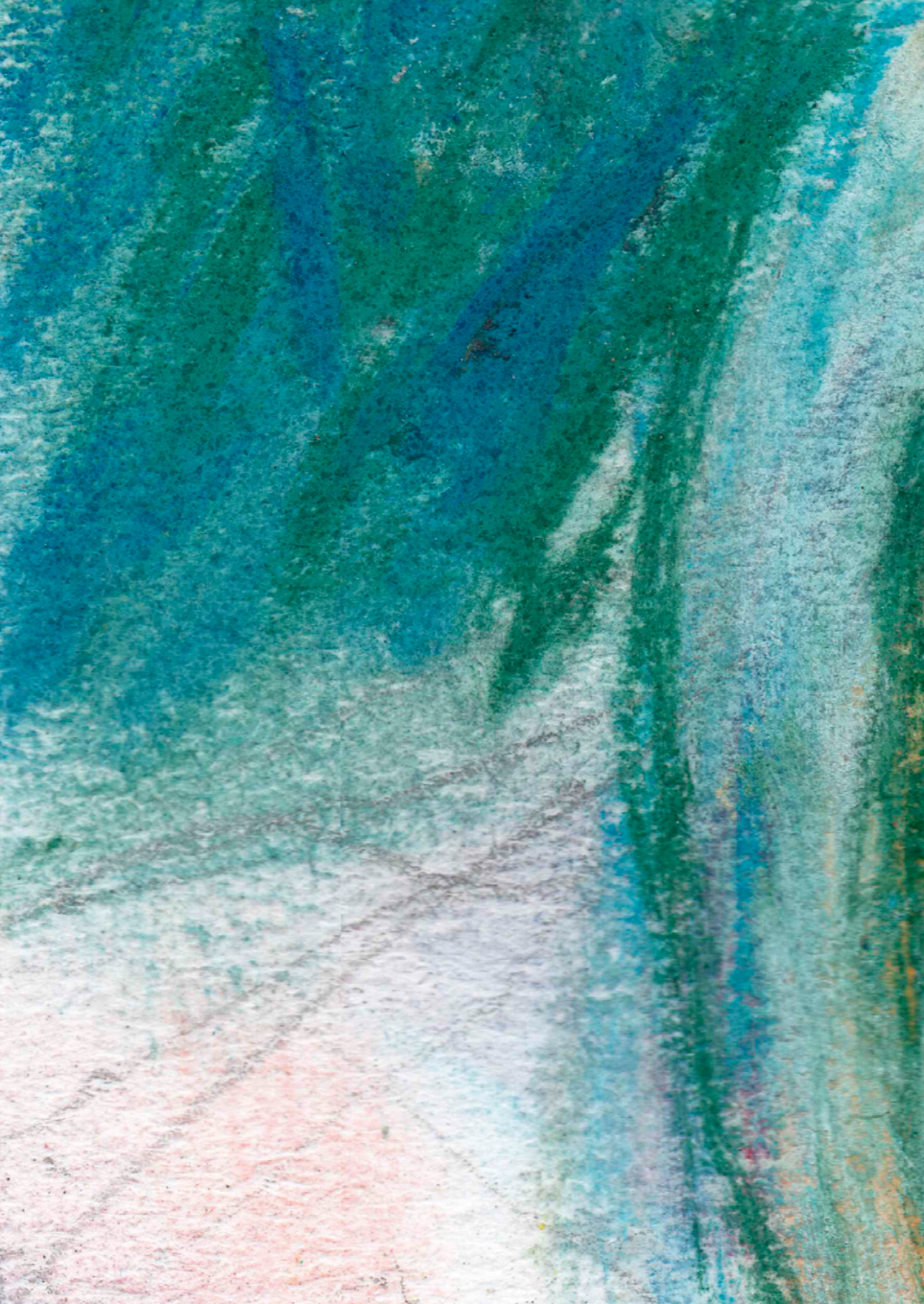

Chapter 9

Time course of coronary flow capacity impairment in ST-segment elevation myocardial infarction

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Eur Heart J Acute Cardiovasc Care. 2020:2048872620918706.
https://doi.org/10.1177/2048872620918706

Abstract

Background

Microvascular dysfunction in the setting of ST-elevated myocardial infarction (STEMI) plays an important role in long-term poor clinical outcome. Coronary flow reserve (CFR) is a well-established physiological parameter to interrogate the coronary microcirculation. Together with hyperaemic average peak flow velocity, CFR constitutes the coronary flow capacity (CFC), a validated risk stratification tool in ischaemic heart disease with significant prognostic value. This mechanistic study aims to elucidate the time course of the microcirculation as reflected by alterations in microcirculatory physiological parameters in the acute phase and during follow-up in STEMI patients.

Methods

We assessed CFR and CFC in the culprit and non-culprit vessel in consecutive STEMI patients at baseline (n = 98) and after one-week (n = 64) and six-month follow-up (n = 65).

Results

A significant trend for culprit CFC in infarct size as determined by peak troponin T ($p = 0.004$), time to reperfusion ($p = 0.038$), the incidence of final Thrombolysis In Myocardial Infarction 3 flow ($p = 0.019$) and systolic retrograde flow ($p = 0.043$) was observed. Non-culprit CFC linear contrast analysis revealed a significant trend in C-reactive protein ($p = 0.027$), peak troponin T ($p < 0.001$) and heart rate ($p = 0.049$). CFC improved both in the culprit and the non-culprit vessel at one-week (both $p < 0.001$) and six-month follow-up ($p = 0.0013$ and $p < 0.001$) compared with baseline.

Conclusion

This study demonstrates the importance of microcirculatory disturbances in the setting of STEMI, which is relevant for the interpretation of intracoronary diagnostic techniques which are influenced by both culprit and non-culprit vascular territories. Assessment of non-culprit vessel CFC in the setting of STEMI might improve risk stratification of these patients following coronary reperfusion of the culprit vessel.

Introduction

Primary percutaneous coronary intervention (PCI) is considered the cornerstone for treating ST-segment elevation myocardial infarction (STEMI), and the implementation of dedicated revascularization networks has resulted in a remarkable decline in cardiac morbidity and mortality.[1] Despite these advancements, a significant proportion of patients have a poor outcome, which is attributed to changes in the microvascular function and integrity due to the ischaemic event.[2] It is increasingly recognized that the impact of the acute ischaemic event on the functional and structural integrity of the microcirculation may yield opportunities to further enhance clinical outcomes in STEMI patients.[3]

Coronary flow reserve (CFR) is a well-validated index that assesses the contribution of obstructive, diffuse and microcirculatory involvement to coronary flow impairment in ischaemic heart disease.[4–6] In the past decades it has been extensively used to elucidate the role of microvascular dysfunction for the prognosis of myocardial infarction. However, assessing the coronary microcirculation solely by means of CFR is inherently cumbersome in STEMI patients, since residual effects of the ischaemic events and changes in (regional) cardiac workload may influence resting or hyperaemic flow and thereby obscure microvascular function assessment by CFR values.[7]

Recently the coronary flow capacity (CFC) concept has been validated as a cross modality platform for the diagnosis, prognosis and risk-stratification in ischaemic heart disease.[7,8] It integrates both the coronary vasodilatory reserve as well as maximal achievable flow, thereby providing comprehensive insight into coronary haemodynamics.[9] Accordingly, CFC was documented to be less prone to alterations in systemic haemodynamics.[10] In the present study we aimed to document the impact of STEMI on CFC in 1) the ischaemic region of the myocardium and 2) in myocardial territories remote from the infarction at baseline, one-week and six-month follow-up.

Methods

Between April 1997 and August 2000, 98 consecutive patients with a first anterior wall STEMI treated by primary PCI were enrolled in the study, for whom the initial results have been reported previously.2,11 All patients were treated in the Amsterdam University Medical Centres – location AMC, a large tertiary referral centre in Amsterdam, The Netherlands.

Anterior STEMI was defined as chest pain lasting >30 min in the presence of persistent ST-segment elevation in ≥2 precordial leads. Primary PCI was performed within 6 h after the onset of symptoms according to standard clinical practice, with provisional bare metal stent implantation. Major exclusion criteria comprised prior anterior wall myocardial infarction, acute left-side heart failure (Killip class >II), prior coronary artery bypass grafting, known left ventricular ejection fraction of <40%, left ventricular hypertrophy, absence of thoracic windows for echocardiography, three-vessel coronary artery disease, Thrombolysis In Myocardial Infarction (TIMI) grade 2 or 3 flow at initial angiography before PCI, or unsuccessful PCI defined as TIMI grade 0 or 1 flow or >50% residual stenosis in the infarct-related artery after PCI. The study protocol was approved by the local ethics committee and all patients gave informed consent.

Cardiac catheterization and periprocedural measurements

Five to 10 minutes after successful reperfusion, intracoronary blood flow velocity was measured in the infarct related artery using a 0.014-inch sensor equipped guide wire (Philips/Volcano, Rancho Cordova, California, USA). Additionally, measurements were performed in an angiographic normal non-culprit coronary artery, defined as a coronary artery with <30% diameter stenosis on visual estimation. Non-culprit vessel measurements were performed in the left circumflex coronary artery, unless a stenosis of >30% was present, in which case the right coronary artery was used. At one-week and six-month follow-up, 64 and 65 respectively patients underwent repeat angiography with assessment of intracoronary Doppler flow velocity, of which the initial results have been reported previously.[2,11] The flow diagram in Figure 1 shows the number of patients included in the analysis at each time frame. Hyperaemia was induced by an intracoronary bolus of adenosine (40 μg). Before and after

PCI, coronary angiography suitable for quantitative coronary angiographic analysis was performed for offline analysis of TIMI flow and myocardial blush grade. Left ventricular function was evaluated by means of echocardiographic 16-segment wall motion score index performed immediately before primary PCI.

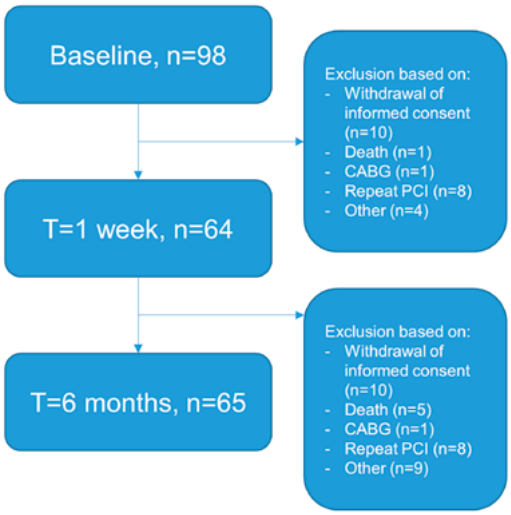

Figure 1. Flow diagram.
CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention.

