The Prevalence of Endothelial Dysfunction in Patients With and Without Coronary Artery Disease

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ABSTRACT

Background: Endothelial dysfunction (ED) is frequently present in patients presenting with acute or stable coronary artery disease (CAD), but it is also found in patients presenting with chest pain without angiographic coronary lesions.

Hypothesis: We hypothesized that even in patients without CAD, the presence of cardiovascular (CV) risk factors will correlate with the presence of ED.

Methods: Our study included a total of 341 consecutive patients referred for coronary angiography. We used pulse wave analysis with a finger plethysmograph (peripheral arterial tonometry) to determine endothelial function. Hyperemia ratio was calculated as the ratio of the postischemic hyperemia response relative to baseline measurement.

Results: The hyperemia ratio was significantly higher in patients without CAD (2.02 ± 0.52) compared with patients with chronic CAD (1.81 ± 0.44 , $P = 0.001$) or acute CAD (1.74 ± 0.49 , $P < 0.001$). Prevalence of ED was 33%, 46%, and 58%, respectively. In multivariate analysis, the presence of CAD, diabetes, and cigarette smoking, and the total number of CV risk factors, were strong predictors of ED. In 67% of the patients without CAD but with ≥ 3 CV risk factors, ED was present.

Conclusions: Prevalence of ED in patients with chest pain depends on the presence of CAD and CV risk factors. Patients without CAD but with ≥ 3 risk factors frequently presented with ED. Such patients may be at increased risk for future CV events and may profit from intensified therapy to control CV risk factors.

Introduction

Endothelial dysfunction (ED) promotes coronary artery disease (CAD) and has been shown to precede angiographic or ultrasonic evidence of atherosclerosis.^{1–3} In patients with ED, the balance between vasoconstriction and vasodilation is disturbed, and permeability, platelet aggregation, leukocyte adhesion, and generation of cytokines are increased.^{3–6} ED is frequently present in patients presenting with acute or stable CAD, but also in patients presenting with chest pain without angiographic coronary lesions. Furthermore, it has been shown that ED is associated with cardiovascular (CV) risk factors like hypercholesterolemia, smoking, diabetes mellitus (DM), and family history of premature CAD.^{7–9}

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In the present study, we used reactive hyperemia peripheral arterial tonometry (RH-PAT)^{10,11} to assess the prevalence of ED in patients presenting with chest pain but without CAD and compared this prevalence with patients presenting with stable and acute CAD. Furthermore, we examined the relationship between CV risk factors and ED in the 3 patient groups.

Methods

Study Protocol

This prospective study enrolled consecutive patients with chest pain referred to the Luzerner Kantonsspital for acute coronary angiography (ie, patients with unstable angina pectoris, non-ST-segment-elevation myocardial infarction, or ST-segment-elevation myocardial infarction) or elective coronary angiography. Patients in cardiogenic shock and hemodynamically unstable patients depending on inotropes were not included. There were no other exclusion criteria. Patient history and clinical data were recorded and endothelial function was measured in fasting state the morning after the coronary angiography. After measurement of endothelial function, blood was drawn (in fasting state) for laboratory analyses. We measured high-density lipoprotein cholesterol (HDL; normal

value >1.0 mmol/L), low-density lipoprotein cholesterol (LDL; >3.0 mmol/L), triglycerides (<2.0 mmol/L), fasting glucose (3.9–6.4 mmol/L), creatinine (59–104 μ mol/L in men, 45–84 μ mol/L in women), blood urea nitrogen (<8.3 mmol/L), and glycated hemoglobin A_{1c} (HbA_{1c}; 4.8%–5.9%). Blood pressure and heart rate were measured on the right arm before the measurement of endothelial function. Figure 1 summarizes the study protocol. For the purpose of this study, patients were categorized into 3 groups according to clinical presentation and angiography result: 1) patients presenting with chest pain but without evidence of a relevant CAD (no stenosis $\geq 50\%$ on coronary angiography), 2) patients presenting with stable CAD referred for elective coronary angiography (≥ 1 stenosis of $\geq 50\%$), and 3) patients with acute coronary syndrome (unstable angina pectoris, non-ST-segment-elevation myocardial infarction, or ST-segment-elevation myocardial infarction) referred for emergent coronary angiography. The study was approved by the local ethics committee for clinical research, and all patients provided written informed consent.

