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PROGNOSTIC IMPACT OF CORONARY ENDOTHELIAL DYSFUNCTION ON LONG-TERM ADVERSE OUTCOME IN PATIENTS WITH CHEST PAIN AND NON-OBSTRUCTIVE CORONARY ARTERY DISEASE

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Key words: acetylcholine, angina, coronary atherosclerosis, endothelium, prognosis.

Summary

Coronary endothelial dysfunction is known to be related with adverse cardiovascular outcome. We obtained a long-term follow-up of patients without significant coronary atherosclerosis, complaining of chest pain, in whom intracoronary acetylcholine testing was performed in order to assess endothelial function. The study included 41 patient (35 with endothelial dysfunction, 6 with preserved endothelial function). Events considered as adverse outcome were cardiovascular death, acute myocardial infarction, unstable angina pectoris, percutaneous coronary intervention, coronary-aortic by-pass grafting, ischemic stroke and peripheral artery revascularization. A high cardiovascular event rate was observed in patients with and without endothelial dysfunction, 34,3% and 50% respectively. Adverse outcome was related not only to endothelial dysfunction but also to traditional cardiovascular risk factors. Thus, evaluation of endothelial function or its determinants seems to be helpful in identifying a subgroup of patients at high risk.

Introduction

Patients, complaining of angina-like chest pain but found to have no significant atherosclerotic lesions in coronary angiograms, comprise up to one third of patients undergoing cardiac catheterization [1, 2]. It used to be believed that these patients had a good long-term prognosis with regard to survival and occurrence of major cardiovascular events [3]. However, recent investigations indicate that the prognosis is not as benign as previously thought [4-9]. The poor prognosis of this group of patients has been related to coronary vasodilator dysfunction – a state of impaired endothelial homeostasis, which results in coronary vasoconstriction, prothrombotic vascular environment and atherosclerosis development [10, 11]. Experimental and clinical data suggest that endothelial dysfunction (ED) may be a marker of atherosclerotic disease progression [12] and increased risk of cardiovascular events [13].

Despite quite a few and newly developing methods of endothelial function assessment, intracoronary acetylcholine (Ach) testing remains the gold-standard method for establishing the diagnosis of coronary endothelial dysfunction [2, 14-16]. However, there are few studies that assess endothelial function invasively in the coronary arteries and there are discrepancies regarding findings. Also, in most cases the follow-up is probably too short for events to manifest.

The purpose of this study is to address the following question: whether patients, who experience angina-like chest pain but show no evidence of significant coronary atherosclerosis and using intracoronary acetylcholine are diagnosed to have endothelial dysfunction, are of poor cardiovascular prognosis. It may be hypothesized that symptomatic patients with established diagnosis of coronary endothelial dysfunction are at a higher risk of developing cardiovascular events than symptomatic ones with preserved endothelial function.

The aim of the study was to compare the cardiovascular event rates during long-term follow-up in symptomatic patients with diagnosed ED and those with normal endothelial function, when assessed using intracoronary acetylcholine.

Material and methods

A follow-up of patients, who participated in the study carried out by dr. Dalia Jarasuniene from 2001 to 2003 at Klaipeda Seamen' hospital, was performed. The study had enrolled 50 patients, complaining of angina-like chest pain but having no significant coronary atherosclerosis. According to coronary angiograms patients were classified as having either smooth coronary arteries or non-obstructive coronary artery disease. Intracoronary acetylcholine tes-

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Table 1. Basic patient characteristics

