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Prognostic value of an abnormal response to acetylcholine in patients with angina and non-obstructive coronary artery disease: Long-term follow-up of the Heart Quest cohort☆

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ABSTRACT

Background: This study aims to determine whether small vessel disease (SVD) or vasospastic disease (VSD) has an impact on prognosis.
Methods: The prospective cohort embraced 718 patients with angina equivalent symptoms and no coronary stenosis ≥50% recruited between 1997 and 2008. At baseline, patients were classified as having SVD, VSD, other cardiac disease or non-cardiac problem based on intracoronary acetylcholine application and fast atrial pacing during coronary angiography. Patients underwent follow-up between 2007 and 2015. Prognostic significance of the diagnosis on cardiovascular events (cardiovascular death or non-fatal myocardial infarction) was evaluated using Cox proportional hazards models adjusted for age and sex.
Results: The mean follow-up duration was 11.3 ± 2.7 years. Only 11 patients (1.5%) were lost to follow-up, resulting in an analyzed population of 707 patients. Patients with SVD (HR: 4.9, 95% CI: 1.1–22.4, P = 0.040) and VSD (HR: 4.8, 95% CI: 1.0–23.4, P = 0.050) had an increased risk of suffering cardiovascular events compared to patients with non-cardiac problems. Among SVD patients, those with the presence of endothelial dysfunction had a particularly high risk (HR: 7.3, 95% CI: 1.5–35.5, P = 0.015). Among patients with SVD or VSD, those having persisting or worsening angina during follow-up had a higher risk than patients in whom angina improved (HR: 4.8, 95% CI: 1.9–12.3, P = 0.001).
Conclusions: Our study shows that patients with SVD or VSD have an increased risk of cardiovascular events. This particularly applies to SVD patients with endothelial dysfunction. Symptoms should be taken seriously in SVD and VSD patients.
Trial registration: ClinicalTrials.gov Identifier: NCT01318629.

1. Introduction

There is an ongoing controversy over diagnosis, management and prognosis of patients with chest pain and normal coronary angiography. Patel et al. showed that elective coronary angiography has a low diagnostic yield for obstructive coronary artery disease (CAD) and that better strategies for risk stratification are needed [1]. Subsequently, and by performing additional invasive testing with intracoronary acetylcholine administration or fast atrial pacing during coronary angiography, we showed that 72.1% of patients with angina but no significant CAD had a cardiac cause of their symptoms [2]. The most frequently found cardiac diseases were small vessel disease and vasospastic disease. In accordance with us, Lee et al. recently showed that with a comprehensive invasive assessment during angiography (e.g., measurement of coronary flow reserve) a majority of these patients have coronary abnormalities and that the assessment can be performed safely [3].

Nonetheless, prognosis in these patients, which has impact on management, remains controversial. Earlier studies postulated a favorable prognosis, but most did not distinguish patients according to underlying etiologies [4–14]. Later studies revealed that prognosis might be less

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beneficial in these patients, in particular if coronary sclerosis, myocardial ischemia or endothelial dysfunction is present [15–21]. We therefore assessed long-term follow-up in a prospective cohort of patients who had normal coronary angiography despite angina and who received additional invasive testing during the angiography for precise diagnostic classification of the cause of angina.

2. Methods

2.1. Study population

This long-term follow-up study embraced all patients from the Heart Quest cohort. Baseline findings have been previously published [2]. In brief, the prospective cohort included patients who underwent coronary angiography at the Luzerner Kantonsspital (Luzern, Switzerland) between January 1st 1997 and July 31st 2008 for the evaluation of angina or angina equivalent symptoms and in whom angiography revealed no CAD (defined as no coronary stenosis ≥50%). We excluded patients in whom the origin of angina was evident after coronary angiography (i.e. patients with severe valvular disease, hypertrophic cardiomyopathy, severe heart failure or dilated cardiomyopathy). We also excluded patients in whom the additional invasive examinations according to the study protocol were not possible due to logistic reasons (such as a lack of personnel during nighttime or a lack of insurance contracts of patients from certain geographic regions). All study participants provided written informed consent. The local ethical committee (Luzern, Switzerland) approved the study (approval no. 11014), which complied with the declaration of Helsinki.

