Coronary Collaterals

Jeroen Koerselman

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coronary *adjective* **1.** *anatomy* designating blood vessels, nerves, ligaments, etc. that encircle a part or structure. **2.** *noun*. [17th century: from Latin *corōnārius* belonging to a wreath or crown]

coronary (artery) *noun* either of the two arteries branching from the aorta and supplying blood to the heart.

collateral *noun* **1.** security pledged for the repayment of a loan. **2.** a person, animal, or plant descended from the same ancestor as another but through a different line. ~*adjective* **3.** situated or running side by side. **4.** descended from a common ancestor but through different lines. **5.** serving to support or coroborate. [14th century: from Medieval Latin, from Latin *com-* together + *laterālis* of the side, from *latus* side].*

* Adopted from Collins English Dictionary and Thesaurus. Glasgow, HarperCollins Publishers, 1993

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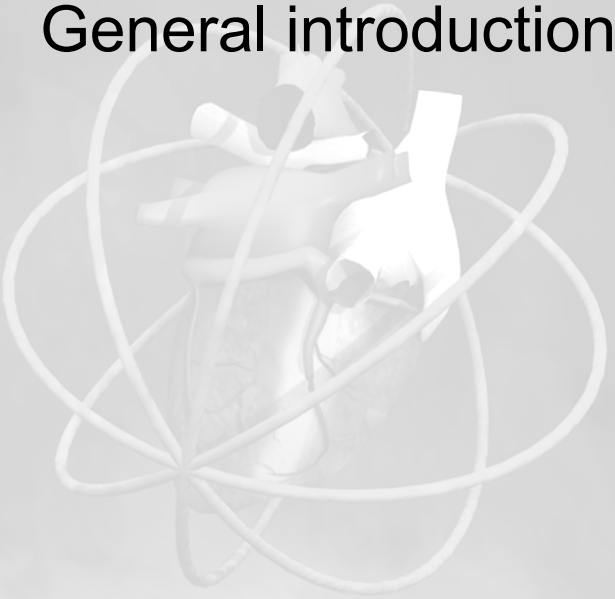
Contents

List of abbreviations

AAA - abdominal aortic aneurysm
ACC - American College of Cardiology
ACE - angiotensin converting enzyme
a-FGF - acidic fibroblast growth factor
AHA - American Heart Association
AP - angina pectoris
ARB - angiotensin receptor blockers
ATP III - Adult Treatment Panel III
b-FGF - basic fibroblast growth factor
BMI - body mass index
BP - blood pressure
CABG - coronary artery bypass grafting
CAD - coronary artery disease
CAG - coronary angiogram
CC - coronary collateral
CFI - collateral flow index
CHD - coronary heart disease
CI - confidence interval
CK-MB - MB-fraction of creatine kinase
CT - computed tomography
CV - cardiovascular
CVD - cardiovascular disease
DBP - diastolic blood pressure
ECG - electrocardiogram
GM-CSF - granulocyte-macrophage colony-stimulating factor
HDL - high-density lipoprotein
HOMA-IR - homeostasis model assessment determined insulin resistance
HR - hazard ratio
hs-CRP - high sensitive C-reactive protein
LAD - left anterior descending coronary artery
LCX - left circumflex coronary artery
LDL - low-density lipoprotein
LVH - left ventricular hypertrophy
MACE - major adverse coronary event
MCP-1 - monocyte chemo-attractant protein-1
MI - myocardial infarction
MRI - magnetic resonance imaging
NS - not significant
NYHA - New York Heart Association
OR - odds ratio
PDGF - platelet derived growth factor
PTA - percutaneous transluminal angioplasty
PTCA - percutaneous transluminal coronary angioplasty
QUICKY - quantitative insulin sensitivity check index
R - Rentrop
RCA - right coronary artery
SBP - systolic blood pressure
SD - standard deviation
SEM - standard error of the mean
SMART - Second Manifestations of ARTerial disease
TGF-α - transforming growth factor-α
TGF-β - transforming growth factor-β
TIA - transient ischemic attack
UMC Utrecht - University Medical Center Utrecht
UPW - unit(s) per week
VEGF - vascular endothelial growth factor

Chapter 1

General introduction



General introduction

The coronary collateral circulation has been a topic of interest since long time. Well-developed collaterals may offer an important alternative source of blood supply in case the original vessel fails to provide sufficient blood to the myocardium. The development of coronary collaterals consists of collateral recruitment and collateral growth.[1] *Collateral recruitment* denotes that pre-existing collateral vessels increase their lumen by passive dilatation, thereby enhancing collateral flow to the jeopardized ischemic regions. *Collateral growth* includes the proliferation of capillaries in the ischemic area (*angiogenesis*), and the maturation of pre-existing collateral vessels into functional muscular collateral arteries (*arteriogenesis*), with the latter being more relevant in humans.[1]

However, not every individual has well-developed collateral vessels, if developed at all. Some individuals, with normal hearts or with angiographically normal coronary arteries, may already have preformed coronary collaterals[2], some even already at birth.[3] Yet, other individuals may develop collateral arteries in the course of their lives. These differences in the potential of individuals to develop coronary collaterals have so far been largely neglected. Such differences may characterize the myocardial vulnerability of an individual. Moreover, knowledge on determinants and mechanisms involved may lead the way to treatments that promote collateral formation. For instance, in hearts with typical findings of coronary disease at autopsy, the number of coronary collaterals was increased.[3] **Chapter 2** addresses this issue, and proposes why coronary collaterals are important, and why the individual potential to develop collaterals should be considered an additional indicator of cardiac vulnerability. In addition, **Chapter 2** reviews the determinants that are known to play a role in collateral coronary blood supply.

The mechanism of the development of coronary collaterals is actually subject to increasing preclinical and clinical research. In addition to myocardial ischemia,

pressure gradient and shear stresses, and growth factors, as reviewed in **Chapter 2**, genetic factors and a number of other patient characteristics have been proposed to play a role in collateral development. These include age, smoking and alcohol, physical exercise, body mass index, hyperlipidemia, hyperhomocysteinemia, hypertension, diabetes mellitus, and the use of various cardiovascular drugs, among which statins, angiotensin converting enzyme inhibitors, and β-blockers.[1,4-21] Yet, results of these studies are conflicting and, therefore, their pathophysiologic role and importance is still unclear.[22-24]

The first objective of this thesis was therefore to study several determinants of the presence and extent of coronary collateral circulation collectively in a single group of patients. The results are presented in **Chapter 3**. We assessed the role of cardiac ischemic burden (**Chapter 3.1**), high blood pressure (**Chapter 3.2**), smoking and alcohol (**Chapter 3.3**), and the metabolic syndrome (**Chapter 3.4**) as potential determinants of coronary collaterals.

Coronary collaterals may also play an important prognostic role in patients with coronary artery disease both during episodes of acute and unexpected myocardial ischemia and during chronic ischemia. In the event of an acute myocardial infarction, well-developed coronary collaterals may determine the short-term outcome of a patient, by minimizing the infarct area, and by preserving myocardial viability and left ventricular function. Moreover, the period of time available until successful coronary reperfusion may be extended, which will improve the chances of survival.[25-28] In patients with stable coronary artery disease, a reduction in ischemic events and a better mid- to long-term prognosis has been reported when collaterals are present.[29,30] In patients with an acute myocardial infarction, overall, similar mid- to long-term findings have been reported,[31,32] although some other studies reported no effect,[33,34] or an adverse effect.[35,36] These different findings may, in part, be attributed to statistical and technical factors, but also to differences in study design, study population, definition of and methods used to assess coronary collaterals, definition of outcome, and duration of follow-up. Furthermore, there is marked interindividual

variability in the extent of coronary collateral circulation.[23] In addition, these studies were done with selected groups of patients.

From a pathophysiologic point of view, a direct and positive relationship between collaterals and better outcome is to be expected. At the same time, however, the presence of collaterals is related to, among others, the duration and extent of ischemic disease and thus a marker of its severity.[1,22,23] Therefore, it is at present not clear whether the presence of coronary collaterals in patients with ischemic heart disease, reflects the severity of coronary artery disease and thus a worse prognosis in the long term, or whether its presence helps to prevent future occurrence of cardiovascular events by protecting against ischemia.

Further examination of the relationship between collaterals and patient outcome and its strength is thus essential. It may help risk stratification and patient management. One may think of patient-tailored treatment and follow-up on the basis of risk. It may also stimulate the development of novel therapeutic strategies aimed for the induction of vascular growth, if collaterals (whatever their origin) proof to be protective.[37,38] Therapeutic induction of vascular growth may actually provide an attractive treatment option, in particular for those patients with myocardial or peripheral ischemia, who are unsuitable for conventional revascularization therapies.[1,39,40]

Therefore, the second objective of this thesis was to study the presence and extent of coronary collaterals as a long-term prognostic determinant of cardio-vascular outcome. The results are presented in **Chapter 4**. We studied the prognostic significance of coronary collaterals with data obtained from two different studies with different study populations: the SMART Study[41] (**Chapter 4.1**), and the Octopus Study[42] (**Chapter 4.2**). Finally, **Chapter 5** reflects on the results presented in this thesis, and **Chapter 6** summarizes the results.

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Chapter 2

Coronary collaterals: an important and underexposed aspect of coronary artery disease

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Introduction

Important risk factors for cardiovascular disease (CVD) have been identified, but they fail to explain why some patients with atherosclerosis become symptomatic and have recurrent symptomatic disease, and others do not. Probably, apart from, among others, the extent of coronary atherosclerosis, the sensitivity of organs to episodes of ischemia is of importance. An organ may be less sensitive to episodes of ischemia, if supplied with sufficient blood flow by well-developed collateral vessels. Unfortunately, some organs or even some individuals do not appear to have well-developed collateral vessels, if developed at all. Currently, it is not clear why there are differences between individuals in their capability of developing a sufficient collateral circulation. The potential of individuals to develop coronary collateral circulation has so far been largely neglected, but may play a major role in determining myocardial vulnerability.

In this article, we propose why coronary collaterals are important, and why this individual potential to develop collaterals should be considered an additional indicator of cardiac vulnerability. Also, we review determinants that play a role in collateral coronary blood supply.

Coronary collateral circulation: current knowledge

Coronary collaterals, or "natural bypasses", are anastomotic connections without an intervening capillary bed, between portions of the same coronary artery and between different coronary arteries (Figure 1).[1] Collateral circulation potentially offers an important alternative source of blood supply when the original vessel fails to provide sufficient blood.[2] Timely enlargement of collaterals may even avoid transmural myocardial infarction (MI) and death in symptomatic patients.[3] As early as in 1956, Baroldi et al. demonstrated the presence at birth of, mostly

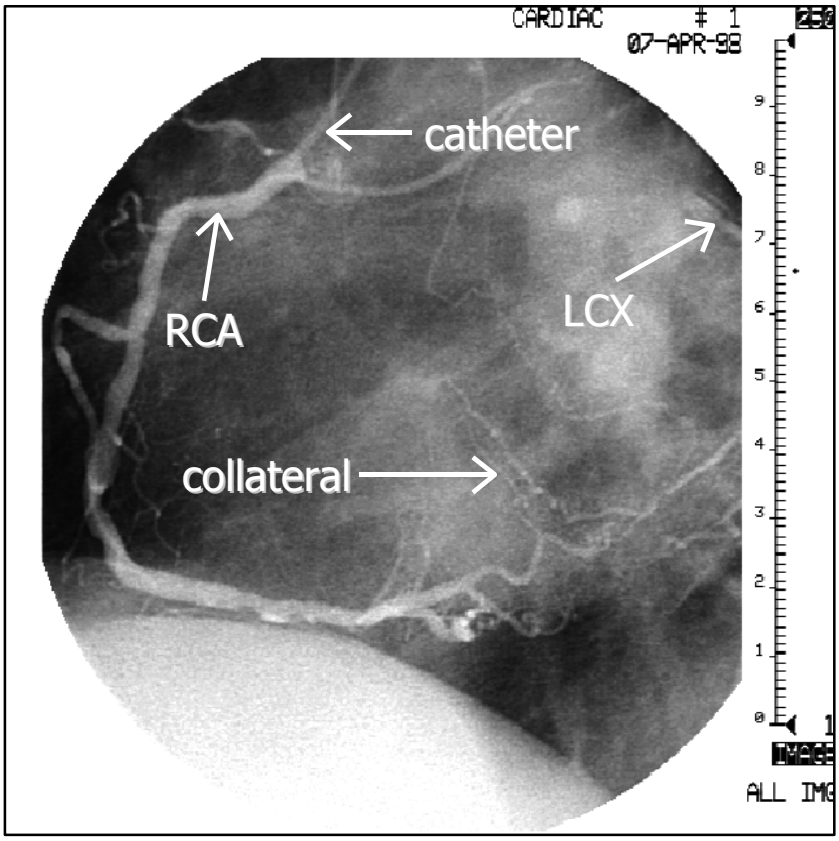

Figure 1. Left anterior oblique view of the right coronary arteriogram. The left circumflex coronary artery (LCX) is proximally occluded, and fills completely by means of collateral circulation from the right coronary artery (RCA). Image courtesy of the Department of Cardiology at the Heronimus Bosch Hospital, Den Bosch, The Netherlands.

"corkscrew"-shaped, collaterals in normal human hearts, with a lumen diameter of 20 to 350 μm and lengths ranging from 1 or 2 cm to 4 or 5 cm.[4] In hearts with typical findings of coronary disease at autopsy, the number of coronary collaterals was increased, notably in cases with a history of slowly evoluted coronary obstruction.[4] Avascular areas were found in acute myocardial infarcts. Baroldi et al. suggested that functional coronary collateral circulation results from hypertrophic evolution of vessels, present in normal hearts.[4] Indeed, in 1964,

Fulton et al. showed that the longer the history of angina, the larger the number of large caliber coronary collaterals at post-mortem examination.[5] When lumen diameter measurements were translated into capacity for blood flow, the functional importance of a few large channels was overwhelming compared to a large number of small channels.

Since then, much research has been done into understanding the mechanisms of collateral vessel growth: vasculogenesis, angiogenesis, and arteriogenesis.[6-12] Vasculogenesis refers to the initial events in vascular growth in which endothelial cell precursors (angioblasts) migrate to discrete locations, differentiate *in situ*, and assemble into solid endothelial cords, later forming a plexus with endocardial tubes.[10] The term angiogenesis was formerly used to describe the formation of new capillaries by sprouting out from preexisting post-capillary venules.[9] Currently, angiogenesis is considered the subsequent growth, expansion and remodeling of these primitive vessels into a complex, mature vascular network.[10] Finally, arteriogenesis refers to the transformation of pre-existing (collateral) arterioles into functional (muscular) collateral arteries, as a thick muscular coat is added, concomitant with acquisition of viscoelastic and vasomotor properties.[10]

Risk factors, trigger factors and myocardial vulnerability

Risk factors of cardiovascular disease

Much is known about the pathogenesis of atherosclerosis,[13] and about risk factors for the initiation and progression of the disorder.[14] Factors strongly associated with CVD, include among others age, male gender, smoking, elevated serum-cholesterol, disturbed carbohydrate metabolism and elevated blood pressure.[15] This knowledge is, however, insufficient to adequately predict the initiation and progression of CVD and the occurrence of (new) ischemic symptoms. Secondary prevention aims at detection and treatment of these risk factors, in order to slow down the progression of the atherosclerotic process, and prevent further morbidity

and mortality.[16] Yet, most patients with symptomatic CVD have similar levels of traditional risk factors and all have atherosclerosis to a larger or lesser degree.[17]

Probably, apart from the extent of coronary atherosclerosis, the sensitivity of organs to episodes of ischemia is of importance. Therefore, other factors may play a role as well: notably, the presence of a collateral circulation. An organ may be less sensitive to episodes of ischemia, if it is supplied with sufficient blood flow by well-developed collateral vessels. Coronary collaterals thus may protect the heart, and prevent ischemic cardiac events.

Trigger factors

Oliver, already in 1986, introduced a scheme summarizing the most important determinants for the occurrence of cardiovascular events in the presence of atherosclerosis: coronary atherosclerosis, trigger factors, and myocardial vulnerability (Figure 2).[18] The presence of atherosclerosis or a vulnerable myocardium in itself does not have to result in the occurrence of symptomatic events. At this point, trigger factors may play an important role. Trigger factors are factors that promote rapid occlusion of arterial vessels already compromised by atherosclerosis, thus "triggering" sudden reductions of coronary flow, and ischemia.[18] Although particularly clear for coronary heart disease, this is likely to apply to the occurrence of ischemic events in other vascular beds as well, such as the brain. The concept of "trigger factors" is of vital importance in understanding the final phase of atherosclerotic CVD, when it shifts from asymptomatic to symptomatic disease. A phase in which thrombosis is central.[14] Plaque rupture with superimposed thrombosis is the main cause of acute coronary syndromes, including unstable angina, MI and sudden cardiac death.[19] Many mechanical and biologic factors are involved in determining plaque stability, and in the process leading to plaque rupture, including among others plaque architecture (thickness of fibrous cap, location of lipid core), mechanical forces (shear stress, repetitive deformation), extracellular matrix biology (synthesis and degradation), and inflammation.[20] Recently, Moons et al. showed that tissue

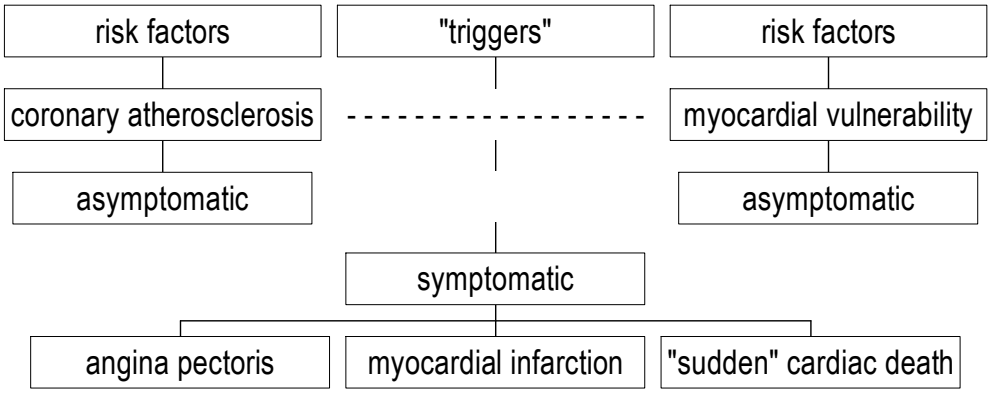

Figure 2. Risk factors, trigger factors and myocardial vulnerability in atherosclerosis and coronary heart disease (scheme modified after Oliver[18] and Grobbee[14]).

factor, a potent initiator of the coagulation cascade, may play a key role in determining plaque thrombogenicity.[19]

In addition to thrombogenic factors, other candidates may act as "trigger factors", although they may eventually affect thrombogenesis as well, such as sympathetic nervous system activity, vasoactive hormones, smoking and psychosocial stress.[14,21]

Myocardial vulnerability

Equally important is the concept of myocardial sensitivity to episodes of ischemia due to reduced coronary flow. The ischemic episode has to exceed a specific threshold-value in duration or severity, in order to produce clinical events, such as sudden myocardial infarction or even sudden cardiac death. This threshold-value depends on the sensitivity of the myocardium to ischemia, which is determined among others by its level of protection, for example by the presence of a collateral circulation.

At present, there are few methods to simply measure the sensitivity of the myocardium to ischemia due to sudden partial or complete reduction of blood supply.[17,18] Important factors that have been shown to negatively affect myocardial vulnerability include left ventricular hypertrophy (LVH), diastolic heart failure, and previous MI. These conditions are frequently present in older individuals.[14,22] The presence of LVH predisposes to ischemia due to several mechanisms.[23] There is an inadequate coronary growth relative to muscle mass, resulting in a decreased capillary density. The increased wall thickness increases the epicardial-endocardial distance resulting in greater transmural loss of, and lower subendocardial perfusion pressure. Coronary remodelling occurs with increased medial thickness and perivascular fibrosis. This results in an altered coronary vascular resting tone, and a limited ability to increase myocardial perfusion and coronary flow, and a rise in oxygen demand, in response to stress. A vicious circle is created in which LVH predisposes to ischemia, the ischemia causes an exaggerated impairment of relaxation in the heart with LVH, and this in turn worsens the severity of the subendocardial ischemia.[23]

Other factors that affect myocardial vulnerability include smoking, chronic renal insufficiency, diabetes mellitus, systemic hypertension, restrictive cardiomyopathy (most often amyloidosis), aortic valve stenosis, and hypertrophic cardio-myopathy.[22]

Determinants of coronary collateral circulation

Myocardial ischemia

Recurrent and severe myocardial ischemia is assumed to stimulate the development of coronary collateral circulation.[2] Takeshita et al. suggested that coronary collaterals develop in response to intermittent myocardial ischemia, and that these collaterals are preserved even if they are closed at rest, in order to offer immediately function upon acute coronary artery occlusion, following

recruitment.[24] Indeed, Herlitz et al. showed that patients with chronic angina pectoris (AP) prior to an acute MI had smaller infarcts compared to patients with AP of short duration prior to an acute MI. They had, however, a higher one-year mortality rate and a higher risk of reinfarction. This probably reflects more extensive coronary artery disease in these patients, with a higher risk of death. Besides, the fact that the patients with chronic AP had smaller infarcts might leave them with a larger area at risk, and thus they would be more likely to develop a reinfarction.[25] Myocardial ischemia, per se, can be a sufficient stimulus to induce coronary collateral development, possibly through biochemical signals, including release of angiogenic growth factors.[2] Exposure to low oxygen levels, both in vitro and in vivo, induce accumulation of VEGF mRNA.[10] Many other genes directly or indirectly involved in angiogenesis, are also upregulated in response to hypoxia, among others the VEGF receptors and TGF-β. A transcriptional complex, composed of hypoxia inducible factors, serves to augment expression of several of the genes involved in angiogenesis and cell survival.[10] However, the growth of collateral arteries through arteriogenesis is not dependent on ischemia.[8,11] Collateral arteries develop in non-hypoxic tissue. While angiogenesis is induced by hypoxia, arteriogenesis is induced by an increase in shear stress. The chemokines and growth factors involved in both processes also differ. Factors inducing angiogenesis (among others TGF-α, VEGF, b-FGF) induce proliferation of endothelial cells, whereas factors stimulating arteriogenesis (among others TGF-β, GM-CSF, b-FGF) also induce proliferation of smooth muscle cells.[11]

Pressure gradient and shear stresses

The process of arteriogenesis is mediated mechanically through an increase in shear stresses.[11] For example, in the event of a haemodynamically relevant stenosis of a main feeding artery, a pressure gradient is created and collateral arteries are recruited. Due to the decrease in arterial pressure distal of the stenosis, blood flow is redistributed through the pre-existent arterioles that now connect a high-pressure with a low-pressure area.[2,11] This results in an increased flow velocity and therefore increased shear stress in the pre-existent collateral

arteries, which leads to a marked activation of the endothelium, upregulation of cell adhesion molecules, and increased adherence of monocytes, that transform into macrophages. Subsequently, several morphological changes and vascular remodeling occur.[10,11]

Growth factors

Different growth factors and chemokines are involved in angiogenesis and arteriogenesis.[10,11] These include VEGF (vascular endothelial growth factor), TGF-α (transforming growth factor-α), and a-FGF (acidic fibroblast growth factor) in angiogenesis, GM-CSF (granulocyte-macrophage colony-stimulating factor), MCP-1 (monocyte chemoattractant protein-1), and TGF-β (transforming growth factor-β) in arteriogenesis. Some growth factors play a role in both processes, for example, b-FGF (basic fibroblast growth factor) and PDGF (platelet derived growth factor).[10,11] In ischemic tissue, enhanced expression of several angiogenic factors and their receptors has been demonstrated.[10] Conversely, impaired collateral circulation in diabetes, hyperlipidemia, and aging has been associated with reduced expression of angiogenic factors.[26] Several studies have reported increased levels of circulating angiogenic factors in patients with ischemic heart disease, stroke or limb ischemia, probably in response to tissue ischemia and injury.[12] Finally, Sasayama et al. observed that mast cells are associated with neovascularization by increasing endothelial cell migration as the earliest event in the formation of a capillary sprout.[2] They even proposed to treat ischemic heart disease with drugs (heparin) to promote the development of coronary collateral circulation. Since then, this concept of therapeutic angiogenesis and arteriogenesis has attracted much attention.[11] Interesting results have recently been published on therapeutic angiogenesis in peripheral artery disease by enhancing collateral development through administration of angiogenic growth factors.[27,28] In ischemic heart disease, early studies, using recombinant proteins, or genes encoding for vascular growth factors, showed encouraging results with clinical improvement, and suggested slightly improved myocardial perfusion in the treated area. However, subsequent trials failed to demonstrate a treatment effect.[11,12]

Collateral circulation and prognosis

Coronary collaterals may help protect the myocardium in patients with CAD. They limit myocardial ischemia during coronary occlusion in patients.[29] Fukai et al. found that well-developed coronary collaterals may minimize the infarct area, and predict the presence of viable myocardium in patients with a history of anteroseptal MI.[30] Sabia et al. demonstrated that the myocardium may remain viable for a prolonged period in patients with a recent acute MI and an occluded infarct-related coronary artery in the presence of collaterals.[31] Myocardial viability appeared to be associated with the presence of coronary collateral blood flow within the infarct bed. In case of an acute MI, the presence of coronary collaterals may extend the period of time available until successful coronary reperfusion.[32,33]

Collateral circulation can be visualized on coronary angiography.[34] The degree of collateral filling on angiography has been related to AP and the extent of previous MI in patients with CAD.[29,30] Similarly, the degree of collateral filling could predict the presence of residual viable myocardium in patients with an old MI.[30] However, studies in which collateral extent and function are studied as prognostic determinants of vascular outcome are hardly available. Only recently, Antoniucci et al. published a study on the significance of pre-intervention angiographic evidence of coronary collateral circulation in patients with acute MI, who underwent primary angioplasty or stenting within 6 hours of symptom onset.[35] At 6 months, the mortality rate was lower in patients with coronary collateral circulation compared to patients without collaterals, without clear effects on clinical outcomes.[35]

However, this study only considers the presence of coronary collaterals in patients with acute MI. Also, the duration of follow-up was rather short. Clearly, cardiovascular end-point studies with long-term follow-up are needed, in which collateral extent and function are studied as prognostic determinants of vascular outcome in patients with significant atherosclerosis.

We postulate that the potential of individuals to develop collaterals should be considered an additional indicator of cardiac vulnerability. The ability to develop collaterals is likely to provide an important response to vascular occlusive disease and to determine in part the severity of ischemic tissue damage.

Conclusion

The potential of individuals to develop coronary collateral circulation is often neglected, but of potential major importance in myocardial vulnerability. Well-developed coronary collaterals may help protect the myocardium from infarction during episodes of ischemia, and may extend the limited number of valuable "golden hours" from the onset of an acute myocardial infarct to successful coronary reperfusion. Promising results have recently been published on gene therapy in cardiovascular disease by promoting collateral development through the administration of angiogenic growth factors. Still, cardiovascular endpoint-studies with long-term follow-up, in which collateral extent and function are studied as prognostic determinants of vascular outcome, are needed to determine the position of collaterals in the mechanisms leading to ischemic events in patients with significant atherosclerosis. This may indicate new opportunities for prevention of re-events in patients suffering from coronary artery disease, or for prevention of events in those with advanced coronary atherosclerosis.

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Chapter 3

Determinants of coronary collaterals

Chapter 3.1

Cardiac ischemic burden determines the presence of coronary collateral circulation

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Abstract

Objective: The presence of coronary collaterals (CCs) is of vital importance during acute ischemia, however, marked interindividual variability exists. We examined the extent to which the burden of cardiac ischemia affects coronary collateral presence.

Methods: Cross-sectional study in 244 patients, admitted for elective coronary angioplasty. Collaterals were graded with Rentrop's classification. CC-presence was defined as Rentrop-grade ≥1. Cardiac ischemic burden, expressed as sum-score (range 0-4), was calculated by adding 1 point for each of the following four clinical factors present: angina pectoris (AP) on exertion, AP during emotions, previous myocardial infarction, and previous coronary intervention. These four clinical factors were chosen because they can be easily assessed in every patient. We used logistic regression with adjustment for gender, age, hypertension, diabetes mellitus, and hyperlipidemia.

Results: The extent of cardiac ischemic burden (OR 1.8 per score-point; 95% CI 1.3-2.5) was strongly associated with CC-presence. Additional adjustment for multi-vessel coronary disease left the relation essentially unchanged. Also, if the definition of collateral presence was limited to Rentrop-grade 2 and 3, the results were effectively the same.

Conclusion: The extent of cardiac ischemic burden determines the presence of coronary collaterals, and may provide a new index for simple assessment of collateral vascular development.

Introduction

The ability to develop collateral circulation provides an important response to vascular occlusive disease and determines in part the severity of ischemic tissue damage.[1-3] Coronary collaterals, or "natural bypasses", are anastomotic connections without an intervening capillary bed between portions of the same coronary artery and between different coronary arteries.[4] An organ will be less sensitive to episodes of ischemia if supplied with sufficient blood flow by well-developed collateral vessels. It is assumed that the presence and absence of coronary collaterals determines the prognosis of patients with coronary artery disease both during episodes of acute and unexpected ischemia, and during chronic ischemia. During acute cardiac ischemia coronary collaterals may extend the number of "golden hours" from the onset of the acute occlusion to the initiation of coronary reperfusion. Several mechanisms have been proposed to promote coronary collateral circulation, among which is recurrent and severe myocardial ischemia.[1-3] There is, however, marked interindividual variability in the presence and extent of collateral circulation. In this respect, also, the influence of the total burden of cardiac ischemia in an individual is largely unknown. In the present study, we examined the extent to which indicators of cardiac ischemic burden can be related to the presence of coronary collateral circulation.