	Patients with ED (35)	Patients with preserved endothelial function (6)	*p* value
Gender, M/F	12/23	1/5	0,645
Age	56,43 ± 10,47	63,67 ± 8,87	0,119
Angiographic evidence of atherosclerosis	11 (31,43)	1 (16,67)	0,651
Previous ACS	24 (68,57)	6 (100)	0,167
Positive family history of CAD	10 (28,57)	2 (33,33)	1,000
Hypertension	25 (71,43)	4 (66,67)	1,000
Smoking	3 (8,57)	0	1,000
Body mass index	28,99 ± 4,05	24,94 ± 2,86	0,022*
Dyslipidemia	23 (65,71)	5 (83,33)	0,645
Total serum cholesterol, mmol/l	5,86 ± 1,20	6,14 ± 0,70	0,596
LDL-C, mmol/l	3,74 ± 1,11	3,98 ± 0,74	0,637
HDL-C, mmol/l	1,44 ± 0,21	1,40 ± 0,41	0,715
Triglycerides, mmol/l	1,45 ± 0,73	1,12 ± 0,20	0,323
Number of risk factors	3,26 ± 1,17	3,17 ± 0,98	0,860

Table 2. Cardiovascular events during long-term follow-up

Event, n (%)	Ach+ group, n=35	Ach– group, n=6	*p* value
Adverse outcome (number of patients)	12 (34,29)	3 (50)	0,651
Cardiovascular death	5 (14,29)	1 (16,67)	1,000
Non-fatal MI	2 (5,71)	0	1,000
Unstable angina pectoris	3 (8,57)	1 (16,67)	0,483
PCA	4 (11,43)	0	1,000
CABG	0	1 (16,67)	0,146
Ischemic stroke	3 (8,57)	1 (16,67)	0,483
Peripheral artery revascularization	1 (2,86)	0 (0)	1,000
Total events	18	4	

ting had been performed in all the participants in order to assess endothelial function. Acetylcholine was infused at two stages: at stage I the suppositional Ach concentration in the artery was 10^{-6} mol/l; II – 3,3 x 10^{-6} mol/l. Patients in whom acetylcholine injection was followed by coronary vasoconstriction >5% of artery diameter (Ach+ group) were diagnosed to have endothelial dysfunction (n=42 [84%]), and those who did not (the coronary arteries dilated or coronary vasoconstriction was <5%) – were assumed to have normal endothelial function (Ach- group, n=8 [16%]).

The follow-up was performed at Klaipeda Seamen' hospital from February to March 2012. The patients were invited for an ordinary health check-up and/or hospital records were reviewed. Follow-up was obtained in 41 patient (82%). 9 patients were excluded because follow-up could not be obtained (2 with normal endothelial function and 7 with ED). Basic patient characteristics are presented in Table 1.

Values are presented either by mean±SD or absolute number and percentage; M/F – male/female; ACS – acute coronary syndrome.

Data regarding adverse cardiovascular outcome was obtained during follow-up: cardiovascular death (death due to a myocardial or cerebral infarction or documented sudden cardiac death), myocardial infarction (MI), unstable angina pectoris (hospitalization due to worsening of angina), percutaneous coronary intervention (PCI), coronary-aortic bypass grafting (CABG), ischemic stroke (clinical evidence of stroke without intracranial hemorrhage on brain imaging studies), revascularization of peripheral arteries. Also, initial data regarding traditional cardiovascular risk factors were obtained: age (>45 years at presentation for men, >55 years for women), family history of coronary artery disease (a first-degree relative had documented coronary artery

disease under 65 years of age), body mass index (BMI) >25 kg/m^2, smoking (current smokers/quitted <3 months ago), arterial hypertension (established diagnosis, receiving antihypertensive treatment), dyslipidemia (total cholesterol level >5,2 mmol/l), number of cardiovascular risk factors per patient.

Statistical analysis. Baseline demographic and biochemistry analytical information is presented as mean ± SD for continuous variables and as absolute number (percentage) for categorical variables. Differences between baseline characteristics of the 2 groups were assessed by the use of Student's *t* test for continuous variables and χ^2 test for categorical variables. All statistical tests were performed with SPSS 16.0 (statistical package for social science, SPSS Inc). Values of $p < 0,05$ were considered significant.

Results

Patients were followed up for an average of 9,5 years.