CFC

From the recorded data, CFR was calculated as the ratio of hyperaemic average peak flow velocity (hAPV) to baseline average peak flow velocity (bAPV). The CFC concept was applied according to that recently derived for invasive coronary flow measurements. Normal CFC was defined as a CFR ≥2.8, with its corresponding hAPV ≥ 49.0 cm/s.[12] Mildly reduced CFC was defined as a CFR < 2.8 but >2.1, and corresponding hAPV < 49.0 and >33.0 cm/s, respectively. Moderately reduced CFC was defined as CFR ≤ 2.1 and >1.7, and the corresponding hAPV ≤33.0 and >26.0 cm/s, respectively.[13] Finally, severely reduced CFC was defined as a CFR ≤ 1.7, and the corresponding hAPV ≤26.0 cm/s.[5]

Haemodynamic data analysis

Microvascular resistance was calculated at baseline and during hyperaemia, respectively the ratio between mean aortic pressure and mean distal flow

velocity at baseline (BMR), and during hyperaemia (HMR), in the culprit and in the absence of significant epicardial disease in the non-culprit vessel. The delta microvascular resistance from resting to hyperaemic conditions (dMR) was determined by calculating the absolute difference between BMR and HMR.

Statistical analysis

Normality of the data was tested using the Shapiro–Wilk test, and homogeneity of variance was tested with Levene's test. All continuous variables are presented as mean ± standard deviation or median (25th to 75th percentile) according to their normal or non-normal distribution. Categorical variables are presented as counts and percentages. Analyses of linear trends across CFC categories were performed with polynomial contrasts.

Improvement of CFC in the culprit and non-culprit vessel between baseline, one week and six months was assessed by a Kruskal–Wallis test with pairwise post hoc correction for multiple comparisons. A p-value < 0.05 was considered statistically significant.

The STATA version 13.1 (StataCorp, College Station, Texas, USA) software package was used to perform statistical analyses.

Results

In total, 98 patients were included in the study at baseline, for which the baseline characteristics are listed in Table 1. The mean age of this cohort was 56 ± 12 years, and 81% were male. Repeat coronary angiography and intracoronary measurements at one-week and six-month follow-up have been performed in a total of 64 and 65 patients respectively.

Relationship of CFC with procedural characteristics

Across CFC groups determined in the culprit vessel directly after primary PCI, linear contrast analysis revealed a significant trend in infarct size as determined by peak troponin T ($p = 0.004$), time to reperfusion ($p = 0.038$), the incidence of respectively final TIMI 3 flow ($p = 0.019$) and systolic retrograde flow ($p = 0.043$) (Supplemental file 1 online). For CFC determined for the non-culprit vessel linear contrast analysis revealed a significant trend in C-reactive protein

(p = 0.027), peak troponin T (p < 0.001) and heart rate (p = 0.049) across the different groups of CFC (Supplementary file 2).

Table 1. Baseline characteristics.

Demographics	
n	98
Age, y	56±12
Male	80 (81)
Risk factors	
Smoking	52 (53)
Hypertension	24 (24)
Family history	40 (40)
Hyperlipidemia	26 (26)
Diabetes mellitus	6 (6)
Prior medication use	
β-Blocker	13 (13)
Calcium antagonist	8 (8)
Angiotensin-converting enzyme inhibitors	5 (5)
Nitrates	4 (4)
Lipid-lowering drugs	8 (8)
Aspirin	11 (11)

Data are presented as mean ± SD or frequency (%).

Time course of culprit vessel CFC

Figure 2(a) to (c) shows the scatterplots of the time course of CFC in the culprit vessel. At this stage of the procedure, 10% of the patients showed a normal CFC, 29% a mildly reduced CFC, 19% a moderately reduced CFC and 42% a severely reduced CFC (Supplementary file 3). A significant linear trend across CFC groups was observed for CFR, bAPV, hAPV, BMR, HMR and dMR (p < 0.001 for all measurements except for dMR, p = 0.002).

At one-week follow-up, measurements in the culprit artery were obtained in 64 patients. In 28% of patients a normal CFC was found, in 44% a mildly reduced CFC, in 19% a moderately reduced and in 9% a severely reduced CFC. A significant linear trend across CFC groups was observed for CFR, bAPV and hAPV (p = 0.004, p < 0.001 and p < 0.001, respectively), but not for BMR (p = 0.183), HMR (p = 0.163) and dMR (p = 0.279). At six-month follow-up measurements in the culprit artery were obtained in 65 patients. In 69% of patients a normal CFC was found, in 20% a mildly reduced CFC, in 6% a moderately reduced and in 5% a severely reduced CFC (Supplementary file 3). A significant linear trend across CFC groups was observed for CFR, bAPV (p < 0.001), hAPV (p < 0.001), HMR (p < 0.001) and dMR (p = 0.02), but not for BMR (p = 0.142).

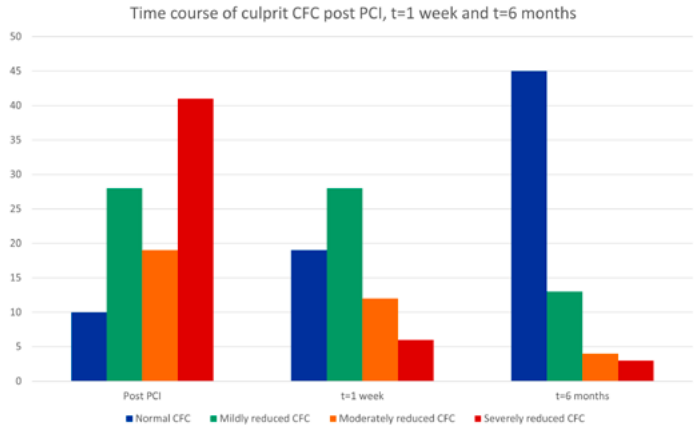

Figure 2. Scatterplot of the time course of coronary flow capacity (CFC) in the culprit vessel ((a), (b) and (c)) and non-culprit vessel ((d), (e) and (f)) after primary percutaneous coronary intervention, at one-week follow-up and six-month follow-up. The rectangles represent CFC categories; blue: normal CFC; green: mildly reduced CFC; orange: moderately reduced CFC; red: severely reduced CFC.

CFVR: coronary flow velocity reserve; hAPV: hyperaemic average peak flow velocity; PPCI: primary percutaneous coronary intervention.

Time course of non-culprit vessel CFC

Figure 2(d) to (f) shows the scatterplots of the time course of CFC in the non-culprit vessel. At the index procedure, CFC was also determined post PCI in a non-culprit vessel derived from measurements obtained in 97 patients with angiographically normal coronary arteries (<30% diameter stenosis): the left circumflex coronary artery was assessed in 87 patients (90%) and the right coronary artery in 10 patients (10%) (Supplementary file 4). CFC in the non-culprit vessel was normal in 27%, mildly reduced in 45%, moderately reduced in 25% and severely reduced in 3% of patients. A significant linear trend was observed for CFR and hAPV ($p<0.001$ and $p<0.001$), but not for bAPV ($p=0.160$). In addition, linear trend analysis of microvascular resistance parameters revealed a significant trend in HMR as well as in dMR ($p<0.001$ and $p<0.001$), but not in BMR ($p=0.428$).

At one-week follow-up, CFC was derived from measurements obtained in 64 patients: the left circumflex coronary artery was assessed in 60 patients (94%), and the right coronary artery in four patients (6%). One week after acute myocardial infarction (AMI), CFC in the non-culprit vessel was normal in 45%, mildly reduced in 52%, and moderately reduced in 3% of patients. A

statistically significant difference between normal and mildly reduced CFC was observed for CFR ($p < 0.001$) and hAPV ($p < 0.001$), but not for bAPV ($p = 0.077$). At six-month follow-up, non-culprit vessel measurements were obtained in the same non-culprit vessel as during one-week follow-up: in 65 patients. Six months after AMI, CFC in the non-culprit vessel was normal in 92% and mildly reduced in 8% of patients. A statistically significant difference between normal and mildly reduced CFC was observed for CFR ($p = 0.003$), hAPV ($p = 0.003$) and HMR ($p < 0.001$).

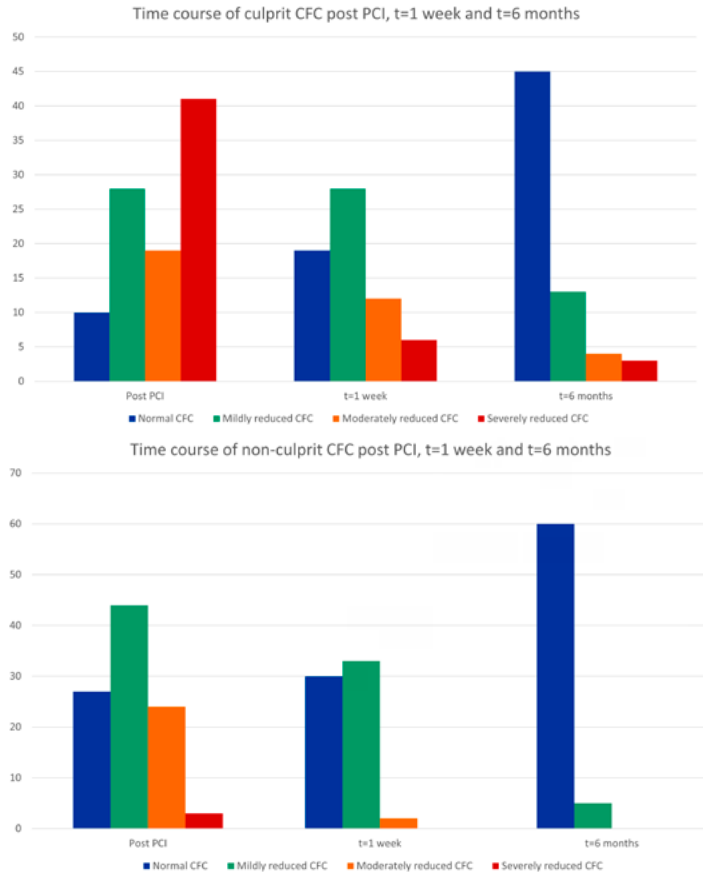

Figure 3. Time course of coronary flow capacity (CFC) in the culprit **(a)** and the non-culprit vessel **(b)** post primary percutaneous coronary intervention (PCI), at one-week and at six-month follow-up. In the culprit vessel, CFC improved significantly post PCI compared with one-week and six-month follow-up ($p < 0.001$) and one-week compared with six-month follow-up ($p = 0.0013$). In the non-culprit vessel, CFC improved post PCI compared with one-week and six-month follow-up, and one-week compared with six-month follow-up (all $p < 0.001$).