Methods

The study was approved by the Medical Ethics Review Committee of the University Medical Center Utrecht (UMC Utrecht). Written informed consent was obtained from all patients. The study was performed in accordance with the principles of the Declaration of Helsinki.

Study population

A cross-sectional study was performed as part of the "Second Manifestations of ARTerial disease (SMART)" study. The latter study is an ongoing prospective cohort study conducted at the UMC Utrecht, designed to determine the prevalence of concomitant arterial disease and risk factors for atherosclerosis in a high risk population.[5] At enrollment, medical history is recorded using a standardized questionnaire, and height, weight, and blood pressure are measured. Blood and urine samples are taken. For the purpose of the present analyses, the baseline diagnostic coronary angiograms of 244 patients, who were referred for elective percutaneous transluminal coronary angioplasty (PTCA), and included in SMART between January 1, 1998 and July 8, 2002, were reviewed.

Coronary collateral circulation

The presence of coronary collaterals on each baseline coronary angiogram (CAG) was defined and visually assessed with the Rentrop's classification (grade 0 - no filling of collateral vessels; grade 1 - filling of collateral vessels without any epicardial filling of the recipient artery; grade 2 - partial epicardial filling by collateral vessels of the recipient artery; and grade 3 - complete epicardial filling by collateral vessels of the recipient artery).[6] Coronary collateral presence was defined as the presence of minimal or well-developed collaterals (grade 1, 2 or 3).[7,8] Grading was done independently by a trained research physician (J.K.) and a cardiologist (P.P.Th.d.J.), who were blinded to the clinical data. If an angiogram was graded differently, consensus was obtained. The pre-PTCA angiograms were graded in random order. To assess the interobserver variability of the grading, 100 randomly selected CAG's were scored by another cardiologist, not involved in the study and unaware of the results of the reading of the two other observers and of the clinical data, during a separate session. The strength of agreement between the two observers (J.K. & P.P.Th.d.J.) and the other cardiologist was good (Kappa 0.65, 95% confidence interval (CI) 0.51 - 0.79). Previously, the reproducibility of the Rentrop's score has already been described as high (Kappa 0.85, 95% CI 0.77-0.93).[9]

Indicators of cardiac ischemic burden

Indicators of cardiac ischemia were derived from self-administrated, standardized questionnaires: angina pectoris, previous myocardial infarction, previous coronary intervention, and duration since first occurrence. Severity of angina pectoris was classified as angina pectoris on brisk walking or climbing stairs ("on exertion"), or angina pectoris during emotions. The extent of vessel disease was defined by visual assessment of the coronary angiogram. Distinction was made between single (1) and multi-vessel (2 or 3) coronary disease on the basis of ≥ 50% luminal narrowing in at least one view.[10] The burden of cardiac ischemia in a patient was expressed as a sum-score (range 0 - 4), and calculated by adding 1 point for each of the following four clinical factors present, notably angina pectoris on exertion, angina pectoris during emotions, previous myocardial infarction, and a history of PTCA or coronary artery bypass grafting (CABG). These four clinical factors were chosen because they can be easily assessed in every patient, either being present or absent.

Data-analysis

The primary outcome of interest was the presence of coronary collaterals, defined as a Rentrop-grade ≥ 1.[7,8] Unless specified otherwise, data are presented as count with percentage or mean ± standard error of the mean. Continuous variables were checked for normal distribution. The variables that defined duration of angina pectoris, duration since myocardial infarction, and duration since first coronary intervention until the index-PTCA, were transformed first by subtraction of the corresponding mean value, and then by insertion of the value zero for every patient, to whom the corresponding previous event did not apply.

The association between the presence and absence of coronary collaterals, and each potential indicator of cardiac ischemia was quantified with logistic regression analysis with adjustment for gender, age, hypertension, diabetes mellitus, and hyperlipidemia. Similarly, the association between the presence and absence of coronary collaterals, and the cardiac ischemic burden sum-score was quantified with logistic regression analysis, first only with adjustment for the confounders

mentioned above, and in addition also with adjustment for multi-vessel coronary disease.

Finally, the analyses were repeated with a different, but frequently used definition of coronary collateral presence, limited to the presence of well-developed collaterals only (grade 2 or 3), while grade 0 or 1 collaterals were considered to be absent.[9,11-14]

Odds ratios with 95% confidence interval are presented. A two-sided (multivariate) P-value < 0.05 was considered statistically significant. The statistical package used was SPSS for Windows, release 11.0.1 (SPSS Inc., Chicago, Illinois, USA).

Results

Patient characteristics

Baseline- and clinical characteristics of the study population are presented in Table 1. Coronary collaterals were present in 91 patients (37%): 13 patients (14%) had grade 1 (no epicardial filling), 33 patients (36%) had grade 2 (partial epicardial filling), and 45 patients (50%) had grade 3 collaterals (complete epicardial filling).

Table 1. Baseline- and clinical characteristics of the study population (n = 244).

characteristic	n (valid %) or mean ± SD
demographics:	
male gender	203 (83.2%)
age at index-PTCA (yrs)	58.1 ± 9.2
cardiovascular risk factors:	
current smoking	69 (28.5%)
current alcohol consumption	186 (76.9%)
hypertension	91 (38.2%)
diabetes mellitus	49 (20.1%)
hyperlipidemia	203 (83.5%)
obesity (BMI ≥ 30 kg/m^2)	43 (18.0%)
angina:	
AP on exertion	171 (71.5%)
AP during emotions	77 (32.4%)
prior angina pectoris (AP)	224 (92.2%)
previous conditions:	
previous TIA or stroke	24 (9.9%)
previous myocardial infarction	106 (43.8%)
previous PTCA or CABG	77 (31.6%)
previous non-cardiac vascular surgery	20 (8.2%)
angiographic characteristics:	
multi-vessel coronary disease	101 (41.4%)
impaired left-ventricle function*	90 (41.5%)
coronary collaterals present (Rentrop-grade ≥ 1)	91 (37.3%)
Rentrop-grade 1	13 (14%)
Rentrop-grade 2	33 (36%)
Rentrop-grade 3	45 (50%)

* In 27 patients the ventriculogram turned out not to be performed.
AP = angina pectoris; BMI = body mass index; CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty; SD = standard deviation; TIA = transient ischemic attack.

Indicators of cardiac ischemic burden and the presence of coronary collaterals

Table 2 summarizes the results of the analyses, both unadjusted, and adjusted for gender, age, hypertension, diabetes mellitus, and hyperlipidemia in relation to the presence of coronary collaterals, defined as Rentrop-grade ≥ 1. Angina pectoris on exertion, angina pectoris during emotions, previous myocardial

infarction, duration since very first PTCA or CABG (if prior) until the index-PTCA, and multi-vessel coronary disease, each were positively associated with the presence of coronary collaterals. The other indicators of cardiac ischemia, e.g. prior angina pectoris, or a history of PTCA or CABG, were not associated with coronary collateral presence.

The extent of cardiac ischemic burden, expressed as a sum-score, was strongly associated with the presence of coronary collateral circulation (Table 2). Additional adjustment for multi-vessel coronary disease left the relation essentially unchanged (odds ratio [OR] 1.6 per score-point; 95% confidence interval [CI] 1.2-2.3). Figure 1 displays the percentage of patients with coronary collateral circulation per total number of patients across categories of the cardiac ischemic burden sum-score.

Finally, if the definition of coronary collateral presence was limited to well-developed collaterals only (Rentrop-grade 2 or 3), the results were effectively the same: angina pectoris on exertion (OR 4.8; 95% CI 2.1-11.2), angina pectoris during emotions (OR 1.8; 95% CI 0.9-3.4), prior angina pectoris (OR 1.5; 95% CI 0.5-5.1), previous myocardial infarction (OR 1.4; 95% CI 0.8-2.7), a history of PTCA or CABG (OR 1.1; 95% CI 0.6-2.2), duration of anginal complaints (OR 1.0 per year; 95% CI 1.0-1.1), duration since previous myocardial infarction (OR 1.1 per year; 95% CI 1.0-1.2), duration since very first PTCA or CABG (OR 1.1 per year; 95% CI 1.0-1.2), multi-vessel coronary disease (OR 3.3; 95% CI 1.7-6.3), and the extent of cardiac ischemic burden (OR 1.8 per score-point; 95% CI 1.3-2.5). Also, after additional adjustment for multi-vessel coronary disease, the relation between the extent of cardiac ischemic burden and the presence of coronary collaterals remained virtually unchanged (OR 1.6 per score-point; 95% CI 1.1-2.3).

Table 2. Indicators of cardiac ischemic burden and their association with the presence of coronary collateral circulation (Rentrop-grade ≥ 1).

indicators of cardiac ischemic burden	**collaterals present (n = 91)** Rentrop = 1, 2, or 3 **n (valid %) or mean ± SEM**	**collaterals absent (n = 153)** Rentrop = 0 **n (valid %) or mean ± SEM**	**unadjusted OR (95% CI)**	**adjusted OR* (95% CI)**
AP on exertion	72 (80.9%)	99 (66.0%)	2.2 (1.2-4.1)	4.1 (1.9-8.9)
AP during emotions	34 (38.6%)	43 (28.7%)	1.6 (0.9-2.7)	1.8 (1.0-3.4)
prior angina pectoris (AP)	85 (93.4%)	139 (91.4%)	1.3 (0.5-3.6)	2.0 (0.6-6.5)
previous myocardial infarction (MI)	46 (50.5%)	60 (39.7%)	1.6 (0.9-2.6)	2.0 (1.1-3.6)
previous PTCA or CABG	29 (31.9%)	48 (31.4%)	1.0 (0.6-1.8)	1.0 (0.5-1.8)
duration AP until index-PTCA (yrs)	3.7 ± 0.7	3.0 ± 0.4	1.0 (1.0-1.1)	1.0 (1.0-1.1)
duration since MI until index-PTCA (yrs)	5.0 ± 1.2	3.1 ± 0.6	1.1 (1.0-1.1)	1.1 (1.0-1.1)
duration since first PTCA or CABG until index-PTCA (yrs)	4.9 ± 1.2	2.2 ± 0.7	1.1 (1.0-1.2)	1.1 (1.0-1.2)
multi-vessel coronary disease	52 (57.1%)	49 (32.0%)	2.8 (1.7-4.8)	3.2 (1.7-6.0)
cardiac ischemic burden sum-score † (range 0 - 4)	2.0 ± 0.09	1.6 ± 0.08	1.5 (1.1-2.0)	1.8 (1.3-2.5)

* Odds ratios and 95% confidence intervals adjusted for gender, age, hypertension, diabetes mellitus, and hyperlipidemia.
† The cardiac ischemic burden sum-score (range 0 - 4) is calculated by adding 1 point for each of the following four clinical factors present, notably AP on exertion, AP during emotions, previous MI, and a history of PTCA or CABG.
AP = angina pectoris; CABG = coronary artery bypass grafting; CI = confidence interval; MI = myocardial infarction; OR = odds ratio; PTCA = percutaneous transluminal coronary angioplasty; SEM = standard error of the mean.

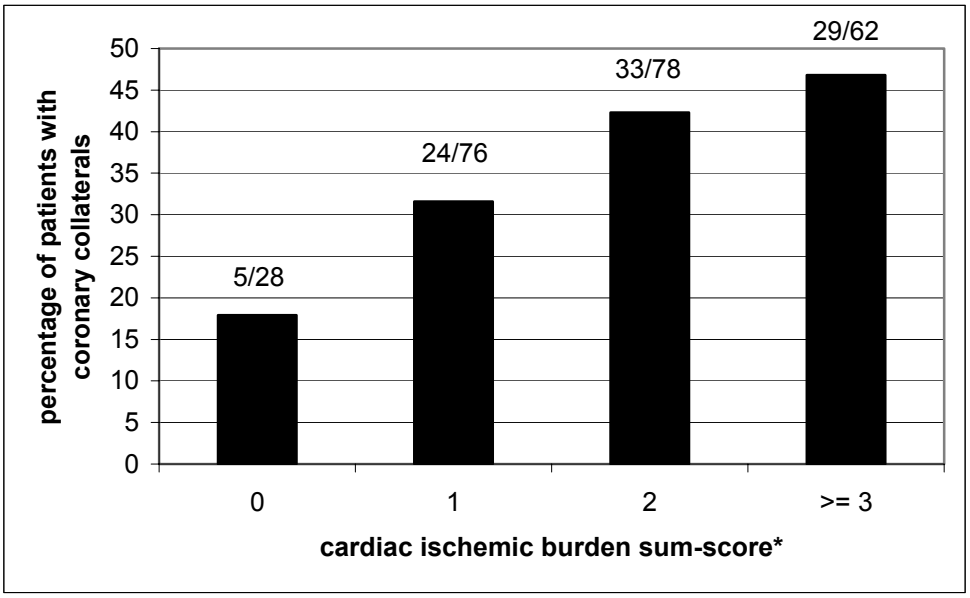

Figure 1. Percentage of patients with coronary collateral circulation (Rentrop-grade ≥ 1) per total number of patients across categories of the cardiac ischemic burden sum-score.
* The cardiac ischemic burden sum-score (range 0 - 4) is calculated by adding 1 point for each of the following four clinical factors present, notably angina pectoris on exertion, angina pectoris during emotions, previous myocardial infarction, and a history of percutaneous transluminal coronary angioplasty or coronary artery bypass grafting.

Discussion

In the present study among 244 patients referred for elective PTCA, we found that angina pectoris on exertion, angina pectoris during emotions, a history of myocardial infarction, time since first coronary intervention, and multi-vessel coronary disease were clear indicators of coronary collaterals in patients with documented coronary artery disease and referred for PTCA. In addition, the extent of cardiac ischemic burden in an individual, expressed as the "cardiac ischemic burden sum-score", using four clinical factors, that can be easily assessed in every patient, was strongly associated with the presence of coronary collaterals. These clinical factors involved the presence or absence of angina pectoris on exertion, angina pectoris during emotions, a history of myocardial

infarction, and a history of PTCA or CABG. This finding remained unchanged even after additional adjustment for severity of coronary disease, or if the definition of collateral presence was limited to well-developed coronary collaterals only (Rentrop-grade 2 or 3).

To appreciate these results, some aspects of this cross-sectional study need to be addressed. First, we investigated the presence or absence of coronary collateral circulation, but not the development of collaterals over time. This makes causal inference regarding the role of ischemia in promoting development of collaterals preliminary.

Second, the use of angiography to define and assess coronary collaterals may have influenced our observations. Coronary angiography, although the most frequently used diagnostic technique for the assessment of collateral vessels, can only identify vessels > 100 μm in diameter, whereas most collateral vessels are smaller.[15] Furthermore, even though the overlap between quantitative measures and qualitative angiographic degrees of collateral flow has been demonstrated to be quite large[12], quantitative indices of collateral circulation may be better markers of the functional significance of collateral vessels, in particular in recruitable (Rentrop-grade 1) collaterals.[9,16] A recent study, nonetheless, reported good correlation between a novel angiographic method of assessment and function.[17] This is to be expected considering the fundamental physical law describing that vessel radius is related to the fourth power of flow.[18] It is, thus, likely that the morphologic degree of collaterals used in this study, is closely related with the functional degree of coronary collateral circulation. In the present study, we therefore applied two definitions of the presence of coronary collaterals, either with, or without Rentrop-grade 1 collaterals included. The results obtained were, however, essentially the same, in particular with regard to the estimated total burden of cardiac ischemia and its relation with the presence of coronary collateral vessels.

Finally, a last source of unquantifiable bias could have been introduced by the selection of patients, admitted for elective coronary angioplasty. This selection is highly restrictive even within the domain of patients with known coronary artery disease. It must be acknowledged that patients with sufficient collaterals may not undergo diagnostic catheterization or angioplasty. At the other extreme, patients with extensive coronary artery disease with or without collaterals may be referred for coronary surgery and not angioplasty.

The mechanism of the formation of coronary collaterals is subject to intense preclinical and clinical research. In addition to ischemic burden as explored in the present study, genetic factors and a number of other patient characteristics including age, physical exercise, body mass index, hyperlipidemia, hyper-homocysteinemia, diabetes mellitus, hypertension, and use of various cardiovascular drugs have been proposed.[7,11,19-29] Yet, results of these studies are conflicting and, therefore, their pathophysiologic role and importance is still unclear.[1-3]

The finding that separate indicators of cardiac ischemic burden are positively associated with presence of coronary collateral circulation, is in agreement with other reports in the literature. Several studies have indicated coronary lesion severity to be a major determinant of collateral vascular growth.[14,26,27,30] Unfortunately, in the present study, quantitative coronary angiography could not be performed, due to the use of retrieved pre-PTCA coronary angiograms. Piek et al. also found that, in addition, proximal location, and the duration of angina independently predicted the presence of recruitable coronary collaterals.[27] Recent findings of Miura et al., suggest that the duration and severity of angina are associated with the development of coronary collateral circulation in patients with angina, who underwent coronary angiography.[21] As in the present study, they found that coronary collaterals were present more frequently in patients with multi-vessel coronary disease.[21] In a study of 248 patients with acute myocardial infarction, Fujita et al. found that a history of angina pectoris prior to the acute event was a positive indicator of well-developed (Rentrop-grade 2 or 3) coronary

collaterals.[11] Finally, in accordance with the data of the present study, Kilian et al. found that a longer time since diagnosis of ischemic heart disease was positively associated with the presence of Rentrop-grade 3 collaterals.[24]

However, the influence of the total burden of cardiac ischemia in an individual, exerted on the presence of the coronary collateral circulation, is at present largely unknown. In view of the findings summarized above, it would be likely though, that a higher cardiac ischemic burden would be associated with a more frequent presence of coronary collaterals. In the present study, we therefore specifically investigated the extent to which the burden of cardiac ischemia affects the presence of coronary collaterals. We developed a cardiac ischemic burden sum-score, that uses four clinical factors, that can easily be assessed in each individual, notably angina pectoris on exertion, angina pectoris during emotions, a history of myocardial infarction, and a history of coronary intervention. Indeed, the extent of cardiac ischemic burden, defined by this sum-score, was strongly associated with the presence of coronary collateral circulation, even if severity of coronary disease was taken into account, or if the definition of collateral presence was limited to well-developed coronary collaterals only (Rentrop-grade 2 or 3). In addition, this estimated total cardiac ischemic burden may also provide a new index for simple, non-invasive assessment of collateral vascular development.

In conclusion, the results of this study indicate that the estimated total burden of cardiac ischemia in an individual is strongly associated with the presence of coronary collaterals. In addition, the cardiac ischemic burden sum-score, developed in this study, may provide a new index for simple, non-invasive assessment of the presence of coronary collateral vessels.

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Appendix

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Chapter 3.2

High blood pressure is inversely related with presence and extent of coronary collaterals

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Abstract

Background: Patients with hypertension have an increased case-fatality during acute myocardial infarction. Coronary collateral circulation has been proposed to reduce the risk of death during acute ischemia. We determined whether and to which degree high blood pressure affects the presence and extent of coronary collateral circulation.

Methods: Cross-sectional study in 237 patients (84% males), admitted for elective coronary angioplasty between January 1998 and July 2002. Collaterals were graded with Rentrop's classification (grade 0 - 3). Coronary collateral presence was defined as Rentrop-grade ≥1. Blood pressure was measured twice with an inflatable cuff-manometer in seated position. Pulse pressure was calculated by systolic blood pressure (SBP) - diastolic blood pressure (DBP). Mean arterial pressure was calculated by DBP + 1/3*(SBP-DBP). Systolic hypertension was defined by a reading ≥140 mmHg. We used logistic regression with adjustment for putative confounders.

Results: Systolic blood pressure (odds ratio (OR) 0.86 per 10 mmHg; 95% confidence-interval (CI) 0.73-1.00), diastolic blood pressure (OR 0.67 per 10 mmHg; 95% CI 0.49-0.93), mean arterial pressure (OR 0.73 per 10 mmHg; 95% CI 0.56-0.94), systolic hypertension (OR 0.49; 95% CI 0.26-0.94), and antihypertensive treatment (OR 0.53; 95% CI 0.27-1.02), each were inversely associated with the presence of coronary collaterals. Also, among patients with coronary collaterals, there was a graded, significant inverse relation between levels of systolic blood pressure, levels of pulse pressure, and collateral extent.

Conclusion: There is an inverse relationship between blood pressure and the presence and extent of coronary collateral circulation in patients with ischemic heart disease.

Introduction

Pre-infarction systolic blood pressure strongly relates to death and increased case-fatality in patients with an acute myocardial infarction.[1] In a prospective analysis from the Finnmark Study, in which 46% of the 760 patients with myocardial infarction died during follow-up, Njolstad and Arnesen found systolic blood pressure at baseline to lead to a relative risk of 1.22 (95% confidence interval 1.13-1.31) per 15 mmHg. The prognosis of patients with an acute myocardial infarction may be beneficially affected by the presence of coronary collateral circulation.[2,3] Coronary collaterals, or "natural bypasses", are anastomotic connections without an intervening capillary bed between portions of the same coronary artery and between different coronary arteries.[4] Well-developed coronary collaterals may minimize the infarct area and predict the presence of viable myocardium in patients with a history of anteroseptal myocardial infarction.[5] Moreover, coronary collaterals may increase the number of "golden hours" from the onset of an acute myocardial infarction to successful coronary reperfusion. There appears, however, to be marked interindividual variability in the extent of collateral circulation.[2]

High blood pressure has been suggested to influence the development of coronary collaterals, but conflicting results remain, and the exact mechanism is still unknown, at present.[6-11] In the present study, we sought to determine whether high blood pressure is related to the presence and extent of coronary collateral circulation.

Methods

The study was approved by the Medical Ethics Review Committee of the University Medical Center Utrecht (UMC Utrecht). Written informed consent was obtained from all patients.

Study population

A cross-sectional study was performed as part of the "Second Manifestations of ARTerial disease (SMART)" study. The SMART study is an ongoing prospective cohort study conducted at the UMC Utrecht.[12] For the purpose of the present analyses, the baseline diagnostic coronary angiograms of 237 patients, who were referred for elective percutaneous transluminal coronary angioplasty (PTCA) and took part in the SMART study between January 1, 1998 and July 8, 2002, were reviewed. At enrollment, medical history was recorded with a standardized questionnaire, and height, weight, and blood pressure was measured. Blood and urine samples were taken.

Coronary collateral circulation

The presence of coronary collaterals on each baseline coronary angiogram (CAG) was defined and visually assessed with the Rentrop's classification (grade 0 - no filling of collateral vessels; grade 1 - filling of collateral vessels without any epicardial filling of the recipient artery; grade 2 - partial epicardial filling by collateral vessels of the recipient artery; and grade 3 - complete epicardial filling by collateral vessels of the recipient artery).[13] Grading was done independently by a trained research physician (J.K.) and a cardiologist (P.P.Th.d.J.), who were blinded to the clinical data. If an angiogram was graded differently, consensus was obtained. The pre-PTCA angiograms were graded in random order. Previously, the reproducibility of the Rentrop's score has already been described as high (Kappa 0.85, 95% CI 0.77-0.93).[14]

Measures of blood pressure

At enrollment in the SMART study, blood pressure (BP) was measured by trained observers, at each arm with an inflatable cuff-manometer (Omron M5-1, Intelli Sense, Omron Matsusaka Co., Ltd. Japan; cuff size Typ M or L depending on the patient's arm circumference), according to a standardized protocol. The patients were seated on a chair with their arms lying on a table. Blood pressure was measured twice about 15 minutes apart. The mean value of these two blood pressure readings at each arm was used. Pulse pressure was calculated by

systolic BP - diastolic BP. Mean arterial pressure was calculated by diastolic BP + 1/3 x (systolic BP - diastolic BP).[15] Systolic hypertension was defined as systolic BP ≥ 140 mmHg, and diastolic hypertension as diastolic BP ≥ 95 mmHg. A history of hypertension and use of antihypertensive treatment was derived from the self-administrated, standardized questionnaires.

Data-analysis

The primary outcome of interest was the presence of coronary collaterals, defined as a Rentrop-grade ≥ 1.[16-18] Unless specified otherwise, data are presented as count with percentage, or mean ± standard deviation. The association between the presence and absence of coronary collaterals, and each separate measure of blood pressure was quantified with binary logistic regression analysis with adjustment for gender, age, history of myocardial infarction, time-interval since myocardial infarction (if previous), and diabetes mellitus. A history of myocardial infarction and diabetes mellitus were entered into the model to adjust for potential confounding of the relation between blood pressure and the presence of coronary collateral circulation.[7,8] Subsequently, the analyses were repeated with additional adjustment for other putative confounders, namely number of types of antihypertensive medication, time-interval since diagnosis of hypertension, hyperlipidemia, use of statins, current smoking, number of packyears, duration of anginal complaints, presence of coronary occlusion, degree of most severe coronary obstruction, and multi-vessel coronary disease.

The relation between the extent of coronary collateral circulation and measures of blood pressure (as a continuous variable, notably systolic BP, diastolic BP, pulse pressure, and mean arterial pressure) was quantified with linear logistic regression analysis with adjustment for gender, age, a history of myocardial infarction, and diabetes mellitus. Then, the analyses were repeated with further adjustment for the same, putative confounders, mentioned above. Odds ratios, betas, and 95% confidence interval are presented. A two-sided (multivariate) P-value < 0.05 was considered significant. The statistical package used was SPSS for Windows, release 12.0.1 (SPSS Inc., Chicago, Illinois, USA).

Table 1. Baseline- and clinical characteristics of the study population (n = 237).

characteristic	all patients (n = 237)	collaterals present (n = 88) Rentrop = 1 - 3	collaterals absent (n = 149) Rentrop = 0	P-value
demographics:				
male gender	198 (84%)	77 (88%)	121 (81%)	0.21
age at index-PTCA (yrs)	57.9 ± 9.2	57.6 ± 9.5	58.1 ± 9.1	0.64
cardiovascular risk factors:				
current smoking	68 (29%)	36 (41%)	32 (22%)	< 0.01
current alcohol consumption	181 (77%)	68 (77%)	113 (76%)	0.87
hypertension	90 (38%)	26 (30%)	64 (43%)	0.04
diabetes mellitus	47 (20%)	24 (27%)	23 (15%)	0.03
hyperlipidemia	196 (83%)	72 (82%)	124 (84%)	0.70
obesity (BMI ≥ 30 kg/m^2)	41 (17%)	14 (16%)	27 (18%)	0.68
blood pressure (BP):				
systolic BP (mmHg)	135 ± 21	132 ± 18	137 ± 22	0.04
diastolic BP (mmHg)	77 ± 10	76 ± 9	78 ± 10	0.06
pulse pressure (mmHg) *	58 ± 17	56 ± 14	59 ± 18	0.16
mean arterial pressure (mmHg) †	97 ± 12	94 ± 11	98 ± 12	0.03
mean number of types of antihypertensive drugs	1.5 ± 0.8	1.5 ± 0.8	1.5 ± 0.9	0.82
duration since diagnosis hypertension (yrs)	11.0 ± 12.5	9.0 ± 10.1	12.0 ± 13.5	0.28
previous conditions:				
prior angina pectoris	219 (92%)	82 (93%)	137 (92%)	0.73
previous myocardial infarction	102 (43%)	44 (50%)	58 (39%)	0.11
previous PTCA or CABG	74 (31%)	28 (31%)	46 (31%)	0.88
previous TIA or stroke	24 (10%)	5 (6%)	19 (13%)	0.08
previous non-cardiac vascular surgery	19 (8%)	9 (10%)	10 (7%)	0.34
angiographic characteristics:				
degree of coronary stenosis:				
50-90% ‡	149 (63%)	20 (23%)	129 (87%)	-
90-99%	39 (17%)	30 (34%)	9 (6%)	< 0.01
100%	49 (21%)	38 (43%)	11 (7%)	< 0.01
coronary occlusion	49 (21%)	38 (43%)	11 (7%)	< 0.01
multi-vessel coronary disease	98 (41%)	50 (57%)	48 (32%)	< 0.01
impaired left-ventricle function §	87 (41%)	34 (43%)	53 (41%)	0.71
1-vessel coronary disease ‡	139 (59%)	38 (43%)	101 (68%)	-
2-vessel coronary disease	77 (33%)	38 (43%)	39 (26%)	< 0.01
3-vessel coronary disease	21 (9%)	12 (14%)	9 (6%)	< 0.01

Table 1 is continued on the next page.

Table 1. Continued.

characteristic	all patients (n = 237)	collaterals present (n = 88) Rentrop = 1 - 3	collaterals absent (n = 149) Rentrop = 0	P-value
type of antihypertensive drugs used:				
beta-adrenergic receptor antagonists	184 (78%)	70 (80%)	114 (77%)	0.59
diuretics	20 (8%)	5 (6%)	15 (10%)	0.24
ACE-inhibitors	44 (19%)	17 (19%)	27 (18%)	0.82
calcium channel-blockers	96 (41%)	34 (39%)	64 (42%)	0.65
alpha-1 receptor antagonists	1	-	1	‖
combined prescription medicines	4	4	-	‖
selective imidazoline receptor agonists	1	-	1	‖
angiotensin II receptor blockers	3	-	3	‖
other type of antihypertensive drugs	1	-	1	‖
statins:				
use of statins	130 (55%)	52 (59%)	78 (52%)	0.31

Number of patients (valid %) or mean ± SD.
* Pulse pressure = systolic BP - diastolic BP.
† Mean arterial pressure = diastolic BP + 1/3 x (systolic BP - diastolic BP).
‡ Reference-category.
§ In 27 patients the ventriculogram turned out not to be performed.
‖ Too few data.
BMI = body mass index; BP = blood pressure; CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty; SD = standard deviation; TIA = transient ischemic attack.