Event rate. During follow-up, a total of 15 (36,6%) patients experienced 22 cardiovascular events, cardiovascular death being the most common (27,3%). Frequency of cardiovascular events in Ach+ and Ach- groups is presented in Table 2.

Adverse outcome. Among patients who had adverse outcome 10 (66,7%) were women, 2 (13,3%) smokers, 13 (86,7%) with a previous ACS, 5 (33,3%) had a positive family history, 12 (80%) were dyslipidemic, 11 (73,3%) had hypertension, 6 (40%) had non-obstructive CAD and 12 (80%) were Ach+. Those with an adverse outcome were older (61,67 ± 9,63 vs. 55,08 ± 10,35), had a higher number of risk factors (3,53 ± 0,83 vs. 3,08 ± 1,26), lower BMI (27,53 ± 3,52 vs. 28,90 ± 4,43), higher total cholesterol level (5,99 ± 0,82 vs. 5,85 ± 1,31), a similar HDL-cholesterol (1,45 ± 0,29 vs. 1,43 ± 0,21) and LDL-cholesterol level (3,80 ± 0,51 vs. 3,76 ± 1,25) and lower triglycerides concentration (1,27 ± 0,56 vs. 1,47 ± 0,74). However, all the differences were not statistically significant.

Cardiovascular death. All in all, 6 (14,6%) of the followed-up patients died, all of a cardiovascular reason. In Ach+ group 3 women died of sudden death, all of them with normal angiograms at presentation, 1 – with positive family history of CAD. One more woman in this group died of ischemic stroke, also presenting with smooth coronary arteries. There was one man in Ach+ group with non-obstructive CAD at presentation, who later developed acute MI, underwent PCI and consequently died of chronic heart failure. Cardiovascular death occurred in 1 patient of Ach- group: a woman with angiographically normal arteries later developed CAD and died after CABG surgery. None of the patients, who died of a cardiovascular reason, was a smoker. 4 (66,7%) of them had a previous ACS, only 1 (16,7%) had a positive family history, 5 (83,3%) were dyslipidemic and all – hypertensive. Also, these patients were older (64,5 ± 11,19 vs. 56,29 ± 10,03), more obese (28,82 ± 3,79 vs. 28,33 ± 4,23), had more risk factors (3,67 ± 0,52 vs. 3,17 ± 1,2), a higher cholesterol (6,28 ± 0,91 vs. 5,84 ± 1,18), LDL-C (3,87 ± 0,54 vs. 3,76 ± 1,13), HDL-C (1,48 ± 0,42 vs. 1,43 ± 0,2) and triglycerides level (1,5 ± 0,76 vs. 1,39 ± 0,69). However, all differences were not statistically significant.

Myocardial infarction. 2 patients (1 man, 1 woman) developed acute MI during follow-up, both of them in Ach+ group ($p = 0,726$) and with non-obstructive coronary atherosclerosis at presentation ($p = 0,08$).

Percutaneous coronary intervention. 4 (50%) patients with non-obstructive CAD at presentation later underwent PCI, whereas none of the patients with smooth coronary arteries did ($p = 0,005$). The number of risk factors was higher among patients later presenting for PCI (4,25 ± 0,5 vs. 3,14 ± 1,13), although the difference was not statistically significant ($p = 0,061$).

Ischemic stroke. Patients who experienced ischemic stroke during follow-up were older (66,05 ± 9,04 vs. 56,51 ± 10,25), but not significantly ($p = 0,07$).

Malignancy. 3 (8,6%) patients in ED group and 1 (16,7%) in Ach- group developed cancer during follow-up ($p = 0,483$). A higher number of risk factors (4 ± 0,00 vs. 3,16 ± 1,16) was observed in patients who developed cancer ($p < 0,001$). Separate traditional risk factors did not differ significantly between groups.