Definition of Cardiovascular Risk Factors

DM was defined as 2 measurements of fasting blood glucose ≥ 7 mmol/L or previously established diabetes with oral antidiabetic drug or subcutaneous insulin treatment. Hypertension was defined as blood pressure at rest $\geq 140/90$ mm

Hg or established diagnosis with antihypertensive drug treatment. Hypercholesterolemia was defined as fasting LDL ≥ 3.6 mmol/L or established cholesterol-lowering drug treatment. Patients were classified as previous smokers if they had stopped smoking at ≥ 1 month before the study. Patients who had smoked ≥ 1 cigarette during the last month were classified as current smokers. Positive family history was present if myocardial infarction occurred in male first-degree relatives age <50 years and in female first-degree relatives age <60 years. In addition, male sex was reckoned among CV risk factors.

Measurement of Endothelial Function

Patients were instructed to start fasting the night before testing and to refrain from smoking and taking any vasoactive medication. Pulse wave amplitude was measured noninvasively using RH-PAT (Itamar Medical Ltd, Caesarea, Israel). The principle of RH-PAT has been previously described.¹² Briefly, a PAT finger probe was placed on each index finger, and after a baseline period of 5 minutes, total occlusion was performed with a blood-pressure cuff on the right arm for 5 minutes. The cuff was inflated to supra-systolic pressures, and the signal of the RH-PAT displayed on the notebook was used to ensure complete occlusion. Thereafter, the hyperemic response of the occluded arm was recorded and compared to the nonoccluded, control arm (relative hyperemia index). The whole test was stored and analyzed with a computerized, automated algorithm (Itamar Medical). RHI values <1.67 were considered as ED.^{13,14}

Statistical Analysis

Statistical analysis was performed using SPSS 15 (SPSS Inc., Chicago, IL). If not indicated otherwise, data are presented as mean $\pm$ SD for continuous variables and as number and frequencies for categorical variables. Continuous variables were compared using the Student *t* test and categorical variables using the χ^2 test. A Mantel-Haenszel χ^2 test was used to detect linear association between the number of CV risk factors and the prevalence of ED. Univariate logistic regression analysis was performed to estimate odds ratio and 95% confidence interval for the presence of ED. The covariates that were included in the model were all CV risk factors, age, and the presence or absence of CAD. Significant covariates in univariate analysis were used as covariates for multivariate analysis. A 2-sided *P* value of <0.05 was considered statistically significant.

Results

Study Population

A total of 341 patients (79 without CAD, 177 with stable CAD, and 85 with acute CAD) were included. Patients presented with Canadian Cardiovascular Society angina

Figure 1. Flow chart of the study protocol. Abbreviations: RH-PAT, reactive hyperemia peripheral arterial tonometry.

class I (44%), II (28%), III (11%), and IV (17%). A stress test prior to the coronary angiography was performed in 63% of the nonacute patients, and yielded a positive result in 46%. Among patients without relevant CAD, 10 (13%) had vessel-wall irregularities, whereas the remaining had smooth coronary vessels. Baseline characteristics of the 3 patient groups are summarized in Table 1. Compared with patients with stable or acute CAD, patients without CAD were significantly younger and more often female. Blood pressure did not differ, but heart rate was higher in patients with acute CAD than in patients with chronic CAD and without CAD. As expected, patients without CAD were less frequently treated with CV medications such as aspirin, clopidogrel, statins, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or β -blockers.

Cardiovascular Risk Factors

Except for a family history of premature CAD, the prevalence of CV risk factors differed significantly among the 3 groups, being more frequent in patients with chronic or acute CAD. However, CV risk factors were frequently present in patients without CAD: 9% had DM, 44% had hypercholesterolemia, 42% had hypertension, and 38% were current or previous smokers. Regarding laboratory parameters, HDL was highest in those without CAD (1.5 ± 0.5), which was significantly higher than in patients with acute CAD (1.2 ± 0.4 , $P < 0.001$) or stable CAD (1.4 ± 0.6 , $P < 0.001$). LDL was highest in patients with acute CAD. Patients without CAD exhibited the lowest fasting glucose and the lowest HbA_{1c}. The number of CV risk factors, including DM, current cigarette smoking, hypercholesterolemia, hypertension, male sex, and a family history of CAD, was significantly lower in patients without CAD.

