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High-sensitivity cardiac troponin T in patients with intermittent claudication and its relation with cardiovascular events and all-cause mortality — The CAVASIC Study

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ABSTRACT

Background. Serum concentrations of high-sensitivity cardiac troponin T (hs-cTnT) are elevated in various diseases. The role of this marker in peripheral arterial disease (PAD) has not been fully investigated. **Methods**. Hs-cTnT was measured in the CAVASIC Study, a male cohort of 235 patients diagnosed with intermittent claudication and 249 age- and diabetes-matched controls. Patients with symptomatic PAD were prospectively followed for a median time of 7 years. The association of hs-cTnT with PAD, cardiovascular disease (CVD) at baseline as well as incident CVD and all-cause mortality during follow-up was analyzed. **Results**. Detectable hs-cTnT was associated with an 84% higher probability for symptomatic PAD at baseline: OR = 1.84, 95%CI 1.05–3.21, $p = 0.03$. Inclusion of ln-NT-proBNP or prevalent CVD abolished this association (both OR = 1.22, $p = 0.52$). However, detectable hs-cTnT was associated with prevalent CVD ($n = 69$) in PAD patients independent from ln-NT-proBNP: OR = 3.42, $p = 0.001$. In the adjusted Cox regression analysis detectable (HR = 2.15, $p = 0.05$) and especially hs-cTnT ≥14 ng/L (HR = 5.06, $p < 0.001$) were predictive for all-cause mortality ($n = 39$) independent from ln-NT-proBNP. Furthermore, hs-cTnT ≥14 ng/L was significantly associated with incident CVD ($n = 66$): HR = 3.15, 95%CI 1.26–7.89, $p = 0.01$. **Conclusions**. This study in male patients with intermittent claudication and age- and diabetes-matched controls revealed hs-cTnT to be associated with PAD and prevalent CVD. The latter association was even significant after considering NT-proBNP. Prospectively, in PAD patients hs-cTnT was predictive for incident cardiovascular diseases and all-cause mortality. Thus, hs-cTnT could be a surrogate marker for cardiomyocyte damage also in symptomatic PAD patients.

1. Introduction

Patients with peripheral arterial disease (PAD) have an increased risk for cardiac and cerebrovascular diseases [1]. Mortality rates are on average more than twice as high in case of symptomatic PAD defined as intermittent claudication compared to patients with symptom-less PAD or without PAD [2,3]. Rates of all-cause as well as cardiovascular mortality and morbidity tremendously increase especially in elderly PAD patients. About a quarter of patients with PAD die due to non-cardiovascular causes [4,5].

Cardiac troponin T (cTnT) is an important structural component of the cardiac muscular contraction system. Cardiomyocyte damage leads to an increase of cTnT blood concentrations. Clinical symptoms and electrocardiography often do not provide a clear diagnosis of this damage. Therefore, the measurement of cTnT blood

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concentrations above the 99th percentile of the upper reference limit of the general population is a required and established threshold to diagnose diseases such as acute coronary syndrome (ACS). Cardiac troponins have been reported to be highly predictive for death and recurrent myocardial infarction [6–14]. Increased cTnT concentrations were also detected in individuals with prevalent or incident chronic heart failure and other types of cardiovascular disease, diabetes mellitus, sepsis as well as renal failure and acute pulmonary embolism [13,15–22]. A recent genome-wide association study based on two prospective cohorts in more than 9000 European Americans and 2000 African Americans without coronary heart disease and heart failure detected an association of hs-cTnT above the 99th percentile threshold with TNNT2, a gene encoding the cardiac troponin T protein. In a subsequent large case-control study hs-cTnT associated single nucleotide polymorphisms (SNPs) were not related to coronary heart disease, but one SNP within TNNT2 was significantly associated with incident heart failure [23]. However, the exact mechanism of cTnT increase is still unclear [24].

Whether cTnT concentrations also play a role in diseases such as symptomatic PAD particularly in patients at a less advanced disease stage has not been investigated in detail yet. One quite small cross-sectional study described an elevation of cTnT levels in PAD patients with Fontaine stage II to IV and a relation to N-terminal pro-B-type natriuretic peptide (NT-proBNP) [25]. A small prospective study and one of moderate size in patients with acute limb ischemia found elevated cTnT to be a predictor of worse outcome [26,27]. A more recent report in symptomatic PAD patients with Fontaine stage IIb to IV described cTnT levels to be elevated and associated with all-cause mortality and higher amputation rates [28].