Results

Patient characteristics

Baseline- and clinical characteristics of the study population are presented in Table 1. Coronary collaterals were present in 88 patients (37%): 13 patients (15%) had grade 1 (no epicardial filling), 31 patients (35%) had grade 2 (partial epicardial filling), and 44 patients (50%) had grade 3 collaterals (complete epicardial filling).

Blood pressure and presence of coronary collaterals

Table 2 summarizes the results of the analyses regarding measures of blood pressure and the presence of coronary collateral circulation, both unadjusted, and adjusted for gender, age, history of myocardial infarction, and diabetes mellitus. Systolic blood pressure, diastolic blood pressure, mean arterial pressure, systolic hypertension, and antihypertensive treatment, were each inversely associated with the presence of coronary collaterals. Pulse pressure and diastolic hypertension were not associated with coronary collateral presence. Further adjustment for number of types of antihypertensive medication, time-interval since diagnosis of hypertension, hyperlipidemia, use of statins, current smoking, number of packyears, duration of anginal complaints, presence of coronary occlusion, degree of most severe coronary obstruction, and multi-vessel coronary disease, left the relations essentially unchanged. However, in this full model, antihypertensive treatment (OR 0.85; 95% CI 0.32-2.27) was no longer associated with collateral presence.

Table 2. Measures of blood pressure and their association with the presence of coronary collaterals.

measures of blood pressure (BP)	collaterals present (n = 88) Rentrop = 1, 2, or 3 n (valid %) or mean ± SEM	collaterals absent (n = 149) Rentrop = 0 n (valid %) or mean ± SEM	unadjusted OR (95% CI)	adjusted OR* (95% CI)	P-value after adjustment*
systolic BP (mmHg)	132 ± 1.9	137 ± 1.8	0.87 (0.76-1.00)§	0.86 (0.73-1.00)§	0.05
diastolic BP (mmHg)	76 ± 1.0	78 ± 0.8	0.76 (0.57-1.01)§	0.67 (0.49-0.93)§	0.02
pulse pressure (mmHg)†	56 ± 1.5	59 ± 1.5	0.89 (0.75-1.05)§	0.91 (0.75-1.11)§	0.34
mean arterial pressure (mmHg)‡	94 ± 1.1	98 ± 1.0	0.77 (0.61-0.97)§	0.73 (0.56-0.94)§	0.02
systolic hypertension (SBP ≥ 140 mmHg)	26 (29.5%)	64 (43.0%)	0.56 (0.32-0.98)	0.49 (0.26-0.94)	0.03
diastolic hypertension (DBP ≥ 95 mmHg)	2 (2.3%)	9 (6.0%)	0.36 (0.08-1.71)	0.33 (0.07-1.59)	0.17
antihypertensive treatment	22 (25.6%)	52 (37.4%)	0.58 (0.32-1.04)	0.53 (0.27-1.02)	0.06

* Odds ratios and 95% confidence intervals adjusted for gender, age, history of myocardial infarction (MI), time-interval since MI, and diabetes mellitus.
† Pulse pressure = systolic BP - diastolic BP
‡ Mean arterial pressure = diastolic BP + 1/3 x (systolic BP - diastolic BP)
§ Odds ratio and 95% confidence interval expressed per 10 mmHg.
BP = blood pressure; CI = confidence interval; DBP = diastolic blood pressure; OR = odds ratio; SBP = systolic blood pressure; SEM = standard error of the mean.

Blood pressure and extent of coronary collateral circulation

Among patients with coronary collaterals, there was a graded and significant inverse relation between levels of systolic blood pressure, levels of pulse pressure, and the extent of coronary collaterals (see Table 3). Diastolic blood pressure and mean arterial pressure were not associated with coronary collateral extent. Additional adjustment for number of types of antihypertensive medication, time-interval since diagnosis of hypertension, hyperlipidemia, use of statins, current smoking, number of packyears, duration of anginal complaints, presence of coronary occlusion, degree of most severe coronary obstruction, and multi-vessel coronary disease, did not materially change the findings. Bar graphs are presented, displaying the relation between each continuous measure of blood pressure and each degree of coronary collateral circulation (see Figures 1 through 4).

Table 3. Blood pressure and its relation with the extent of coronary collateral (CC) circulation.

measures of blood pressure (BP)	**CC-grade 1 (n = 13)** Rentrop = 1 *reference-category*	**CC-grade 2 (n = 31)** Rentrop = 2	**CC-grade 3 (n = 44)** Rentrop = 3	**unadjusted Beta* (95% CI)**	**adjusted Beta*† (95% CI)**	**P-value after adjustment†**
	mean ± SEM	**mean ± SEM**	**mean ± SEM**			
systolic BP (mmHg)	141 ± 6.5	133 ± 3.4	128 ± 2.0	-0.11 (-0.19;-0.02)	-0.11 (-0.20;-0.01)	0.03
diastolic BP (mmHg)	76 ± 2.7	75 ± 1.8	76 ± 1.3	0.04 (-0.13; 0.21)	-0.01 (-0.20; 0.18)	0.94
pulse pressure (mmHg)‡	65 ± 5.0	58 ± 2.6	51 ± 1.7	-0.18 (-0.28;-0.07)	-0.17 (-0.29;-0.05)	< 0.01
mean arterial pressure (mmHg)§	97 ± 3.6	95 ± 2.1	94 ± 1.4	-0.08 (-0.23; 0.07)	-0.10 (-0.26; 0.06)	0.21

* Betas and 95% confidence intervals expressed per 10 mmHg.
† Betas and 95% confidence intervals adjusted for gender, age, history of myocardial infarction (MI), time-interval since MI, and diabetes mellitus.
‡ Pulse pressure = systolic BP - diastolic BP
§ Mean arterial pressure = diastolic BP + 1/3 x (systolic BP - diastolic BP)
BP = blood pressure; CC = coronary collateral; CI = confidence interval; SEM = standard error of the mean.

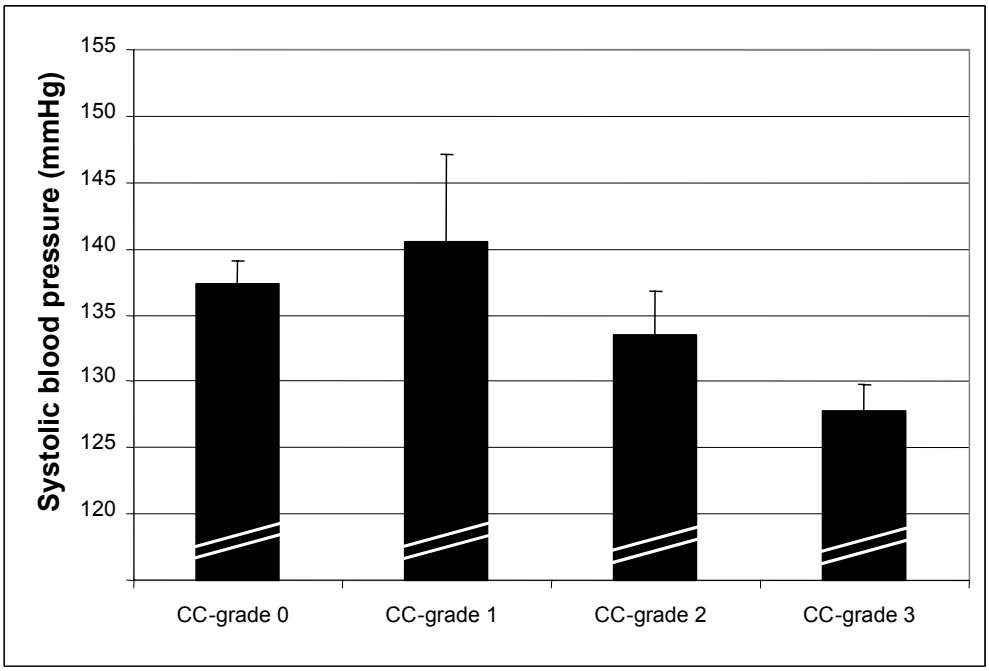

Figure 1. Systolic blood pressure across degrees of coronary collateral circulation.
Mean value and standard error of the mean. CC = coronary collateral; grade 0 = no filling of collateral vessels; grade 1 = filling of collateral vessels without any epicardial filling of the recipient artery; grade 2 = partial epicardial filling by collateral vessels of the recipient artery; grade 3 = complete epicardial filling by collateral vessels of the recipient artery.

Discussion

In the present study among 237 patients referred for elective PTCA, we found that high levels of blood pressure were inversely related with the presence and extent of coronary collaterals. This was particularly pronounced for the systolic blood pressure and pulse pressure.

To appreciate these results, some aspects of this study need to be addressed. First, we investigated the presence or absence of coronary collateral circulation cross-sectionally, but not the development of collaterals over time. This makes

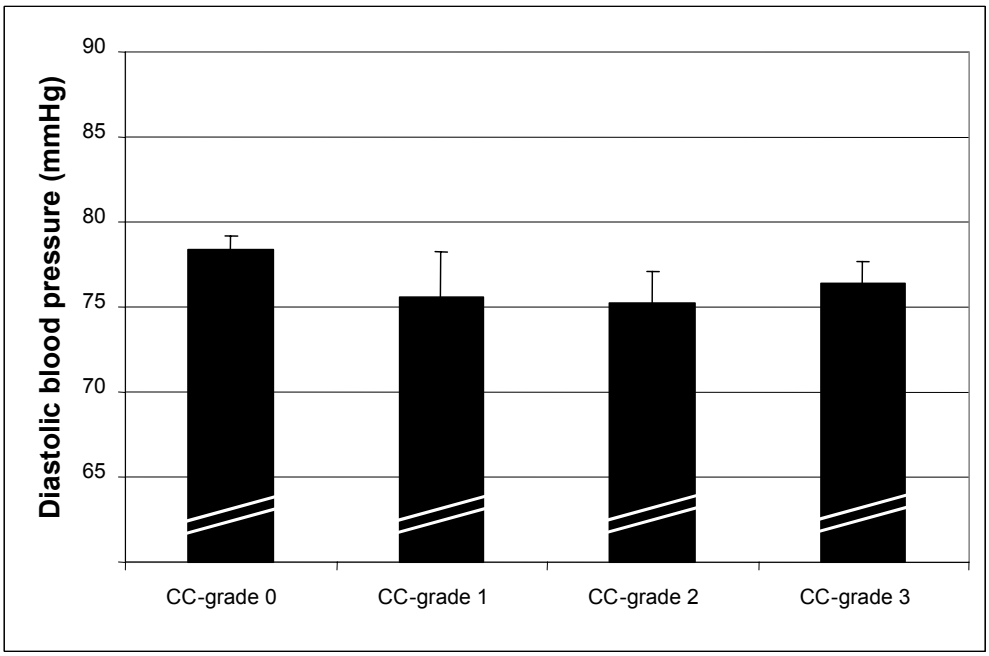

Figure 2. Diastolic blood pressure across degrees of coronary collateral circulation.
Mean value and standard error of the mean. CC = coronary collateral; grade 0 = no filling of collateral vessels; grade 1 = filling of collateral vessels without any epicardial filling of the recipient artery; grade 2 = partial epicardial filling by collateral vessels of the recipient artery; grade 3 = complete epicardial filling by collateral vessels of the recipient artery.

causal inference regarding the role of high blood pressure in reducing development of collaterals preliminary.

Second, the use of angiography to define and assess coronary collaterals may have influenced our observations. Coronary angiography, although the most frequently used diagnostic technique for the assessment of collateral vessels, can only identify vessels > 100 μm in diameter, whereas most collateral vessels are smaller.[19] Furthermore, even though the overlap between quantitative measures and qualitative angiographic degrees of collateral flow has been demonstrated to be quite large[20], quantitative indices of collateral circulation may be better markers of the functional significance of collateral vessels, in particular in recruitable (Rentrop-grade 1) collaterals.[14,21,22] A recent study, nonetheless,

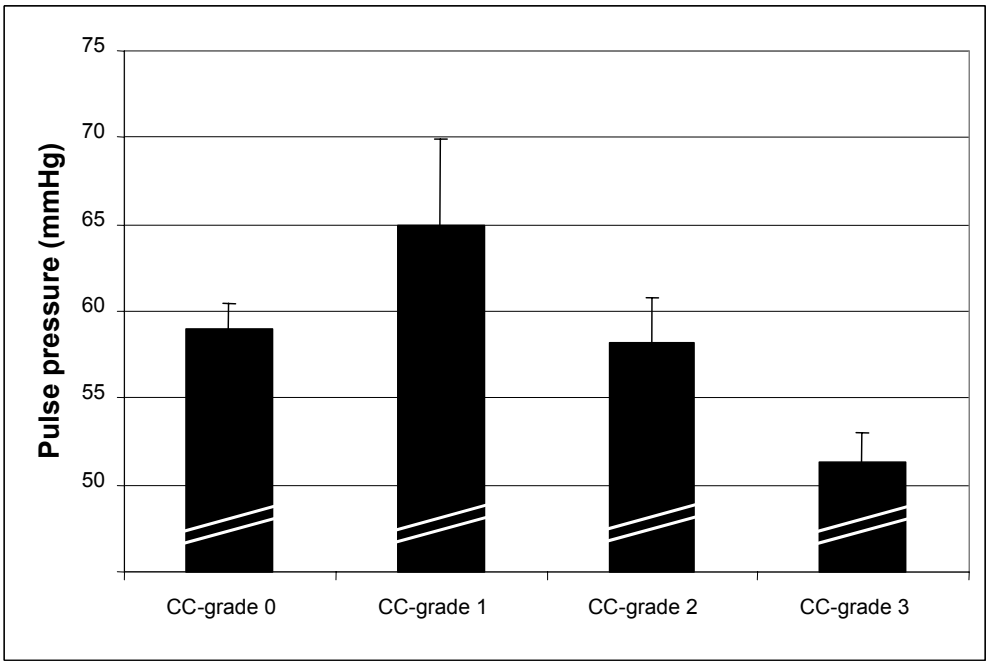

Figure 3. Pulse pressure across degrees of coronary collateral circulation.
Mean value and standard error of the mean. CC = coronary collateral; grade 0 = no filling of collateral vessels; grade 1 = filling of collateral vessels without any epicardial filling of the recipient artery; grade 2 = partial epicardial filling by collateral vessels of the recipient artery; grade 3 = complete epicardial filling by collateral vessels of the recipient artery.

reported good correlation between a novel angiographic method of assessment and function.[23] This is to be expected considering the fundamental physical law describing that vessel radius is related to the fourth power of flow.[24] It is, thus, likely that the morphologic degree of collaterals used in this study, is closely related with the functional degree of coronary collateral circulation. Indeed, in the present morphologic study, as in other quantitative collateral studies[25,26], we found coronary lesion severity to be strongly associated with the presence of coronary collaterals as well (odds ratio 5.80 per degree of stenosis; 95% confidence interval 3.73-9.00).

Finally, a last source of unquantifiable bias could have been introduced by the selection of patients, admitted for elective coronary angioplasty. This selection is

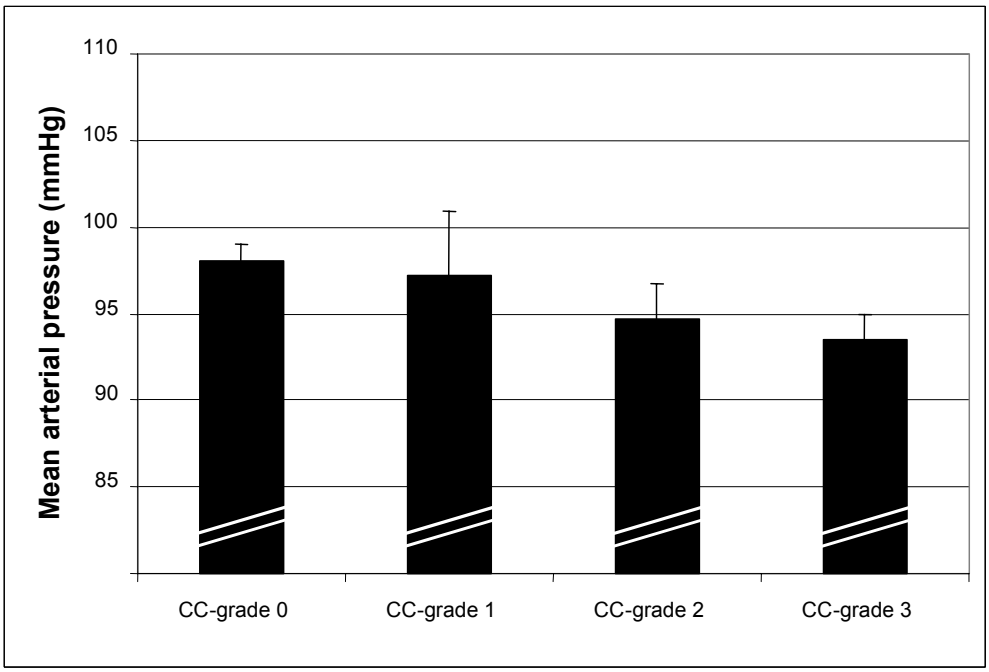

Figure 4. Mean arterial pressure across degrees of coronary collateral circulation.
Mean value and standard error of the mean. CC = coronary collateral; grade 0 = no filling of collateral vessels; grade 1 = filling of collateral vessels without any epicardial filling of the recipient artery; grade 2 = partial epicardial filling by collateral vessels of the recipient artery; grade 3 = complete epicardial filling by collateral vessels of the recipient artery.

highly restrictive even within the domain of patients with known coronary artery disease. It must be acknowledged that patients with sufficient collaterals may not undergo diagnostic catheterization or angioplasty. At the other extreme, patients with extensive coronary artery disease with or without collaterals may be referred for coronary surgery and not angioplasty.

The mechanism of the formation of coronary collaterals is subject to intense preclinical and clinical research. In addition to high blood pressure as explored in the present study, genetic factors and a number of other patient characteristics including age, myocardial ischemia, physical exercise, smoking, body mass index, hyperlipidemia, hyperhomocysteinemia, diabetes mellitus, and use of various cardiovascular drugs have been proposed.[6-9,16,26-36] Yet, results of these

studies are conflicting and, the pathophysiologic role and importance of these patient characteristics is still unclear.[2,3,37]

To our knowledge, this is the first study to show an inverse association between (high) blood pressure and the presence and extent of coronary collaterals. This inverse relation continued to exist even after additional adjustment for, among other things, the duration of hypertension, number of types of antihypertensive drugs, duration of anginal complaints, coronary lesion severity, and the presence of coronary occlusion.

Two studies, in patients with carotid artery disease, also reported a lower prevalence of cerebral collateral circulation among the patients with hypertension.[38,39] Yet, three other studies found hypertension to be positively associated with the presence of coronary collaterals.[7,9,10] Kyriakides et al. compared 61 hypertensive patients with total or subtotal occlusion of a single coronary artery, with 252 normotensive patients with similar angiographic findings, and found that the coronary collateral circulation was more extensive in the hypertensive group.[9] Karpanou et al. studied 433 male patients with angiographically documented coronary artery disease, and found that coronary collaterals were more frequently present in the patients with arterial hypertension, especially high-grade coronary collaterals.[10] Finally, in a series of 200 patients with an occlusion of a single coronary artery, Kilian et al. found a positive relation between hypertension and the number of collaterals with Rentrop-grade 3.[7] Yet, this was only the case in univariate analysis.

In three other studies, no association between hypertension and coronary collateral presence was found.[6,8,11] In a consecutive group of 112 patients with a chronic total coronary occlusion, hypertension was equally distributed among the patients, independent of coronary collateral presence or grade.[6] Fujita et al. studied 248 patients undergoing coronary angiography within 12 hours after the onset of a first acute myocardial infarction, and found hypertension to be equally present among the patients with and without well-developed coronary collaterals

(defined as Rentrop-grade 2 or 3).[8] Finally, Heinle et al. studied 248 patients undergoing selective coronary angiography, and found no difference in the occurrence of hypertension among the patients with and without coronary collaterals.[11]

The controversy regarding the role of blood pressure or hypertension in determining the presence and extent of coronary collaterals, may in part be explained by differences in the patients studied and the methods used. A positive relation between blood pressure or hypertension and the presence of coronary collaterals may be explained by an increased myocardial oxygen demand, which may trigger the formation or development of collaterals[10], or enlargement of collateral arteries.[9]

Another potential explanation for this controversy may be in the vasculature under study. We examined functional collateral vessels, that were spontaneously visible with contrast-angiography, thus vessels of at least 100 μm. The inverse relation, currently found between (high) blood pressure and coronary collateral presence may also be explained by functional and structural remodeling of the coronary arterioles and microvasculature and venules in response to increased blood pressure, as proposed by Boudier and Vicaut.[40-42] This arteriolar remodeling has been referred to as *microvascular rarefaction* (or rarification or rarefication) and ultimately involves the obliteration of preexisting blood vessels.[42] This destructive process affects the microvascular network, in particular the arteriolar vessels that are 100 to 150 μm in diameter, where a large part of the systemic pressure gradient takes place.[41,42] Microvascular rarefaction is completely different from angiogenesis (the proliferation of capillaries in ischemic areas) or arteriogenesis (the maturation of pre-existing collateral vessels into functional muscular collateral arteries), that generally involve vessels less than 100 μm in diameter.[29]

Microvascular rarefaction has been observed even in very early stages of the development of hypertension. The ensuing reduction in blood vessels not only may contribute to hypertensive lesions of target organs, but may also maintain or

even amplify the increased blood pressure by augmenting the peripheral vascular resistance, thus creating a vicious circle. Microvascular changes in hypertension may also lead to an increase in pulse pressure, which may subsequently induce lesions of the vessel walls, and of the endothelium of the large arteries.[40] Both genetic and fetal mechanisms have been proposed to be involved.[41]

Just recently, in a large prospective cohort study with 2451 normotensive people and 10 years follow-up, the potentially important role of the narrowing of the small blood vessels in the pathogenesis of hypertension was clearly determined.[43] Wong et al. showed that people with smaller retinal arteriolar diameters were more likely to develop hypertension over a 10-year period, than people with larger arteriolar diameters, independent of known risk factors for hypertension. They also found that the combined exposure to higher pre-existing blood pressure at baseline and narrowed arterioles was associated with a higher risk of hypertension, than the effect of either alone. This finding supports the theory of microvascular rarefaction described above, that higher blood pressure may cause arteriolar vasoconstriction, vascular remodeling, and higher peripheral vascular resistance, leading to further increases in blood pressure and the maintenance of the hypertensive state.[40,43]

Perspectives

In conclusion, the results of this study show that high blood pressure, and notably elevated systolic blood pressure and increased pulse pressure, is inversely associated with the presence and extent of coronary collateral (arteriolar) circulation. Microvascular rarefaction in response to increased blood pressure may explain our findings. We postulate that the increased case-fatality in hypertensive patients with an acute myocardial infarction[1] may be related to these findings.

Acknowledgments

These data were presented previously in part as a poster, entitled "High blood pressure is inversely related with presence and extent of coronary collaterals", at the 14th European Meeting on Hypertension of the European Society of Hypertension 2004 (Paris, France).

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Appendix

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Chapter 3.3

Coronary collateral circulation: the effects of smoking and alcohol

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Submitted for publication

Abstract

Background: The presence or absence of coronary collaterals is of vital importance during acute ischemia. Smoking and alcohol have been suggested to play a role, but data are scarce. We examined the extent to which smoking and alcohol use affect the presence of coronary collateral circulation.

Methods: Cross-sectional study in 242 patients, admitted for PTCA. Collaterals were graded with Rentrop's classification. Coronary collateral presence was defined as Rentrop-grade ≥ 1. Smoking was defined as past, current or never (reference-category). Packyears were calculated. Alcohol consumption was defined as past or current, and categorized into never-users (reference-category); < 1; 1-10; 11-20; and ≥ 21 units per week (UPW). We used logistic regression with adjustment for putative confounders. Smoking and alcohol were adjusted for each other.

Results: Current smoking (odds ratio (OR) 3.39; 95% confidence interval (CI) 1.18-9.73) was positively associated, while number of packyears (OR 0.97 per packyear; 95% CI 0.94-0.99) was inversely associated with coronary collateral presence. Current alcohol intake showed a J-shaped association: < 1 UPW: OR 0.49 (95% CI 0.12-2.06); 1-10 UPW: OR 0.35 (95% CI 0.12-1.03); 11-20 UPW: OR 0.17 (95% CI 0.04-0.67); and ≥ 21 UPW: OR 2.33 (95% CI 0.62-8.81), while past moderate alcohol consumption (OR 0.12; 95% CI 0.01-0.95) was inversely associated with presence of coronary collateral circulation.

Conclusions: Current smoking is positively related with presence of coronary collaterals, while packyears is inversely related. Past and current moderate alcohol consumption are associated with reduced, while high alcohol intake with increased coronary collateral presence.

Introduction

The presence of coronary collaterals may have a protective role during acute myocardial ischemia, potentialy reducing sudden cardiac death, the amount of myocardial cell loss and infarct size.[1-3] Also, coronary collaterals may extend the number of "golden hours" from the onset of an acute myocardial infarction to successful coronary reperfusion. Coronary collaterals, or "natural bypasses", are anastomotic connections without an intervening capillary bed between portions of the same coronary artery and between different coronary arteries.[4] There is, however, marked interindividual variability in the extent of collateral circulation.[3]

Smoking and alcohol have among others been suggested to play a role in the presence of coronary collaterals. However, data are very scarce, and the mechanism whereby these life-style factors may affect collateral formation is at present still unknown. [5-9] While smoking is a well-established risk factor for cardiovascular disease and acute myocardial infarction[10-13], moderate alcohol intake has been associated with a reduced incidence of, and mortality from, coronary heart disease.[14,15] In the present study, we examined the extent to which smoking and alcohol use affect the presence of coronary collaterals in patients with documented coronary artery disease.

Methods

The study proposal, as well as the manner in which informed consent was obtained from subjects, was approved by the Medical Ethics Review Committee of the the University Medical Center Utrecht (UMC Utrecht). Written informed consent was obtained from all patients.The study was performed in accordance with the principles of the Declaration of Helsinki.

Study population

A cross-sectional study was performed as part of the "Second Manifestations of ARTerial disease (SMART)" study. The latter study is an ongoing prospective cohort study conducted at the UMC Utrecht, designed to determine the prevalence of concomitant arterial disease and risk factors for atherosclerosis in a high risk population.[16] At enrollment, medical history is recorded with a standardized questionnaire, and height, weight, and blood pressure are measured. Blood and urine samples are taken. For the purpose of the present analyses, the baseline diagnostic coronary angiograms of 242 patients, who were referred for elective percutaneous transluminal coronary angioplasty (PTCA) and took part in the SMART study between January 1, 1998 and July 8, 2002, were reviewed.

Coronary collateral circulation

The presence of coronary collaterals on each baseline coronary angiogram (CAG) was defined and visually assessed with the Rentrop's classification (grade 0 - no filling of collateral vessels; grade 1 - filling of collateral vessels without any epicardial filling of the recipient artery; grade 2 - partial epicardial filling by collateral vessels of the recipient artery; and grade 3 - complete epicardial filling by collateral vessels of the recipient artery).[17] Coronary collateral presence was defined as the presence of minimal or well-developed collaterals (grade 1, 2 or 3).[18,19] Grading was done independently by a trained research physician (J.K.) and a cardiologist (P.P.Th.d.J.), who were blinded to the clinical data. If an angiogram was graded differently, consensus was obtained. The pre-PTCA angiograms were graded in random order. To assess the interobserver variability of the grading, 100 randomly selected CAG's were scored by another cardiologist, not involved in the study and unaware of the reading of the two other observers and of the clinical data, during a separate session. The strenght of agreement between the two observers (J.K. & P.P.Th.d.J.) and the other cardiologist was good (Kappa 0.65; 95% confidence interval [CI] 0.51-0.79). Previously, the reproducibility of the Rentrop's score has already been described as high (Kappa 0.85; 95% CI 0.77-0.93).[20]

Smoking and alcohol

Information on smoking and alcohol was derived from the self-administrated, standardized questionnaires. Smoking was defined as never (reference-category), past or current smoking within 1 year before inclusion. Number of packyears was calculated with the formula:

(((ending-year smoking - starting-year smoking) - (number of years temporarily quit smoking)) x mean number of cigarettes smoked per day) / 20 cigarettes per pack.

Alcohol consumption was defined as past or current alcohol use within 1 year before inclusion. Subsequently, current alcohol intake was categorized into never-users (reference-category); < 1; 1-10; 11-20; and ≥ 21 units per week (UPW). One unit of alcohol was defined as 250 mL of beer (one beer glass) with an average alcohol percentage of 4-6 percent, or 125 mL of wine (one wine glass), or 35 mL of liquor (one shot glass).

Data-analysis

The outcome of interest was the presence of coronary collaterals, defined as a Rentrop-grade ≥ 1.[18,19] Unless specified otherwise, data are presented as count with percentage, or mean with standard deviation. The association between each measure of smoking and alcohol intake (notably current smoking, past smoking, number of packyears, current alcohol consumption (categorized), and past alcohol consumption), and the presence of coronary collaterals, was quantified with one logistic regression model. Gender, age, hypertension, diabetes mellitus, hyperlipidemia, a history of myocardial infarction, time-interval since myocardial infarction (if prior), a history of PTCA or coronary artery bypass grafting, and time-interval since first coronary intervention (if prior) were entered into the model to adjust for potential confounding of the relation between smoking and alcohol consumption and the presence of coronary collaterals. Smoking and alcohol use were adjusted for each other. Odds ratios with 95% confidence interval are presented. A two-sided (multivariate) P-value < 0.05 was considered significant. The statistical package used was SPSS for Windows, release 11.0.1 (SPSS Inc., Chicago, Illinois, USA).