CFC improved significantly both in the culprit and the non-culprit vessel, when compared at baseline post PCI with one-week follow-up ($p = 0.036$ and $p < 0.001$), and one-week follow-up compared with six-month follow-up ($p = 0.0013$ and $p < 0.001$) (Figure 3; Supplementary file 5).

Discussion

The present study is one of the first to document the impact of STEMI on myocardial perfusion using the validated CFC framework to comprehensively assess the consequences of focal obstructive, diffuse and microcirculatory causes of myocardial blood flow impairment. We have previously reported that microvascular function assessed by Doppler flow velocity is altered in the setting of STEMI, even in non-ischaemic regions at distance from the infarcted myocardial tissue and the independent association with long-term fatal cardiac events.

We observed a trend in infarct size for both the culprit vessel post PCI as well as the non-culprit vessel across CFC groups. In addition, an increase in time to reperfusion was associated with worsening of CFC determined after primary PCI in the both the culprit and the non-culprit vessel. CFC at the different time points resulted from an alternating contribution of the individual components that determine CFC group allocation; CFR, hAPV and bAPV. Of note, bAPV showed a significant trend across culprit vessel CFC groups after primary PCI and at one-week and six-month follow-up, but did not differ between groups in the non-culprit vessel.

CFC in the acute setting

First derived from positron emission tomography, the CFC concept integrates CFR with maximal hyperaemic flow velocity.[7,9,14] It thereby captures all components of coronary flow physiology and provides a comprehensive tool to depict myocardial blood flow impairment due to a combination of obstructive, diffuse and microcirculatory involvement of the coronary vasculature. Hence, in the absence of epicardial disease the CFC concept provides insights into the microvascular function. In addition, it has been shown to provide an improvement in risk discrimination for adverse clinical outcomes compared with CFR alone.[9]

This concept is of particular interest when assessing microvascular function in the acute setting of STEMI, where mechanical and neurohumoral factors can have an effect on both resting and hyperaemic coronary flow,[11] resulting in prolonged activation of the sympathetic nervous system,[15,16] subsequently inducing a vasoconstrictive response of the coronary resistance vessels by

upregulated catecholamines.[3] The current study utilized the CFC concept to document the time course of microvascular function in the setting of STEMI in both the culprit and the non-culprit arteries.

It also revealed that despite restored epicardial patency of the culprit, a substantial number of patients remained having a severely reduced CFC, which improved over time. As previously documented for CFR, we also observed an impaired CFC in the non-culprit artery remote from the ischaemic region. However, compared with the culprit vessel, CFC in the non-culprit vessel was less impaired in the acute setting and improved more rapidly over time.

Previous studies on microvascular function in STEMI

Myocardial tissue perfusion remains compromised in 30–40% of STEMI patients despite rapid and successful mechanical revascularization.[17,18] Whereas culprit vessel flow abnormalities have been ascribed to numerous pathophysiological mechanisms, including reperfusion injury, distal embolization of plaque and thrombus material, endothelial dysfunction, leucocyte plugging and external compression of the microvasculature, the pan-myocardial nature of microvascular dysfunction is less well-understood, but has partly been ascribed to metabolic consequences of STEMI.[3,19] Microvascular dysfunction in the infarct related artery as well as remote regions from the infarct related myocardium observed after primary PCI are associated with a significantly increased long-term clinical outcome and mortality.[11,20–23] In addition, CFR obtained directly after primary PCI is an independent predictor of long term global as well as regional recovery of left ventricular function.[24,25] However, microvascular dysfunction in the setting of STEMI is often disclosed as a decrease in hyperaemic flow and increase in resting flow. The ratio of these, that is, the coronary flow reserve, does not provide insights into the relative contribution of both components.

Clinical implication

Risk stratification in the setting of AMI has long remained to be elucidated, and recent findings of large clinical trials have led to a revived interest in the approach to STEMI patients with multivessel disease. Revascularization of multivessel

disease in STEMI patients roughly has three different approaches: angiography, optical coherence tomography (OCT) and invasive coronary physiology assessment. The COMPLETE (Complete vs Culprit-only Revascularization to Treat Multi-vessel Disease After Early PCI for STEMI) trial suggests complete revascularization in STEMI patients with multivessel disease based on angiography, independent of infarct size.[26] A sub study of the COMPLETE trial and several other studies suggest OCT assessment of obstructive non-culprit lesions containing complex vulnerable plaque morphology and subsequent treatment of these lesions.[27–29] Coronary physiology assessment by using Fractional Flow Reserve (FFR) in STEMI patients with multivessel disease has been evaluated in several trials, and showed a decrease in major adverse cardiac events for FFR-guided PCI of the non-culprit; however, this effect is mainly driven by the complete revascularization at baseline and subsequent prevention of inevitable revascularization at a later stadium.[30,31] Additionally, non-culprit instantaneous wave-free ratio (iFR) has been assessed in the iSTEMI trial, during the acute ischaemic event and ≥16 days post-STEMI. iFR was significantly lower during the acute ischaemic event compared with follow-up, potentially due to a higher baseline flow in the setting of STEMI, resulting in a potential overtreatment of these lesions compared with FFR.[32] The ongoing trials iModern (iFR Guided Multi-vessel Revascularization During Percutaneous Coronary Intervention for Acute Myocardial Infarction, NCT03298659) and FRAME-AMI (FFR Versus Angiography-Guided Strategy for Management of AMI With Multivessel Disease, NCT02715518) both evaluate non-culprit lesions with iFR and/or FFR in the setting of AMI. However, certainly FFR, and potentially to a lesser extent iFR, are affected by the coronary microcirculation and microvascular resistance in particular, so these indices have to be interpreted cautiously if these are assessed in the setting of STEMI.[33,34] On the contrary, non-culprit vessel CFR has important prognostic value as reflected by a 4.09-fold increase in long-term cardiac mortality if non-culprit vessel CFR <2.0 in STEMI patients with multivessel disease.[11] Non-culprit vessel CFC assessment post primary PCI of the culprit has a significant benefit to determine long term prognosis and clinical outcome. Hence, patients with lower CFC in the non-culprit vessel after primary PCI of the culprit in the setting of STEMI require more intensive treatment and monitoring.

Limitations

There has been an extensive debate on the amount of adenosine needed to achieve a maximally vasodilated state. More recently, the dose–response relationship of intracoronary hyperaemia has been investigated, and no significant differences in FFR-values between low and high dose intracoronary adenosine were documented.[35] In this study we used an intracoronary bolus of 40 µg adenosine, which induced a sufficient state of hyperaemie to allow accurate assessment of coronary flow characteristics.

The acquisition of coronary flow velocity was performed by a sensor-equipped guidewire that assessed only coronary flow. We assessed only non-culprit vessel haemodynamics in coronary arteries without significant epicardial narrowing and assumed distal pressure to equal aortic pressure. Therefore, a potential role of subclinical atherosclerosis of the conduit artery in the absence of focal narrowing in the impairment of non-culprit vessel flow and pressure cannot be excluded. However, resting coronary flow is unlikely to be disturbed by coronary stenoses up to 85% of the vessel diameter, without interference of compensatory vasodilation of the distal vascular bed.[36]

Conclusion

These observations underline the impact of the coronary microcirculation both in the culprit and non-culprit vessel in the setting of STEMI on intracoronary diagnostic techniques. The coronary microcirculation recovers over time at six-month follow-up, as shown by an improvement in CFC. Both culprit and non-culprit vessel CFC assessment in the setting of STEMI might provide valuable insight into the recovery of the coronary circulation, emphasizing the importance of intracoronary physiology assessment following primary PCI in AMI.

Conflict of interest

The authors have no conflicts of interest to declare.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported in part by the European Community's Seventh Framework Program (FP7/2007–2013) under grant agreement no. 224495 (euHeart project), and by a grant from the Dutch Heart Foundation (2006B186).

Supplemental material

Supplemental material for this article is available online. https://journals.sagepub.com/doi/suppl/10.1177/2048872620918706/suppl_file/sj-pdf-1-acc-10.1177_2048872620918706.pdf

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Chapter 10

General discussion and future perspectives

Coronary flow unequivocally plays a dominant role in cardiac function, and thus, routine coronary flow or flow velocity assessment is a prerequisite for our insight into the hemodynamics of coronary syndromes. Although the development of coronary flow velocity techniques stagnated over the past years, recent research in the field of coronary flow velocity and flow velocity reserve led to a novel understanding of the macro and microcirculatory involvement in ischemic heart disease,[1, 2] and has reinvigorated interest in coronary flow (velocity) technology.

Over the years, knowledge about the abnormal values of the baseline and hyperemic blood flow velocity in non-IRA following a heart attack has become of paramount importance.

Recently, studies have been conducted in which STEMI patients treated with PPCI underwent additional PCI of their non-culprit multivessel lesions remote of the infarcted area. The question if multivessel PCI is indicated at the time of myocardial infarction is of clinical relevance since multivessel disease exists in half of the patients admitted with STEMI. Studies comparing culprit vessel-only with multivessel PCI have reported conflicting results[3-11] Previous clinical practice guidelines recommended culprit-only strategy PCI in STEMI patients. In 2015 however, the prior Class III (harm) recommendation was upgraded to a Class IIb recommendation (level of evidence B-R) to consider multivessel PCI in stable STEMI patients, either at the time of PPCI or as a planned, staged procedure.[12] Interestingly, the most recent, randomized studies demonstrate the benefit of multi-vessel PCI treatment at the time of PPCI as well as a staged procedure.

Since it is known that the angiographic severity of the stenosis does not indicate its functional significance in patients with stable coronary artery disease, it is conceivable that physiological measurements of non-culprit lesions may be used to determine the need for adjunctive or preventive PCI in the context of a STEMI. Determining the severity of the non-culprit stenosis was done by FFR measurement in several studies.[8, 10, 11] In the recently published COMPLETE study, comparing complete revascularization during or after the index hospitalization versus conservative medical treatment, the randomization was done after eyeballing of the severity of the non-culprit lesions. If the lesion severity was 50-

70% an FFR less than 0.80 was necessary to enter randomization. Remarkably, FFR was done in less than 1% of the included patients.[11, 13]

In the DANAMI-3 – PRIMULTI study patients with multivessel disease at the time of PPCI were randomized to either FFR-guided complete revascularization or no further invasive treatment.[8] FFR guided revascularization was performed two days after PPCI. Only two third of the patients who on eyeballing of the severity of the non-culprit lesions entered the study, had an FFR below the discrimination value of 0.80. The primary endpoint driven by less revascularizations occurred in favor of the complete revascularization group.