2.2. Baseline evaluation and diagnostic classification

All patients received extensive baseline evaluation. Medical history, including symptoms, was recorded. Height, weight, blood pressure and blood lipids were measured. Electrocardiogram (ECG) and stress testing were performed. Cardiovascular risk factors were diagnosed according to standard criteria. Hypertension was defined as a repeatedly elevated blood pressure > 140/90 mm Hg [22]. Dyslipidemia was defined as total cholesterol >193 mg/dL (5.0 mmol/L) or low-density lipoprotein cholesterol >117 mg/dL (3.0 mmol/L) [23]. Diagnosis of diabetes mellitus was made if fasting plasma glucose was ≥126 mg/dL (≥7.0 mmol/L) on at least two different days or if postprandial plasma glucose was ≥200 mg/dL (≥11.1 mmol/L) [24].

During coronary angiography, all participating patients received acetylcholine applied in the right and/or left coronary artery with subsequent contrast media application and angiographic depiction [25–27]. The investigators noted any occurring symptoms and judged diameter changes of the coronary vessels by visual impression [28]. Patients in whom diagnosis was unclear after acetylcholine received a temporary pacemaker. The investigators then noted any symptoms or arrhythmias occurring during fast atrial pacing (increasing frequency from 100/min to Wenckebach point) [29].

Based on the additional testing during angiography, we classified patients into the following four diagnosis groups. The diagnostic classification used in this cohort has been previously published in detail [2]. (A) Small vessel disease was diagnosed, if there was no relevant coronary diameter change (<50% reduction of lumen diameter) after acetylcholine, but there were typical symptoms after acetylcholine, during contrast media application, during atrial pacing, during femoral puncture and/or during extra beats [29]. Patients with small vessel disease were further classified into those with endothelial dysfunction (i.e. had coronary diameter change ≥10% and <50% after acetylcholine that was reversible after nitroglycerine) and those without (i.e. <10% reduction of lumen diameter after acetylcholine). (B) Vasospastic disease was diagnosed, if there was a vasospasm (defined as localized reduction of lumen diameter of ≥50% after acetylcholine application) and prompt vasodilatation after nitroglycerine [25–27]. All remaining patients were classified (C) into a group with other cardiac diseases (i.e. rhythm disorders or hypertensive heart disease) or (D) a group with non-cardiac problems. Non-cardiac problems were assumed, if angiography and the additional testing during angiography did not reveal a cardiac cause for the symptoms but rather another problem as cause (e.g. pulmonary hypertension, psychosomatic disorders, esophageal disease or musculoskeletal pain).

2.3. Follow-up and outcomes

We performed follow-up evaluations between January 1st 2007 and January 31st 2015. Patients were invited to receive a follow-up evaluation at the hospital, including ECG recording and stress testing. For patients who refused the in-hospital follow-up, a standardized phone questionnaire was used. From each patient we obtained medical interim history, including persisting angina or angina equivalent symptoms, prescribed drugs and occurrence of any cardiovascular events since study inclusion. As an additional source of information, we reviewed medical records from the hospital for each patient. Further, we communicated with the primary care physician of those patients whose medical interim history remained unclear or who were not contactable. To search for "untraceable" patients we used information from phone directories and municipal authorities. Municipal authorities reliably assess where patients move to or when patients died. For patients who died, the cause of death was ascertained through information from relatives, primary care physicians, in-hospital medical records and/or the death registry from Swiss statistics. A diagnosis of myocardial infarction was based on symptoms, ECG, and/or cardiac enzymes, and conformed to prevailing guidelines in use at the time of the event [30]. The primary outcome was a combined endpoint of cardiovascular events, defined as death from cardiovascular cause (i.e. death from fatal myocardial infarction, fatal heart failure, sudden death or fatal stroke) or non-fatal myocardial infarction. Secondary outcomes included: death from cardiac cause, which was defined as death from fatal myocardial infarction, fatal heart failure, or sudden death; death from cardiovascular cause, which was defined as death from cardiac cause or from stroke; and, revascularization by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).