Table 1. Baseline- and clinical characteristics of the 242 study-patients.

characteristic	all patients (n = 242)	collaterals present (n = 91) Rentrop = 1 - 3	collaterals absent (n = 151) Rentrop = 0	P-value
demographics:				
male gender	202 (84%)	79 (87%)	123 (82%)	0.28
age at index-PTCA (yrs)	58.0 ± 9.2	57.9 ± 9.6	58.1 ± 9.1	0.84
cardiovascular risk factors:				
hypertension	91 (38%)	26 (30%)	65 (44%)	0.03
diabetes mellitus	48 (20%)	25 (28%)	23 (15%)	0.02
hyperlipidemia	201 (83%)	75 (82%)	126 (84%)	0.75
obesity (BMI ≥ 30 kg/m^2)	42 (18%)	15 (17%)	27 (18%)	0.80
smoking and alcohol:				
current smoking	69 (29%)	37 (41%)	32 (21%)	< 0.01
past smoking	121 (50%)	38 (42%)	83 (55%)	0.05
number of packyears (yrs) *	26.2 ± 18.7	25.3 ± 16.5	26.7 ± 20.1	0.61
plasma hemoglobin (mmol/L)	9.0 ± 0.7	9.1 ± 0.6	9.0 ± 0.7	0.46
current alcohol consumption	186 (77%)	70 (77%)	116 (77%)	0.99
past alcohol consumption	16 (7%)	4 (4%)	12 (8%)	0.28
previous conditions:				
prior angina pectoris	223 (92%)	85 (93%)	138 (91%)	0.57
previous myocardial infarction	106 (44%)	46 (51%)	60 (40%)	0.10
previous PTCA or CABG	77 (32%)	29 (32%)	48 (32%)	0.99
previous TIA or stroke	23 (10%)	5 (6%)	18 (12%)	0.10
previous non-cardiac vascular surgery	20 (8%)	10 (11%)	10 (7%)	0.23
duration since MI until index-PTCA (yrs)	4.0 ± 6.1	5.0 ± 7.6	3.1 ± 4.7	0.14
duration since first PTCA or CABG until index-PTCA (yrs)	3.2 ± 5.4	4.9 ± 6.4	2.2 ± 4.5	0.05
angiographic characteristics:				
1-vessel coronary disease †	142 (59%)	39 (43%)	103 (68%)	†
2-vessel coronary disease	79 (33%)	40 (44%)	39 (26%)	< 0.01
3-vessel coronary disease	21 (9%)	12 (13%)	9 (6%)	< 0.01
multi-vessel coronary disease	100 (41%)	52 (57%)	48 (32%)	< 0.01
impaired left-ventricle function ‡	89 (41%)	35 (43%)	54 (41%)	0.76

Table 1 is continued on the next page.

Table 1. Continued.

characteristic	all patients (n = 242)	collaterals present (n = 91) Rentrop = 1 - 3	collaterals absent (n = 151) Rentrop = 0	P-value
type of antihypertensive drugs used:				
beta-adrenergic receptor antagonists	188 (78%)	72 (79%)	116 (77%)	0.68
diuretics	21 (9%)	6 (7%)	15 (10%)	0.37
ACE-inhibitors	44 (18%)	17 (19%)	27 (18%)	0.88
calcium channel-blockers	98 (41%)	36 (40%)	62 (41%)	0.82
alpha-1 receptor antagonists	1	-	1	§
combined prescription medicines	4	4	-	§
selective imidazoline receptor agonists	1	-	1	§
angiotensin II receptor blockers	3	-	3	§
other type of antihypertensive drugs	1	-	1	§
antidiabetic treatment:				
use of antidiabetic medication	26 (12%)	12 (14%)	14 (10%)	0.37
statins:				
use of statins	131 (54%)	53 (58%)	78 (52%)	0.32

Number of patients (valid %) or mean ± SD.
* Only concerns current and past smokers.
† Reference-category.
‡ In 27 patients the ventriculogram turned out not to be performed.
§ Too few data.
BMI = body mass index; BP = blood pressure; CABG = coronary artery bypass grafting; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; SD = standard deviation; TIA = transient ischemic attack.

Results

Patient characteristics

Baseline- and clinical characteristics of the study population are presented in Table 1. Coronary collaterals were present in 91 patients (38%): 13 patients (14%) had grade 1 (no epicardial filling), 33 patients (36%) had grade 2 (partial epicardial filling), and 45 patients (50%) had grade 3 collaterals (complete epicardial filling).

Smoking and alcohol intake, and presence of coronary collateral circulation

Table 2 summarizes the results of the analyses, both unadjusted, and adjusted for gender, age, hypertension, diabetes mellitus, hyperlipidemia, prior myocardial infarction, time since myocardial infarction, prior PTCA or coronary artery bypass grafting, and time since first coronary intervention. Smoking and alcohol use were adjusted for each other. Current smoking was positively associated, while number of packyears was inversely associated with coronary collateral presence. Current alcohol intake showed a J-shaped association with the presence of coronary collaterals (see Figure 1), while past alcohol consumption was inversely associated. The majority of these past drinkers had been moderate or infrequent alcohols users (13 out of 16; 81%). Past smoking was not associated with coronary collateral presence. Additional adjustment for severity of coronary disease did not materially change the results: current smoking (odds ratio [OR] 3.48; 95% confidence interval [CI] 1.17-10.3), past smoking (OR 0.62; 95% CI 0.23-1.69), number of packyears (OR 0.97 per packyear; 95% CI 0.95-1.00), current alcohol intake < 1 UPW: OR 0.50 (95% CI 0.12-2.22); 1-10 UPW: OR 0.39 (95% CI 0.13-1.15); 11-20 UPW: OR 0.20 (95% CI 0.05-0.79); and ≥ 21 UPW: OR 2.78 (95% CI 0.71-10.9), and past alcohol consumption (OR 0.13; 95% CI 0.02-1.00).

Table 2. Smoking and alcohol intake, and their association with the presence of coronary collaterals.

measures of smoking and alcohol	collaterals present (n = 91) Rentrop = 1, 2, or 3 n (valid %) or mean ± SEM	collaterals absent (n = 151) Rentrop = 0 n (valid %) or mean ± SEM	unadjusted OR (95% CI)	adjusted OR* (95% CI)	P-value after adjustment*
never smoked†	16 (18%)	36 (24%)	1.0†	1.0†	†
current smoking	37 (41%)	32 (21%)	2.54 (1.17-5.51)	3.39 (1.18-9.73)	0.02
past smoking	38 (42%)	83 (55%)	1.03 (0.51-2.10)	0.57 (0.22-1.51)	0.26
number of packyears (yrs)‡	25.3 ± 2.0	26.7 ± 1.9	0.99 (0.97-1.01)	0.97 (0.94-0.99)	0.01
categories of current alcohol consumption:					
never-users†	17 (19%)	23 (15%)	1.0†	1.0†	†
< 1 UPW	8 (9%)	14 (9%)	0.95 (0.34-2.65)	0.49 (0.12-2.06)	0.33
1-10 UPW	37 (41%)	68 (45%)	0.91 (0.46-1.78)	0.35 (0.12-1.03)	0.06
11-20 UPW	10 (11%)	22 (15%)	0.76 (0.30-1.91)	0.17 (0.04-0.67)	0.01
≥ 21 UPW	15 (17%)	12 (8%)	2.08 (0.82-5.29)	2.33 (0.62-8.81)	0.21
past alcohol consumption	4 (4%)	12 (8%)	0.53 (0.17-1.70)	0.12 (0.01-0.95)	0.04

* Odds ratios and 95% confidence intervals adjusted for gender, age, hypertension, diabetes mellitus, hyperlipidemia, prior myocardial infarction, time since myocardial infarction, prior percutaneous transluminal coronary angioplasty or coronary artery bypass grafting, and time since first coronary intervention. Smoking and alcohol use adjusted for each other.
† Reference-category.
‡ Only concerns current and past smokers.
CI = confidence interval; OR = odds ratio; SEM = standard error of the mean; UPW = unit(s) per week.

Discussion

In the present study among 242 patients referred for elective PTCA, we found that current smoking was positively associated with the presence of coronary collaterals, while a higher number of packyears was inversely related. We also found that current alcohol intake was associated with the presence of coronary collaterals in a J-curve fashion with moderate alcohol intake associated with a reduced, and high alcohol intake with an increased presence of coronary collaterals. Furthermore, past moderate alcohol consumption was inversely associated.

To appreciate these results, some aspects of this study need to be addressed. First, we investigated the presence or absence of coronary collateral circulation cross-sectionally, but not the development of collaterals over time. This makes causal inference regarding the role of smoking and alcohol intake in promoting development of collaterals preliminary. However, from a pathophysiologic point of view, one may understand the relation between these determinants and the presence of collaterals.

Second, the use of angiography to define and assess coronary collaterals may have influenced our observations. Coronary angiography, although the most frequently used diagnostic technique for the assessment of collateral vessels, can only identify vessels > 100 μm in diameter, whereas most collateral vessels are smaller.[21] Furthermore, even though the overlap between quantitative measures and qualitative angiographic degrees of collateral flow has been demonstrated to be quite large[22], quantitative indices of collateral circulation may be better markers of the functional significance of collateral vessels, in particular in recruitable (Rentrop 1) collaterals.[20,23,24] A recent study, nonetheless, reported good correlation between a novel angiographic method of assessment and function.[25] This is to be expected considering the fundamental physical law describing that vessel radius is related to the fourth power of flow.[26] It is, thus,

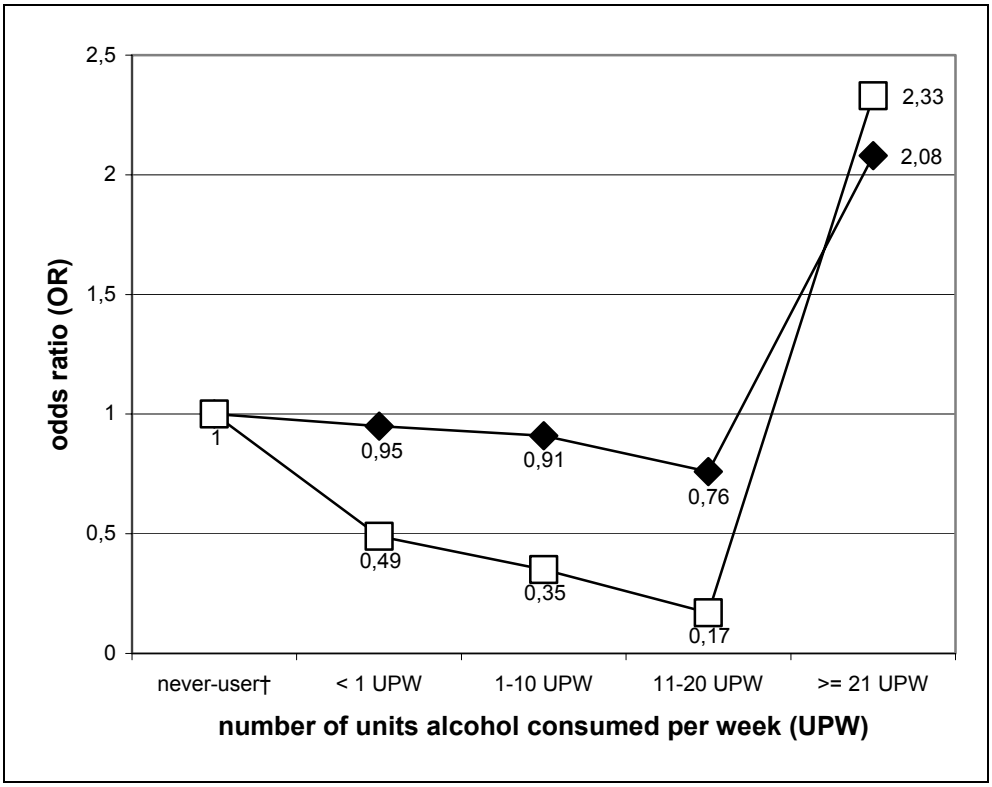

Figure 1. The J-shaped association between current alcohol intake and the presence of coronary collaterals.

♦ = Univariate analysis.

□ = Multivariate analysis with adjustments made for gender, age, smoking-status, number of packyears, hypertension, diabetes mellitus, hyperlipidemia, prior myocardial infarction, time since myocardial infarction, prior percutaneous transluminal coronary angioplasty or coronary artery bypass grafting, and time since first coronary intervention.

† = Reference category.

OR = odds ratio; UPW = unit(s) per week.

likely that the morphologic degree of collaterals used in this study, is closely related with the functional degree of coronary collateral circulation.

A third limitation of this study might be the use of a self-administrated, standardized questionnaire to assess the patient's lifestyle with respect to smoking and alcohol consumption. However, while self-reports have limitations, their validity and reliability has been established sufficiently.[27-29]

Finally, a last source of unquantifiable bias could have been introduced by the selection of patients, admitted for elective coronary angioplasty. This selection is highly restrictive even within the domain of patients with known coronary artery disease. It must be acknowledged that patients with sufficient collaterals may not undergo diagnostic catheterization or angioplasty. At the other extreme, patients with extensive coronary artery disease with or without collaterals may be referred for coronary surgery and not angioplasty.

The mechanism of the formation of coronary collaterals is subject to intense preclinical and clinical research. In addition to smoking and alcohol as explored in the present study, genetic factors and a number of other patient characteristics including age, myocardial ischemia, physical exercise, body mass index, hyperlipidemia, hyperhomocysteinemia, hypertension, diabetes mellitus, and use of various cardiovascular drugs have been proposed.[1,5-9,30-39] Yet, results of these studies are conflicting and, therefore, their pathophysiologic role and importance is still unclear.[2,3,40]

Smoking and presence of coronary collaterals

To our knowledge, this is the first study to show an association between current smoking and the presence of coronary collaterals. Smoking, a major risk factor for cardiovascular disease, was previously found not to be associated with the presence of coronary collaterals.[5,7-9] However, tobacco smoke contains more than 4,000 chemical compounds that might have an effect on human coronary collaterals. Collateral growth includes the proliferation of capillaries in the ischemic area (angiogenesis), and the maturation of pre-existing collateral vessels into functional muscular collateral arteries (arteriogenesis), with the latter being more relevant in humans.[1] Interestingly, nicotine was recently identified as a potent angiogenic agent, effective through an endogenous nicotinic cholinergic pathway, present in endothelial cells that is involved in physiological, as well as pathological angiogenesis.[41,42] Nicotine may also promote arteriogenesis, possibly

mediated in part by activation of endothelial-monocyte interactions involved in arteriogenesis.[6]

Other pathophysiologic mechanisms may be involved as well, such as smoking-induced chronic hypoxia and endothelial dysfunction.[43,44] Chronic and recurrent ischemia and arteriogenesis play an important role in the development of collateral circulation.[3] Interestingly, smoking has been associated with an up to twofold lower risk of dying in-hospital after an acute cardiac event, which is called the "smokers' paradox".[11,13] This has been explained by a greater case-fatality before hospital-admission in smokers suffering an acute cardiac event.[13] In addition, smokers, in general, are younger and have a more favourable coronary anatomy, such as single vessel disease and the preferential involvement of the right coronary artery and inferior wall.[11] Apart from these more beneficial characteristics, the present study, however, offers an alternative explanation for the "smokers' paradox", as our results demonstrate the presence of more coronary collaterals in current smokers. This may protect the patient against life-threatening arrhythmias and extensive myocardial damage during an acute infarction.

The number of packyears was inversely associated with the presence of coronary collaterals, after adjustment for cardiovascular risk factors and prior coronary events. In addition, after adjustment for cardiovascular risk factors and prior coronary events, past smoking was inversely associated with coronary collateral presence as well, but not significant. This is not necessarily in contradiction with the findings described above. Acute cigarette smoking in occasional smokers resulted in arterial vasoconstriction without altering vascular responsiveness.[45] Therefore, current smoking can be seen as an acute ischemic stimulus, inducing angiogenesis and collateral growth as shown in the case of nicotine[6], while the number of packyears is a well established risk factor for the ontogenesis and course of the atherosclerotic process. The relationship between the packyears of cigarette smoking and coronary heart disease risk has been convincingly demonstrated by Burns, showing an increasing risk with increasing duration of

smoking.[10] It cannot be excluded, however, that the inverse relation between packyears and collaterals is caused by smoking-induced, impaired endothelial vasodilation and inappropriate vasoconstriction[43,46], making the collaterals less visible.

Alcohol and presence of coronary collaterals

We found that alcohol consumption has an association with the presence of coronary collaterals. At variance with the data of Kilian et al.[7], we found a biphasic, J-shaped association between current alcohol consumption and the presence of coronary collaterals, with high intake levels associated with an increased frequency of coronary collaterals. Furthermore, past moderate alcohol consumption was inversely associated. These associations persisted after adjustment for cardiovascular risk factors and prior coronary events, and also after additional adjustment for severity of coronary disease. This is in accordance with epidemiological data, revealing a biphasic relationship between alcohol and atherosclerotic cardiovascular disease. Actually, this biphasic, J-shaped association between alcohol use and coronary collateral presence represents the inverse of the protective effect of alcohol on atherosclerosis. A protective effect is observed with moderate consumption, but an increased risk of stroke and coronary artery disease with heavy alcohol consumption.[14,15] Low-dose alcohol has been proposed to favourably influence other risk factors, outweighing other alcohol-related side-effects, such as hypertension and dyslipidemia.[14] Furthermore, there is increasing evidence that wine, and in particular red wine, contains ethanol-independent pharmacologically active substances, protecting the individual from atherosclerosis and myocardial infarction.[15] In addition, animal studies reveal that alcohol has a protective effect on endothelium in case of moderate alcohol exposure, but a detrimental influence in case of heavy exposure.[14]

Finally, in a chick embryo model, moderate levels of ethanol were found to induce expression of vascular endothelial growth factor (VEGF) and stimulate angiogenesis, thus providing a theoretical basis for speculating that the cardiovascular-protective effects of moderate alcohol consumption may be mediated in part through VEGF-induced angiogenesis.[47]

Therefore, moderate alcohol consumption would imply less cardiac ischemic burden, thus less trigger for the presence of coronary collaterals. If this were true, then moderate alcohol use would protect for the occurrence of a first myocardial infarction (due to a reduction in cardiac ischemic burden), while on the other hand, a similar level of alcohol use would increase the risk of a fatal cardiac event, once a myocardial infarction has already occurred (due to less coronary collaterals present). Indeed, in men with a previous myocardial infarction, moderate alcohol consumption was associated with a higher case fatality in the event of (another) myocardial infarction, while moderate alcohol use in men with no previous myocardial infarction was associated with a lower case fatality.[48]

In conclusion, smoking and alcohol use are associated with the presence of coronary collaterals in patients with documented coronary artery disease. Current smoking is positively associated with the presence of coronary collaterals, while a higher number of packyears was inversely related to the presence of coronary collaterals. Current, regular alcohol intake is associated with the presence of coronary collateral circulation in a biphasic, J-curve fashion with moderate intake levels associated with a reduced, and high intake levels with an increased presence of coronary collaterals. Also, past moderate alcohol consumption is inversely associated. The results support the view that life-style factors may affect the formation of coronary collaterals in patients with ischemic cardiac disease.

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Appendix

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Chapter 3.4

Presence of the metabolic syndrome does not impair coronary collateral vessel formation in patients with documented coronary artery disease

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Abstract

Objective: The metabolic syndrome confers an increased risk for cardiovascular morbidity and mortality. The presence of coronary collaterals may have beneficial effects during myocardial ischemia and may improve cardiovascular outcome in patients with coronary artery disease. Impaired collateral formation could be one of the reasons for the increased cardiovascular risk in patients with the metabolic syndrome. Aim of the present study was to determine the influence of the metabolic syndrome and insulin resistance on the presence of coronary collaterals.

Research designs and methods: A cross-sectional study in 227 patients referred for elective percutaneous transluminal coronary angioplasty to the University Medical Center Utrecht. Metabolic syndrome was diagnosed according to Adult Treatment Panel III and HOMA-IR and QUICKI were used to quantify insulin resistance. Coronary collaterals were graded with Rentrop's classification. Rentrop-grade ≥ 1 indicated the presence of collaterals. Results were adjusted for age, sex and severity of coronary artery disease.

Results: 103 patients (45%) were diagnosed with the metabolic syndrome. There was no association between the metabolic syndrome and the presence of coronary collateral formation (odds ratio [OR] 1.2; 95% confidence interval [CI] 0.7-2.0). Also, the degree of insulin resistance was not related to the presence of coronary collaterals. OR for HOMA-IR (highest versus lowest tertile) was 0.7 (95% CI 0.3-1.5) and for QUICKI (lowest versus highest tertile) 0.8 (95% CI 0.4-1.6).

Conclusions: The metabolic syndrome and insulin resistance are not related to the presence of coronary collaterals in patients with documented coronary artery disease.

Introduction

The metabolic syndrome is a cluster of generally accepted cardiovascular risk factors such as impaired glucose metabolism, elevated blood pressure, dyslipidemia and central obesity.[1] Also other, often not routinely measured cardiovascular risk factors (like inflammation, increased oxidative stress, increased small dense LDL-cholesterol, impaired fibrinolysis, hypercoagulability and hyperinsulinemia), cluster in this syndrome.[2] The underlying pathophysiology is still not fully clarified, but insulin resistance is a major characteristic. Increased adipose tissue mass is involved in the development of insulin resistance by changes in the production of cytokines.[3,4]

The prevalence of the metabolic syndrome is high, amounting to 24% in an apparently healthy westernised population.[5] In patients with manifest vascular disease the prevalence is 46%.[6] The number of subjects with the metabolic syndrome is likely to increase in the coming years due to the increased prevalence of obesity. Patients with the metabolic syndrome are at an increased risk for cardiovascular morbidity and mortality.[7-12] Several studies report a two to three fold increased risk.[13-15] This increased risk can at least partially be explained by the risk factors clustering in the metabolic syndrome.

Well-developed coronary collaterals are associated with improved cardiovascular outcome in terms of limiting infarction size, prevention of ventricular aneurysm formation[16,17], and future ischemic events[18,19] in patients with coronary artery disease. Repetitive myocardial ischemia and increased shear stress are important determinants of coronary collateral development.[20,21] Adequate collateral formation has been suggested to be critically dependent on endothelial function and nitric oxide bioavailability.[22,23] Abaci et al. demonstrated a decreased presence of coronary collaterals in diabetic patients, which may be attributed to impaired endothelial function.[24] However, this could not be confirmed by others.[25-

[28] To our best knowledge, no information on coronary collaterals is available in patients with the metabolic syndrome.

Insulin resistance may be linked to endothelial dysfunction by several mechanisms including, inflammation (as reflected by elevated high sensitive C-reactive protein [hs-CRP] plasma levels), disruption of insulin receptor signalling cascades, increased production of cytokines and activation of the renin angiotensin system.[29,30] Adiponectin, an adipocyte-derived protein, stimulates the production of nitric oxide in vascular endothelial cells in vitro[31], and hypo-adiponectinemia is associated with insulin resistance.[32,33] We hypothesize that impaired coronary collateral formation caused by endothelial dysfunction and decreased nitric oxide production contributes to increased cardiovascular risk in metabolic syndrome patients.

Aim of the present study is to determine the relation of the metabolic syndrome and insulin resistance with coronary collateral formation in patients referred for elective percutaneous transluminal coronary angioplasty (PTCA).

Research design and methods

Study population

Patients originated from the SMART study (Second Manifestations of ARTerial disease), an ongoing prospective cohort study at the University Medical Center Utrecht designed to establish the prevalence of concomitant arterial diseases and risk factors for atherosclerosis in a high risk population.[34] The local Ethics Committee approved the study and all participants gave their written informed consent. For the present cross-sectional study 227 patients referred for elective percutaneous transluminal coronary angioplasty (PTCA) and included in SMART between January 1, 1998 and July 8, 2002 were enrolled.

Study design and methods

At the time of enrolment, clinical information was obtained using a standardized health questionnaire for all patients. Length, body weight, waist circumference and blood pressure were measured. Fasting blood was sampled to determine lipid, serum glucose, homocysteine, creatinine, adiponectin, hs-CRP and insulin levels. Insulin was measured with an immunometric assay (Diagnostic Products Corporation, Los Angeles, USA), adiponectin with a quantitative enzyme immunoassay technique (R&D Systems, Minneapolis, USA). Two experienced observers blinded to all patient characteristics independently reviewed all pre-PTCA coronary angiograms. Rentrop's classification was used to determine the extent of collateralization (grade 0 - no filling of collateral vessels; grade 1 - filling of collateral vessels without any epicardial filling of the recipient artery; grade 2 - partial epicardial filling by collateral vessels of the recipient artery; and grade 3 - complete epicardial filling by collateral vessels of the recipient artery).[35] Severity of coronary artery disease was defined by visual assessment of the pre-PTCA coronary angiograms (single-, two- or three-vessel disease) and a ≥ 50% diameter reducing stenosis was regarded as significant.[36]

Definitions

Metabolic syndrome was diagnosed according to the Adult Treatment Panel III criteria, including three or more of the following metabolic abnormalities: abdominal obesity (waist circumference > 102 cm in men and > 88 cm in women), high blood pressure (≥ 130 mmHg systolic or ≥ 85 mmHg diastolic), hypertriglyceridemia (serum triglycerides ≥ 1.70 mmol/L [150 mg/dL]), low high-density lipoprotein (HDL) cholesterol (serum HDL-cholesterol < 1.04 mmol/L [40 mg/dL] in men and < 1.29 mmol/L [50 mg/dL] in women), high fasting glucose (fasting serum glucose ≥ 6.1 mmol/L [110 mg/dL]).[1] Patients on glucose-lowering agents or anti-hypertensive medication were regarded as having high fasting glucose and high blood pressure, respectively. Waist circumference was not measured until January 1, 1999. If waist circumference was not available, a body mass index (BMI) cut point of 30 kg/m^2 was used as determinant for obesity.[37] A

fasting glucose ≥ 7.0 mmol/L in patients with no history of diabetes mellitus was considered as newly diagnosed diabetes mellitus. Established diabetes was defined as self-reported diabetes.

Homeostasis model assessment (HOMA) determined insulin resistance (HOMA-IR) and Quantitative insulin sensitivity check index (QUICKI) were used as quantitative estimates of insulin resistance. HOMA-IR was calculated using the formula: HOMA-IR = (fasting serum glucose x fasting serum insulin)/22.5,[38] and QUICKI according to the equation: (1/(log fasting serum glucose + log fasting serum insulin).[39]

The presence of coronary collaterals was defined as a Rentrop score ≥ 1. Severity of coronary artery disease was categorized in two groups (single- versus multi-vessel [including two- or three-vessel] disease). HOMA-IR and QUICKI were categorized in tertiles.

Data analyses

Differences between patients with and without metabolic syndrome were tested with chi-square (categorical variables), unpaired T-test (continuous normal distributed variables) or Mann-Whitney U (continuous skewed variables).
Rentrop-score was dichotomised (score 0 indicating the absence and score ≥ 1 indicating the presence of coronary collaterals). The relation between the presence or absence of coronary collaterals and metabolic syndrome was quantified using binary logistic regression model. Subsequently, this association was adjusted for age, sex and severity of coronary artery disease. These analyses were also performed with the values of HOMA-IR (categorized in tertiles), QUICKI (categorized in tertiles) and the number of components of the metabolic syndrome as independent variables respectively and the presence of collaterals as dependent variable. HOMA-IR and QUICKI were only calculated in patients not on glucose lowering agents. Hs-CRP values > 15 mg/L were

excluded from analyses since they may indicate the presence of an active inflammatory disease.

All statistical analyses were performed using the Statistical Package for the Social Sciences for Windows 10.1 (SPSS, Chicago, IL, USA).

Results

Table 1 describes the baseline characteristics of the study population, according to the presence of the metabolic syndrome: 103 patients (45%) with the metabolic syndrome, and 124 patients without (55%). In 58 patients waist circumference was not available. Substituting a BMI cut point of 30 kg/m^2 as determinant for obesity classified only two more patients with the metabolic syndrome (103 patients vs. 101 patients when BMI was not substituted). In one patient both waist circumference as BMI were missing. Age and smoking habits were equally distributed. Patients with the metabolic syndrome had a higher creatinine clearance compared to non-metabolic syndrome patients (85 mL/min vs. 79 mL/min, P-value = 0.009). Metabolic syndrome patients had higher hs-CRP plasma levels (3.2 vs. 2.0 mg/L, P-value <0.001) and lower adiponectin levels (4.1 mg/L vs. 5.3 mg/L, P-value = 0.002) compared to their non-metabolic syndrome counterparts. Severity of coronary artery disease was classified as single-vessel disease in 55% and as multi-vessel disease in 45% of the metabolic syndrome patients versus 65% and 35% in non-metabolic syndrome patients (P-value 0.2). As expected, all 5 diagnostic parameters of the metabolic syndrome were more common in patients with the metabolic syndrome than in patients without the metabolic syndrome.