The COMPARE-ACUTE study was an FFR-guided complete revascularization study in STEMI patients with multivessel disease.[10] FFR of the non-IRA stenosis at the time of PPCI was mandatory for inclusion of the study. This study showed a reduction of the primary endpoint, again driven by a reduction of subsequent revascularizations in patients in the complete-revascularization group.

The question arises whether FFR measurements can be used to evaluate remote coronary arteries in the context of STEMI. Adequate interrogation of the non-IRA with FFR measurement depends on obtaining maximum hyperemic blood flow velocity as dictated by the definition. Alteration of the blood flow velocity in the non-IRA, basically a reduction of the coronary flow reserve as shown by Uren,[14] or more specifically a reduction of hyperemic blood flow as a result of an increased hyperemic microvascular resistance will erroneously increase the FFR value. The consequence might be that a significantly stenosed non-IRA will not be revascularized. It is unclear after what time window following STEMI FFR measurement will result in a veracious outcome on which reliable decisions can be based. The incorrect increase of FFR value might be less pronounced in case of smaller myocardial infarctions due to less disturbed microvascular function, less increased hyperemic resistance, and thus hyperemic blood flow that can approach normal values.

To avoid erroneous decision making based on altered hyperemic blood flow values, iFR measurement could be considered due to the non-hyperemic nature of this measurement. However, the baseline blood flow(velocity) in a non-culprit vessel is changed during STEMI either. Increased baseline flow in the

non-infarct arteries affects iFR measurement. Choi et al. stated that changes in FFR and iFR for the non-culprit stenosis of myocardial infarction patients were not significantly different from those in patients with stable ischemic heart disease.[15] De Waard et al. clarified in his editorial why this conclusion could be drawn.[16]

Two third of the analyzed patients were suffering a non-ST-segment elevation myocardial infarction (with other effects on microvascular resistance than with STEMI, partly due to the absence of deleterious effects of reperfusion), only 39% had an anterior wall infarction and both the CK-MB peak levels and the post-infarction left ventricular ejection fraction indicated small infarctions. Small infarctions will have little influence on coronary hemodynamic status whereas the coronary hemodynamic status might be disturbed after large STEMI and reperfusion effects with extensive microcirculatory dysfunction in both the culprit and the non-culprit areas.

The iSTEMI study evaluated with iFR the non-culprit stenoses during PPCI and after a median of 16 days.[17] Acute iFR was 0.89 and follow-up iFR increased to 0.91. With follow-up iFR as a reference, acute iFR had a positive predictive value of 68%, and a negative predictive value of 89%. Using follow-up FFR ≤0.80 as a reference, it was 67% and 77% respectively. The potential risk to overtreatment of non-culprit lesions in the PPCI-setting is shown clearly.

The results of the ongoing iModern study, comparing iFR-guided complete revascularization with staged complete revascularization based on CMR-proved ischemia evaluated 6 weeks after STEMI (https://clinicaltrials.gov/ct2/show/NCT03298659) and the FRAME-AMI study, comparing FFR-guided complete revascularization at the time of PPCI with angiography-only strategy (https://clinicaltrials.gov/ct2/show/NCT02715518), will have to answer the question if acute iFR or FFR measurement can be used for decision making in the treatment strategy for non-infarct artery lesions at the time of STEMI as well as the timing of PCI for non-culprit lesions. On theoretical grounds, it is conceivable that decision-making at the time of PPCI is only possible if it concerns limited infarct sizes in true STEMI patients where the microvascular characteristics of the remote areas are not disturbed by the STEMI itself. Currently, it is not known from what infarct size affects microvascular resistance making iFR and FFR in non-culprit vessels not reliable for decision making. Also, the size of the area subtended by the non-IRA vessel plays a role. Smaller areas need a tighter

lesion to be physiological significant. The six-week interval for the detection of ischemia by CMR may be relevant, since the baseline and hyperemic blood flow will be less disturbed than in the acute phase of myocardial infarction, including remote areas. The time window might be shorter since CFC in non-IRA was near normal at 1-week post STEMI in our recent studies.

The results of the studies presented in this thesis indicate that one has to be careful with the interpretation of physiological measurements in non-culprit vessels during the acute phase of myocardial infarction. For the time being, the results of the COMPLETE trial are in favor of a staged procedure for non-culprit lesions in the weeks after AMI. At that time, the microcirculatory disturbances induced by AMI have been partly or completely resolved allowing to use physiological diagnostic techniques for the right decision making and avoiding unnecessary interventions.

Furthermore, extensive research into the long-term predictive value of impaired microvascular function in non-IRA at the time of STEMI is needed, as well as into the intervention options to improve microvascular function.

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Chapter 11

Summary

Samenvatting

Introduction

The purpose of this thesis was to evaluate coronary microvascular function during and after reperfusion of an anterior ST-elevation myocardial infarction using coronary blood flow velocity characteristics. In addition, we wanted to investigate the association of the post-reperfusion microcirculatory function to left ventricular function recovery and long-term mortality.

Coronary microvascular integrity determines the effectiveness of the function of the myocardium. At the time of myocardial infarction, microvascular function in the area subtended by the infarct-related artery (IRA) is abnormal. It was unclear how fast and to what extent microvascular function will recover after reperfusion therapy. Microvascular dysfunction in the non-infarct-related arteries (non-IRA) was a virtually unknown area at the time that the studies described in this thesis were performed.

The microvascular function cannot be directly visualized with standard techniques in the catheterization laboratory. The measurement methods developed so far are still in their infancy due to difficult or time-consuming use in daily clinical practice and interpretation requires consideration of potentially confounding coronary and patient-related disorders. In addition, the understanding of the coronary microvasculature is not facilitated by the use of numerous abbreviations of indices to estimate the hemodynamics of the coronary microcirculation.

Chapter 1 briefly provides the development of ST-elevation myocardial infarction (STEMI) with the potential consequences of impaired left ventricular function and cardiac death. Although the current treatment consists of timely mechanical reperfusion in addition to medical therapy, the effects of this reperfusion are not only favorable for the microvascular integrity know as reperfusion injury that partly determines the ultimate outcome of the treatment of the myocardial infarction. Many experimental and clinical studies of complementary therapies intended to prevent, or limit reperfusion injury did not reveal promising results. In order to further improve the outcomes of myocardial infarction treatment, more in-depth knowledge is needed about the mechanisms that play a role in the microvascular recovery phase

after reperfusion. Microvascular status and function are important predictors of event-free survival but are not readily visible and available at the time of reperfusion.

A brief description is provided on coronary blood flow regulation and microvascular function and how these factors are influenced by local (patho) physiological conditions.

Since it was unclear at the end of the last century when and to what extent microvascular integrity would restore after reperfusion of the infarcted artery, we designed the study described in **chapter 2**. It was for the first time possible to measure the blood flow velocity in the coronary artery using a Doppler crystal mounted on a coronary guidewire. In Japan, the first studies had been performed that showed various abnormal Doppler flow velocity patterns in the setting of acute myocardial infarction (AMI) to describe microvascular dysfunction. Kern et al. demonstrated that using the Doppler technique, the coronary flow velocity reserve (CFVR or CFR) was a more relevant derivative measure of myocardial blood flow than the TIMI flow and TIMI frame-count, to determine the result of reperfusion.

The study in **chapter 2** describes the prospective evaluation of 100 patients with an anterior myocardial infarction in single vessel disease, who were treated with primary PCI (PPCI). Immediately after reperfusion, Doppler flow parameters were assessed including baseline flow velocity, adenosine-stimulated maximum blood flow velocity, calculated CFR, microvascular resistance at rest and during hyperemia in both the infarct and non-infarct related artery (IRA and non-IRA). Doppler measurements were repeated, for the first time, at 1 week and 6 months after myocardial infarction. Echocardiograms were made before reperfusion, at 24 hours after the infarction as well as after 1 week and 6 months of follow-up to relate microvascular function to left ventricular recovery. In the 73 patients eligible for follow-up and without restenosis in the previously treated vessel, the Doppler flow determined CFR appeared to be the only independent 6-month predictor of global and regional restoration of LV function and thus a better prognostic marker than the usual measurements such as TIMI flow and TIMI frame count.

The same cohort of patients was used to study the course of the coronary (including microvascular) hemodynamics after the first anterior wall infarct and thus indirectly the autoregulation in both the IRA and the non-IRA. In **chapter 3** it is described that the microvascular function, determined by the microvascular resistance, improves in both territories over time after the acute infarct. As a result, the rate-pressure corrected baseline flow rate decreases slightly and the hyperemic flow rate increases significantly. The adjusted baseline microvascular resistance in the infarct vessel, decreased in the acute phase, increased by approximately 28% in 6 months of follow-up. The same development (an increase of approximately 31%) was documented in the non-IRA. Hyperemic (or minimal) microvascular resistance in the acute phase of myocardial infarction is higher than usual in both the IRA and non-IRA and declines rapidly in both areas in the first week after AMI. In non-IRA this value drops to normal in the first week, in IRA it takes longer, and recovery is complete at 6 months. The minimum resistance in the infarct area decreases by approximately 44% and in the non-IRA area by 18%. This study provides a time perspective for the restoration of microvascular function for both the infarct area and the distant areas.

Chapter 4 reviews briefly how the Doppler-tipped guidewire functions and how it can be used in the setting of PPCI, for example. The value of the various parameters, obtained in the setting of acute infarct angioplasty, are described such as coronary flow velocity reserve (CFR), diastolic deceleration time (DDT), systolic flow velocity reversal and is put into perspective with myocardial contrast echocardiography (MCE) and cardiac magnetic resonance imaging (CMR). In the setting of PPCI, the Doppler wire technique can be easily applied to assess microvascular obstruction and dysfunction and yields information to predict recovery of the left ventricular function following anterior wall infarction.

We showed that in the acute phase of the anterior wall infarct the microcirculation in remote areas was also disturbed. It was unknown whether this altered microcirculation in non-obstructive regions yields prognostic information. **Chapter 5** describes the mortality after 10 years in the patients from the cohort discussed earlier. For this analysis, the patient cohort was divided into post-procedural CFR values in the non-IRA below or above 2.1. We

found that an abnormal remote CFR value was associated with a 4.09 increase in 10-year cardiac mortality hazard. This predictive value of measurements in the non-IRA during PPCI had not been previously described. The impaired CFR in the non-IRA was due to an increased hyperemic microvascular resistance (and thus decreased hyperemic blood flow rate) in combination with a slightly decreased baseline microvascular resistance.