Arrhythmia. 6 (17%) patients in Ach+ group developed new heart rhythm disorders, whereas none of the patients did in the Ach- group. However, the difference was not statistically significant ($p = 0,567$).

Gender. Cardiovascular event rate was similar between men (38,5%) and women (35,7%), $p = 0,865$. However, CAD was more prevalent among men (6 men, 3 women, $p < 0,001$). 82% of women had a positive Ach test versus 92,3% of men ($p > 0,05$).

Body mass index. Ach+ patients had significantly higher BMI (28,99 ± 4,05 vs. 24,94 ± 2,86, $p = 0,015$).

Discussion

Interpretation of findings. The obtained follow-up of patients, complaining of angina-like chest pain and not having obstructive CAD revealed high rates of adverse outcome both in Ach+ and Ach- group, 34,3% and 50% respectively, the main event being cardiovascular death (27,3%). There are a few studies analysing the prognostic impact of ED diagnosed using intracoronary Ach test on long-term

adverse outcome [5-9] and none of the study reported such a high event rate: number of patients with adverse events varied between studies ranging from 5% [9] to 30% [6]. There may be a few explanations for this discrepancy: firstly, some studies had enrolled patients who were healthier and had fewer risk factors than did the participants of our study. For example, Bugiardini et al. did not include patients who had dyslipidemia; Schächinger et al. together with Suwaidi et al. excluded patients who had previous ACS and/or uncontrolled hypertension. Secondly, we have registered a higher variety of cardiovascular events during follow-up and included all the events, not only the one that occured first. Thirdly, the follow-up time differed between studies and among patients of one study, varying from 1 to 10 years. Moreover, the treatment of our patients was not standartised and the patients were not checked-up regularly, as it was done in other studies [9].

Also, we would like to pay the reader‘s attention to the prevalence of ED in our study group. None of the studies reported such a high ED rate among the observed patients: Sánchez-Recalde et al. – 65%, Bugiardini et al. – 52%, Schächinger et al. – 66%, Suwaidi et al. – 31%. We speculate this finding may be accidental – our population sample was quite small and we might have accidentally enrolled more patients with impaired endothelial function than those with normal one. Besides, all of our patients were symptomatic and had more coronary risk factors, while other investigators included asymptomatic patients as well.

One more explanation for a high ED rate in our study may be the technique and the evaluation of the Ach test. None of the investigators performed intracoronary Ach testing in the way it was done in our study. Suppositional Ach concentration in the artery, infusion rate and coronary artery diameter change indicating presence of ED differed between studies. Also, some of the studies did not include patients with coronary atherosclerosis [6,9], which is assumed to be related with ED.

Interestingly, none of the recent studies found cardiovascular death as the main adverse event during follow-up, as it was observed in our study. Most commonly, investigators reported worsening of angina as the most frequent cardiovascular event [6,9]. All observed deaths in our study population were of cardiovascular origin, whereas other authors report deaths from other causes [6].

In other studies all episodes of acute MI and coronary revascularisation were observed in Ach+ group. By contrast, one our patient in Ach- group underwent CABG and therefore died.

All of our patients were symptomatic, however CAD was significantly more prevalent among men. This finding agrees with notion that women complaining of chest pain tend to have normal coronary arteries [17,18].

Development of cancer was observed in only one study [7] investigating ED relation to cardiovascular events and the incidence was lower than in our study population (1,4% vs. 4,7%). It is interesting to note that patients who developed cancer in our study had significantly more cardiovascular risk factors than those who did not. This finding lets us presume that a higher number of coronary risk factors enhances the chance of developing cancer. We speculate this relationship might be explained having in mind that coronary risk factors induce oxidative stress [19,20] which, in turn, promotes cancer development [21].