Table 1. Baseline characteristics of the study population.

characteristic	metabolic syndrome		P-value
	yes (n=103)	no (n=124)	
male gender	77%	88%	0.03
age (years)[a]	58 ± 8	58 ± 10	0.8
body mass index (kg/m^2)[a]	29 ± 3	26 ± 4	<0.001
smoking *	77%	81%	0.6
severity of coronary vessel disease †			0.2
single-vessel disease	55%	65%	
multi-vessel disease	45%	35%	
total cholesterol (mmol/L)[b]	5.4 (4.7-6.1)	5.0 (4.4-5.7)	0.001
adiponectin (mg/L)[b]	4.1 (3.0-6.4)	5.3 (3.7-7.5)	0.002
hs-CRP (mg/L)[b]	3.2 (2.0-6.6)	2.0 (1.1-3.9)	<0.001
creatinine clearance (Cockcroft) mL/min[a]	85 ± 17	79 ± 17	0.009
fasting serum insulin ‡ (mIU/L)[b]	19 (11-35)	15 (9-25)	0.05
diabetes mellitus §	40%	7%	<0.001
glucose lowering agents	18%	3%	0.001
anti-hypertensive drugs	43%	20%	0.001
lipid lowering agents	55%	46%	0.1
components of metabolic syndrome			
waist circumference (cm)[a]	101 ± 8	95 ± 9	
blood pressure systolic (mmHg)[a]	140 ± 18	132 ± 21	
blood pressure diastolic (mmHg)[a]	80 ± 9	76 ± 10	
HDL-cholesterol (mmol/L)[b]	0.93 (0.82-1.10)	1.15 (0.96-1.32)	
triglycerides (mmol/L)[b]	2.25 (1.78-3.22)	1.38 (1.06-1.63)	
fasting serum glucose (mmol/L)[b]	6.5 (5.7-8.1)	5.6 (5.2-5.9)	

All data in percentages, or as indicated: [a] mean ± standard deviation, or [b] median with interquartiles range.
* Still smoking, recently stopped smoking or previously smoking.
† According to pre-PTCA angiograms.
‡ Patients on glucose lowering agents excluded from analyses.
§ Fasting serum glucose ≥ 7.0 mmol/L or self-reported diabetes.
Hs-CRP: high sensitive C-Reactive Protein (plasma values > 15 mg/L excluded from analyses).

Table 2. Relation of the metabolic syndrome, the number of components (according to ATP III criteria[1]) and the presence of coronary collaterals according to Rentrop's classification[35].

	collaterals present Rentrop-grade ≥ 1 (n = 86)	**collaterals absent Rentrop-grade = 0** (n = 141)
metabolic syndrome		
no	35% (44)	65% (80)
yes	41% (42)	59% (61)
number of components		
0	36% (5)	64% (9)
1	34% (16)	66% (31)
2	37% (23)	64% (40)
3	43% (22)	57% (29)
4	42% (13)	58% (18)
5	33% (7)	67% (14)

All data in percentages (number of patients).

Rentrop-grade ≥ 1 was present in 41% of the metabolic syndrome patients and in 35% of the non-metabolic syndrome patients. Coronary collaterals were present in 36% of the patients without any components of the metabolic syndrome, in 34% of the patients with 1 component, in 37% of the patients with 2 components, in 43% of the patients with 3 components, in 42% of the patients with 4 components and in 33% of the patients with all components of the metabolic syndrome (Table 2).

Table 3. Relation of the metabolic syndrome, the number of components (according to the ATPIII criteria[1]) and the presence of coronary collaterals.

	crude	adjusted for age and sex	adjusted for age, sex and severity of coronary artery disease*
metabolic syndrome	1.3 (0.7-2.1)	1.3 (0.8-2.3)	1.2 (0.7-2.0)
number of components			
0	†	†	†
1	0.9 (0.3-3.2)	0.9 (0.3-3.1)	1.1 (0.3-4.1)
2	1.0 (0.3-3.5)	1.0 (0.3-3.5)	1.2 (0.3-4.1)
3	1.4 (0.4-4.7)	1.4 (0.4-4.8)	1.5 (0.4-5.3)
4	1.3 (0.4-4.8)	1.4 (0.4-5.1)	1.3 (0.3-4.9)
5	0.9 (0.2-3.7)	1.0 (0.2-4.0)	1.0 (0.2-4.3)

All data: odds ratio's (95% confidence interval).
* According to pre-PTCA angiograms (single-vessel versus multi-vessel disease).
† Reference category.

No difference was found in the presence of coronary collaterals between patients with and patients without the metabolic syndrome (crude odds ratio [OR] 1.3; 95% confidence interval [CI] 0.7-2.1). Age, sex and the severity of coronary artery disease did not influence the relationship between the metabolic syndrome and coronary collaterals (adjusted OR 1.2; 95% CI 0.7-2.0). The number of single components of the metabolic syndrome similarly showed no association with coronary collateral formation (Table 3). When patients with established diabetes mellitus were excluded from analyses, results remained the same (data not shown).

In Table 4 it is shown that quantitative estimates of insulin resistance are not associated with the presence of coronary collaterals. Odds ratio for HOMA-IR (highest versus lowest tertile) was 0.7 (95% CI 0.3-1.5) and for QUICKI (lowest versus highest tertile) 0.8 (95% CI 0.4-1.6) after adjustment for age, sex and severity of coronary artery disease.

Table 4. Relation of quantitative estimates of insulin resistance (HOMA-IR and QUICKI) and the presence of coronary collaterals.*

	crude	adjusted for age and sex	adjusted for age, sex and severity of coronary artery disease†
HOMA-IR tertiles			
1	‡	‡	‡
2	1.0 (0.5-2.0)	1.0 (0.5-2.1)	0.8 (0.4-1.8)
3	0.8 (0.4-1.7)	0.8 (0.4-1.7)	0.7 (0.3-1.5)
QUICKI tertiles			
1	0.9 (0.4-1.8)	0.9 (0.4-1.8)	0.8 (0.4-1.6)
2	1.0 (0.5-2.1)	1.1 (0.5-2.2)	0.8 (0.4-1.8)
3	‡	‡	‡

All data: odds ratio's (95% confidence interval).
* Patients on glucose lowering agents excluded from analyses.
† According to pre-PTCA angiograms (single-vessel versus multi-vessel disease).
‡ Reference category.
HOMA-IR: homeostasis model assessment determined insulin resistance (fasting serum glucose x fasting serum insulin)/22.5.[38]
QUICKI: quantitative insulin sensitivity check index (1/(log fasting serum glucose + log fasting serum insulin).[39]

Conclusions

The metabolic syndrome is associated with an increased risk for cardiovascular morbidity and mortality.[7-15] Impaired coronary collateral formation has been reported in diabetes mellitus and may also contribute to the increased cardio-vascular risk in metabolic syndrome patients. However, in the present study we could not detect a relation between the metabolic syndrome and the presence of coronary collaterals in patients referred for elective PTCA. Moreover, also no association was found between insulin resistance and coronary collaterals.

To our best knowledge this is the first clinical study examining the association between the metabolic syndrome (according to the ATP III criteria) and the presence of coronary collaterals. There are several studies with contradictory

findings on coronary collateralization in diabetic patients. In their angiographic study, Abaci et al. showed that diabetic patients developed a less extensive coronary collateral circulation compared to non-diabetic patients.[24] Endothelial dysfunction and blunted nitric oxide production, both associated with diabetes, were suggested to underlie this decreased collateralization. A recently performed study found no difference in coronary collateral vessel formation between diabetic and non-diabetic patients using Rentrop's classification.[28]

In an insulin resistant state hyperinsulinemia is associated with endothelial dysfunction by the release of the potent vasoconstrictor endothelin. Also, the increased production of cytokines, low-grade inflammation, defects in insulin signalling pathways, activation of the renin angiotensin system and increased oxidative stress, all associated with insulin resistance, could contribute to endothelial dysfunction.[30] However, we showed that, in patients referred for PTCA the metabolic syndrome and insulin resistance are not associated with impaired coronary collateral formation. This may be due to several reasons. Firstly, we studied patients with advanced coronary artery disease. These patients may already have an impaired endothelial function to such an extent that the influence of insulin resistance on endothelial function could be neglected. Despite the fact that patients with the metabolic syndrome have significantly higher plasma levels of hs-CRP (3.2 vs. 2.0 mg/L, P-value <0.001) and significantly lower plasma levels of adiponectin (4.1 mg/L vs. 5.3 mg/L, P-value 0.001) (hs-CRP positively and adiponectin negatively associated with endothelial dysfunction) compared to non-metabolic syndrome patients, we did not find a difference in coronary collateralization.

Secondly, vasoactive drugs, as angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB) and statins could have positive effects on endothelial function.[40-42] Moreover, statin use has been shown to be associated with enhanced collateralization in patients with documented coronary artery disease.[43] Although use of lipid lowering agents was equally distributed in our study population, patients with the metabolic syndrome significantly more often

use ACE inhibitors or ARB compared to patients without the metabolic syndrome (28% vs. 11%, P-value 0.001). This could have ameliorated the endothelial dysfunction in metabolic syndrome patients. However, in the present study we did not find a significant association between the use of ACE inhibitors or ARB and coronary collateralization (data not shown).

Finally, the technique used to visualize coronary collaterals could only identify blood vessels which diameter exceeds 100 μm. With this technique, contrary to myocardial contrast echocardiography, intramural collaterals can also not be demonstrated so coronary collateral blood flow can only be semi-quantitatively assessed. It may be possible that patients with the metabolic syndrome have an impaired formation of collateral vessels with a diameter < 100 μm, or intramural situated collaterals. In addition to coronary angiography to determine coronary collateral development, several studies use intracoronary pressure and/or flow velocity assessments. Although this quantitative assessment of coronary collaterals is considered superior to the angiographic grading method used in this study[44-46], a major limitation of this technique is that it can only be performed during angioplasty which restricts its applicability to a limited population. To investigate the influence of the metabolic syndrome on coronary collateral development in subjects without coronary artery disease non-invasive imaging techniques for coronary collateral assessment should be developed.

We conclude that there is no significant association between the metabolic syndrome or insulin resistance and the presence of coronary collaterals in patients with documented coronary artery disease.

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Appendix

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Chapter 4

Prognostic significance of coronary collaterals

Chapter 4.1

Prognostic significance of coronary collaterals in patients with ischemic heart disease (the SMART Study)

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Submitted for publication

Abstract

Background: The presence and extent of coronary collateral (CC) circulation are of vital importance in acute myocardial ischemia. However, its prognostic significance at long-term in unselected patients with ischemic cardiac disease, is uncertain. We examined CC-presence and extent as prognostic determinant of cardiovascular (CV) outcome.

Methods and results: Prospective case-cohort study in 655 patients, admitted for elective coronary angioplasty. Median follow-up time: 2.6 years (range 0.2-4.6). Outcome was defined as first CV-event during follow-up, and a composite of CV-death, non-fatal myocardial infarction (MI), non-fatal stroke, or any CV-intervention. Baseline coronary angiograms were reviewed for the control-group (a 20% random sample at baseline), and all cases, in total 244 patients. CCs were graded with Rentrop's classification (grade 0-3). CC-presence was defined as Rentrop-grade $\geq$1. Data were analyzed with the unweighted Cox proportional-hazards model, stratified for Framingham coronary heart disease (CHD) risk-score, and adjusted for gender, age, previous MI, previous coronary intervention, and multi-vessel coronary disease. CCs were present in 91 patients (37%). A first CV-event occurred in 141 patients (58%): CV-death (n=3), non-fatal MI (n=26), non-fatal stroke (n=4), and any CV-intervention (n=108). Overall, CC-presence at baseline was related to a higher risk of subsequent CV-events, particularly in high-risk patients (hazard ratio [HR] 2.2; 95% confidence interval [CI] 1.1-4.6). Grade 1-collaterals were related to the highest risk of subsequent CV-events (HR 8.1; 95% CI 3.1-20.8).

Conclusions: In patients with ischemic heart disease, CC-presence marks an unfavourable prognosis, particularly in relatively high-risk patients, and if present to only a limited extent (Rentrop-grade 1).

Introduction

The presence and extent of coronary collaterals may determine the prognosis of patients with coronary artery disease both during episodes of acute and unexpected myocardial ischemia, and during chronic ischemia.[1-3] Coronary collaterals, or "natural bypasses", are anastomotic connections without an intervening capillary bed between portions of the same coronary artery and between different coronary arteries.[4] In the event of an acute myocardial infarction, well-developed coronary collaterals may determine the short-term outcome of a patient, by minimizing the infarct size, by preserving myocardial viability and left ventricular function, and by extending the period of time available until successful coronary reperfusion.[5-8] In patients with stable coronary artery disease, a reduction in ischemic events and a better mid- to long-term prognosis has been reported when collaterals are present.[9,10] In patients with an acute myocardial infarction, overall, similar mid- to long-term findings have been reported,[11,12] although some other studies reported no effect,[13,14] or an adverse effect.[15,16] These different findings may, in part, be attributed to statistical and technical factors, but also to differences in study design, study population, definition of and methods used to assess coronary collaterals, definition of outcome, and duration of follow-up. Furthermore, there is marked interindividual variability in the extent of coronary collateral circulation.[3] In addition, these studies were done with selected groups of patients.

From a pathophysiologic point of view, a direct and positive relationship between collaterals and better outcome is to be expected. At the same time, however, the presence of collaterals is related to, among others, the duration and extent of ischemic disease and thus a marker of its severity.[1-3] Therefore, it is at present not clear, whether the presence of coronary collaterals in unselected patients with ischemic heart disease, reflects the severity of coronary artery disease and thus a worse prognosis in the long term, or whether its presence helps to prevent future occurrence of cardiovascular events by protecting against ischemia. In the

present study, we examined the presence and extent of coronary collaterals as a long-term prognostic determinant of cardiovascular outcome, in an unselected group of patients, referred for elective coronary angioplasty. In addition, patients were stratified according to cardiac risk (estimated with the Framingham coronary heart disease risk-score[17]) to examine whether the prognostic significance of coronary collaterals varies by disease severity.

Methods

The study was approved by the Institutional Review Board of the University Medical Center Utrecht (UMC Utrecht). Written informed consent was obtained from all patients. The procedures followed were in accordance with the institutional guidelines.

Patients

A prospective case-cohort study was separately performed within the "Second Manifestations of ARTerial disease (SMART)" study. The latter study is an ongoing prospective cohort study conducted at the UMC Utrecht.[18] At enrollment, medical history is recorded with a standardized questionnaire, and height, weight, and blood pressure are measured. Blood and urine samples are taken. Information on occurrence of new fatal or non-fatal cardiovascular disease, and cardiovascular interventions during follow-up is obtained by contacting the patients every six months. Follow-up for the present study ended March 1, 2003.

For the purpose of the present study, we used a case-cohort design.[19] The study population consisted of all 655 patients, who were admitted for elective percutaneous transluminal coronary angioplasty (PTCA) and took part in SMART between January 1, 1998 and July 8, 2002. For the control-group a 20% random sample of 131 of the 655 (20%) patients was selected. Cases consisted of all

patients in whom a cardiovascular event occurred during follow-up, in total 152 patients, 25 of whom had also been selected into the random sample.

Coronary collateral circulation

In total, baseline angiographic data on 258 PTCA-patients were to be retrieved (131 + 152 - 25 = 258). Baseline diagnostic coronary angiograms (CAG's) could not be retrieved for 14 patients (3 from the control-group; 11 cases), and subsequently, these patients were excluded from the study. Therefore, baseline CAG's were reviewed for 244 PTCA-patients (258 - 14 = 244). The presence and extent of coronary collaterals on each baseline CAG was defined and visually assessed with the Rentrop's classification (grade 0 - no filling of collateral vessels; grade 1 - filling of collateral vessels without any epicardial filling of the recipient artery; grade 2 - partial epicardial filling by collateral vessels of the recipient artery; and grade 3 - complete epicardial filling by collateral vessels of the recipient artery).[20] Coronary collateral presence was defined as the presence of minimal or well-developed collaterals (Rentrop-grade 1, 2 or 3).[21,22] Grading was done independently by a trained research physician (J.K.) and a cardiologist (P.P.Th.d.J.), who were blinded to the clinical data. If an angiogram was graded differently, consensus was obtained. The pre-PTCA angiograms were graded in random order. To assess the interobserver variability of the grading, 100 randomly selected CAG's were scored by another cardiologist, not involved in the study and unaware of the results of the reading of the two other observers and of the clinical data, during a separate session. The strength of agreement between the two observers (J.K. & P.P.Th.d.J.) and the other cardiologist was good (Kappa 0.65, 95% confidence interval (CI) 0.51 - 0.79). Previously, the reproducibility of the Rentrop's score has already been described as high (Kappa 0.85, 95% CI 0.77-0.93).[23]

Cardiovascular outcome

In the present study, we considered the presence of coronary collaterals as a measure of an individual to form collaterals in vascular areas other than the heart, such as the brain and peripheral circulation. Therefore, we defined cardiovascular outcome as a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, any cardiovascular intervention, or any amputation of lower extremities. The outcome of interest was defined as the first cardiovascular event occurring during follow-up. In case potential outcomes of interest occurred, additional information was collected from either the patients' specialist or general practitioner.

Cardiovascular death was defined as fatal cerebral infarction, fatal myocardial infarction, sudden death, or fatal rupture of an abdominal aortic aneurysm. Non-fatal myocardial infarction was defined by at least two out of the three following characteristics present: (1) ischemic chestpain of $\geq$ 30-min duration, (2) an increase in MB-fraction of creatine kinase (CK-MB) to more than twice the upper level of normal, and (3) characteristic changes on the electrocardiogram consistent with the diagnosis. Non-fatal stroke was defined as focal brain injury persisting for more than 24 hours, combined with an increase in handicap of at least one point on the Rankin Scale. A distinction was made between a cerebral infarction and a cerebral hemorrhage, based on computed tomography (CT) or magnetic resonance imaging (MRI), if available. A cardiovascular intervention was defined as any coronary artery bypass grafting (CABG), PTCA, carotis endarterectomy, or revascularization (surgical or with percutaneous transluminal angioplasty [PTA]) of the aorta or one of its branches, or of the iliac, femoral, or crural arteries. An amputation of lower extremities was defined as any amputation (or part) of a toe, foot or leg due to chronic ischemia.[18] All events were reviewed by three members of an independent Clinical Event Committee for final diagnosis and classification, and coded as described previously.[18] If an event was classified differently, consensus was obtained.

Data-analysis

Unless specified otherwise, data are presented as count with percentage or mean ± standard deviation. First, the association between the presence and absence of coronary collaterals, and cardiovascular outcome was quantified with the unweighted Cox proportional-hazards model by Prentice, particularly suitable to analyze case-cohort data.[19] This weighting method is incorporated in a SAS macro written by Barlow and Ichikawa, and made available through Statlib on the Internet (*http://lib.stat.cmu.edu/general/robphreg*).[24] Subsequently, the analyses were repeated with adjustment for variables, known to potentially affect the association examined, notably male gender, age, a history of myocardial infarction, a history of PTCA or CABG, and multi-vessel coronary disease.

Second, the relation between the extent of coronary collateral circulation (Rentrop-grades 1, 2, 3, versus 0 taken as the reference-category), and cardiovascular outcome was quantified with the unweighted Cox proportional-hazards model by Prentice[19], both unadjusted, and with adjustment for the variables, mentioned above. Finally, to examine whether the prognostic significance of coronary collaterals varies by disease severity (the amount of cardiovascular disease already present), the analyses were repeated with the patients stratified according to cardiac risk, estimated with the Framingham coronary heart disease risk-score.[17] Patients were classified as relatively low- or high-risk, with the distinction based on the median estimated risk-score.

Hazard ratios with robust 95% confidence interval are presented. A two-sided P-value < 0.05 was considered statistically significant. The statistical package used was the SAS System for Windows, release 8.02 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Patient characteristics

Baseline- and clinical characteristics of the 244 patients studied, are presented in Table 1. Coronary collaterals were present in 91 patients (37%): 13 patients had grade 1 (no epicardial filling), 33 patients had grade 2 (partial epicardial filling), and 45 patients had grade 3 collaterals (complete epicardial filling). The median estimated Framingham coronary heart disease (CHD) risk-score was 13% (range 1 - 53). Therefore, patients with a CHD risk-score < 13% were classified as relatively low-risk. Consequently, patients with a risk-score ≥ 13% were classified as relatively high-risk.

Table 1. Baseline- and clinical characteristics of the study population.

characteristic	all patients studied (n = 244)	cases (n = 141)	non-cases (n = 103)	P-value
demographics:				
age at index-PTCA (yrs)	58.1 ± 9.2	58.5 ± 9.1	57.5 ± 9.4	0.40
male gender	203 (83%)	121 (86%)	82 (80%)	0.20
cardiovascular risk factors:				
current smoking	69 (29%)	38 (27%)	31 (30%)	0.64
current alcohol-consumption	186 (77%)	105 (76%)	81 (79%)	0.57
diabetes mellitus	49 (20%)	34 (24%)	15 (15%)	0.07
hypertension	91 (38%)	54 (40%)	37 (36%)	0.59
hyperlipidemia	203 (84%)	121 (86%)	82 (80%)	0.16
obesity (BMI ≥ 30 kg/m^2)	43 (18%)	28 (20%)	15 (15%)	0.28
Framingham CHD risk*:				
CHD risk (%)	15.4 ± 9.9	16.3 ± 10.6	14.2 ± 8.8	0.12
Low CHD-risk (< 13%)†	109 (46%)	59 (44%)	50 (50%)	†
High CHD-risk (≥ 13%)	126 (54%)	75 (56%)	51 (51%)	0.41
angina:				
prior angina pectoris (AP)	224 (92%)	132 (94%)	92 (89%)	0.15
AP on exertion	171 (72%)	103 (76%)	68 (66%)	0.10
AP during emotions	77 (32%)	45 (33%)	32 (31%)	0.78
previous conditions:				
previous TIA or stroke	24 (10%)	9 (6%)	15 (15%)	0.04
previous MI	106 (44%)	71 (51%)	35 (34%)	< 0.01
previous PTCA or CABG	77 (32%)	51 (36%)	26 (25%)	0.07
previous non-cardiac vascular surgery	20 (8%)	14 (10%)	6 (6%)	0.25
angiographic characteristics:				
coronary collaterals present (Rentrop-grade ≥ 1)	91 (37%)	58 (41%)	33 (32%)	0.15
1-vessel coronary disease†	143 (59%)	79 (56%)	64 (62%)	†
2-vessel coronary disease	80 (33%)	46 (33%)	34 (33%)	0.75
3-vessel coronary disease	21 (9%)	16 (11%)	5 (5%)	0.08
multi-vessel coronary disease	101 (41%)	62 (44%)	39 (38%)	0.34
impaired left-ventricle function‡	90 (42%)	53 (42%)	37 (40%)	0.75

Number of patients with events (valid %) or mean ± SD.
* = in 9 patients (7 cases, 2 non-cases) the Framingham CHD risk could not be calculated due to missing data; † = reference category; ‡ = in 27 patients the ventriculogram turned out not to be performed.
AP = angina pectoris; BMI = body mass index; CABG = coronary artery bypass grafting; CHD = coronary heart disease; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; SD = standard deviation; TIA = transient ischemic attack.

Table 2. Cardiovascular outcome and the presence and extent of coronary collateral circulation.

first cardio-vascular event after index-PTCA	Rentrop 0 (collaterals absent)	Rentrop 1 (not epicardial)	Rentrop 2 (partial epicardial)	Rentrop 3 (complete epicardial)	all patients studied
	(n = 153)	(n = 13)	(n = 33)	(n = 45)	(n = 244)
cardiovascular death	-	-	1 (3%)	2 (4%)	3 (1%)
- sudden death	-	-	1 (3%)	1 (2%)	2 (1%)
- congestive heart failure	-	-	-	1 (2%)	1 (0.4%)
non-fatal myo-cardial infarction	17 (11%)	5 (39%)	1 (3%)	3 (7%)	26 (11%)
non-fatal stroke	1 (1%)	-	-	3 (7%)	4 (2%)
(repeat) cardiovascular interventions	65 (43%)	5 (39%)	20 (61%)	18 (40%)	108 (44%)
- CABG	12 (8%)	-	6 (18%)	9 (20%)	27 (11%)
- PTCA	47 (31%)	4 (31%)	11 (33%)	9 (20%)	71 (29%)
- PTA	3 (2%)	1 (8%)	2 (6%)	-	6 (3%)
- AAA surgery	1 (1%)	-	-	-	1 (0.4%)
- other vascular surgery	2 (1%)	-	1 (3%)	-	3 (1%)
patients with events	83 (54%)	10 (77%)	22 (67%)	26 (58%)	141 (58%)

Number of patients with events (valid %).
AAA = abdominal aortic aneurysm; CABG = coronary artery bypass grafting; PTA = percutaneous transluminal angioplasty; PTCA = percutaneous transluminal coronary angioplasty.

Follow-up and cardiovascular outcome

Median follow-up time was 2.6 years (range 0.2 - 4.6). A first cardiovascular event occurred in 141 patients (58%). Three patients died of cardiovascular disease: sudden death occurred in two patients, and one patient died of congestive heart failure. In 26 patients a non-fatal myocardial infarction occurred, in four patients a non-fatal ischemic stroke, and 108 patients had a cardiovascular intervention (see Table 2).

Table 3. Risk of any first cardiovascular event in relation to presence and extent of coronary collateral circulation, unadjusted, adjusted, and stratified for Framingham coronary heart disease risk at baseline (case-cohort study in 655 elective PTCA-patients).

coronary collaterals	low CHD-risk * (< 13%)	high CHD-risk * (≥ 13%)	all strata	P-value
	59 cases; 50 non-cases	75 cases; 51 non-cases	141 cases; 103 non-cases	all strata
unadjusted				
collateral presence (Rentrop ≥ 1)	0.96 (0.58-1.59)	2.23 (1.28-3.89)	1.41 (0.98-2.04)	0.07
collateral extent †				
- Rentrop 1	0.62 (0.13-2.93)	6.96 (2.73-17.8)	1.48 (0.35-6.22)	0.59
- Rentrop 2/3	1.02 (0.60-1.72)	2.05 (1.16-3.61)	1.40 (0.97-2.02)	0.07
adjusted ‡				
collateral presence (Rentrop ≥ 1)	1.04 (0.60-1.78)	2.22 (1.08-4.55)	1.34 (0.91-1.98)	0.14
collateral extent †				
- Rentrop 1	0.78 (0.16-3.74)	8.07 (3.13-20.8)	1.91 (0.45-8.06)	0.38
- Rentrop 2/3	1.08 (0.61-1.90)	1.78 (0.82-3.86)	1.27 (0.86-1.89)	0.23

Hazard ratio (robust 95% confidence interval).
* = in 9 patients (7 cases, 2 non-cases) the Framingham CHD risk could not be calculated due to missing data.
† = Rentrop-grade 0 is reference category.
‡ = adjusted for male gender, age, a history of myocardial infarction, a history of PTCA or CABG, and multi-vessel coronary disease.
CABG = coronary artery bypass grafting; CHD = coronary heart disease;
PTCA = percutaneous transluminal coronary angioplasty.

Cardiovascular outcome and the presence and extent of coronary collateral circulation

Table 3 summarizes the results of the analyses regarding the presence and extent of coronary collateral circulation, and the risk of a first cardiovascular event, both unadjusted, and adjusted for male gender, age, a history of myocardial infarction, previous coronary intervention, and multi-vessel coronary disease. Overall, the presence of coronary collaterals at baseline was related to a

higher risk of subsequent cardiovascular events. This adverse effect was most pronounced in patients with relatively high CHD-risk (hazard ratio [HR] 2.22; 95% confidence interval [CI] 1.08 - 4.55), but less obvious in relatively low-risk patients (HR 1.04; 95% CI 0.60 - 1.78).

The risk of subsequent cardiovascular events also depended on the extent of coronary collateral circulation. Overall, Rentrop-grade 1 coronary collaterals were related to the highest risk, particularly in relatively high-risk patients (HR 8.07; 95% CI 3.13 - 20.8), but not in patients with a relatively low CHD-risk (HR 0.78; 95% CI 0.16 - 3.74).

If the analyses were restricted to cardiac outcome alone, defined as a composite of cardiac death, non-fatal myocardial infarction, or any cardiac intervention (PTCA or CABG) during follow-up, the results were essentially similar.

Discussion

In the present, prospective case-cohort study among 655 patients with ischemic heart disease and referred for elective PTCA, with a median follow-up time of 2.6 years (range 0.2 - 4.6), we found that, overall, the presence of coronary collaterals at baseline was related to a higher risk of subsequent cardiovascular events, particularly in relatively high-risk patients, and if present to only a limited extent (Rentrop-grade 1). If cardiac outcome alone was considered, these findings were essentially similar.

To appreciate these results, some aspects of this study need to be addressed. First, we examined the presence and extent of coronary collaterals as prognostic determinant of cardiovascular outcome in a population, who was referred for elective PTCA. Therefore, we first calculated the hazard ratios for adverse cardiovascular outcome without adjustment. Subsequently, we calculated these

hazard ratios with adjustment for variables that are known to potentially affect this relation, since they may not only be associated with the outcome, but also with the presence and extent of coronary collaterals. Nonetheless, the factors responsible for the presence or development of collaterals, including genetic factors, are still subject of investigation.[1-3,25-33]

In addition, the use of angiography to define and assess coronary collaterals may have influenced our observations. Coronary angiography, although the most frequently used diagnostic technique for the assessment of collateral vessels, can only identify vessels > 100 μm in diameter, whereas most collateral vessels are smaller.[6] Furthermore, even though the overlap between quantitative measures and qualitative angiographic degrees of collateral flow has been demonstrated to be quite large[34], quantitative indices of collateral circulation may be better markers of the functional significance of collateral vessels, in particular in recruitable (Rentrop-grade 1) collaterals.[23,35,36] A recent study, nonetheless, reported good correlation between a novel angiographic method of assessment and function.[37] This is to be expected considering the fundamental physical law describing that vessel radius is related to the fourth power of flow.[38] It is, thus, likely that the morphologic degree of collaterals used in this study, is closely related with the functional degree of coronary collateral circulation.

Furthermore, it is plausible that the fate of the patient will ultimately be determined by the balance between severity of disease and the presence and extent of coronary collateral circulation. Presumably, a gradient of risk is present. Therefore, we repeated the analyses with the patients stratified according to cardiac risk at baseline, estimated with the Framingham coronary heart disease risk-score.[17] Although, this risk-score is primarily intended to predict the risk of coronary heart disease in patients without overt coronary heart disease, the prediction rule also provides an efficient method to simply rank patients according to their estimated cardiac risk, if disease is already present.