Permanently disturbed CFR values in the non-IRA 6 months post-myocardial infarction, based on low baseline microvascular resistance (and therefore high baseline flow rate), associated with a 10.7-fold increase in the risk of cardiac mortality. The size of myocardial infarction as measured by the wall motion score index obtained at 6 months of follow-up was not related to an increase in long-term cardiac mortality risk.

Notable, low CFR, the presence of systolic flow reversal, or short diastolic deceleration time in the IRA did not identify patients at high risk for long-term cardiac death. CFR in the IRA was associated with an increased risk of early cardiac mortality but not long-term mortality.

Chapter 6 is the only chapter in this thesis that investigates cardiac microcirculation in patients outside the setting of an AMI. It demonstrates the relevance of knowledge of microcirculatory function in obstructive coronary artery disease for risk stratification. In these patients, CFR assessments were performed with a Doppler FloWire in reference coronary arteries without significant stenosis. In 77 out of 178 patients, the CFR value was abnormally low (below 2.7) in the reference arteries, mainly due to a higher baseline blood flow velocity (lower baseline microvascular resistance), while no significant impaired hyperemic flow velocity or resistance was measured, indicating autoregulatory disturbances throughout the heart. After multivariate adjustment, these patients had a significantly increased hazard ratio of 3.3 for cardiac death. This underlines the fact that microvascular disease in stable coronary artery disease is an important factor for risk stratification and, hence, treatment strategies. In conjunction with the results in chapter 5, this CFR yields prognostic information in both stable and unstable coronary syndromes.

Since reduction of baseline microvascular resistance, not increase of hyperemic resistance, is the main driver of the lower CFR it is suggestive that impaired basal microvascular autoregulation plays a pivotal role as opposed to a diminished vasodilator reserve.

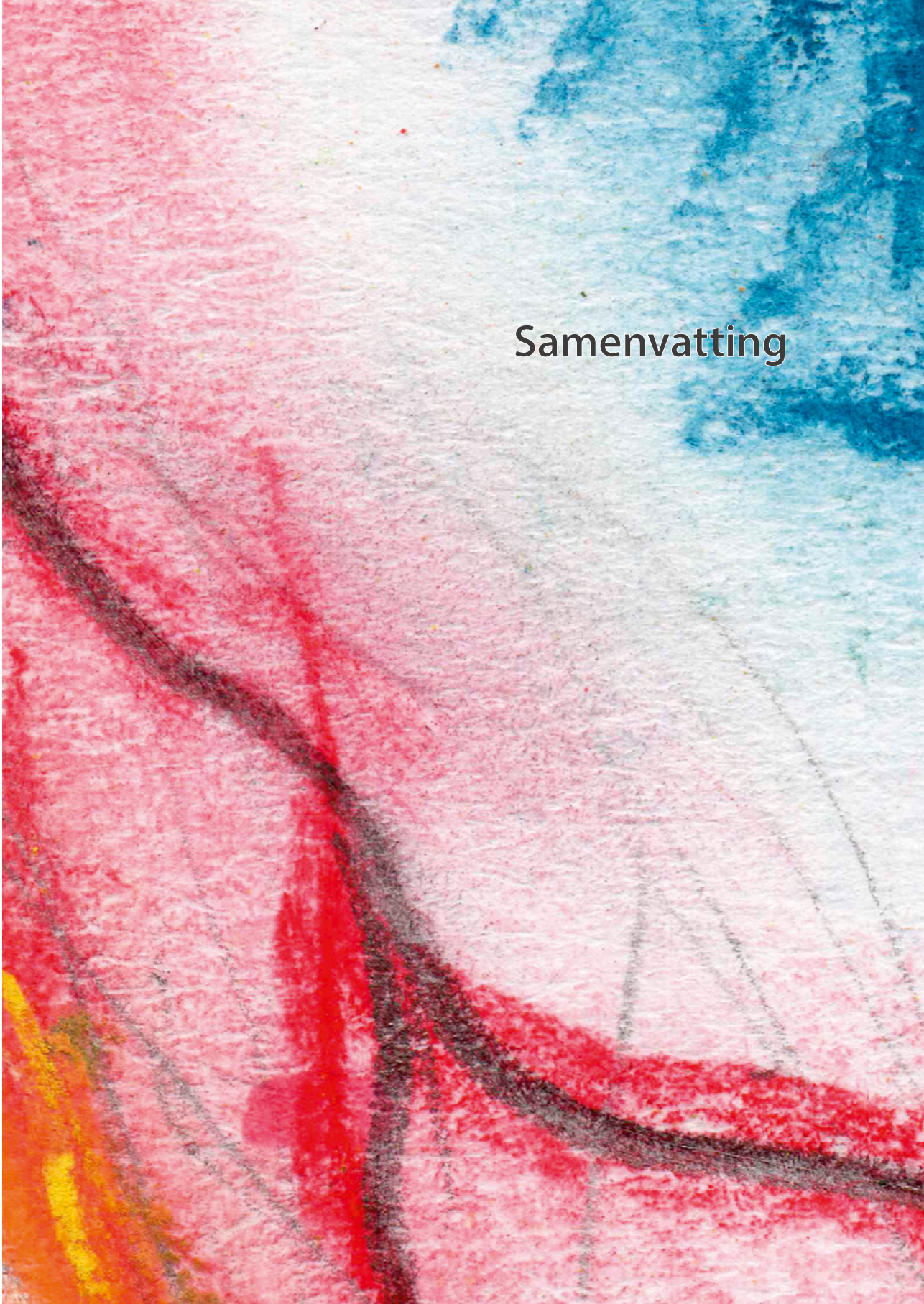
Chapter 7 describes the results of the research into a subpopulation from the HEBE study. It concerns 62 patients who underwent a PPCI for AMI. The HEBE study was designed to evaluate the effect of bone marrow mononuclear cell therapy on left ventricle improvement after STEMI. In this sub-study, Doppler-derived intracoronary hemodynamic evaluation was performed within 1 week and after 4 months after PPCI. Outcomes are related to left ventricular function (LVF) determined by CMR at 4 days, 4 months, and 2 years. CFR was not significantly associated with LVEF at 2 years in a multivariate regression model. This is in contrast to the findings described in chapter 2. CFR measurement was performed 1 to 4 days after reperfusion. The CFR may have increased in the first few days after reperfusion due to a decreased hyperemic microvascular resistance. The lower CFR in larger sized infarctions, mainly based on higher hyperemic microvascular resistance (and thus lower blood flow velocity) also plays a role. Subdivision by infarct size (separated by the median infarct size of 24.2% of LV on CMR) showed an association between absolute CFR improvement and LVEF improvement in patients with larger infarcts. Also, patients with a greater decrease in hyperemic microvascular resistance showed significant improvement in LVEF. Neither effect was seen in the group with smaller infarcts.

To elaborate on factors influencing microvascular dysfunction during acute anterior wall myocardial infarction, we described in **Chapter 8** the influence of serum glucose levels in non-diabetics on blood flow velocity and microvascular resistance in the IRA and non-IRA. In some patients, stress-related metabolic changes in the acute phase of the infarct led to glucose intolerance and elevated serum glucose levels. Serum glucose values were significantly associated with peak troponin T levels. In the adjusted multivariate analysis, elevated glucose levels were significantly associated with decreased baseline microvascular resistance (i.e., higher baseline flow velocity) and decreased CFR in the non-IRA. This association disappeared at 1-week and 6-months follow-

up. It is noteworthy that these associations were not found in the IRA, possibly less detectable due to other (patho)physiological mechanisms.

Since the effect of increased admission glucose levels on baseline microvascular resistance was more pronounced than on the hyperemic resistance in non-IRA, it suggests that the autoregulatory function is negatively affected by elevated blood glucose levels. The disappearance of the associations at follow-up suggests, at least in part, recovery of the autoregulation in non-IRA.

Coronary flow capacity (CFC) has recently been developed as a tool for diagnosis, prognosis, and risk stratification in patients with stable ischemic heart disease with known coronary flow and resistance values. CFC depicts the relationship between hyperemic flow and CFR, is less prone to alteration in hemodynamics as it corrects for variation in baseline flow. **Chapter 9** describes the evaluation of CFC in patients with acute anterior wall myocardial infarction. Patients were divided into 4 groups based on their CFC (normal and mild, moderate, or severely abnormal). A significant association was found with infarct size based on peak troponin value across the 4 categories for both IRA and non-IRA. CFC improved during follow-up for both IRA and non-IRA. A moderately and severely reduced CFC of IRA was present in 61% of the patients at the time of PPCI, 28% at 1 week, and 11% at 6 months. For the non-IRA, this was 28%, 3%, and 0% respectively. This illustrates the usefulness of CFC to assess the hemodynamics of the coronary microcirculation in the setting of an acute anterior wall STEMI.



Samenvatting

Introductie

Het doel van dit proefschrift was het evalueren van de coronaire microvasculaire functie tijdens en na reperfusie van een voorwand ST-elevatie myocardinfarct door middel van coronaire bloedstroomsnelheid karakteristieken. Bovendien wilden we de associatie onderzoeken van de microcirculatoire functie na reperfusie op het herstel van de linkerventrikelfunctie en sterfte op lange termijn.

Coronaire microvasculaire integriteit bepaalt de effectiviteit van de prestaties van de hartspiercellen. Op het moment van een myocardinfarct is de microvasculaire functie in het gebied dat wordt voorzien door de infarctgerelateerde slagader (IRA) abnormaal. Het was onduidelijk hoe snel en tot welk niveau de microvasculaire functie zal herstellen na reperfusietherapie. Microvasculaire disfunctie in de niet-infarctgerelateerde slagaders (Non-IRA) was een vrijwel onbekend gebied op het moment dat de onderzoeken beschreven in dit proefschrift werden uitgevoerd.

Microvasculaire functie kan niet direct worden gevisualiseerd met standaardtechnieken in het katheterisatielaboratorium. De tot nu toe ontwikkelde meetmethoden staan nog in de kinderschoenen vanwege moeilijk of tijdrovend gebruik in de klinische praktijk en interpretatie vereist overweging van mogelijk van invloed zijnde coronaire en patiënt gerelateerde aandoeningen. Bovendien wordt het begrip van de coronaire microvasculatuur niet vergemakkelijkt door het gebruik van talrijke afkortingen van indices om de hemodynamiek van de coronaire microcirculatie te schatten.