Furthermore, the prevalence of CV risk factors differed between men and women. Men were more frequently current smokers (27% vs 16%, $P = 0.035$), but women presented more often with a family history of premature CAD (44% vs 33%, $P = 0.047$).

Prevalence of Endothelial Dysfunction

The PAT hyperemia ratio was significantly higher in patients without CAD (2.02 ± 0.52) than in patients with chronic CAD (1.81 ± 0.44 , $P = 0.001$) or acute CAD (1.74 ± 0.49 , $P < 0.001$). As shown in Figure 2, 33% of the patients without CAD had ED (defined as a PAT hyperemia ratio < 1.67), which was significantly less than patients with chronic stable CAD (46%, $P = 0.045$) and acute CAD (58%, $P = 0.001$). In patients without relevant coronary atherosclerosis, RH-PAT was not different between those with smooth coronary arteries and those with vessel-wall irregularities (2.04 ± 0.58 vs 2.11 ± 0.54 for patients with and without lumen irregularities, respectively, $P = 0.716$).

The number of risk factors was the same in both groups (2.0 ± 1.3 vs 1.7 ± 0.8 in patients with and without lumen irregularities, respectively, $P = 0.300$).

The results of univariate regression analysis for the different CV risk factors are shown in Table 2. The presence of CAD (β coefficient = 2.0, $P = 0.008$), DM ($\beta = 2.3$, $P = 0.007$), and current cigarette smoking ($\beta = 1.9$, $P = 0.014$) were significantly associated with a higher prevalence of ED. In multivariate analysis, DM was shown to have the strongest predictive value for ED, followed by current cigarette smoking and presence of CAD (Table 3).

Because both CV risk factors (except family history) and ED were more frequently present in patients with stable or acute CAD than in those without relevant coronary atherosclerosis, we analyzed the prevalence of ED according to the number of CV risk factors. Figure 3 shows that in patients with 0–2 risk factors, ED was significantly less frequent in patients without CAD (23%) than in those with acute (46%) or stable CAD (48%; $P = 0.010$ for overall comparison). However, in patients with ≥ 3 risk factors, this difference disappeared and the prevalence of ED did not differ among the 3 patient groups.

Discussion

This study identifies a number of observations regarding the prevalence of ED in patients presenting with chest pain but no evidence of CAD, compared with patients presenting with stable CAD and with acute CAD. First, ED is most frequently present in patients presenting with acute CAD. Overall, 58% of these patients had ED, compared with 46% of the patients with stable CAD and 33% of the patients without CAD. Second, the prevalence of ED also depends on the number of CV risk factors. We showed that patients with DM or current cigarette smoking had a higher prevalence of ED than those without these risk factors. Third, the difference in the prevalence of ED between patients presenting with chest pain but without CAD and patients with stable and acute CAD was only evident in those with a low number (0–2) of CV risk factors. In subjects with ≥ 3 risk factors, this difference disappeared, and patients with chest pain but without CAD frequently presented with ED. It is known that atherosclerosis is a major cause of ED. However, the presence of a larger number of CV risk factors greatly increased the prevalence of ED in patients without CAD.

Comparison With Previous Studies

Previous studies have shown that ED is more frequent in patients with CV risk factors such as high serum cholesterol,^{7,15–18} male sex,^{7,8,18} family history of premature CAD,^{7,17} hypertension,¹⁶ cigarette smoking,^{8,18} DM,¹⁸ age,^{8,16} the total number of CV risk factors,^{16,17,19} and the presence of CAD.^{15,19} In the present study, the presence of