The fact that the hazard ratios for adverse outcome were different across the two categories of cardiac risk and dependent on collateral extent, and the fact that the adjusted hazard ratios were essentially similar to the unadjusted estimates, emphasizes the role of coronary collaterals in predicting future events. The different effect of collaterals in the various risk groups may explain the conflicting evidence on the protective role of collaterals, reported in the literature, so far.[9-16,39,40] From this point of view, it would thus be interesting to estimate the mean (Framingham) cardiac risk-score at baseline for each of these studies to allow better comparison of the results. Unfortunately, due to lack of specific and individual data, for instance on mean total cholesterol or mean systolic blood pressure, we were not able to do so.

The results of the present study indicate that, overall, in patients with ischemic cardiac disease, the presence of coronary collaterals represents a prognostic indicator of adverse cardiovascular outcome, especially if present to only a limited extent (Rentrop-grade 1), rather than a favorable sign. Yet, in patients with relatively low cardiac risk, the presence of well-developed coronary collaterals may protect against subsequent cardiovascular or cardiac events. It is likely, that in these relatively low-risk patients, the presence of well-developed collaterals marks sufficient collateral blood flow to adequately counterbalance the adverse effects of ischemic heart disease.[37] At the same time, in particular in relatively high-risk patients, the presence of barely developed coronary collaterals (Rentrop-grade 1) may indicate such limited collateral function, that it does not succeed in compensating for the severity of disease, thus putting the patient at an even higher risk.

In conclusion, in patients with ischemic heart disease, the presence of coronary collaterals marks an unfavourable prognosis, in particular in relatively high-risk patients, and if present to only a limited extent (Rentrop-grade 1).

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Appendix

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Chapter 4.2

Determinants and prognostic significance of collaterals in patients undergoing coronary revascularization (the Octopus Study)

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Abstract

Background: There is evidence that coronary collaterals improve the prognosis in patients with acute myocardial infarction. However, there is limited clinical information on the protective role of collaterals in patients with stable coronary artery disease. This information may help risk stratification and the development of novel therapies such as arteriogenesis and angiogenesis.

Methods: The relation between collaterals and cardiac death or myocardial infarction at one year after coronary revascularization, was studied in 561 patients who were enrolled in a randomized study comparing stent implantation and bypass surgery. Collaterals were assessed on the angiogram using the Rentrop's classification and considered present if Rentrop-grade >1. Unadjusted and adjusted odds ratios for cardiac death or myocardial infarction at one year were calculated using univariate and multivariate regression analysis. In addition, determinants of collaterals were assessed using univariate and multivariate analysis.

Results: Collaterals were present in 176 patients (31%). The adjusted odds ratio of cardiac death or infarction was 0.18 (95% CI 0.04-0.78) in the presence of collaterals. Independent determinants of collaterals were age (odds ratio 0.97; 95% CI 0.95-0.99), multi-vessel disease (odds ratio 1.60; 95% CI 1.02-2.51), impaired ventricular function (odds ratio 1.85; 95% CI 1.04-3.29), type-C lesion (odds ratio 3.72; 95% CI 2.33-5.95), and stenosis severity> 90% (odds ratio 9.08; 95% CI 4.65-17.7).

Conclusions: In patients with stable coronary artery disease, the presence of collaterals protects against cardiac death and myocardial infarction. Variables that reflect the duration and severity of the atherosclerotic and ischemic burden determine their presence.

Introduction

There is evidence that coronary collaterals protect the myocardium during acute ischemia and in patients with stable coronary artery disease. They may limit infarct size, preserve viability and prevent of ventricular aneurysm formation during an episode of acute coronary occlusion.[1-4] In patients with stable coronary artery disease, a reduction in ischemic events and a better prognosis has been reported when collaterals are present.[5,6]

From a pathophysiologic point of view, a direct and positive relationship between collaterals and better outcome is to be expected. Yet, due to the small number of studies and patients, this relationship and its strength needs further examination. It may help risk stratification and patient management. One may think of tailoring the intensity of treatment and follow-up on the basis of risk. It may also stimulate the development of novel therapeutic strategies (e.g. angiogenesis) if inter-arterial connections, whatever their origin (preexisting and potentially recruitable or angiogenetic in nature) proof to be protective.[7,8] We investigated the determinants and prognostic significance of collaterals in a series of 561 patients who were enrolled in a randomized study that compared stent implantation and bypass surgery with a follow-up period of one year.[9,10]

Methods

Study population

The population comprised the 561 patients enrolled in the Octopus Study. This study consisted of two randomized trials in which bypass surgery on the beating heart with the Octopus stabilizer (off-pump surgery) was compared to stent implantation and bypass surgery with cardiopulmonary bypass (on-pump surgery). These two trials were conducted in parallel to each other in the same

time frame in three centers. The study and main findings have recently been reported.[9,10]

In brief, patients referred for coronary angioplasty were randomized to stent implantation or off-pump surgery (138 and 142 patients, Octostent Study), whereas patients referred for surgery were randomized to on- or off-pump surgery (139 and 142 patients, Octopump Study). Patients were eligible, if they had stable or unstable angina (Braunwald class I-II, B) and/or documented ischemia, irrespective of the extent of vessel disease provided that off-pump surgery was technically feasible and expected to lead to a similar degree of revascularization in comparison to stent implantation or on-pump surgery. The objective was to achieve complete functional revascularization by stenting or arterial grafting of the major coronary arteries. Patients were excluded in case of left main stem stenosis, the need of more than one graft for complete revascularization of the left circumflex artery, or a poor ventricular function. Patients were also excluded in case of emergency revascularization, Q-wave myocardial infarction in the last six weeks, previous surgery, and angioplasty in the last six months or in-stent restenosis.

Coronary collaterals

The presence of collaterals was defined by the visual assessment of the baseline angiogram using the Rentrop classification.[11] This morphologic assessment has been shown to correlate with the quantitative or functional assessment in patients with stable angina and angiographic documented coronary artery disease.[12,13] Grade 0 is defined by the absence of filling of collateral vessel(s); grade 1 by the filling of collateral vessel(s) without any epicardial filling of a recipient artery; grade 2 by the partial epicardial filling; and grade 3 by the complete epicardial filling of the recipient artery.[11] Collaterals were considered present in case of epicardial filling of the recipient artery (Rentrop-grade > 1). The angiograms were graded in random order by two cardiologists who were blinded for the treatment assignment and clinical data. Inter-observer variability of the grading was

assessed earlier. The reproducibility of the Rentrop's score has been described as high (Kappa 0.85; 95% CI 0.77-0.93).[14]

Baseline characteristics and cardiac outcome

Multi-vessel disease was defined by the presence of a significant stenosis (> 50% diameter obstruction) in at least 2 major coronary arteries. Ventricular function was defined by the visual assessment of the angiogram in the right anterior oblique view and categorized into normal, moderate and poor. Lesion severity was scored according to the ACC/AHA classification. Details of all baseline variables have been reported elsewhere.[9,10]

For the purpose of the present analysis, cardiac outcome was defined by the composite of cardiac death or non-fatal myocardial infarction (MI) in descending order of severity (mutually exclusive analysis). In addition, non-cardiac death, non-fatal stroke and repeated coronary revascularization (surgery or angioplasty) were analyzed as well. Death was considered cardiac unless documented otherwise, stroke was defined as focal brain injury persisting for more than 24 hours, combined with an increase in handicap of at least one grade on the Rankin Scale.[9,10] Within seven days, a non-Q wave MI was defined by the increase in the serum creatine kinase isoenzyme myocard brain (CK-MB) five times the upper limit of normal after surgery or 3 times after stenting. A Q-wave MI was defined using the same enzymatic criteria in combination with the occurrence of new pathological Q-waves. Seven days after surgery, a non-Q-wave MI was diagnosed in case the CK-MB to total creatine kinase ratio exceeded 0.1 and a Q-wave MI if new pathological Q-waves appeared.[9,10] An independent Clinical Event Committee evaluated all events.

Data-analysis

The primary objective of the study was to determine the association between the presence of collaterals and one-year cardiac outcome. The association between collaterals and cardiac outcome was determined by calculating the crude odds ratio using an univariate regression analysis. By means of multivariate regression analysis, the crude odds ratio was adjusted for variables considered confounders of the association examined. Distinction was made between patients with and without collaterals to identify potential indicators of collateral presence. The independent contribution between putative determinants was analyzed using multivariate logistic regression analysis. Chi-square or student-t-tests were used to discern statistical significant differences. All reported P-values were two-sided. A P-value <0.05 was considered statistically significant. Event-free survival was estimated using the Kaplan-Meier method and groups were compared with the logrank test. All data were analyzed using SPSS version 10.0.

Table 1. Baseline characteristics of patients with and without collaterals.

characteristic	all patients (n=561)	collaterals present Rentrop > 1 (n=176)	collaterals absent Rentrop 0 -1 (n=385)	P-value
demographics:				
age (years; mean value)	60.7	60.3	60.9	0.48
male sex	70%	71%	69%	0.84
cardiovascular risk factors:				
diabetes	12%	10%	13%	0.30
history of smoking	75%	72%	77%	0.23
hypertension	37%	34%	38%	0.30
hypercholesterolemia	64%	69%	62%	0.08
obesity (BMI > 30 kg/m^2)	15%	14%	15%	0.85
family history of cardiovascular disease	40%	41%	40%	0.85
stable angina	70%	77%	67%	0.05
previous myocardial infarction	28%	38%	23%	<0.01
angiographic characteristics:				
multi-vessel disease	51%	68%	44%	<0.01
impaired left-ventricular function	16%	24%	13%	<0.01
LAD-disease	93%	94%	93%	0.71
LCX-disease	30%	34%	27%	0.09
RCA-disease	41%	63%	31%	<0.01
coronary stenosis > 90%	65%	94%	53%	<0.01
type-C coronary lesion	48%	78%	35%	<0.01

BMI = body mass index; LAD = left anterior descending coronary artery;
LCX = left circumflex coronary artery; RCA = right coronary artery.

Results

The baseline characteristics are summarized in Table 1. Collaterals were present in 31% of the patients. Most patients were male and had a normal ventricular function. Multi-vessel disease was present in 51% of the patients (39% had double and 13% triple vessel disease). Complete myocardial revascularization was achieved in 90% of the patients.

Table 2. Independent determinants of collaterals in patients undergoing myocardial revascularization.

determinant	odds ratio (95% CI)	P-value
age	0.97 (0.95 - 0.99)	0.03
female sex	1.27 (0.76 - 2.13)	0.34
diabetes	0.72 (0.36 - 1.41)	0.33
history of smoking	0.74 (0.44 - 1.24)	0.25
history of hypertension	0.78 (0.50 - 1.26)	0.33
history of hypercholesterolemia	1.19 (0.75 - 1.89)	0.45
obesity	1.14 (0.62 - 2.10)	0.66
previous myocardial infarction	1.51 (0.93 - 2.45)	0.09
stable angina	1.19 (0.73 - 1.93)	0.33
multi-vessel coronary disease	1.60 (1.02 - 2.51)	0.04
impaired left ventricular function	1.85 (1.04 - 3.29)	0.04
type-C coronary lesion	3.72 (2.33 - 5.95)	<0.01
coronary lumen stenosis > 90%	9.08 (4.65 - 17.73)	<0.01

Odds ratio's and 95% confidence intervals (CI).

By univariate analysis, stable angina, hypercholesterolemia, previous MI, multi-vessel disease, impaired ventricular function, left circumflex and right coronary disease, coronary stenosis > 90%, and type-C coronary lesion were identified as strong indicators of the presence of collaterals (Table 1). Diabetes and a history of smoking were indicative of absence of collaterals without reaching statistical significance. There was no relation between age and gender and collaterals (Table 1). Multivariate analysis disclosed that coronary stenosis > 90% was the strongest independent determinant of the presence of collaterals, followed by type-C lesion, multi-vessel disease, impaired ventricular function, previous MI, and young age (Table 2).

Table 3. First cardiac event at one-year in descending order of severity.

first cardiac event	**off-pump** (n=284)	**on-pump** (n=139)	**stent** (n=138)	**all patients** (n=561)
cardiac death	2 (0.7%)	2 (1.5%)	-	4 (0.7%)
myocardial infarction (MI)	9 (3.9%)	8 (5.9%)	4 (2.9%)	21 (3.7%)
cardiac outcome (cardiac death or MI)	11 (4.6%)	10 (7.4%)	4 (2.9%)	25 (4.4%)
non-cardiac death	4 (1.4%)	-	-	4 (0.7%)
stroke	1 (0.4%)	1 (0.7%)	-	2 (0.4%)
repeated bypass surgery	3 (1.1%)	1 (0.7%)	3 (2.1%)	7 (1.2%)
repeated angioplasty	8 (2.8%)	2 (1.5%)	14 (10.0%)	24 (4.3%)
patients with any event	27 (9.5%)	14 (10.3%)	21 (15.0%)	62 (11.1%)
patients free from events	258 (90.5%)	122 (89.7%)	119 (85.0%)	499 (88.9%)

Number of patients with events (valid %).

At one-year, cardiac death or MI had occurred in 25 patients (4.4%). Death, MI, stroke or repeat revascularization had occurred in 62 patients (11.1%) (Table 3). The crude odds ratio for cardiac death or MI during one year of follow-up in the presence of collaterals was 0.17 (95% CI 0.04-0.74) (Table 4). After adjustment for age and sex the odds ratios were 0.19 and 0.18, respectively. Further adjustment for previous MI, multi-vessel disease and impaired ventricular function did not materially change the odds ratio 0.18 (95% CI 0.04-0.78, Table 4).

Table 4. Unadjusted and adjusted risk of one-year cardiac death or myocardial infarction in relation to presence of collaterals (Rentrop-grade > 1).

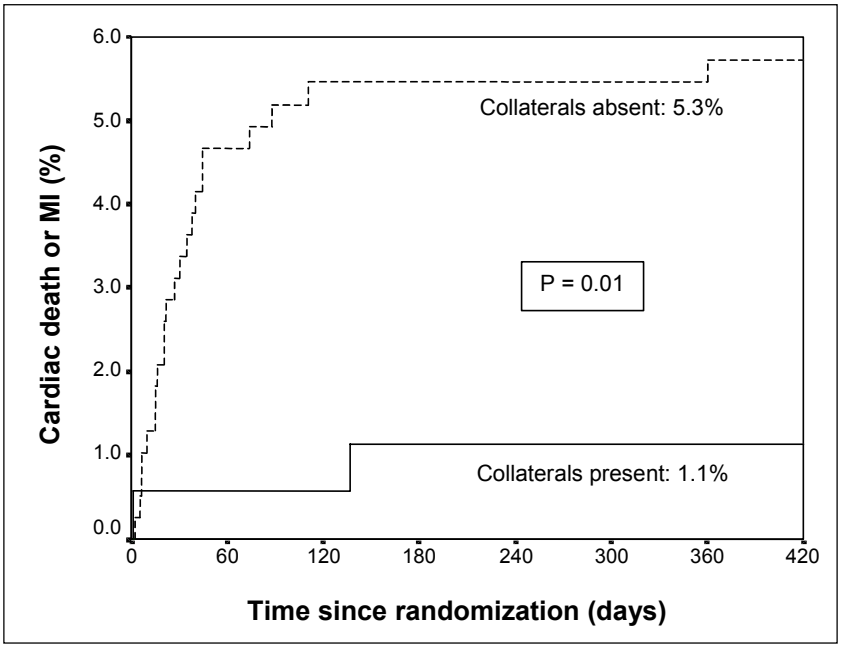
coronary collaterals	odds ratio (95% CI)	P-value
presence of coronary collaterals, unadjusted	0.17 (0.04 - 0.74)	0.019
presence of coronary collaterals, adjusted for:		
- age	0.19 (0.04 - 0.84)	0.026
- sex	0.18 (0.04 - 0.78)	0.022
- previous myocardial infarction	0.18 (0.04 - 0.79)	0.023
- multi-vessel coronary disease	0.16 (0.04 - 0.68)	0.013
- impaired left ventricular function	0.18 (0.04 - 0.77)	0.020
- all variables mentioned above	**0.18 (0.04 - 0.78)**	**0.021**

Odds ratio's and 95% confidence intervals (CI).

Kaplan Meier graphs of the occurrence of cardiac death or MI and any first event in patients with and without collaterals are shown in Figure 1. The presence of collaterals was associated with a significantly lower risk of cardiac death or MI ($P = 0.01$) and of any first event ($P < 0.01$).

Discussion

The main finding of the present study is that collaterals protect the patient with stable coronary artery disease against future events. The nature and strength of the relationship between collaterals and outcome must be viewed and interpreted in the context of the study and methods of assessment. With respect to the latter, we first calculated the unadjusted odds of adverse outcome in the presence of collaterals, followed by the calculation of adjusted odds ratios. This was done since, in accordance with other studies, we postulated that collaterals protect the patient against adverse events even in the presence of variables that are known to be associated with poor outcome but which are also (causally) related to the presence of collaterals. The extent of disease and ventricular function, for



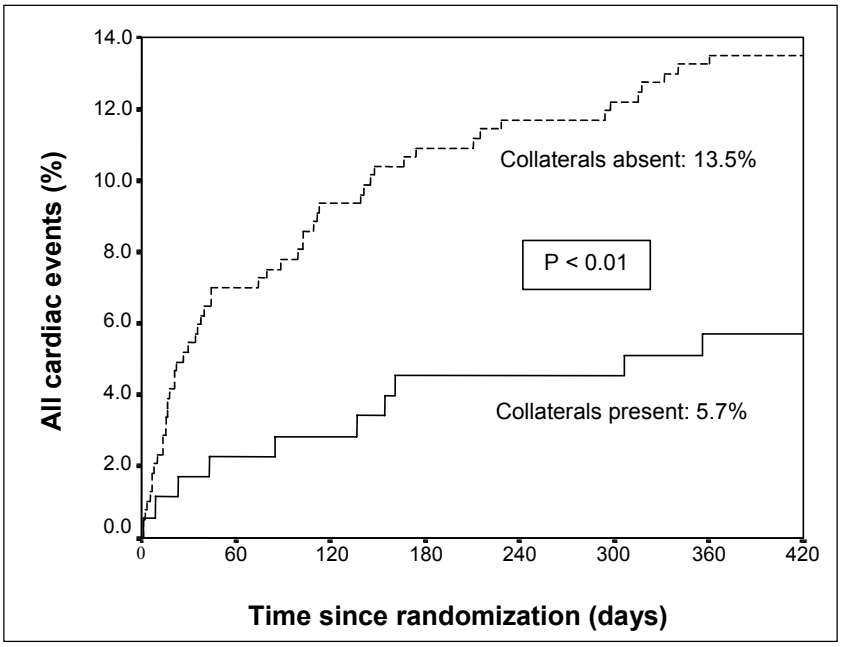


Figure 1. Kaplan-Meier estimates of proportion first events at one year after myocardial revascularization, stratified by collaterals. P-values were calculated with the log-rank test. Upper panel: cardiac death or non-fatal myocardial infarction (MI). Lower panel: all-cause death or non-fatal stroke or non-fatal MI or repeated coronary revascularization.

instance, are known to affect outcome but also induce collaterals. The balance between harm of disease and benefit from collaterals will ultimately define the fate of the patient. Most likely, a gradient of risk is present. Patients with low-grade disease will benefit most from collaterals, while those with advanced disease or high cardiovascular risk will not, even in the presence of adequate collaterals.

In the present low risk population with few events during a period of one year, overall protection by collaterals was found. Given the homogeneity of the study population, no meaningful further stratification of risk groups was possible. The protection from collaterals is in agreement with two other studies that found a lower incidence of ischemic events in patients with stable angina and well-developed collaterals. The fact that the adjusted odds ratios did not really differ from the unadjusted odds ratio, underscores the role of collaterals in the protection against future events.[5,6]

In addition to the methods of analysis, the use of angiography for the definition of collaterals and the threshold value (Rentrop Score > 1) to discern their presence or absence may have influenced our observations. Quantitative assessment, which is considered to be superior to morphologic assessment, was not used.[15] We may, thus, have underestimated the protective effects of collaterals. Recent studies, however, report a good correlation between angiographic and functional methods of assessment in patients with stable angina referred for coronary angioplasty.[12,13] As a result of the low-risk population studied with low number of ischemic events, the relationship between the various grades of collaterals according to the Rentrop Score and outcome could not be explored.

The determinants of the presence of collaterals were assessed cross-sectionally using the baseline measurements of the cohort, but not in a dedicated prospective study. From a pathophysiologic point of view, one may understand the relation between these determinants and the presence of collaterals. The determinants can be considered as a measure of the severity and duration of the atherosclerotic process and ischemic burden and, thus, the time during which the

coronary artery tree has been subjected to a different and changing intracoronary pressure distribution. Hemodynamic factors have been shown to be the main cause of recruitment and growth of collaterals.[16] This is in accordance with the relation between the ischemic burden and collaterals reported by others.[15,17]

Still, it is unclear why collaterals are present in some patients of the same population and not in others. Most likely other factors play a role as well. Physical activity, high cholesterol levels, hypertension, nicotine and the use of statins or angiotensin converting enzyme inhibitors have all been reported to be positively associated with collaterals while homocysteine and diabetes appear to be inversely associated with collaterals.[18-26] This needs further elucidation considering the nature of the evidence. If true, this knowledge may open new therapeutic frontiers. This may especially be the case for drugs such as statins and angiotensin converting enzyme inhibitors considering their presumed pleiotropic action.[27,28]

In conclusion, this study in a large and well-defined low risk population with stable coronary artery disease, supports the view that the presence of coronary collaterals is a strong and independent predictor of improved outcome. Variables that reflect the duration of the atherosclerotic process and ischemic burden are determinants for their presence.

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Chapter 5

General discussion

General discussion

Current knowledge on coronary collaterals

Coronary collaterals, or "natural bypasses", may already be present at birth, or in normal human hearts, but they may also develop during life.[1-4] Coronary collaterals might protect the heart and prevent ischemic cardiac events by providing sufficient and alternative blood flow to the myocardium, making it less vulnerable to episodes of ischemia. Actually, the most important determinants for the occurrence of cardiovascular events in the presence of atherosclerosis are coronary atherosclerosis, trigger factors, and myocardial vulnerability.[5] Trigger factors are factors that promote rapid occlusion of arterial vessels already compromised by atherosclerosis, thus "triggering" sudden reductions of coronary flow and ischemia. This ischemic episode has to exceed a specific threshold value in duration or severity, in order to produce clinical events, such as a myocardial infarction or even sudden cardiac death. This threshold value depends on the susceptibility of the myocardium to ischemia, which is determined by (among other factors) its level of protection, for example, by the presence of well-developed collateral arteries.

The most important determinants of coronary collaterals, identified so far, are recurrent and severe myocardial ischemia,[6-8] and the existence of an arterial pressure gradient and shear stresses.[9,10] Furthermore, different circulating growth factors and chemokines are involved in angiogenesis (such as vascular endothelial growth factor [VEGF]), and arteriogenesis (for instance, granulocyte-macrophage colony stimulating factor [GM-CSF]).[9,10] In addition, several growth factors are currently being studied as a novel treatment in peripheral artery disease to enhance the development of collateral vessels.[11,12] The findings of these trials will be of potential importance in patients who are unsuitable for conventional interventions, either in case of peripheral artery disease, [13] or ischemic heart disease.[9,14]

Finally, well-developed coronary collaterals may play an important prognostic role in patients with coronary artery disease. They may determine the outcome of a patient in the event of an acute myocardial infarction, by minimizing the infarct area, by preserving myocardial viability and left ventricular function, by extending the limited time available until successful coronary reperfusion, and ultimately by improving the chances of survival.[15-18] However, cardiovascular endpoint-studies with long-term follow-up, in which coronary collaterals are studied as prognostic determinants of vascular outcome, are scanty and with different findings.[19-29]

In order to further clarify these different findings, Table 1 presents a concise, chronologically ordered, overview of the characteristics of these 11 endpoint-studies. Among others, the method used to assess the presence or absence of coronary collaterals, the population and outcome studied, the duration of follow-up, and the results obtained, are reviewed for each study. In short, the prognostic significance of coronary collaterals has mainly been studied in patients with stable coronary artery disease (4 studies[19,20,26,29]), or in patients admitted for an acute myocardial infarction (6 studies[21-23,25,27,28]). The number of patients studied ranged from 20 to 1164. In fact, 2 studies were too small in size to draw conclusions from.[24,25] Furthermore, different methods and definitions have been used to assess the presence of coronary collaterals, either qualitative with angiography[19,21-25,27-29], or quantitative with pressure- or doppler-derived collateral flow index.[20,26] Issues related to the assessment of coronary collaterals are discussed in more detail in Section 3. Lastly, the study-populations were classified according to estimated low or high coronary heart disease-risk at baseline, based on severity of coronary artery disease at inclusion, population homogeneity, additional in- and exclusion criteria if applicable, and event-rates reported. Essentially, this resulted in 4 studies with low-risk populations, notably those in patients with stable coronary artery disease.[19,20,26,29] The 5 sufficiently sized studies in patients with an acute myocardial infarction had higher risk populations.[21-23,27,28]

This distinction between low and high coronary heart disease risk at baseline revealed an important finding regarding the different results on the prognostic significance of coronary collaterals, reported by the cardiovascular endpoint-studies listed in Table 1. The studies in low-risk populations reported a protective effect of coronary collaterals with a subsequent reduction in future cardiac ischemic events.[19,20,26,29] However, the studies in high-risk populations either reported no effect[21,27], or even an adverse effect[22,28], if coronary collaterals were found to be present at baseline. Just one study in a higher risk population reported a beneficial effect of pre-existent coronary collaterals.[23] However, this study only considered the influence of coronary collaterals on in-hospital death from an anterior acute myocardial infarction, while the potential occurrence of cardiac events during follow-up after hospital-discharge was left out of consideration.

Table 1. Overview of coronary collaterals and cardiovascular endpoint follow-up

1st author	study-design	study-population	mean follow-up	outcome
Hansen[29] **Am Heart J 1989**	cohort	stable coronary artery disease n=96 coronary artery occlusion at diagnostic coronary angiogram - no acute myocardial infarction (MI) < 3 months - no overt heart failure - no unstable angina pectoris - no diastolic hypertension - no severe non-cardiac disease - no significant valvular disease	11-19 years	death
Gohlke[28] **Am J Cardiol 1991**	cohort	acute anterior Q-wave myocardial infarction (MI) at < 40 years old n=102 (98 male; 4 female) - survivor of acute anterior Q-wave MI at < 40 years old - 1-vessel disease - culprit lesion in proximal LAD (before 1st septal branche)	1-12 years	death

studies (in chronological order).

1st author	coronary collaterals	co-variables	event-rate / results	conclusion
Hansen[29] **Am Heart J 1989**	<u>method by Bruschke:</u> good collaterals: collaterals and epicardial arteries well visualized (= Rentrop 2/3) *versus* poor collaterals: collaterals or epicardial arteries faint or absent (= Rentrop 0/1)	<u>strata:</u> - angina pectoris y/n - heart failure y/n <u>covariables:</u> - clinical history - ECG - stenosis or occlusion of coronary arteries	no details given on number of deaths <u>survival-rate at 10 yrs:</u> - good collaterals: 51.5% - poor collaterals: 34.5% [p<0.1] - with angina pectoris and good collaterals: 59.5% - with angina pectoris and poor collaterals: 41.2% [p<0.05] - good collaterals and no heart failure: 64.8% - good collaterals and heart failure: 24.4% [p<0.001] - poor collaterals and no heart failure: 58.3% - poor collaterals and heart failure: 16.1% [p<0.01]	good collaterals protect the myocardium by prevention of acute MI and heart failure, and thus may improve survival
Gohlke[28] **Am J Cardiol 1991**	<u>method by Goldstein:</u> 0 = no vessels (= Rentrop 0) 1 = few small; faint (= R 1) 2 = many small, or 1 large; dense opacification (= R 2/3) 3 = 1 large and ≥ 1 small; dense (= R 3) 4 = ≥ 2 large; dense (= R 3) - each donor vessel assessed separately - total score > 4 possible at least moderate collaterals: score ≥ 2 *versus* none or faint collaterals: score 0 - 1	degree of stenosis	no details given on number of deaths <u>8-yr mortality rate:</u> - collateral-score ≥ 2: 21% - none or faint collaterals: 8% [p<0.034]	collateral vessels after an anterior Q-wave acute MI before age 40 years do not protect against adverse events

Table 1. Overview of coronary collaterals and cardiovascular endpoint follow-up

1st author	study-design	study-population	mean follow-up	outcome
Boehrer[27] **Am J Cardiol 1992**	case-control	first acute myocardial infarction (MI) n=146 (108 male; 38 female) - first acute MI - occluded infarct artery - follow-up available - no disease of other coronary arteries - no acute MI related angioplasty - no CABG for refractory angina	12.5 years	morbid events: - unstable angina pectoris - recurrent acute MI - congestive heart failure - death
Pijls[26] **JACC 1995**	case-control	stable coronary artery disease n=120 (91 male; 29 female) - 1-vessel disease - NYHA III stable angina pectoris ≥ 3 months - positive exercise-test pre-PTCA - elective coronary angiogram at inclusion - no previous myocardial infarction - no previous PTCA or CABG	16 months (6-22 months)	composite of: - death - myocardial infarction - unstable angina pectoris

studies (in chronological order) - continued.