Hoofdstuk 1 geeft in het kort de ontwikkeling van ST-elevatie myocardinfarct (STEMI) met de potentiele gevolgen van een verminderde linkerventrikelfunctie en cardiale dood. Hoewel de actuele behandeling naast medicamenteuze therapie ook uit een tijdige mechanische reperfusie bestaat, zijn de effecten van deze reperfusie niet louter gunstig voor de microvasculaire integriteit, bekend als reperfusieschade, die medebepalend is voor de uiteindelijke uitkomst van de behandeling van het myocardinfarct.

Veel experimentele en klinische onderzoeken naar complementaire therapieën bedoeld om reperfusieschade te voorkomen of te beperken, leverden geen veelbelovende resultaten op.

Om de uitkomsten van een myocardinfarctbehandeling verder te verbeteren, is meer diepgaande kennis nodig over de mechanismen die een rol spelen in de microvasculaire herstelfase na reperfusie. Microvasculaire status en functie zijn belangrijke voorspellers van gebeurtenisvrije overleving, maar zijn niet direct zichtbaar en beschikbaar op het moment van reperfusie.

Er wordt een korte beschrijving gegeven van coronaire bloedstroomregulatie en microvasculaire functie en hoe deze factoren worden beïnvloed door lokale (patho)fysiologische condities.

Omdat het eind vorige eeuw onduidelijk was wanneer en in welke mate de microvasculaire integriteit zou herstellen na reperfusie van de geïnfarceerde slagader, hebben we de studie ontworpen die beschreven is in **hoofdstuk 2**. Het was voor het eerst mogelijk om de bloedstroomsnelheid te meten in de kransslagader met behulp van een Doppler-kristal gemonteerd op een coronaire voerdraad. In Japan waren de eerste onderzoeken uitgevoerd die verschillende abnormale Doppler-stroomsnelheidspatronen lieten zien in de setting van een acuut myocardinfarct (AMI) om microvasculaire disfunctie te beschrijven. Kern et al. toonde aan dat bij gebruik van de Doppler-techniek de coronaire stroomsnelheidsreserve (CFVR of CFR) een relevantere afgeleide maat was voor de myocardiale bloedstroom dan de TIMI-flow en "TIMI-frame count", om het resultaat van reperfusie te bepalen.

Het onderzoek in **hoofdstuk 2** beschrijft de prospectieve evaluatie van 100 patiënten met een voorwandinfarct, bij monovasculair lijden, die werden behandeld met primaire PCI (PPCI). Direct na reperfusie werden de Doppler flow parameters beoordeeld, waaronder de baseline-stroomsnelheid, door adenosine gestimuleerde maximale bloedstroomsnelheid, berekende CFR, microvasculaire weerstand in rust en tijdens hyperemie in zowel de infarct- als de niet-infarct gerelateerde slagader (IRA en non-IRA). Doppler metingen werden voor de eerste keer herhaald na 1 week en 6 maanden na het hartinfarct.

Echocardiogrammen werden gemaakt vóór reperfusie, 24 uur na het infarct en na 1 week en 6 maanden follow-up om de microvasculaire functie te relateren aan het linke ventrikel herstel. Bij de 73 patiënten die zonder restenose in het eerder behandelde vat in aanmerking kwamen voor follow-up was de door Doppler bepaalde CFR de enige onafhankelijke 6 maanden voorspeller van globaal en regionaal herstel van de LV-functie en dus een betere prognostische marker dan de gebruikelijke metingen zoals als TIMI-flow en TIMI-frame count.

Hetzelfde cohort patiënten werd gebruikt om het beloop van de coronaire (inclusief microvasculaire) hemodynamica na het eerste voorwandinfarct en dus indirect de autoregulatie in zowel de IRA als de non-IRA te bestuderen. In **hoofdstuk 3** wordt beschreven dat de microvasculaire functie, bepaald door de microvasculaire weerstand, verbetert in beide stroomgebieden in de tijd na het acute infarct. Als resultaat neemt het voor "rate-pressure product" gecorrigeerde baseline stroomsnelheid enigszins af en neemt de hyperemische stroomsnelheid significant toe. De aangepaste microvasculaire weerstand bij aanvang in het infarctvat, verlaagd in de acute fase, nam toe met ongeveer 28% in 6 maanden follow-up. Dezelfde ontwikkeling (een stijging van ongeveer 31%) werd gedocumenteerd in de non-IRA. Hyperemische (of minimale) microvasculaire weerstand in de acute fase van het myocardinfarct is hoger dan normaal in zowel de IRA als non-IRA en neemt in beide gebieden snel af in de eerste week na AMI. Bij non-IRA daalt deze waarde in de eerste week al tot normaal, bij IRA duurt het langer en is herstel compleet na 6 maanden. De minimale weerstand in het infarctgebied neemt af met ongeveer 44% en in het non-IRA-gebied met 18%. Deze studie biedt een tijdsperspectief voor het herstel van de microvasculaire functie voor zowel het infarctgebied als de gebieden op afstand.

Hoofdstuk 4 bespreekt in het kort hoe de Doppler-getipte voerdraad functioneert en hoe deze bijvoorbeeld kan worden gebruikt in de setting van PPCI. De waarde van de verschillende parameters, verkregen ten tijde van het acute hartinfarct, worden beschreven zoals coronaire stroomsnelheid reserve (CFR), diastolische vertragingstijd (DDT), systolische stroom omkering en wordt in perspectief geplaatst met myocardiale contrast-echocardiografie (MCE) en cardiale magnetische resonantie beeldvorming (CMR). In de setting van PPCI kan de Doppler-draadtechniek gemakkelijk worden toegepast om

microvasculaire obstructie en disfunctie te beoordelen en levert dit informatie op om het herstel van de linkerventrikelfunctie na een voorwandinfarct te voorspellen.

Wij toonden aan dat in de acute fase van het voorwandinfarct ook de microcirculatie in niet-infarct gebieden gestoord was. Het was niet bekend of deze veranderde microcirculatie in niet-obstrueerde gebieden prognostische informatie oplevert. **Hoofdstuk 5** beschrijft de mortaliteit na 10 jaar bij de patiënten uit de eerder besproken cohort. Voor deze analyse werd het cohort onderverdeeld in post-procedurele CFR-waarden in de non-IRA onder of boven 2.1. We ontdekten dat een gestoorde CFR-waarde in het niet-infarct gebied geassocieerd was met een toename van 4,09 in het 10-jaars risico op cardiale dood. Deze voorspellende waarde van metingen in de non-IRA tijdens PPCI was niet eerder beschreven. De gestoorde CFR in de non-IRA was toe te schrijven aan een verhoogde hyperemische microvasculaire weerstand (en dus verlaagde hyperemische bloedstroomsnelheid) in combinatie met een licht verlaagde baseline microvasculaire weerstand.

Permanent gestoorde CFR-waarden in de non-IRA 6 maanden na het hartinfarct, op basis van lage baseline microvasculaire weerstand (en daarmee hoge baseline stroomsnelheid), associeerde met een 10,7-voudige toename van het risico op cardiale mortaliteit. De omvang van het hartinfarct gemeten aan de hand van de wall motion score index verkregen na 6 maanden follow-up, was niet gerelateerd aan een toename van het risico op cardiale sterfte op de lange termijn.

Opvallend was de bevinding dat een lage CFR, de aanwezigheid van systolische stroomomkering, of korte diastolische vertragingstijd in de IRA geen patiënten identificeerden met een hoog risico op cardiale dood op lange termijn. CFR in de IRA was wel geassocieerd met een verhoogd risico op vroege cardiale moraliteit maar niet op mortaliteit op lange termijn.

Hoofdstuk 6 is het enige hoofdstuk in dit proefschrift dat cardiale microcirculatie onderzoekt bij patiënten *buiten* de setting van een AMI. Het toont de relevantie aan van kennis van de microcirculatoire functie bij obstructieve coronaire hartziekte voor risicostratificatie. Bij deze patiënten

werden CFR-bepalingen uitgevoerd met een Doppler-FloWire in referentie-kransslagaders zonder significante stenose. Bij 77 van de 178 patiënten was de CFR-waarde abnormaal laag (lager dan 2,7) in de referentieslagaders, voornamelijk als gevolg van een hogere baseline bloedstroomsnelheid (lagere baseline microvasculaire weerstand), terwijl er geen significante gestoorde hyperemische stroomsnelheid of weerstand werd gemeten, wat wijst op autoregulatoire stoornissen in het gehele hart. Na multivariate aanpassing hadden deze patiënten een significant verhoogde hazard ratio van 3,3 voor hartdood. Dit onderstreept het feit dat microvasculaire aandoeningen bij stabiele coronaire hartziekte een belangrijke factor zijn voor risicostratificatie en dus voor behandelstrategieën. In combinatie met de resultaten in hoofdstuk 5 levert deze CFR prognostische informatie op bij zowel stabiele als onstabiele coronaire syndromen.

Aangezien een afname van de baseline microvasculaire weerstand en niet de verhoging van hyperemische weerstand de belangrijkste oorzaak is van de lagere CFR, is het aannemelijk dat verminderde basale microvasculaire autoregulatie een cruciale rol speelt vergeleken met een verminderde vasodilatatie reserve.

Hoofdstuk 7 beschrijft de resultaten van het onderzoek in een subpopulatie uit het HEBE-studie. Het betreft 62 patiënten die een PPCI hebben ondergaan in het kader van een AMI. De HEBE-studie was ontworpen om het effect van beenmerg mononucleaire celtherapie op verbetering van de linkerhartkamer na STEMI te evalueren. In dit deelonderzoek werd door Dopplertechniek verkregen intracoronaire hemodynamische evaluatie uitgevoerd binnen 1 week en na 4 maanden na PPCI. De resultaten zijn gerelateerd aan de linkerventrikelfunctie (LVF), bepaald door CMR na 4 dagen, 4 maanden en 2 jaar. CFR was niet significant geassocieerd met LVEF na 2 jaar in een multivariate regressiemodel. Dit is in tegenstelling met de bevindingen beschreven in hoofdstuk 2. CFR-meting werd 1 tot 4 dagen na reperfusie uitgevoerd. De CFR kan in de eerste dagen na reperfusie al zijn toegenomen als gevolg van een verminderde hyperemische microvasculaire weerstand. De lagere CFR bij grotere infarcten, voornamelijk gebaseerd op hogere hyperemische microvasculaire weerstand (en dus lagere bloedstroomsnelheid), speelt ook een rol. Onderverdeling naar infarctgrootte (gescheiden door de mediane infarctgrootte van 24,2% van

LV op CMR) toonde een verband tussen absolute CFR-verbetering en LVEF-verbetering bij patiënten met grotere infarcten. Ook vertoonden patiënten met een grotere afname in hyperemische microvasculaire weerstand een significante verbetering in LVEF. Beide effecten werden niet waargenomen in de groep met kleinere infarcten.

