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Cardiac Ischemic Score Determines the Presence of Coronary Collateral Circulation

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Summary. Purpose: **The presence of coronary collaterals is of vital importance during acute ischemia, however, marked interindividual variability exists. We examined the extent to which the burden of cardiac ischemia, expressed as a cardiac ischemic score, affects coronary collateral presence.**

Methods: **Cross-sectional study in 244 patients, admitted for elective coronary angioplasty. Collaterals were graded with Rentrop's classification. Coronary collateral presence was defined as Rentrop-grade ≥1. The cardiac ischemic score (range 0–4) was calculated by adding 1 point for each of the following four clinical factors present: angina pectoris on exertion, angina pectoris 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 the cardiac ischemic score (odds ratio 1.8 per score-point; 95% confidence interval 1.3–2.5) was strongly associated with coronary collateral presence. Additional adjustment for multivessel coronary disease left the relation essentially unchanged. Also, if the definition of collateral presence was limited to Rentrop-grade 2 and 3, results were effectively the same.**

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

Key Words. **collateral circulation, coronary disease, ischemia, epidemiology, angiography**

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 ischemia, expressed as a "cardiac ischemic score," can be related to the presence of coronary collateral circulation.

Methods

Ethics

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

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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 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 inter-observer 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].

The "cardiac ischemic score"

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 multivessel (2 or 3) coronary disease on the basis of $\geq$50% luminal narrowing in at least one view [10]. The burden of cardiac ischemia in a patient was expressed as a sum-score, the "cardiac ischemic 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 and give a clear clinical impression of the severity of the complaints, either being present or absent.

Data-analysis and statistics

The primary outcome of interest was the presence of coronary collaterals, defined as a Rentrop-grade $\geq$1 [7,8]. Unless specified otherwise, data are presented as count with percentage or mean $\pm$ 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. Hypertension was defined as blood pressure $\geq$160 mmHg systolic and/or $\geq$95 mmHg diastolic. Diabetes mellitus was defined as fasting serum glucose $\geq$7.0 mmol/L. Hyperlipidemia was defined as total serum cholesterol $>$5.0 mmol/L and/or serum LDL cholesterol $>$3.20 mmol/L. In addition, patients on antihypertensive medication, or glucose-lowering agents, or cholesterol-lowering drugs, were regarded as having hypertension, diabetes mellitus, and hyperlipidemia, respectively.

Similarly, the association between the presence and absence of coronary collaterals, and the cardiac ischemic score was quantified with logistic regression analysis, first only with adjustment for the confounders mentioned above, and in addition also with adjustment for multivessel 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

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:	
Multivessel 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.

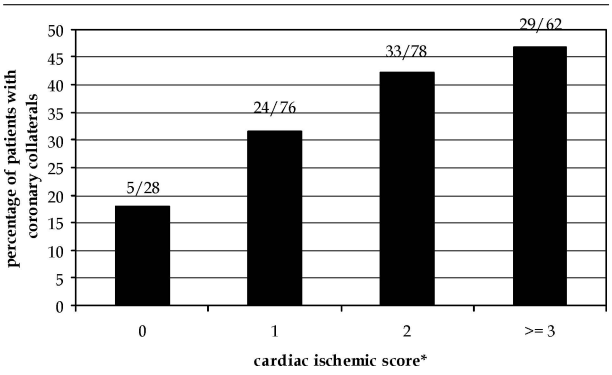

Fig. 1. *Percentage of patients with coronary collateral circulation (Rentrop-grade ≥ 1) per total number of patients across categories of the cardiac ischemic score. *The cardiac ischemic score (range 0–4) is calculated by adding 1 point for each of the following four clinical factors present, notably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

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).

Indicators of cardiac ischemia, the cardiac ischemic score, 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 multivessel 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 the cardiac ischemic score was strongly associated with the presence of coronary collateral circulation (Table 2). Additional adjustment for multivessel 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 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), multivessel coronary disease (OR 3.3; 95% CI 1.7–6.3), and the extent of the cardiac ischemic score (OR 1.8 per score-point; 95% CI 1.3–2.5). Also, after additional adjustment for multivessel coronary disease, the relation between the extent of the cardiac ischemic score and the presence of coronary collaterals

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

Indicators of the cardiac ischemic score	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)
Multivessel coronary disease	52 (57.1%)	49 (32.0%)	2.8 (1.7–4.8)	3.2 (1.7–6.0)
Cardiac ischemic 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 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.

remained virtually unchanged (OR 1.6 per score-point; 95% CI 1.1–2.3).

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 multivessel 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 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], the quantitative indices of collateral circulation were 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 cardiac

ischemic score and its relation with the presence of coronary collateral vessels.

Third, the contemporary assessment of angiographically visible collaterals is based, not only on the Rentrop's classification, but also upon more recent measures of the myocardial blush score [19]. The myocardial blush score is considered a more sensitive angiographic measure of the microcirculatory myocardial status, and could serve as a complementary parameter to assess the efficiency of antegrade and retrograde myocardial circulation. Unfortunately, in the present study, we could not evaluate the myocardial blush score.

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, hyperhomocysteinemia, 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 ischemia, expressed as the cardiac ischemic score, 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 [22]. As in the present study, they found that coronary collaterals were present more frequently in patients with multivessel coronary disease [22]. 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 score 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 the cardiac ischemic 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 the cardiac ischemic 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 cardiac ischemic score may also provide a new index for simple, non-invasive assessment of collateral vascular development.

Lastly, the cardiac ischemic score may add to patient tailored treatment. We believe that the present findings will contribute to further insight in and understanding of coronary collateral development. In addition, the present study will contribute to the development of novel therapeutic strategies aimed for the induction of vascular growth. This may actually provide an attractive treatment option, in particular for those patients with myocardial or peripheral ischemia, who are unsuitable for conventional revascularization therapies.

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

Appendix

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