In the present study we investigated the role of hs-cTnT serum concentrations in symptomatic PAD patients at stages IIa or IIb according to the Fontaine classification with the following aims: 1) We analyzed in a case-control design whether elevated hs-cTnT is associated with symptomatic PAD. 2) In PAD patients we studied whether hs-cTnT is associated with prevalent cardiovascular disease (CVD). 3) We prospectively followed PAD patients for a median time of 7 years and investigated whether baseline hs-cTnT is associated with an increased risk for fatal and non-fatal cardiovascular events as well as all-cause mortality independent from confounders or risk factors and the established cardiac marker NT-proBNP.

2. Methods

2.1. Study participants and study design

The CAVASIC (Cardiovascular Disease in Intermittent Claudication) Study is a case-control study with a prospective follow-up examination primarily initiated to detect atherosclerotic risk factors in patients with intermittent claudication [29,30].

PAD patients ($n = 248$) were enrolled in the study when they presented with a history of intermittent claudication (PAD stages IIa or IIb corresponding to the criteria of Fontaine), irrespective of a former treatment (bypass surgery or intervention). Patients were excluded for any of the following reasons: acute or critical limb ischemia (Fontaine III or IV), malignancy, previous organ transplantation, decreased kidney function (serum creatinine >133 μmol/L), and therapy with corticosteroids or nicotinic acid.

A control cohort of 251 male participants from the same geographic area matched for age and type 2 diabetes mellitus (T2DM) agreed to attend in the study after an invitation in the local newspaper. The same exclusion criteria were applied as for patients. Symptomatic PAD in the control group was considered as exclusion criteria, whereas those with known CVD were allowed to participate.

All subjects provided written informed consent. The examination protocol was approved by the local Ethics Committee of the participating study centers.

Hs-cTnT was measured in 235 patients and 249 controls with available serum samples. All data and analyses at baseline are based on these 484 participants. The design of the baseline investigation is briefly described in Fig. 1.

2.2. Baseline examination

Demographic data, a clinical history as well as an atherosclerosis risk profile were obtained via a standardized interview.

The Supplementary material contains further details on the study design, the baseline investigation such as the ankle-brachial index (ABI) measurement, phenotypic characterization and standard laboratory measurements.

2.3. Follow-up examination

All PAD patients ($n = 256$) of the CAVASIC Study, not only those patients for whom the baseline case-control analysis did contain matching controls, were followed prospectively for a median time of 7 years to collect data on clinical endpoints (fatal and non-fatal cardiovascular events) and all-cause mortality. At the end of the observation period, follow-up information was available in 255 patients. Face-to face interviews including follow-up examinations were performed (in 86%) and/or hospital charts were available (in 100%). Finally, the follow-up investigation for this particular project included 242 PAD patients with available hs-cTnT values. For an overview of the follow-up part of the study see Fig. 1.

2.4. Clinical endpoints in the prospective observation period

Defined clinical endpoints were all-cause mortality (primary endpoint) as well as fatal and non-fatal cardiovascular events (secondary endpoint) between baseline and follow-up. Data on mortality and/or the verification of causes of death as well as all further reported clinical events were obtained through autopsy reports, death certificates, medical reports or information reported by general practitioners. Cardiovascular mortality was defined according to the ICD10 Codes I00-I99, death due to cancer as ICD10 C00-D48 and infectious mortality as ICD10 A00-B99.

The extended definition of cardiovascular events comprised non-fatal myocardial infarction (MI) diagnosed by clinical symptoms, electrocardiography, and an increase in cardiac troponins. In all non-fatal MI cases additionally medical records of coronary angiographies (CAGs) with or without subsequent percutaneous transluminal coronary angioplasty (PTCA) were available. Elective PTCA, aortocoronary bypass, angiographically proven coronary stenosis ≥50%, ischemic cerebral infarction (diagnosed by clinical appearance, computer tomography and/or magnetic resonance imaging), transient ischemic attack (TIA), carotid endarterectomy (CEA) and cardiovascular death were also included in the extended definition.

Major composite cardiovascular events were defined as non-fatal MI, PTCA due to MI, or ischemic cerebral infarction and cardiovascular death (detailed description see above).

2.5. Laboratory measurements

Serum and EDTA plasma samples were taken after an overnight fasting period and stored in aliquots at −80 °C until laboratory measurements were conducted. High-sensitivity cardiac Troponin