Om uit te diepen welke factoren microvasculaire disfunctie beïnvloeden tijdens een acuut voorwandinfarct, wordt in **hoofdstuk 8** de invloed van serumglucosespiegels bij niet-diabetici op de stroomsnelheid en microvasculaire weerstand in de IRA en non-IRA beschreven. Bij sommige patiënten leidden stress gerelateerde metabole veranderingen in de acute fase van het infarct tot glucose-intolerantie en verhoogde serumglucosespiegels. Serumglucosewaarden waren significant geassocieerd met piek troponine T-spiegels. In de adjusted multivariate analyse waren verhoogde glucosespiegels significant geassocieerd met verminderde baseline microvasculaire weerstand (d.w.z. een hogere baseline stroomsnelheid) en verlaagde CFR in de non-IRA. Deze associatie verdween na 1 week en 6 maanden follow-up. Het is opmerkelijk dat deze associaties niet werden gevonden in de IRA, mogelijk overstemt door andere (patho)fysiologische processen.

Aangezien in non-IRA het effect van verhoogde glucosespiegels bij opname op de baseline microvasculaire weerstand meer uitgesproken was dan op de hyperemische weerstand, suggereert dit dat de autoregulatoire functie negatief wordt beïnvloed door verhoogde bloedglucosespiegels. Het verdwijnen van de associaties bij follow-up suggereert, althans gedeeltelijk, herstel van de autoregulatie in non-IRA.

Coronaire doorstromingscapaciteit (CFC) is recentelijk ontwikkeld als hulpmiddel voor diagnose, prognose en risicostratificatie bij patiënten met stabiele ischemische hartziekte met bekende waarden voor coronaire flow en weerstand. CFC geeft de relatie weer tussen hyperemische flow en CFR, is minder vatbaar voor veranderingen in de hemodynamica omdat het corrigeert voor variatie in de baseline flow. **Hoofdstuk 9** beschrijft de evaluatie van CFC bij patiënten met een acuut voorwand myocardinfarct.

Patiënten werden in 4 groepen onderverdeeld op grond van hun CFC (normaal, gering, matig of ernstig afwijkend). Een significante associatie werd vastgesteld met infarctgrootte op basis van peak troponine waarde over de 4 genoemde categorieën voor zowel IRA als non-IRA. CFC verbeterde gedurende de follow-up voor zowel IRA als non-IRA. Een matig en ernstig verminderde CFC van IRA was aanwezig bij 61% van de patiënten op het moment van PPCI, 28 % na 1 week en 11% na 6 maanden. Dit was voor de non-IRA 28%, 3% en 0% respectievelijk. Dit illustreert het nut van CFC om de hemodynamica van de coronaire microcirculatie te beoordelen in de setting van een acute voorwand STEMI.

Appendix

List of abbreviations

ACE angiotensin-converting enzyme
AMI acute myocardial infarction
ANOVA one-way analysis of variance
APV average peak velocity
bAPV baseline average peak flow velocity
BMI body mass index
BMR baseline microvascular resistance
BMRI baseline microvascular resistance index
CFC coronary flow capacity
CFR coronary flow reserve
CFVR coronary flow velocity reserve
CK-MB creatine kinase myocardial band
CMR cardiac magnetic resonance
cTfc corrected TIMI frame count
dMR delta microvascular resistance from resting to hyperaemic conditions
DDT diastolic deceleration time
ECG electrocardiogram
hAPV hyperaemic average peak flow velocity
HMR hyperaemic microvascular resistance
HMRI hyperaemic microvascular resistance index
IRA infarct-related artery
IS infarct size
LAD left anterior descending (coronary artery)
LCX left circumflex (coronary artery)
LV left ventricle
LVEDV left ventricular end-diastolic volume
LVEF left ventricular ejection fraction
LVESV left ventricular end-systolic volume
LVF left ventricular function
MCE myocardial contrast echocardiography
MI myocardial infarction
MR microvascular resistance
MVO microvascular obstruction
PCI percutaneous coronary intervention
PPCI primary percutaneous coronary intervention
PTCA percutaneous transluminal coronary angioplasty
RCA right coronary artery
refCFVR reference coronary flow velocity reserve
SRF systolic retrograde flow
STEMI ST-elevation myocardial infarction
TIMI Thrombolysis In Myocardial Infarction
WIA wave intensity analysis
WMI wall motion index
WMSI wall motion score index

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PhD Portfolio

PhD student: Matthijs Bax

PhD period: 1997 - 2021

PhD supervisors: Prof. Dr. J.J. Piek, Prof. Dr. R.J. de Winter

PhD Co-supervisors: Dr. K.T. Koch, Prof. Dr. J.P.S. Henriques

PhD training	Year (ECTS)	Workload
Courses		
Developments in diagnostic and therapeutic cardiac catheterization	1998	0.5
Molecular cardiology: Basic developments and clinical implications	1998	0.25
Diagnosis and treatment of unstable coronary syndromes	1998	0.3
Diagnostics and therapy in chronic heart failure	1998	0.2
CVOI course of coagulation and flow	1998	0.3
Presentation of research results in English	1999	1.2
Endovascular therapy course coronary and peripheral, Paris	1999	1.0
Radiation course and Radiation protection for medical specialists (SB level 4a)	2000-2001	1.0
Intracoronary physiology for guidance of percutaneous interventions.	2001	0.2
Echocardiography course in The Hague	2002-2020	4.0
Research at a crossroads	2005	0.4
Percutaneous valve procedures	2009	0.25
Optical Coherence Tomography; Clinical practice and image interpretation	2015	0.1
Developments and state of affairs in intracoronary physiology	2016	0.5
Multimodality course Cardiac CT	2019	0.2
QFR course	2021	0.3
Seminars, workshops and master classes		
ACCSAP	1998-2005	3.9
Wenckebach society	2004-2020	2.5
Center of Excellence Presbyterian Hospital New York	2004	0.7
Management Development courses and training	2009-2015	1.4
Training the trainers	2007	0.5
(inter)national conferences		
NVVC congresses	1999-2020	5.5
Annual Scientific Session of the American College of Cardiology	2000-2014	1.7
Congress on Acute coronary syndromes	2000, 2014	0.5
Limits of cardiovascular interventions	2003	0.25
American heart association congress	2004	1.1
Annual New York Cardiovascular Symposium	2004, 2010	1.4
Amsterdam Cardiology symposium	2005-2008	1.4

Interventional Cardiology of the Benelux	2007	0.4
World congress on controversies in cardiovascular disease	2008	0.6
Transcatheter Cardiovascular Therapeutics conference	2008	0.9
First World Congress on controversies in Cardiovascular diseases	2008	0,5
Euro PCR	2009-2020	5.3
European Society of Cardiology (ESC)	2007-2018	5.2
Chronic Total Occlusion Summit, New York	2009-2013	2.7
Dutch revascularization and Electrophysiology summit	2012-2019	1.5
Meetbaar Beter en NHR-symposia	2013-2020	0.7
Poster/oral presentations		
Cardiovascular Research Institute Amsterdam symposium. (Invited speaker)	1997	0.3
European society of cardiology (ESC), Barcelona. (Oral presentation)	1999	1.8
Clinical Cardiology: Past, Present, and Future, Amsterdam. (Invited speaker)	2000	0.5
Scientific Sessions of the American Heart Association, New Orleans.	2000	1.3
(Oral presentation)		
Annual Scientific Session of the American College of Cardiology, Anaheim.	2000	1.0
(Poster)		
Symposium on Intervention cardiology, elective and acute, Amsterdam.	2001	0.6
(Invited speaker)		
Amsterdam symposium Intervention Cardiology. (Invited speaker)	2002	0.5
Prehospital triage in ST-elevation myocardial infarction (Invited speaker)	2005	0.2
Cardiology symposium The Hague (invited speaker)	2010	0.1
Near Care. Distribution and concentration of hospital functions. Invitational		
conference NVZ (Invited speaker)	2011	0.3
Symposium Jubilee Heart Center Haga Hospital	2017	0.2
Coaching/ mentoring		
Coaching and mentoring of trainees in cardiology	2012-	3.4
Coaching and mentoring fellows interventional cardiology	2008-	14.0
Teaching		
Lecturer cardiology, coronary artery disease for dentist in training ACTA	2000-2003	1.2
Lecturer cardiology for coronary care and intensive care nurses Amsterdam	2000-2003	1.5
Interventional cardiology and workshops on atrial fibrillation for general practitioners	2004	1.0
Acute myocardial infarction. New strategy for the general practitioner	2004	0.3
Interventional cardiology for cardiologists	2004	0.4
Primary PCI in acute myocardial infarction; GGD and cardiology	2008	0.1
Regional campaign 'Heart attack? Call 1-1-2'	2010	0.3
Junior Chamber day	2016	0.4
Other		
Editor Medweb	1997-2004	3.0

Curriculum vitae

Matthijs Bax, geboren op 15 september 1963 te Amsterdam, groeide op in Ede en Bennekom. Na het behalen van het VWO-diploma op het Streeklyceum te Ede in 1981 studeerde hij psychologie aan de Vrije Universiteit te Amsterdam. Na zijn propedeuse psychologie startte hij in 1982 met de studie geneeskunde aan de Universiteit van Amsterdam. Hij behaalde het doctoraalexamen in 1986 en het artsexamen, cum laude, in 1990. In aansluiting op het co-schap kindergeneeskunde in 1989 werd het prille enthousiasme voor wetenschappelijk onderzoek gestimuleerd door Frits Wijburg, resulterend in een voordracht over SIADH bij kinderen met meningitis op het congres voor de Nederlandse vereniging voor kindergeneeskunde.

Het enthousiasme voor de cardiologie werd gewekt tijdens de co-schappen in het AMC bij Barbara Mulder op de hartbewaking en enorm gestimuleerd door de bevlogenheid van Donald Düren op de afdeling klinische cardiologie. De periode als arts-assistent cardiologie in het Zuiderziekenhuis Rotterdam en het Academisch Ziekenhuis Utrecht, werd gevolgd door de opleiding tot cardioloog in het Academisch Medisch Centrum te Amsterdam. (1991-1997; interne geneeskunde prof. dr. J. Vreeken; cardiologie Dr. G.K. David en prof. Dr. K.I. Lie). In 1997 en 1998 volgde de opleiding tot interventiecardioloog (opleider prof. dr J.J. Piek). In deze tijd startte het onderzoek naar de effecten van het acute voorwandinfarct en de primaire PCI op de coronaire en microvasculaire hemodynamica in relatie tot het mogelijke herstel van de linkerventrikelfunctie, zoals beschreven in dit proefschrift.