Endothelial dysfunction and outcome. It is already known that acute coronary syndrome and sudden cardiac death cannot be predicted by nor are necessarily associated with significant obstructive coronary artery disease [22,23]. These events are likely to be dependent on the vascular wall properties and components of the plaque – elements regulated by the endothelium. Until now, all studies investigating prognostic impact of coronary ED to adverse cardiovascular outcome find a direct relationship: Suwaidi et al. and Recalde et al. concluded that ED and hypertension were independent predictors of cardiovascular events; Halcox et al. found that ED together with increasing age, CAD and higher BMI were independently associated with adverse events.

It is assumed that endothelial dysfunction may cause adverse events in several ways. One possible mechanism is myocardial ischemia secondary to ED related vasoconstriction [24-26], as demonstrated by Suwaidi et al. The authors showed that reduction of coronary blood flow as a response to acetylcholine infusion was related to myocardial perfusion defects.

Also, coronary endothelial dysfunction may contribute to cardiac events through acceleration of coronary atherosclerosis, as evidenced by the development of obstructive coronary artery disease in ED patients [7,9].

Study Limitations

There are a few limitations of the study that have to be considered. First of all, our patient population was relatively small. Secondly, there was quite a difference in ED+ and ED- groups regarding the number of patients in each group. Moreover, long-term evaluation was not a prespecified end point at the time of coronary vasoreactivity testing – that is why patients had not been checked-up regularly nor the treatment had been standartised.

Conclusion

In summary, the results of the present study demonstrate that patients complaining of chest pain but found to have no significant coronary atherosclerosis are at a high risk of developing a cardiovascular event. Poor prognosis of this patient population is determined by coronary endothelial dysfunction together with traditional cardiovascular risk factors. Thus, evaluation of endothelial function or its determinants may help identify a subgroup of patients at high risk. Whether medical treatment and/or lifestyle interventions that improve endothelial function would improve prognosis needs to be studied prospectively.

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VAINIKINIŲ ARTERIJŲ ENDOTELIO DISFUNKCIJOS, NUSTATYTOS PACIENTAMS, BESISKUNDŽIANTIEMS KRŪTINĖS SKAUSMU, BET NETURINTIEMS REIKŠMINGŲ PAKITIMŲ VAINIKINĖSE ARTERIJOSE, ĮTAKA NEPALANKIOMS BAIGTIMS

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Raktažodžiai: acetilcholinas, angina, koronarai, aterosklerozė, endotelis, prognozė.

Santrauka

Yra žinoma, kad vainikinių arterijų endotelio disfunkcija yra susijusi su didesne kardiovaskulinių įvykių rizika. Mes nustatėme kardiovaskulinių įvykių dažnį per ilgą sekamąjį laikotarpį tarp pacientų, kuriems dėl skausmų krūtinėje buvo atliekama koronarografija, o, neradus reikšmingų aterosklerozinių pakitimų vainikinėse arterijose, buvo įvertinta endotelio funkcija, atliekant acetilcholino mėginį. Kardiovaskulinių įvykių dažnis per vidutiniškai 9,5 metų laikotarpį buvo nustatytas 41 pacientui (35 - turintiems endotelio disfunkciją, 6 - su normalia endotelio funkcija). Nepalankia kardiovaskuline baigtimi buvo laikomi šie įvykiai: kardiovaskulinė mirtis, ūmus miokardo infarktas, nestabili krūtinės angina, perkutaninė koronarinė intervencija, aortokoronarinio šuntavimo operacija, išeminis insultas ir periferinių arterijų revaskuliarizacijos operacija. Kardiovaskulinių įvykių dažnis per sekamąjį laikotarpį buvo didelis tiek pacientų grupėje su endotelio disfunkcija, tiek be jos – atitinkamai 34,3% ir 50%. Nepalankių baigčių atsiradimą mūsų tirtiems ligoniams lėmė tiek endotelio disfunkcija, tiek tradiciniai kardiovaskuliniai rizikos veiksniai. Taigi, endotelio funkcijos ir ją sąlygojančių veiksnių įvertinimas gali padėti nustatyti didelės kardiovaskulinės rizikos pacientus.

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