1st author	coronary collaterals	co-variables	event-rate / results	conclusion
Boehrer[27] **Am J Cardiol 1992**	method by Helfant: collateral presence: if portion distal to site of occlusion was filled by accessory blood vessels (= ± Rentrop 3) *versus* collateral absence	none only univariate analysis (chi-square test, student's T test)	unstable angina pectoris: - collaterals present: 23 (19%) - collaterals absent: 8 (31%) [NS] recurrent acute MI: - collaterals present: 14 (12%) - collaterals absent: 2 (8%) [NS] congestive heart failure: - collaterals present: 19 (16%) - collaterals absent: 3 (12%) [NS] cardiac death: - collaterals present: 19 (16%) - collaterals absent: 5 (19%) [NS]	angiographic evidence of collateral filling of the infarct artery in surviving acute MI-patients exerts no demonstrable influence on long-term morbidity or mortality
Pijls[26] **JACC 1995**	pressure-derived collateral flow index (CFI) high CFI ≥ 0.24 *versus* low CFI < 0.24 additionally: Rentrop 0-3	none only univariate analysis (relative risk; chi-square test)	16 ischemic events: - high CFI: 1/16 - low CFI: 15/16 - Rentrop 2/3: 3/16 Rentrop 0 often associated with low CFI Rentrop 1 or 2 does not guarantee high CFI	pressure derived CFI reliable method to distinguish sufficient versus insufficient collateral circulation sufficient collateral flow is beneficial

Table 1. Overview of coronary collaterals and cardiovascular endpoint follow-up

1st author	study-design	study-population	mean follow-up	outcome
Kodama[25] **JACC 1996**	case-control	first acute myocardial infarction (MI) n=21 (20 male; 1 female) - acute MI < 24 hours - unsuccessful reperfusion therapy - proximally occluded LAD in acute phase, and at 1 month - no collaterals in acute phase - no previous MI - no cardiomyopathy, severe valvular disease, ventricular septal defect, or cardiogenic shock	short term: 1 month long term: 2.12 ± 0.79 years	left ventricular dilation and function
Shen[24] **Am J Cardiol 1998**	case-series	total left main (LM) coronary artery occlusion n=20 (18 male; 2 female) - total LM coronary artery occlusion - CABG performed - post-operative survivor	10 years (1.5-18 years)	death after CABG

studies (in chronological order) - continued.

1st author	coronary collaterals	co-variables	event-rate / results	conclusion
Kodama[25] **JACC 1996**	new collaterals at 1 month after index-myocardial infarction (MI) method of Saito: - grade 0 = none (= Rentrop 0) - grade 1 = poor (= R 1) - grade 2 = well-developed (= R 2/3) well-developed = grade 2 *versus* absent or poor = grade 0 or 1	- gender - age - body surface area - duration follow-up - defect volume - ejection fraction - left-ventricle end-diastolic (LVED) volume - left-ventricle end-systolic (LVES) volume - TIMI-flow grade	well-developed collateral-group: decrease in LVED- and LVES-volumes at 2 years absent or poor collateral-group: increase in LVED- and LVES-volumes after 2 years	newly developed collaterals after acute MI prevent subsequent ventricular dilation and deterioration of left-ventricle-function over 2 years, but not within 1 month after infarction
Shen[24] **Am J Cardiol 1998**	Rentrop 0 - 3 total collateral score score 4 - 6 = well-developed collaterals *versus* score 0 - 3 = poor collaterals	univariate and multivariate (but no information on co-variables)	9 patients died: - score 4 - 6: 4 (29%) - score 0 - 3: 5 (83%) univariate: collateral score weakly associated with survival [p=0.12] life-table: lower collateral score worse prognosis than higher score [hazard ratio (HR) 2.5] cox multivariate: lower collateral score weaker association [HR 2.8; p=0.13]	the presence of insufficient collaterals is possible risk factor for decreased survival after CABG for left main coronary artery occlusion

Table 1. Overview of coronary collaterals and cardiovascular endpoint follow-up

1st author	study-design	study-population	mean follow-up	outcome
Perez-Castellano [23] **JACC 1998**	case-control	anterior acute myocardial infarction (MI) n=180 (147 male; 33 female) - anterior acute MI - completely occluded LAD - primary PTCA < 6 hours - left and right coronary angiogram obtained - no previous PTCA or CABG	in-hospital stay after acute MI exact duration not given	in-hospital death cardiogenic shock
Nicolau[22] **Am J Cardiol 1999**	cohort	acute myocardial infarction (MI) n=422 (355 male; 67 female) - acute MI - intravenous streptokinase < 6 hours - coronary angiogram during hospitalization - no terminal disease, no hemorrhagic coagulopathy - no stroke < 3 months - no urinary or digestive tract bleed < 3 months; no peptic ulcer - no surgery < 3 months - no traumatic cardio-pulmonary resuscitation - no pregnancy - no arterial hypertension	3.44 years	death

studies (in chronological order) - continued.

1st author	coronary collaterals	co-variables	event-rate / results	conclusion
Perez-Castellano[23] **JACC 1998**	Rentrop 0 - 3 collaterals present = Rentrop 1 - 3 *versus* collaterals absent = Rentrop 0	- age - previous MI - diabetes - multi-vessel coronary artery disease - PTCA-result final model: - age - previous MI	in-hospital mortality-rate: - collaterals present: 5 (8%) - no collaterals: 26 (23%) - Rentrop 2/3: 2 (6%) - Rentrop 1: 3 (9%) cardiogenic shock: - collaterals present: 4 (6%) - no collaterals: 30 (26%)	pre-existent collateral circulation decreases in-hospital death from anterior acute MI by reducing the incidence of cardiogenic shock
Nicolau[22] **Am J Cardiol 1999**	method of Schwarz et al: - grade 0 = absence (= Rentrop 0) - grade 1 = faint (= R 1) - grade 2 = more than half vessel (= R 2) - grade 3 = normal flow (= R 3) initially: collateral presence = grade 2 or 3 *versus* collateral absence = grade 0 or 1 subsequently: collateral degree = 3 *versus* collateral degree < 3	- left-ventricle global ejection fraction; global, and regional shortening - multi-vessel coronary artery disease - residual obstruction - age - gender - previous MI - non-invasive hemodynamic status - recanalization - dose streptokinase - acute MI wall - time "strepto" - coronary angiogram - time pain - streptokinase - hypotension after "strepto" - reinfarction - definite in-hospital treatment	50 patients died during FUP (no further details given) survival-rate: - grade 2/3: 73.2% - grade 0/1: 85.4% [p=0.16] - grade = 3: 66.0% - grade < 3: 85.1% [p=0.12] cox multivariate: collateral flow degree independent (negative correlation) [p=0.02]	patients treated with intravenous streptokinase during acute MI and with adequate coronary collateral circulation had a worse prognosis than those who developed adequate anterograde flow (= patency of infarct-related artery)

Table 1. Overview of coronary collaterals and cardiovascular endpoint follow-up

1st author	study-design	study-population	mean follow-up	outcome
Antoniucci[21] **Am J Cardiol 2002**	cohort	acute myocardial infarction (MI) n=1164 (906 male; 258 female) - acute MI - primary PTCA < 6 hours - repeat coronary angiogram at 6 months no restrictions based on age, gender, or clinical status on presentation	6 months	death <u>composite of:</u> - death - re-infarction - repeat target vessel re-vascularization < 6 months
Billinger[20] **JACC 2002**	cohort	stable coronary artery disease n=403 (311 male; 92 female) - 1- or 2-vessel disease - PTCA at inclusion - no previous Q-wave myocardial infarction - no previous PTCA or CABG	94 ± 56 weeks (15-202 weeks)	<u>composite of:</u> - cardiac death - myocardial infarction - unstable angina pectoris stable angina pectoris

studies (in chronological order) - continued.

1st author	coronary collaterals	co-variables	event-rate / results	conclusion
Antoniucci[21] **Am J Cardiol 2002**	Rentrop 0 - 3 collateral presence = Rentrop 2 or 3 *versus* collateral absence = Rentrop 0 or 1	- age - gender - previous MI - preinfarction angina pectoris - anterior acute MI - cardiogenic shock - multi-vessel coronary artery disease - total chronic occlusion - TIMI-flow grade <1 - infarct artery stenting - multiple stents - PTCA failure - post-PTCA minimal lumen diameter	mortality rate: - Rentrop 2/3: 11 (4%) - Rentrop 0/1: 80 (9%) [p=0.011] MACE*: - Rentrop 2/3: 58 (22%) - Rentrop 0/1: 226 (25%) [NS] multivariate Cox-model: collateral presence not significant * MACE = major adverse coronary event	coronary collateral presence does not exert a protective effect in patients who undergo primary PTCA in the first hours after acute MI
Billinger[20] **JACC 2002**	pressure- or doppler-derived collateral flow index (CFI) high CFI $\geq$ 0.25 *versus* low CFI < 0.25	none only univariate Kaplan-Meier analysis	MACE + stable angina pectoris: - high CFI: 31 (23%) - low CFI: 55 (20%) [NS] MACE: - high CFI: 3 (2.2%) - low CFI: 24 (9%) [p=0.01] stable angina pectoris: - high CFI: 28 (21%) - low CFI: 31 (12%) [p=0.01]	well-developed collaterals have beneficial impact on future major cardiac ischemic events

Table 1. Overview of coronary collaterals and cardiovascular endpoint follow-up

1st author	study-design	study-population	mean follow-up	outcome
Nathoe[19] **Circulation 2004, *in press***	case-control	stable coronary artery disease n=281 (191 male; 90 female) stable or unstable angina pectoris enrolled in Octopus study randomly assigned to on- or off-pump CABG - no previous CABG - no emergency or other surgery - no Q-wave myocardial infarction < 6 weeks - no poor left-ventricle function	1 year	< 48 hours after surgery: peri-operative myocardial infarction (MI) 1-year follow-up: composite of: - all-cause death - non-fatal stroke - non-fatal MI - repeat re-vascularization (PTCA or CABG)

studies (in chronological order) - continued.

1st author	coronary collaterals	co-variables	event-rate / results	conclusion
Nathoe[19] **Circulation 2004, *in press***	Rentrop 0 -3 collateral presence = Rentrop > 1 *versus* collateral absence = Rentrop 0 - 1	- age - gender - hypertension - hypercholes-terolemia - diabetes - multi-vessel coronary artery disease - ventricular dysfunction - ischemic-time	peri-operative MI in the presence of collaterals: - off-pump: OR 0.34 [p=0.02] - on-pump: OR 1.28 [p=0.74] 1-year event-free survival: - off-pump with collaterals: 87% - off-pump no collaterals: 69% [p=0.01] - on-pump with collaterals: 66% - on-pump no collaterals: 63% [p=0.79]	collaterals protect against peri-operative MI during off-pump but not during on-pump CABG. collaterals are associated with better one-year event-free survival

Current work on coronary collaterals

The first aim of this thesis was to examine several determinants of the presence and extent of coronary collaterals collectively in a single group of patients. For that, we performed a cross-sectional study as part of the "Second Manifestations of ARTerial disease (SMART)" study. The SMART study is an ongoing prospective cohort study conducted at the University Medical Center Utrecht.[30] We assessed the role of cardiac ischemic burden, high blood pressure, smoking and alcohol, and the metabolic syndrome, as potential determinants of coronary collaterals in a group of 244 patients, who were referred for elective coronary angioplasty and took part in the SMART Study between January 1, 1998 and July 8, 2002. Baseline diagnostic coronary angiograms of these patients were reviewed to visually assess the presence and extent of coronary collaterals. Collaterals were graded with the Rentrop's classification, the standard angiographic measure of collateral vessels.[31]

We found that several indicators of cardiac ischemic burden were strongly associated with the presence of coronary collaterals. These included, in order of importance, angina pectoris on exertion, multi-vessel coronary artery disease, a history of myocardial infarction, angina pectoris during emotions, and time since first coronary intervention (if prior). In addition, we also developed a simple sum-score to estimate the total burden of cardiac ischemia in a patient, that uses four clinical factors, that can be easily assessed in every patient. These included angina pectoris on exertion, angina pectoris during emotions, a history of myocardial infarction, and a history of prior coronary intervention. The sum-score was then calculated by adding one point for each clinical factor present (range 0 - 4). We found that the cardiac ischemic burden sum-score was strongly associated with the presence of coronary collaterals, even if severity of coronary artery disease was taken into account.

Furthermore, we found that several measures of blood pressure were inversely related with the presence of coronary collaterals. These included systolic blood

pressure, diastolic blood pressure, mean arterial pressure, systolic hypertension, and the use of antihypertensive treatment. In addition, there was a graded, inverse relation between levels of systolic blood pressure, levels of pulse pressure, and collateral extent.

Subsequently, we found that the life-style factors smoking and alcohol were related to the presence of coronary collaterals, as well. Current smoking was positively associated, while the number of packyears was inversely associated. Current, regular alcohol intake was associated with the presence of collaterals in a biphasic, J-curve fashion, with moderate intake levels associated with a reduced, and high intake levels with an increased presence of coronary collaterals. In addition, past moderate alcohol consumption was inversely related. Finally, we found for the first time, that the metabolic syndrome (a cluster of generally accepted cardiovascular risk factors as impaired glucose metabolism, hypertension, dyslipidemia and central obesity), was not associated with the presence of coronary collaterals.

The second objective of this thesis was to evaluate the presence and extent of coronary collaterals as prognostic determinant of cardiovascular outcome. For that, we studied the prognostic significance of coronary collaterals in two different study populations.

In the unselected group of patients with ischemic heart disease, referred for elective percutaneous transluminal coronary angioplasty (PTCA) and enrolled in the SMART Study[30] between January 1, 1998 and July 8, 2002, we found that, overall, the presence of coronary collaterals at baseline was related to a higher risk of subsequent cardiovascular events, particularly in relatively high-risk patients, and if present to only a limited extent.

In addition, in a large and well-defined low-risk population with stable coronary artery disease, enrolled in the Octopus Study (a randomized study comparing stent implantation and bypass surgery)[32], we found that the presence of coronary

collaterals at baseline protected against subsequent cardiac death and myocardial infarction. These findings are in accordance with the studies summarized in Table 1.

Assessment of coronary collaterals

An important issue regarding the studies presented in this thesis, is the use of angiography for grading the coronary collateral circulation with Rentrop's classification, the standard angiographic measure of collateral vessels.[31] Collaterals were graded: 0 = no filling of collateral vessels; 1 = filling of collateral vessels without any epicardial filling of the recipient artery; 2 = partial epicardial filling by collateral vessels of the recipient artery; and 3 = complete epicardial filling by collateral vessels of the recipient artery. Grade 1 collaterals have been called "recruitable" collaterals, whereas collaterals were classified "spontaneously visible" when they were grade 2 or 3 before coronary occlusion.[31,33] Nonetheless, several definitions for the distinction between the presence and absence of coronary collaterals have been used in the literature. The distinction most frequently reported has been between well-developed collaterals (grade 2 or 3), and absent or poorly developed collaterals (grade 0 or 1).[33-37] Yet, the presence of coronary collaterals has also been defined as the presence of minimal or well-developed collaterals (grade 1, 2 or 3) compared with none (grade 0).[17,38,39] One study discriminated between rich (grade 3) and poor collateral networks (grade 0, 1 or 2).[40] Another study differentiated between good (grade 2 or 3), poor (grade 1), and absent collateral circulation (grade 0).[41] Finally, the four Rentrop-grades have been distinguished seperately.[42,43]

However, the angiographic grading of coronary collaterals has some limitations. Coronary angiography, although the most frequently used diagnostic technique for the assessment of collateral vessels, can only identify vessels > 100 μm in diameter, whereas most collateral vessels are smaller.[16] Also, while it can demonstrate the presence of epicardial collateral vessels, it does not specify the

distribution of collateral flow within the myocardium, contrary to myocardial contrast echocardiography.[16] Thus, coronary collateral blood flow can only be assessed semi-quantitatively by coronary angiography.

Apart from the angiographic grading during vessel patency or occlusion[31], other conventional methods for qualitatively assessing human coronary collaterals include postmortem coronary angiography[44], patient's history of a walking-through angina pectoris[45], nuclear cardiology techniques[46], recording of intracoronary and surface electrocardiogram[47] and coronary wedge pressure during PTCA[48]. More, recently, the use of transthoracic echocardiography before angiography has been reported to demonstrate the presence of coronary collaterals.[49]

Yet, better techniques for practical quantitative assessment of recruitable collaterals were sought. The development of ultra-thin Doppler and pressure angioplasty guidewires, in the early 1990s, made it possible to measure flow velocity or pressure in remote vascular areas, allowing the physiologic assessment of coronary stenoses and recruitable coronary collaterals in humans.[36,50] In 1991 Ofili et al. described the Doppler-derived collateral flow index.[51] Subsequently, in 1993 Pijls et al. described the pressure-derived collateral flow index.[52] The theoretical basis for the use of intracoronary flow velocity or pressure measurements to determine collateral flow, relates to the fact that velocity or perfusion pressure signals (greater than the central venous pressure) obtained distal to an occluded stenosis almost invariably originate from collaterals.[36] The measurement of such signals provides the variables for the calculation of a flow velocity- and pressure-derived collateral flow index, both of which express the amount of flow via collaterals to the vascular region of interest as a fraction of the flow via the normally patent vessel.[36]

The question is, however, how do the qualitative and quantitative assessment of coronary collaterals relate? Accordingly, Seiler et al. in 51 patients, compared Doppler-wire- and pressure-wire obtained collateral indices with each other, and with three traditional methods for the assessment of coronary collaterals.[36] These

included intracoronary electrocardiogram signs of myocardial ischemia, angina pectoris during balloon occlusion, and the angiographic degree of collateralization. The flow velocity-derived collateral index was the most accurate tool for the detection of collateral flow, sufficient to prevent myocardial ischemia during PTCA. Furthermore, intracoronary pressure-derived collateral indices were only slightly more accurate as the angiographic collateral degree (with Rentrop-grade $\geq$ 2 appointed the cut-off value, defining the presence of well-developed collaterals). The presence of angina pectoris during PTCA was the least accurate test. In addition, they also demonstrated that the overlap between the quantitative measures and qualitative angiographic degrees of collateral flow was quite large.[36] Similar findings on the correlation between quantitative and qualitative assessment of collaterals have been reported by others.[35,37,41,43] However, the quantitative indices of collateral circulation might be better markers of the functional significance of collateral vessels than angiographical grading, in particular in recruitable (grade 1) collateral vessels.[35,41,53]

Finally, although quantitative assessment is considered superior to the morphologic assessment used in the studies presented in this thesis,[35,36,53,54] a recent study reported good correlation between a novel angiographic method of assessment and function.[55] The size of the collateral connection diameter was measured with an electronic caliper on enlarged still images and classified into 3 grades: CC-0, no continuous connection between donor and recipient artery; CC-1, continuous, threadlike connection; and CC-2, continuous, small side branch–like size of the collateral throughout its course.[55] However, the applicability of this angiographic method to collaterals in non-occlusive lesions has yet to be established. Nonetheless, in view of the above, it is therefore likely that the morphologic degree of collaterals used in the studies presented in this thesis, is closely related with the functional degree of coronary collateral circulation.

Added value of coronary collaterals

From the work presented in this thesis, it becomes clear that many determinants, already identified as well-established risk factors for cardiovascular morbidity and mortality, play an important role in the presence of coronary collaterals, as well. In addition, in patients with ischemic heart disease, the presence of coronary collaterals may mark an unfavourable prognosis, particularly in patients with relatively high coronary heart disease-risk, and if present to only a limited extent. Yet, in relatively low-risk patients, the presence of well-developed coronary collaterals may protect against subsequent cardiovascular events. Nonetheless, one may question the added value of knowledge on the presence of coronary collaterals.

We believe that the presence of coronary collaterals should be considered an additional indicator of myocardial vulnerability. Myocardial vulnerability involves the susceptibility of the myocardium to episodes of (acute) ischemia due to reduced coronary flow. The ischemic episode has to exceed a specific threshold value in duration or severity, in order to produce clinical events such as sudden myocardial infarction or even sudden cardiac death. This threshold value depends on the susceptibility of the myocardium to ischemia, which is determined by (among other factors) its level of protection, for instance, by the presence of coronary collaterals.

Recently, in an important consensus document on the potential role of vulnerable plaque in a new risk assessment strategy, the term "cardiovascular vulnerable patient" was introduced.[56,57] The term "vulnerable patient" was proposed to define subjects susceptible to an acute coronary syndrome or sudden cardiac death, based on plaque, blood, or myocardial vulnerability (for instance, 1-year risk $\geq$ 5%). After all, atherosclerosis is a diffuse and multi-system, chronic inflammatory disorder involving vascular, metabolic, and immune systems with various local and systemic manifestations. Therefore, it is essential to assess total vulnerability burden, and not just search for a single, unstable coronary plaque. A composite

risk score, that comprises the total burden of atherosclerosis and vulnerable plaque in the coronaries (and other arteries throughout the body), and that includes blood and myocardial vulnerability factors, should be a more accurate method of risk stratification.[56,57]

Accordingly, the authors presented a new risk assessment strategy, because traditional coronary heart disease risk factors have, so far, failed to predict development of coronary heart disease in a large group of cases, despite extensive studies and development of several risk prediction models. The authors proposed the "Cumulative Vulnerability Index", based on vulnerable plaque / artery, vulnerable blood (prone to thrombosis), and vulnerable myocardium (prone to life-threatening arrhythmia), indicating the likelihood that a patient with certain factors will have a clinical event in the coming year.[56,57]

We propose that the presence of coronary collaterals may provide an additional marker of myocardial vulnerability, and therefore, an additional marker to identify the "vulnerable patient". The prognostic significance of coronary collateral presence is, however, considerably modified by the patient's risk-level of coronary heart disease. Coronary collaterals may exert a protective effect in low-risk patients, but an adverse effect in high-risk patients. Therefore, in particular for those patients with myocardial ischemia and at low cardiac risk, who are unsuitable for percutaneous coronary intervention or coronary artery bypass grafting, therapeutic induction of coronary collateral growth may provide an attractive treatment option.[14,58,59]

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Chapter 6

Summary

Summary

Cardiovascular diseases, in particular coronary artery disease, are the leading cause of death and disease in industrialized countries. Atherosclerotic changes of the arterial vessel wall constitute one of the major causes for the occurrence of cardiovascular disease. Important risk factors for cardiovascular disease have been identified, but they fail to explain why some patients with atherosclerosis become symptomatic and have recurrent symptomatic disease, and others do not. Apart from the extent of coronary atherosclerosis (among other factors), the susceptibility of organs to episodes of ischemia is probably of importance. Well-developed collateral vessels, or "natural bypasses", may offer an important alternative source of blood supply, and thereby protect an organ from episodes of ischemia. Unfortunately, not every organ or even individual has well-developed collateral vessels, if developed at all.

Current knowledge on coronary collaterals and its most important determinants involved, are reviewed in **Chapter 2**. The mechanism of the development of coronary collaterals is subject to increasing preclinical and clinical research. Many factors and patient characteristics have already been proposed to play a role in collateral development. For instance, myocardial ischemia, physical exercise, hypertension, and the use of various cardiovascular drugs. So far, however, for many of these factors, results are inconsistent and, therefore, their pathophysiologic role and importance is still unclear.

In addition, the potential clinical relevance of coronary collaterals has attracted much attention. Coronary collaterals may in fact play an important prognostic role in patients with coronary artery disease during episodes of myocardial ischemia. Well-developed coronary collaterals may determine the prognosis of a patient not only in the event of an acute myocardial infarction, but also in stable coronary artery disease. Yet, different findings have been reported so far, as well.

Therefore, we first investigated several determinants of the presence and extent of coronary collaterals collectively in a single group of patients, notably cardiac ischemic burden, high blood pressure, smoking and alcohol, and the metabolic syndrome. Second, we investigated the presence and extent of coronary collaterals as a prognostic determinant of cardiovascular outcome in two different studies with different study populations.

Determinants of coronary collaterals

In **Chapter 3.1** we reported that several indicators of cardiac ischemic burden were strongly associated with the presence of coronary collaterals. These included, in order of importance, angina pectoris on exertion, multi-vessel coronary artery disease, a history of myocardial infarction, angina pectoris during emotions, and time since first coronary intervention (if prior). Actually, the role of cardiac ischemia, either acute or chronic, in determining the development of coronary collaterals, has now been fairly established. In particular, coronary lesion severity and the duration of myocardial ischemic symptoms have consistently been described as influencing collateral vascular growth. However, to the best of our knowledge, these indicators of cardiac ischemic burden have never been summarized into one score. Therefore, in **Chapter 3.1** we also developed a simple sum-score to estimate the total burden of cardiac ischemia in a patient, that uses four clinical factors, that can be easily assessed in every patient. These included angina pectoris on exertion, angina pectoris during emotions, a history of myocardial infarction, and a history of prior coronary intervention. The sum-score was then calculated by adding one point for each clinical factor present (range 0 - 4). We found that the cardiac ischemic burden sum-score was strongly associated with the presence of coronary collaterals, even if severity of coronary artery disease was taken into account. Thus, the results presented in **Chapter 3.1** not only support the view that cardiac ischemia plays an important role in the development of coronary collaterals, but especially indicate the importance of the total burden of cardiac ischemia in an individual.

In **Chapter 3.2** we reported that several measures of blood pressure were inversely related with the presence of coronary collaterals. These included systolic blood pressure, diastolic blood pressure, mean arterial pressure, systolic hypertension, and the use of antihypertensive treatment. In addition, there was a graded, inverse relation between levels of systolic blood pressure, levels of pulse pressure, and collateral extent. So far, a similar finding has only been reported in patients with carotid artery disease, notably a lower prevalence of cerebral collateral circulation among patients with hypertension. Yet, in patients with documented coronary artery disease, either a positive association was found between hypertension and the presence of coronary collaterals, or no association at all. This controversy may in part be explained by differences in the patients studied and the methods used. However, our results firmly indicated an inverse relation between high blood pressure and the presence of coronary collaterals.

In **Chapter 3.2** we proposed that *microvascular rarefaction* may explain our findings. This involves the functional and structural remodeling of the coronary arterioles and microvasculature in response to increased blood pressure, and ultimately results in the obliteration of preexisting blood vessels. Actually, coronary collateral regression has been reported earlier, but in response to successful coronary recanalization. Collateral regression involves two different concepts: functional and anatomical regression. Functional regression means that collateral vessels close after reperfusion of the recipient coronary artery, presumably due to the disappearance of collateral flow. On the other hand, anatomical regression means that matured collateral vessels lose, in part, their well-developed media and luminal size, and the conductance of collateral flow decreases despite a sufficient pressure gradient and time for collateral recruitment. In particular, incompletely matured collateral vessels may be prone to anatomical regression. Accordingly, in **Chapter 3.2** we postulated that the increased case-fatality in hypertensive patients with an acute myocardial infarction may be related to our findings.

In **Chapter 3.3** we reported that the life-style factors smoking and alcohol were related to the presence of coronary collaterals, as well. Current smoking was positively associated, while the number of packyears was inversely associated. Current, regular alcohol intake was associated with the presence of collaterals in a biphasic, J-curve fashion, with moderate intake levels associated with a reduced, and high intake levels with an increased presence of coronary collaterals. In addition, past moderate alcohol consumption was inversely related. Unfortunately, due to the nature of the study, detailed data on the chemical compounds in the tobacco smoke and alcohol were not available. Therefore, to a large part, we could only speculate about the potential pathophysiologic mechanisms involved.

In an earlier study, smoking was reported not to be associated with the presence of coronary collaterals. Interestingly however, nicotine, one of the many chemical compounds in tobacco smoke, has recently been identified to play a role in angiogenesis and arteriogenesis. Smoking is also associated with chronic hypoxia, which in turn may stimulate collateral growth. Interestingly, smokers have a twofold lower risk of dying in-hospital after an acute cardiac event, the "smokers' paradox", assuming that coronary collaterals may protect the patient during an acute infarction. Finally, the number of packyears, a well established risk factor for coronary atherosclerosis, may induce impaired endothelial vasodilation and inappropriate vasoconstriction, potentially making the collaterals less visible.

Data on alcohol and the presence of coronary collaterals are scarce. The biphasic relationship between alcohol and atherosclerotic cardiovascular disease is well established from epidemiologic data. In fact, the biphasic, J-shaped association between alcohol use and the presence of coronary collaterals represents the inverse of the protective effect of alcohol on atherosclerosis: a protective effect is observed with moderate consumption, but an increased risk of symptomatic cardiovascular disease with heavy alcohol consumption. We, therefore, reasoned that moderate alcohol consumption may imply less cardiac ischemic burden, thus

less trigger for the presence of coronary collaterals. This hypothesis is supported by the finding that, in men with a previous myocardial infarction, moderate alcohol intake was associated with a higher case fatality in the event of another myocardial infarction (presumably due to less collaterals present). Yet, in men with no previous myocardial infarction, moderate alcohol use was associated with a lower case-fatality in the event of a first myocardial infarction (presumably due to a reduction in cardiac ischemic burden). In conclusion, **Chapter 3.3** supports the view that life-style factors may affect the development of coronary collaterals in patients with ischemic cardiac disease.

Finally, in **Chapter 3.4** we reported for the first time, that the metabolic syndrome, another risk factor of increased cardiovascular morbidity and mortality, was not associated with the presence of coronary collaterals. The metabolic syndrome encompasses a cluster of generally accepted cardiovascular risk factors as impaired glucose metabolism, hypertension, dyslipidemia and central obesity. Actually, each of these risk factors has so far been separately studied for an association with the presence of coronary collaterals, but conflicting results were reported on diabetes, hypertension, hyperlipidemia, and obesity. The combination of these different effects, when clustered into the metabolic syndrome, may provide another explanation for the fact that we did not find any association between the metabolic syndrome and the presence of coronary collaterals.