Table 1. Baseline Characteristics of the Patient Groups

	No CAD (n = 79)	Stable CAD (n = 177)	Acute CAD (n = 85)	P Value, No vs Stable CAD	P Value, No vs Acute CAD	P Value, Stable vs Acute CAD
Age (y)	54 ± 12	62 ± 9	58 ± 11	<0.001	0.026	0.003
Male sex (%)	53	75	80	0.001	<0.001	0.334
Weight (kg)	76 ± 14	80 ± 13	81 ± 14	0.067	0.024	0.346
Height (cm)	170 ± 9	171 ± 8	172 ± 7	0.737	0.158	0.172
BMI (kg/m ²)	26 ± 4	27 ± 4	28 ± 4	0.046	0.066	0.909
Waist (cm)	92 ± 11	97 ± 12	96 ± 12	0.004	0.050	0.778
Waist/hip ratio	0.91 ± 0.07	0.96 ± 0.08	0.96 ± 0.07	<0.001	<0.001	0.870
BP systolic (mm Hg)	127 ± 18	130 ± 18	130 ± 22	0.357	0.386	0.845
BP diastolic (mm Hg)	76 ± 12	74 ± 11	76 ± 14	0.131	0.936	0.184
Heart rate (/min)	68 ± 10	68 ± 14	73 ± 13	0.963	0.006	0.005
CCS class (1–4)	1.1 ± 0.4	1.8 ± 0.8	3.3 ± 1.1	<0.001	<0.001	<0.001
Chest pain at rest (%)	0	3	57	0.181	<0.001	<0.001
CV risk factors						
DM (%)	9	20	13	0.023	0.404	0.144
Hypercholesterolemia (%)	44	73	62	<0.001	0.021	0.083
Hypertension (%)	42	64	47	0.001	0.496	0.008
Current smoker (%)	19	20	35	0.803	0.019	0.009
Family history (%)	39	36	35	0.576	0.601	0.962
No. of CV risk factors	2.1 ± 1.3	2.9 ± 1.1	2.7 ± 1.1	<0.001	<0.001	0.294
CV medications (%)						
ACE inhibitor	19	48	18	<0.001	0.808	<0.001
β-Blocker	33	54	24	0.002	0.198	<0.001
Statin	22	64	33	<0.001	0.118	<0.001
Aspirin	59	85	44	<0.001	0.066	<0.001
Clopidogrel	4	32	22	<0.001	0.001	0.082
Ca antagonist	6	20	10	0.007	0.398	0.056
Diuretic	17	23	9	0.282	0.142	0.009
Laboratory values						
HDL (mmol/L)	1.5 ± 0.5	1.4 ± 0.6	1.2 ± 0.4	0.856	<0.001	<0.001
LDL (mmol/L)	2.7 ± 1.0	2.6 ± 1.1	3.0 ± 1.0	0.313	0.171	0.013
TG (mmol/L)	1.5 ± 1.3	1.6 ± 1.0	1.7 ± 1.2	0.768	0.489	0.522
Fasting glucose (mmol/L)	5.6 ± 0.7	5.9 ± 1.4	6.5 ± 2.1	0.024	<0.001	0.020

Table 1. Baseline Characteristics of the Patient Groups (Continued)

	No CAD (n = 79)	Stable CAD (n = 177)	Acute CAD (n = 85)	P Value, No vs Stable CAD	P Value, No vs Acute CAD	P Value, Stable vs Acute CAD
HbA _{1c} (%)	5.8 ± 0.5	6.2 ± 0.9	6.0 ± 0.8	0.002	0.037	0.217
Cr (μmol/L)	75 ± 14	81 ± 16	83 ± 32	0.015	0.071	0.491
BUN (mmol/L)	4.9 ± 1.3	5.5 ± 1.6	5.2 ± 1.9	0.002	0.166	0.162

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; Ca, calcium; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; Cr, creatinine; CV, cardiovascular; DM, diabetes mellitus; HbA_{1c}, glycated hemoglobin A_{1c}; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TG, triglycerides.

Figure 2. Prevalence of ED. ED was significantly more frequently present in patients with CAD than in patients without CAD. Abbreviations: CAD, coronary artery disease; ED, endothelial dysfunction.

Table 2. Univariate Analysis of Cardiovascular Risk Factors as Predictors of Endothelial Dysfunction

Variable	β Coefficient	95% CI	P Value
Presence of CAD	2.04	1.20–3.46	0.008
DM	2.27	1.24–4.13	0.007
Hypercholesterolemia	1.37	0.88–2.14	0.169
Hypertension	1.33	0.86–2.04	0.198
Current smoker	1.89	1.14–3.12	0.014
Family history	1.22	0.78–1.90	0.378
Male sex	1.46	0.91–2.36	0.116
Age (per year)	1.009	0.99–1.03	0.377

Abbreviations: CAD, coronary artery disease; CI, confidence interval; DM, diabetes mellitus.