Hij was van 1997 tot 2004 werkzaam als interventiecardioloog in het AMC en van 2000 tot 2004 in een duobaan constructie met Carl Schotborgh in het Slotervaartziekenhuis.

In 2004 trad hij samen met Carl Schotborgh toe tot de gefuseerde maatschappen cardiologie van het Leyenburg ziekenhuis en het Rode Kruis ziekenhuis te Den Haag om het nieuwe hartcentrum in den Haag te helpen ontwikkelen. Dit is inmiddels uitgegroeid tot het regionale hartcentrum met een vrij compleet palet aan cardiologische- en cardiochirurgische zorg en dat de A-opleidingsstatus heeft voor de opleiding tot cardioloog.

In 2005 introduceerde hij met Don Poldermans en de ambulancediensten van den Haag, Delft en Zoetermeer het regionale triage systeem voor de acute hartinfarctzorg. In 2009 organiseerde hij met het ziekenhuis, de GGD, gemeente den Haag, CPA, Veiligheidsregio Haaglanden, regionale cardiologen en huisartsen een regionale campagne "Hartaanval? Bel 1-1-2. De snelste weg naar de beste zorg" om het prehospitale patiënten delay te bekorten bij patiënten met een acuut hartinfarct. In 2015 organiseerde hij met bovengenoemde partijen en in samenwerking met de Hartstichting een vervolg: de regionale 112-campagne "Herken een Hartinfarct, bel direct 112!".

Sinds 2008 is hij medisch manager van het Hartcentrum en sinds 2018 van het Hart Long centrum in het HagaZiekenhuis. Vanaf 2019 is hij tevens medisch manager van de cardiologie in het Reinier de Graaf gasthuis in Delft en in 2020 eveneens van de cardiologie in het LangeLand ziekenhuis te Zoetermeer met als opdracht de lokale en regionale cardiologische zorg te verbeteren en op elkaar af te stemmen.

Hij was voorzitter van de kamer vrij beroep van de medische staf in het HagaZiekenhuis van 2011 tot 2013. Nadien tot 2015 voorzitter van de stafmaatschap HagaZiekenhuis en van 2015 tot en met 2018 voorzitter van het Medisch Specialisten Coöperatief Haga U.A.

Hij is getrouwd met Jannine van den Berg en zij hebben drie dochters Vera, Isabelle en Brenda.

Dankwoord

Het heeft even geduurd… maar nu is mijn proefschrift werkelijk klaar en het promotietraject bijna ten einde. In al die jaren zijn er velen geweest met wie ik mocht samenwerken om dit onderzoekstraject te voltooien. Hun energie, inzet en steun hebben mij enorm geholpen om dit proefschrift af te ronden. Hier ben ik hen zeer dankbaar voor. Door de lange periode tot voltooiing van dit boekje en de grote hoeveelheid betrokken mensen hierbij zal het niet lukken om in dit dankwoord volledig te zijn. Enkelen wil ik in het bijzonder bedanken.

Beste *Jan, Rob en Karel* door jullie enthousiasme voor de interventiecardiologie ben ik aangestoken. In mijn start tot interventiecardioloog was de primaire PCI, dotteren als behandeling voor het acute hartinfarct, net in zwang geraakt. De vele, door ons niet goed begrepen pathofysiologische veranderingen in het microvasculaire vaatbed, teweeggebracht door het hartinfarct en de mechanische reperfusie, leidden met jullie uitgebreide inbreng tot het starten van de FLOMI-studie, de basis van dit proefschrift. Ondanks dat we een kleine interventiegroep eind jaren 90 in het AMC waren, was iedereen altijd bereid, ook 's nachts en in het weekend, aanvullende intracoronaire metingen te doen. Ik heb nooit een wanklank gehoord, integendeel. Dank daarvoor!

Beste *Jan*, ik wil je bedanken voor je tomeloze energie, stimulering, goede ideeën, snelle en grondige reacties op alle manuscripten maar vooral ook het gestelde vertrouwen in mij als onderzoeker, interventiecardioloog en collega. Het was altijd enorm plezierig samenwerken waarbij ik je snelle schakelingen tussen serieus zijn en humor erg heb gewaardeerd. De ruimte die ik van jou als promotor kreeg om onderzoek te doen, ook na mijn vertrek uit het AMC, was groot. Mijn tempo tot afronden van de thesis lag ver onder de gangbare maat. Nooit heb ik je hier een negatieve opmerking over horen maken. Herhaaldelijk begon je mij weer te enthousiasmeren om de draad weer op te pakken en onderzoekers toe te voegen om zo het onderzoek verder te brengen. Veel dank!

Beste *Rob* en *Karel*, dank dat jullie mij zo diep in de interventiecardiologie hebben geïntroduceerd. Daar pluk ik tot op de dag van vandaag de vruchten van. Mede dankzij jullie was niet alleen de studieopzet succesvol maar gold dit ook voor de degelijke metingen en resultaten waarop we de analyses konden

doen. Dank voor jullie vertrouwen en samenwerking. Ik heb mede door de ervaren waardering een plezierig herinnering aan mijn AMC-tijd.

Beste *José*, na je komst uit Zwolle hebben wij een korte periode samengewerkt in het AMC. Dat was zeer plezierig door je enthousiasme, drive en humor. Ik wil je danken dat je mijn copromotor wilde zijn. Veel leerde ik van je door je kritische inbreng over de myocardial blush en ander reflow elementen.

De leden van de promotiecommissie*, prof. dr. S.A.J. Chamuleau, prof. dr. E.T. van Bavel, prof. dr. J.J. Bax, prof. dr. N. Van Royen, prof. dr. R.J.G. Peters* en *dr. P.C. Smits* ben ik zeer erkentelijk voor het kritisch evalueren van mijn proefschrift en om zitting te nemen in de promotiecommissie.

Beste *Carl*, er zijn vele redenen dat ik je mijn dank wil betuigen. Enkele daarvan benoem ik hier. Meer dan 25 jaar collegialiteit en vriendschap is het hoofdbestanddeel. Jij ging mij net voor in de start als interventiecardioloog en ook jij was altijd bereid bij nacht en ontij onderzoek te doen aan de acute infarctpatiënten. We hebben samen hard gewerkt, successen bereikt en veel plezier beleefd aan onze gezamenlijke ontwikkeling waaronder onze nog immer laagdrempelige overleggen over interventies, onze duobaan in het Slotervaart, onze gezamenlijke overstap naar Den Haag om daar een nieuw hartcentrum te helpen bouwen en heel veel meer. Ik waardeer je nog steeds om je gedegen literatuurkennis en bovenal je vrolijke enthousiasme.

Graag wil ik mijn *coauteurs* bedanken voor het vele werk dat zij hebben verricht. Het doet mij deugd dat nog immer uit de FLOMI-database relevante informatie wordt geput. Zonder iemand te kort te doen, wil ik in het bijzonder *Martijn* en *Tim* bedanken voor hun goede onderzoeksideeën en hulp bij de uitvoering van verschillende studies. *Martijn*, dank voor het geniale idee een 10-jaars follow-up van de patiënten te doen. En hoe logisch is dat als je zo lang over je proefschrift doet. Dit gaf tenslotte een nieuwe kijk op en bijzonder gewicht aan de evaluatie van het niet-infarct gerelateerde vat. Wellicht moeten we de 20-jaar follow-up ook in gaan zetten. *Tim*, het is bijzonder hoe jij je in korte tijd ontwikkelde tot een top-deskundige op het gebied intracoronaire fysiologie. Je snelle evaluaties, idee vorming, je mooie schrijfstijl en collegialiteit waardeer ik.

Jan Tijssen ben ik erkentelijk voor de hulp bij de studieontwerpen en de statistische evaluaties.

De patiënten die vrijwel zonder enige bedenking of voorwaarde mee wilden doen aan de onderzoeken wil ik bedanken. Zonder hen geen medische wetenschap of proefschrift.

De groep '*jonge klaren*' van mijn tijd wil ik bedanken voor de mooie tijd dat wij samenwerkten en waarin ik de mogelijkheid en ruimte kreeg om tussen de bedrijven door promotieonderzoek te doen. In het bijzonder komt dank toe aan wijlen *Peter Landzaat*, collegiaal, humoristisch, bijzonder betrokken en altijd bereid in mijn afwezigheid een patiënt te includeren en stipt de onderdelen van het onderzoeksprotocol uit te voeren, ongeacht het tijdstip van de dag.

Veel dank ben ik verschuldigd aan de verpleegkundigen en laboranten van de hartkatheterisatiekamers in het AMC, toen onder leiding van *Martin Meesterman*, die immer bereid waren tot hulp bij het uitvoeren van het onderzoek. Ook de echolaboranten komt deze dank toe. De verpleegkundigen van de hartbewaking ben ik zeer erkentelijk voor het uitvoeren van alle stapjes van de onderzoeksprotocollen en vooral ook *Rob Adams* die alle ECG's altijd weer op de juiste momenten verzameld en beoordeeld had.

Mijn paranimfen *Vera* en *Carl* dank ik voor hun bijstand tijdens mijn verdediging. Ik prijs mij gelukkig dat ik deze ondersteuning van mijn dochter alsook van mijn vriend en collega mag ervaren.

Margreet de Bruin ben ik erkentelijk omdat zij mij door de laatste loodjes bureaucratie en regelwerk heeft geloodst en *Andrea Groenewegen* om haar immer adequate management en secretariële ondersteuning.

Ik dank mijn collega's van mijn vakgroep en mijn managementteam in het HagaZiekenhuis voor de zeer aangename werksfeer. Dit is tenslotte nodig om ook nog tijd aan een promotietraject te kunnen besteden. Deze dank komt ook mijn collega's van mijn vakgroepen in Reiner de Graaf en Lange Land toe.

Mijn ouders ben ik erg dankbaar voor hun warme en enthousiaste ondersteuning in eigenlijk alle keuzes die ik in mijn leven maakte.

Lieve *Jannine*, dank voor je eindeloze en onvoorwaardelijke steun en liefde, niet alleen in dit promotietraject waarin jij ook nog een rol had in de totstandkoming van de 'inclusie pakketten' maar ook in zovele levenszaken. Jouw management en bestuurlijke vaardigheden en deskundigheid coachen mij in mijn andere rollen in de zorg. Maar bovenal ben ik gelukkig en trots met jou als mijn vrouw aan mijn zijde in al ons lief en leed. In liefde een toast op nog vele jaren!
Lieve *Vera*, *Isabelle* en *Brenda* mijn levensgeluk was niet compleet zonder jullie. Wat een toppertjes zijn jullie! En ja, we gaan nog vele reizen maken.