Prognostic significance of coronary collaterals

In **Chapter 4.1** we reported that in the unselected group of patients with ischemic heart disease, referred for elective percutaneous transluminal coronary angioplasty (PTCA) and enrolled in the SMART Study between January 1, 1998 and July 8, 2002, overall, the presence of coronary collaterals at baseline was related to a higher risk of subsequent cardiovascular events, in particular in relatively high-risk patients, and if present to only a limited extent. Accordingly, we supposed that the fate of a patient will ultimately be determined by the balance

between severity of disease and the presence and extent of coronary collaterals. In relatively low-risk patients, the presence of well-developed coronary collaterals may mark sufficient collateral blood flow to adequately counterbalance the adverse effects of ischemic heart disease. At the same time, the presence of barely developed coronary collaterals may indicate such limited collateral function, that it does not succeed in compensating for the severity of disease, thus putting the patient at a higher risk.

In **Chapter 4.2** we reported results in support of this supposition. In a large and well-defined low-risk population with stable coronary artery disease, enrolled in the Octopus Study (a randomized study comparing stent implantation and bypass surgery), the presence of coronary collaterals at baseline protected against subsequent cardiac death and myocardial infarction. We believe that this different effect of coronary collaterals in the various risk groups may explain the conflicting evidence on the protective role of collaterals, reported in the literature, so far.

Added value of coronary collaterals

Finally, in **Chapter 5** we discuss these different findings by several cardiovascular endpoint-studies in greater detail. The prognostic significance of the presence of coronary collaterals appears to be considerably modified by the patient's risk-level of coronary heart disease. Furthermore, we discuss the different methods, that are currently used to assess coronary collateral circulation, and in particular their relationship and limitations. We propose that the presence of coronary collaterals may provide an additional marker of myocardial vulnerability, and therefore, an additional marker to identify the "vulnerable patient". In addition, in particular for those patients with myocardial ischemia and at low cardiac risk, who are unsuitable for conventional coronary interventions, therapeutic induction of coronary collateral growth may provide an attractive treatment option.

Chapter 7

Samenvatting

Samenvatting

Hart- en vaatziekten, in het bijzonder ziekte van de kransslagaderen (coronair arteriën), zijn de belangrijkste oorzaak van ziekte en overlijden in geïndustrialiseerde landen. Aderverkalking (atherosclerose) vormt één van de belangrijkste oorzaken voor het optreden van hart- en vaatziekte. Belangrijke risicofactoren voor hart- en vaatziekte zijn inmiddels geïdentificeerd. Maar, kennis van deze risicofactoren kan niet goed verklaren waarom sommige patiënten met aderverkalking ziekteverschijnselen en steeds terugkerende ziekte-uitingen krijgen, terwijl dit bij andere patiënten met aderverkalking niet het geval is. Behalve onder meer de uitgebreidheid van de aderverkalking van de kransslagaderen, speelt de vatbaarheid van organen voor episodes van plaatselijk tekort aan bloed- en zuurstoftoevoer (ischemie) waarschijnlijk een belangrijke rol. In dat geval zouden goed ontwikkelde, collaterale vaten of "natuurlijke bypasses" een belangrijke bron van alternatieve bloedtoevoer kunnen bieden, en daardoor een orgaan kunnen beschermen tijdens episodes van ischemie. Helaas beschikt niet ieder orgaan, of zelfs individu, over goed ontwikkelde collaterale vaten, als ze al ontwikkeld zijn.

In **Hoofdstuk 2** wordt besproken wat er tot nu al bekend is over de collaterale vaten van de kransslagaderen (coronaire collateralen) en de meest belangrijke factoren, die hierin een rol spelen. Op dit moment wordt er intensief onderzoek verricht naar het mechanisme van de ontwikkeling van coronaire collateralen, zowel in het laboratorium, als in de kliniek. Van veel factoren en patiëntkarakteristieken is al geopperd, dat ze een rol spelen in de ontwikkeling van collateralen, waaronder bijvoorbeeld ischemie van de hartspier, lichaamsbeweging, verhoogde bloeddruk, en het gebruik van diverse soorten medicijnen voor ziekten van hart- en bloedvaten. Maar de resultaten van deze verschillende onderzoeken zijn tot nu toe voor veel van deze factoren met elkaar in tegenspraak. Daarom is de exacte rol en het belang van deze verschillende factoren in de ontwikkeling van coronaire collateralen nog steeds onduidelijk.

Daarnaast heeft het potentiële klinische belang van coronaire collateralen veel aandacht getrokken. Coronaire collateralen kunnen mogelijk namelijk een belangrijke rol spelen bij patiënten met coronairlijden, in het voorspellen van het verloop en de afloop van de ziekte (de prognose) tijdens episodes van ischemie van de hartspier. Goed ontwikkelde coronaire collateralen kunnen mogelijk de prognose van een patiënt bepalen, niet alleen in het geval van een acuut hartinfarct, maar ook bij reeds lang bestaand coronairlijden. Helaas heeft het onderzoek naar dit klinisch belang van coronaire collateralen ook verschillende resultaten opgeleverd.

Het eerste doel van dit promotie-onderzoek was daarom om, in één groep met hoog-risico patiënten, verschillende factoren te onderzoeken die de aanwezigheid en uitgebreidheid van coronaire collateralen bepalen (zogenoemde determinanten), namelijk: de mate van ischemische belasting van het hart, hoge bloeddruk, roken en alcohol, en het "metabool syndroom".[1] Daartoe hebben we van een groep van 244 patiënten, die waren verwezen voor een geplande dotterbehandeling en deelnamen aan het SMART-onderzoek, de oorspronkelijke hartkatheterisatie-films opnieuw bekeken om de aanwezigheid en uitgebreidheid van coronaire collateralen te bepalen.

Het tweede doel van dit promotie-onderzoek was om de invloed van de aanwezigheid en uitgebreidheid van coronaire collateralen te bepalen op de klinische uitkomst op lange termijn (bijvoorbeeld overlijden of een hartinfarct) bij patiënten met reeds aanwezige ischemische hartziekte. Daartoe hebben we de prognostische betekenis van coronaire collateralen onderzocht in twee verschillende patiënten-groepen: een zogenoemde ongeselecteerde groep van hoog-risico patiënten, gevormd door de eerdergenoemde 244 SMART-patiënten,

[1] Het metabool syndroom is een combinatie van vier frequent voorkomende aandoeningen. Dat zijn: hoge bloeddruk, suikerziekte, verhoogd cholesterol, en overgewicht. Daarnaast zien we als vijfde afwijking een verhoging van de eiwit-uitscheiding in de urine. We spreken van het metabool syndroom als er tenminste drie van de vijf genoemde aandoeningen aangetoond zijn.

en een groep van 561 wel-omschreven, laag-risico patiënten, die deelnamen aan het Octopus-onderzoek.

Determinanten van coronaire collateralen

In **Hoofdstuk 3.1** hebben we gemeld dat meerdere indicatoren van ischemische belasting van het hart sterk verbonden zijn met de aanwezigheid van coronaire collateralen. Dit betrof, in volgorde van belangrijkheid, pijn op de borst (angina pectoris) bij inspanning, meertaks-coronairlijden, een eerder doorgemaakt hartinfarct, angina pectoris tijdens emoties, en de tijdsduur sinds de eerste ingreep aan de kransslagaderen (als bijvoorbeeld al een eerdere dotter-behandeling had plaatsgevonden). De rol van cardiale ischemie, zowel acute, als reeds lang bestaande ischemie, in het bepalen van de ontwikkeling van coronaire collateralen is inmiddels inderdaad redelijk vast komen te staan. Met name de ernst van de vernauwing in de kransslagader, en de duur van de klachten door ischemie van de hartspier, worden consequent beschreven als factoren, die de groei van collaterale vaten beïnvloeden. Maar, deze indicatoren van ischemische belasting van het hart zijn, voorzover wij weten, nooit eerder samengevoegd in één score.

In **Hoofdstuk 3.1** hebben we daarom ook een simpele somscore ontwikkeld, om een schatting te maken van de totale hoeveelheid ischemische belasting van het hart in één patiënt. Deze somscore maakt gebruik van vier klinische kenmerken, die gemakkelijk in iedere patiënt kunnen worden vastgesteld, namelijk: angina pectoris bij inspanning, angina pectoris tijdens emoties, een eerder doorgemaakt hartinfarct, en een eerder doorgemaakte ingreep aan de kransslagaderen (bijvoorbeeld een dotterbehandeling of een coronaire bypassoperatie). Vervolgens werd de somscore berekend door voor ieder aanwezig klinisch kenmerk één punt op te tellen. Een patiënt kon minimaal nul punten halen en maximaal vier. Uit ons onderzoek bleek dat deze somscore voor ischemische belasting van het hart sterk verbonden was met de aanwezigheid van coronaire

collateralen, zelfs als rekening werd gehouden met de ernst van het coronairlijden. De resultaten in **Hoofdstuk 3.1** ondersteunen daarom niet alleen de visie dat cardiale ischemie een belangrijke rol speelt in de ontwikkeling van coronaire collateralen, maar geven ook duidelijk het belang aan van de totale hoeveelheid ischemische belasting van het hart in één individu.

In **Hoofdstuk 3.2** hebben we laten zien dat verscheidene maten van bloeddruk omgekeerd gerelateerd zijn aan de aanwezigheid van coronaire collateralen. Dit betrof de bovendruk (systolische bloeddruk), de onderdruk (diastolische bloeddruk), de gemiddelde slagaderdruk, een verhoogde bovendruk (systolische hypertensie), en het gebruik van bloeddrukverlagende medicijnen. Daarnaast was er een omgekeerd, gegradeerd verband tussen de niveaus van systolische bloeddruk, van polsdruk, en de mate van uitgebreidheid van collaterale vaten. Een vergelijkbare bevinding was tot nu toe alleen gemeld bij patiënten met vaatlijden van de halsslagader. Bij die patiënten, die daarnaast ook nog een verhoogde bloeddruk hadden, werden minder vaak collaterale vaten van de hersenslagaders gevonden dan bij patiënten met vaatlijden van de halsslagader en een normale bloeddruk. Daarentegen was bij patiënten met aangetoond coronairlijden tot nu toe, ofwel een positief verband gevonden tussen een verhoogde bloeddruk en de aanwezigheid van coronaire collateralen, ofwel helemaal geen verband. Deze tegenstrijdigheid zou ten dele verklaard kunnen worden door verschillen in de onderzochte patiënten en de gebruikte onderzoeks-methoden. Toch gaven onze resultaten zeer duidelijk een omgekeerd verband aan tussen hoge bloeddruk en de aanwezigheid van coronaire collateralen.

Wij stellen daarom in **Hoofdstuk 3.2** voor dat lokale uitdunning van de kleinste slagaders ("*microvascular rarefaction*") onze bevindingen zou kunnen verklaren. Met *microvascular rarefaction* wordt bedoeld de functionele en structurele uitdunning van de kleinere en kleinste (krans-)slagaders in reactie op een stijging van de bloeddruk, waarbij dit proces uiteindelijk eindigt in het volledig verdwijnen van vooraf aanwezige bloedvaten. Deze uitdunning van coronaire collateralen is zowaar eerder in de literatuur vermeld, maar dan in reactie op het succesvol

doorgankelijk maken van een vernauwde kransslagader. De uitdunning van coronaire collateralen heeft betrekking op twee verschillende concepten: functionele en anatomische uitdunning. Functionele uitdunning betekent dat collaterale vaten sluiten na het opnieuw doorgankelijk maken van de ontvangende kransslagader, waardoor het bloed hier weer vanzelf kan stromen. In de collaterale vaten komt de bloedstroom dan juist tot stilstand, waardoor deze zeer waarschijnlijk dicht gaan. Anatomische uitdunning betekent daarentegen dat reeds volgroeide collaterale vaten gedeeltelijk hun goed ontwikkelde spierlaag (de media) verliezen. Daardoor nemen hun diameter en collaterale doorstromings-capaciteit af, terwijl toch een voldoende groot drukverloop en tijd voor de rekrutering van collaterale vaten blijven bestaan. Met name onvolledig uitgegroeide collaterale vaten kunnen vatbaar zijn voor anatomische uitdunning. Vanuit deze gedachte hebben we in **Hoofdstuk 3.2** voorgesteld dat de hogere sterftekans bij patiënten met verhoogde bloeddruk in het geval van een acuut hartinfarct, verband kan houden met onze bevindingen.

In **Hoofdstuk 3.3** hebben we verslag gedaan van onze bevinding dat ook roken en alcoholgebruik verband houden met de aanwezigheid van coronaire collateralen. Actueel roken was positief, terwijl het aantal gerookte pak-jaren omgekeerd gerelateerd was aan de aanwezigheid van collateralen. Het verband tussen actueel, regelmatig alcoholgebruik en de aanwezigheid van coronaire collateralen had de vorm van een J-curve: gematigd alcoholgebruik hield verband met een verminderde aanwezigheid van collateralen, terwijl bovenmatig alcohol-gebruik juist verband hield met een toegenomen aanwezigheid. Verder was er een omgekeerde relatie tussen voormalig gematigd alcoholgebruik en de aanwezigheid van collateralen. Helaas hadden wij, door de aard van ons onderzoek, niet de beschikking over gedetailleerde gegevens over de chemische samenstelling van de tabaksrook of de alcohol. Daarom hebben wij voor een belangrijk deel slechts kunnen speculeren over de mogelijke achterliggende mechanismen, die hierin een rol kunnen spelen.

In een eerder onderzoek was gemeld dat roken geen verband hield met de aanwezigheid van coronaire collateralen. Interessant genoeg, werd onlangs echter beschreven dat nicotine, één van de vele chemische bestanddelen in tabaksrook, een belangrijke rol speelt in de groei en ontwikkeling van nieuwe bloedvaatjes en kleine slagaders (angiogenese en arteriogenese). Verder is roken gekoppeld aan steeds terugkerend zuurstoftekort, wat op zijn beurt weer een stimulans is voor de groei van collaterale vaten. Opmerkelijk genoeg hebben rokers, in het geval van een acuut hartinfarct, een tweemaal lager risico om vervolgens in het ziekenhuis te overlijden. Dit wordt ook wel de "rokers-paradox" genoemd, waarbij het voorstelbaar is dat goed ontwikkelde coronaire collateralen deze patiënten bescherming bieden in het geval van een acuut hartinfarct. Het aantal gerookte pak-jaren, tot slot, een bekende en belangrijke risicofactor voor het ontstaan van aderverkalking van de (krans-)slagaderen, hield echter omgekeerd verband met de aanwezigheid van collateralen. Maar hoe groter het aantal gerookte pak-jaren, hoe groter ook de kans op een beschadiging van de inwendige bekleding van de bloedvaten (het endotheel) door het roken. Deze endotheelbeschadiging kan weer leiden tot een verminderde vaatverwijding, en zelfs tot een misplaatste vernauwing van de bloedvaten, waardoor collaterale vaten mogelijk minder goed zichtbaar worden.

Gegevens over de relatie tussen alcoholgebruik en de aanwezigheid van collateralen zijn schaars. Uit epidemiologisch onderzoek is echter duidelijk gebleken, dat de relatie tussen alcohol en atheroslerotische hart- en vaatziekte in twee fasen (bifasisch) verloopt. Het nu gevonden bifasische verband tussen alcoholgebruik en de aanwezigheid van coronaire collateralen, in de vorm van een J-curve, verbeeldt eigenlijk het omgekeerde van het bekende, beschermende effect van alcohol op aderverkalking: gematigd alcoholgebruik heeft een beschermende invloed, terwijl overmatig alcoholgebruik juist een verhoogd risico geeft op ziekte-uitingen van hart- en vaatziekte. Wij hebben daarom beredeneerd, dat gematigd alcoholgebruik min of meer gelijk staat aan een lagere ischemische belasting van het hart, en dus minder stimulans is voor de aanwezigheid van coronaire collateralen. Deze veronderstelling wordt gesteund door de bevinding,

dat bij mannen met een eerder doorgemaakt hartinfarct, gematigd alcoholgebruik verband hield met een hogere sterftekans in het geval van nog een hartinfarct (waarschijnlijk door een verminderde aanwezigheid van collaterale vaten). Daarentegen was gematigd alcoholgebruik bij mannen zonder eerder doorgemaakt hartinfarct, juist gerelateerd aan een lagere sterftekans in het geval van een eerste hartinfarct (waarschijnlijk door een afname in de mate van ischemische belasting van het hart). Al met al ondersteunen de bevindingen in **Hoofdstuk 3.3** de visie, dat leefstijlfactoren de groei en ontwikkeling van coronaire collateralen kunnen beïnvloeden bij patiënten met ischemische hartziekte.

Tot slot hebben we in **Hoofdstuk 3.4** voor het eerst laten zien, dat het metabool syndroom (op zichzelf ook een risicofactor voor hart- en vaatziekte) geen verband hield met de aanwezigheid van coronaire collateralen. Zoals eerder aangegeven, omvat het metabool syndroom een cluster van algemeen geaccepteerde risicofactoren voor hart- en vaatziekte, waaronder suikerziekte, verhoogde bloeddruk, een verhoogd cholesterolgehalte, en overgewicht. Eigenlijk is elk van deze risicofactoren tot op heden afzonderlijk onderzocht op een eventueel verband met de aanwezigheid van coronaire collateralen, maar de bevindingen waren voor geen enkele, aparte risicofactor eensluidend. Het is daarom mogelijk, dat juist het samenvoegen van dergelijke, verschillende effecten in één cluster als het metabool syndroom, nog een andere verklaring kan vormen voor het feit, dat we geen enkel verband hebben gevonden tussen het metabool syndroom en de aanwezigheid van coronaire collateralen.

<u>Prognostische betekenis van coronaire collateralen</u>

In **Hoofdstuk 4.1** hebben we de bevindingen vermeld van het onderzoek in de ongeselecteerde groep van patiënten met ischemische hartziekte, die verwezen waren voor een geplande dotterbehandeling, en deelnamen aan het SMART-onderzoek tussen 1 januari 1998 en 8 juli 2002. Over het geheel genomen, was

de aanwezigheid van coronaire collateralen bij aanvang van het onderzoek, in deze groep patiënten gerelateerd aan een hoger risico op een daaropvolgende uiting van hart- en vaatziekte, in het bijzonder in relatief hoog-risico patiënten, en in het geval coronaire collateralen slechts in geringe mate aanwezig waren. Op basis van onze bevindingen, hebben we vervolgens gesteld dat het lot van een patiënt uiteindelijk wordt bepaald door de balans tussen de ernst van ziekte, en de aanwezigheid en uitgebreidheid van coronaire collateralen. In relatief laag-risico patiënten kan de aanwezigheid van goed ontwikkelde coronaire collateralen een aanwijzing zijn voor een collaterale bloeddoorstroming, die toereikend is om de nadelige gevolgen van ischemische hartziekte in voldoende mate te kunnen compenseren. Tegelijkertijd kan de aanwezigheid van amper ontwikkelde coronaire collateralen duiden op een dermate beperkte functie van collaterale vaten, dat deze er niet in slagen om de ernst van de ziekte in voldoende mate te compenseren, waardoor de patiënt uiteindelijk een hoger risico loopt.

Deze veronderstelling wordt gesteund door onze bevindingen in **Hoofdstuk 4.2.** Hier hebben we de resultaten gerapporteerd van ons onderzoek in de grote groep van 561 wel-omschreven, laag-risico patiënten met stabiel coronairlijden, die deelnamen aan het Octopus-onderzoek. In dit onderzoek werd een dotterbehandeling met het plaatsen van een stent, vergeleken met coronaire bypasschirurgie, waarbij de behandeling door loting werd toegewezen. In deze groep patiënten bleek de aanwezigheid van coronaire collateralen bij aanvang van het onderzoek te beschermen tegen een daaropvolgend hartinfarct, of overlijden ten gevolge van de hartziekte. Wij geloven dat deze verschillende invloed van coronaire collateralen in de diverse risicogroepen van patiënten kan verklaren, waarom tot nu toe zulke tegenstrijdige resultaten over de beschermende rol van collateralen zijn beschreven in de literatuur.

De toegevoegde waarde van coronaire collateralen

In **Hoofdstuk 5** bespreken we daarom deze verschillende resultaten van verscheidene overlevingsstudies op het gebied van hart- en vaatziekte in meer detail. De prognostische betekenis van de aanwezigheid van coronaire collateralen blijkt aanmerkelijk veranderd te worden door het risico-niveau van de patiënt met coronaire hartziekte. Verder bespreken we de verschillende methoden, die op dit moment gebruikt worden, om de aanwezigheid en uitgebreidheid van coronaire collateralen te bepalen, of zelfs te meten. Daarbij besteden we in het bijzonder aandacht aan hun onderlinge samenhang en hun beperkingen. Op basis van de onderzoeksresultaten, beschreven in dit proefschrift, stellen wij voor, dat de aanwezigheid van coronaire collateralen kan dienen als een extra indicator voor de kwetsbaarheid van de hartspier, en daarmee als een extra aanwijzing om de “kwetsbare patiënt” te identificeren. Daarnaast kunnen therapieën, gericht op het bevorderen van groei en ontwikkeling van coronaire collateralen, een aantrekkelijke behandelmethode vormen, in het bijzonder voor laag-risico patiënten met ischemische hartziekte, die ongeschikt zijn voor dotterbehandeling of coronaire bypass-chirurgie.

Reeds op dit moment worden verschillende klinische studies verricht, waarin de toediening van groeifactoren, bedoeld om groei en ontwikkeling van collateralen te stimuleren, wordt onderzocht als nieuwe behandeling bij patiënten met ischemische hartziekte of perifeer arterieel vaatlijden, die ongeschikt zijn voor de gebruikelijke therapieën. Daarnaast vinden diverse studies plaats naar de mogelijke angiogene eigenschappen van statines (cholesterolverlagende medicijnen) en ACE-remmers (bloeddrukverlagende medicijnen), en hun rol in het bevorderen van collaterale bloedvoorziening. De bevindingen, beschreven in dit proefschrift, kunnen hier al een rol in spelen.

Dankwoord

Dankwoord

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dat dat nog heel lang zo blijft. Ik ben heel benieuwd welk uitstapje jullie de volgende keer weer bedenken.

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Lieve Papa en Mama, waar ik ook mee bezig ben, in welke sloot ik ook sta, jullie hebben altijd vertrouwen in de goede afloop. Nu was ook ik aan een promotie-onderzoek begonnen. Ik herinner mij de beelden van jullie, avond aan avond aan de typemachine en later de Atari 1024 STE, het boekje met de wijze uil, de verdediging aan de VU, en het feest op de boot. Maar wat er echt allemaal bij komt kijken, dat blijkt toch pas als je er zelf midden in zit. Dit is dan het resultaat. Ik ben jullie erg dankbaar voor jullie liefde, steun, zorg en vertrouwen.

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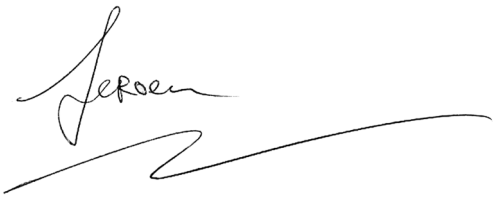

Curriculum Vitae

Curriculum Vitae (Nederlands)

Jeroen Koerselman werd geboren op 17 augustus 1973 te Utrecht. Hij volgde het middelbaar onderwijs aan het Gemeentelijk Gymnasium te Hilversum. In 1991 begon hij zijn medische opleiding aan de Faculteit Geneeskunde van de Universiteit Utrecht. Om nader kennis te maken met de wereld van medisch wetenschappelijk onderzoek, besteedde hij zijn vijfde extra-curriculaire studiejaar aan onderzoek op het gebied van maag en darmen, speciaal de maag-darm motoriek en zuurbranden (reflux). Hij werkte daarom eerst 6 maanden bij de Kliniek van Gastro-intestinale Motoriek van de afdeling Chirurgie en Gastro-enterologie in het Universitair Medisch Centrum Utrecht (supervisor prof. dr. L.M.A. Akkermans). Vervolgens werkte hij nog eens 6 maanden in het Gastro-intestinaal Motoriek Laboratorium van het Department of Medicine at the Graduate Hospital te Philadelphia, Pennsylvania, Verenigde Staten (supervisor prof. dr. D.O. Castell). In augustus 1998 slaagde hij voor het Artsexamen. Van oktober 1998 tot en met september 1999 werkte hij als arts-assistent cardiologie in het St. Antonius Ziekenhuis te Nieuwegein. Daarop werkte hij van oktober 1999 tot en met april 2001 als arts/projectleider bij de afdeling Voedingsfysiologie van TNO Voeding te Zeist.
In juli 2001 ging hij aan de slag als arts-onderzoeker binnen het SMART-onderzoek bij het Julius Centrum voor Gezondheidswetenschappen en Eerstelijns Geneeskunde, Universitair Medisch Centrum Utrecht. Tegelijkertijd begon hij aan het promotie-onderzoek beschreven in dit proefschrift, onder supervisie van prof. dr. Y. van der Graaf en prof. dr. D.E. Grobbee, van het Julius Centrum, en dr. P.P.Th. de Jaegere, van de afdeling Cardiologie. Tijdens zijn aanstelling behaalde hij zijn Master of Science in Klinische Epidemiologie bij het Netherlands Institute for Health Sciences (NIHES), Erasmus Universiteit Rotterdam (Augustus 2003).
Jeroen Koerselman leeft samen met Brenda C. Ruijters. Samen hebben zij een dochter, Veerle.

Curriculum Vitae (English)

Jeroen Koerselman was born on August 17th, 1973, in Utrecht, The Netherlands. He attended secondary school at the Gemeentelijk Gymnasium in Hilversum. In 1991 he started his medical training at the Utrecht University Faculty of Medicine. In order to get acquainted with the world of scientific medical research, he spent his fifth extracurricular study year on gastro-intestinal research: gastro-intestinal motility and gastro-esophageal reflux, in particular. First, six months were spent at the Clinic of Gastro-intestinal Motility of the Department of Surgery and Gastroenterology at the University Medical Center Utrecht (supervised by Professor dr. L.M.A. Akkermans). Then, another six months were spent at the Gastro-intestinal Motility Unit of the Department of Medicine at the Graduate Hospital in Philadelphia, Pennsylvania, USA (supervised by Professor dr. D.O. Castell). In August 1998 he obtained his medical degree. From October 1998 through September 1999 he worked as a resident in cardiology at the St. Antonius Hospital in Nieuwegein. Thereafter, from October 1999 through April 2001 he worked as a research physician at the Department of Nutritional Physiology at TNO Nutrition and Food Research in Zeist.
In July 2001 he started as a research physician on the SMART Study at the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht. At the same time he started the research described in this thesis, supervised by Professor dr. Y. van der Graaf and Professor dr. D.E. Grobbee, from the Julius Center, and Dr. P.P.Th. de Jaegere, from the Department of Cardiology. During this period he obtained his Master of Science degree in Clinical Epidemiology at the Netherlands Institute for Health Sciences (NIHES), Erasmus University Rotterdam (August 2003).
Jeroen Koerselman lives together with Brenda C. Ruijters. Together they have a daughter, Veerle.

List of publications

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Published papers

1. *Koerselman J*, Van der Graaf Y, De Jaegere PPTh, Grobbee DE. Coronary collaterals: an important and underexposed aspect of coronary artery disease. Special review. Circulation 2003; 107: 2507-11.
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1. *Koerselman J*, De Jaegere PPTh, Verhaar MC, Grobbee DE, Van der Graaf Y. Chronic cardiac ischemic burden determines presence of coronary collateral circulation. 2003, ImagO Scientific Meeting. Graduate School ImagO, Utrecht.
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Awards

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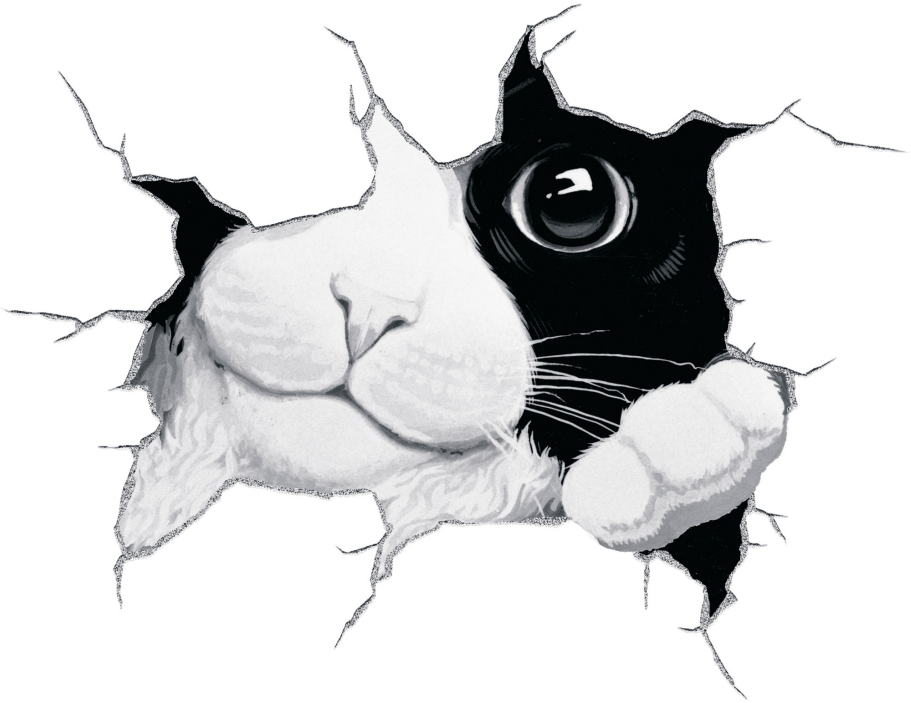
Carpe Diem

Speciaal voor Veerle



"Poe"

Felix Kattenvoer, Nestlé Purina Petcare Nederland BV, with permission.