2.4. Statistical analysis

We calculated the required sample size a priori at 66 patients per group based on the following assumptions: Cox proportional hazards model, exposed group has a two-fold increased risk of events, significance level 0.05, and power 0.80.

We first descriptively analyzed baseline characteristics separate for the four diagnosis groups and compared the characteristics of patients with cardiac disorders to those of patients with non-cardiac problems. Second, Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) to compare the event rates in patients with small vessel or vasospastic disease to patients with a non-cardiac disease [31]. Patients from the group with non-cardiac problems served as reference group. All models were done unadjusted and after adjustment for age and sex. Deviations from the proportional hazards assumption were tested by examining the global test of Schoenfeld residuals. We depicted the times to event with the Kaplan–Meier estimates of the survival function and used the log-rank test to compare the curves. Third, we analyzed the importance of endothelial dysfunction in patients with small vessel disease. Fourth, the prognostic significance of symptoms was analyzed using the Kaplan–Meier estimates of the survival function and log-rank tests for their comparison. Finally, we descriptively analyzed drug therapy during follow-up. For patients who died, the last known drug therapy before death was used in the analysis.

We used Stata 12.1. (StataCorp, College Station, TX, USA) for all analyses. Group differences of continuous variables were compared by use of the t test, if normally distributed, or by the Mann–Whitney test. For categorical variables, the χ^2 test or, if cell counts were <5, the Fisher exact test. In all tests, P values ≤0.05 were considered statistically significant.

3. Results

3.1. Study population

Fig. 1 shows the study flow chart. Of 718 patients included in the Heart Quest cohort, only 11 patients (1.5%) were lost during long-term follow-up: 10 patients had moved to distant countries and were untraceable, and one patient was alive but refused follow-up assessment. Nine of the 10 untraceable patients were citizens from other countries who had worked for some time in Switzerland and subsequently returned to their country of origin. The analyzed population consisted of 707 patients. Of these, 283 patients (40.0%) had small vessel disease, 142 patients (20.1%) had vasospastic disease, and 86 patients (12.2%) had other cardiac diseases. A non-cardiac problem was cause of the angina equivalent in 196 patients (27.7%).

Table 1 shows the baseline characteristics according to the diagnosis. In comparison to patients with non-cardiac problems, patients with small vessel disease were older, more were female, had effort-related symptoms more often, and exercise testing was more frequently abnormal. Patients with vasospastic disease were older and more often had abnormal kinetics and/or hypertrophy on echocardiography than did patients with non-cardiac problems.

3.2. Follow-up and outcomes

The total observation time was 7982 person-years. The mean follow-up duration was 11.3 ± 2.7 years. During follow-up, overall 68 patients (9.6%) died. Ten patients died from cardiac causes (5 of sudden cardiac death, 3 of congestive heart failure, 1 of fatal MI and 1 of endocarditis). A cerebral cause of death was found for 13 patients: seven died from dementia, 3 from stroke, 2 from Parkinson's disease and 1 had a cerebral bleeding after a car accident. Malignancies (solid carcinoma, leukemia or lymphoma) were the cause of death in 22 patients, infectious diseases (mainly pulmonary) in 9 patients and pulmonary embolism in 3 patients. Eleven further patients died from other non-cardiovascular causes (e.g. cachexia, liver cirrhosis, ischemic colitis, suicide, bleeding during surgery). Ten patients (1.4%) had non-fatal myocardial infarction during follow-up.