CAD, DM, and current cigarette smoking were associated with increased prevalence of ED.

In addition, risk factors have also been shown to contribute to ED in the coronary resistance vessels.²⁰ This may be particularly important in patients with acute coronary syndromes, where there is increased oxygen demand

Table 3. Multivariate Analysis of Cardiovascular Risk Factors Predicting Endothelial Dysfunction

Variable	β Coefficient	95% CI	P Value
Presence of CAD	1.85	1.08–3.17	0.025
DM	2.32	1.26–4.28	0.007
Smoker	1.98	1.18–3.33	0.010

Abbreviations: CAD, coronary artery disease; CI, confidence interval; DM, diabetes mellitus.

Figure 3. Prevalence of ED according to number of risk factors. Patients with 0–2 cardiovascular risk factors without CAD have a low prevalence of ED (23%). Patients with 0–2 cardiovascular risk factors and acute (46%) or stable CAD (48%) had a significantly higher prevalence of ED ($P = 0.010$ for overall comparison). However, this difference is not evident for patients with 3–4 or 5–6 risk factors ($P = 0.138$ and $P = 0.186$, respectively). Abbreviations: CAD, coronary artery disease; ED, endothelial dysfunction.

and where resistance vessels would be expected to dilate.^{21,22}

Of note, not only cardiovascular risk factors, but also other factors, such as estrogen deficiency in postmenopausal women and inflammation (including sepsis and

elevation of endothelin-1 concentrations) have been shown to be associated with reduced endothelial function.^{23,24}

Most of these studies measured endothelium-dependent vasodilation of the coronary arteries following infusion of acetylcholine, a test that is invasive and also quite expensive. In the present study, we used PAT, which is a fairly new technique to evaluate endothelial function by assessing the finger pulse wave amplitude. This technique has the advantage of being noninvasive, but it is susceptible to environmental conditions. The most widely used noninvasive method is brachial artery ultrasound measuring flow-mediated dilation after a 5-minute occlusion with suprasystolic pressure. The advantage of this procedure is that it has been used and validated numerous times. The main disadvantages are the intraoperator and interoperator variability and the cost of equipment.²⁵ Furthermore, both PAT and brachial artery ultrasound, as noninvasive methods, may not be able to distinguish between coronary epicardial ED and coronary microvascular ED. The latter (ie, cardiac syndrome X) has been consistently shown to have an excellent prognosis regarding mortality.

Clinical Implications

Initially, it was thought that prognosis of patients presenting with chest pain and normal or only mildly diseased coronary arteries on angiography is benign.^{26–28} However, more recent studies have demonstrated that the prognosis of such patients may not be as benign as initially suggested. ED is frequently present in these patients, and limited endothelium-dependent vasodilation may not only cause myocardial ischemia, but also promote atherosclerosis and thus future CV events.^{29,30} However, the results of our study suggest that patients with chest pain but no CAD presenting with a low number of CV risk factors may have a benign prognosis. This may be due not only to the absence of CV risk factors, but also to the absence of ED. On the other hand, patients with chest pain and no CAD, but with a high number of CV risk factors, may be at increased risk, not only due to the presence of CV risk factors, but additionally due to a high prevalence of ED. Such patients may benefit from intensified risk-reduction therapies.

Further research, including long-term follow-up studies, is needed to evaluate the prognostic significance of this finding.

Study Limitations

Although the number of patients included in this study was relatively high, the study may have been underpowered to detect an association of ED with known predictors such as age, dyslipidemia, or hypertension.

Conclusion

Finger arterial pulse wave amplitude measurement is a noninvasive, easily applied method that may be used in

combination with risk stratification by conventional CV risk factors to assess patients at risk. In the present study, we found that the prevalence of ED in patients with chest pain depends on the presence of CAD and CV risk factors. Patients without CAD and a low number of CV risk factors have a very low prevalence of ED. Therefore, prognosis of such patients may be beneficial. However, patients without CAD but with a high number of CV risk factors frequently present with ED and thus may be at increased risk for future events. Such patients may benefit from an intensified treatment of CV risk factors.

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