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Biomarkers of cardiomyocyte injury and stress identify left atrial and left ventricular remodelling and dysfunction: A population-based study

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ABSTRACT

Background/objectives: The validation of effective screening tools for the identification of patients with subclinical myocardial remodelling is a major clinical need. Thus, we explored the associations of circulating biomarkers of cardiomyocyte injury and stress with subclinical cardiac remodelling and dysfunction, and with biomarkers reflecting collagen turnover.

Methods: We randomly recruited 727 subjects from a general population (51.2% women; mean age 51.3 years). Measurements included echocardiographic left atrial (LA) and left ventricular (LV) structure and function, quantification of high sensitivity cardiac Troponin T (hs-cTnT), NT-proBNP, and biomarkers of collagen types I and III turnover.

Results: In unadjusted and adjusted analyses, the prevalence of LA enlargement (LAE), LV hypertrophy (LVH) and LV diastolic dysfunction (LVDD) increased with higher hs-cTnT ($P \leq 0.031$). NT-proBNP was independently associated with LVDD ($P = 0.009$). Both biomarkers combined yielded significant integrated discrimination and net reclassification improvements ($P \leq 0.014$ and $P \leq 0.009$, respectively) for LAE, LVH and LVDD, over the conventional risk factors, and were independently and positively associated with biomarkers of collagen type I turnover. In a sensitivity analysis, after excluding participants with previous cardiac diseases, our findings remained consistent.

Conclusions: Our population-based study suggested that subclinical LV and LA remodelling were associated with hs-cTnT, and that, in combination with NT-proBNP, hs-cTnT showed incremental diagnostic utility over the conventional risk factors. Both biomarkers were associated with biomarkers of collagen type I turnover. Thus, biomarkers of cardiomyocyte microinjury and hemodynamic stress may stimulate fibrosis-related mechanisms and facilitate the diagnosis of subclinical LA and LV remodelling and dysfunction in the general population.

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Abbreviations: A, peak late diastolic velocity, transmitral; CITP, carboxyterminal telopeptide of type I collagen; E, peak early diastolic velocity, transmitral; e′, peak early diastolic mitral annular velocity; EF, ejection fraction; hs-cTnT, high sensitivity cardiac Troponin T; HF, heart failure; IVRT, isovolumetric relaxation time; LA, left atrial; LAE, left atrial enlargement; LAVI, left atrial volume index; LV, left ventricular; LVDD, left ventricular diastolic dysfunction; LVESV, left ventricular end-systolic volume; LVEDV, left ventricular end-diastolic volume; LVH, left ventricular hypertrophy; NRI, net reclassification improvement; NT-proBNP, amino-terminal pro-brain natriuretic peptide; PICP, carboxyterminal propeptide of procollagen type I; PIIINP, aminoterminal propeptide of procollagen type III; TDI, tissue Doppler imaging; TIMP-1, tissue inhibitor of the matrix metalloproteinase type 1.

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1. Introduction

Heart failure (HF) is a progressive condition that begins with risk factors (e.g., hypertension), proceeds to cardiac remodelling (e.g., left ventricular (LV) hypertrophy and left atrial enlargement) and changes in LV function (e.g., diastolic and systolic dysfunction), and then evolves into clinically overt HF, disability and death [1]. The validation of effective screening tools for the identification of patients at the early stage of LV remodelling (diagnostic markers) is a major clinical need.

The cardiac troponin complex includes troponin T (cTnT) protein which is tightly bound to the cardiac tropomyosin complex [2]. The mechanisms underlying cTnT release from cardiomyocytes might be related to myocyte necrosis and apoptosis, to increased cardiomyocyte wall permeability, or to normal cardiomyocyte turnover [3]. Patients with symptomatic HF outside the context of clinically apparent ischemia (myocardial infarction) have increased levels of circulating cTnT detected with a high sensitivity assay (hs-cTnT) [2]. In the general population, LV hypertrophy (LVH) is associated with elevated hs-cTnT levels [4,5]. Independently of other cardiovascular risk factors, hs-cTnT levels predict incident HF [6] and total mortality [4,6].

Brain natriuretic peptide (BNP) is released from cardiomyocytes in response to an increase of atrial or ventricular diastolic stretch to stimulate natriuresis and vasodilatation and to facilitate LV relaxation [7]. Secreted pro-BNP is subsequently cleaved in the blood into amino terminal-proBNP (NT-proBNP) and BNP. NT-proBNP values vary with the degree of LV diastolic dysfunction (LVDD) [8]. Moreover, in combination with hs-cTnT, NT-proBNP identifies a malignant phenotype of LVH with high risk for HF and cardiovascular death in the general population [9].

Cardiomyocyte microinjury may be associated with dysregulation of the collagen deposition process in elderly patients with HF [10]. Indeed, biological processes related to cardiomyocyte microinjury can activate collagen turnover and, therefore, lead to myocardial fibrosis even in the absence of myocardial infarction [11]. Biomarkers of collagen metabolism relevant to myocardial fibrosis include, among others, carboxyterminal propeptide of procollagen type I (PICP), a marker of type I collagen synthesis; carboxyterminal telopeptide of type I collagen (CITP) and tissue inhibitor of the matrix metalloproteinase type 1 (TIMP-1) as markers of degradation of type I collagen; and aminoterminal propeptide of procollagen type III (PIIINP), a marker of synthesis and degradation of type III collagen [12].

The objective of our study was to gain further insight into the association of subclinical myocardial remodelling, considering not only LV but also left atrial (LA) morphology, with circulating biomarkers of cardiomyocyte injury (hs-cTnT) and cardiomyocyte stress (NT-proBNP). In addition, we also explored the associations of hs-cTnT and NT-proBNP with biomarkers reflecting collagen turnover. All these aspects were investigated in subjects randomly selected from a Flemish population.

2. Methods

2.1. Study participants

The Ethics Committee of the University of Leuven approved the Flemish Study on Environment, Genes and Health Outcomes (FLEMENGHO). Detailed explanation of the study participants is provided in the Data Supplement. Briefly, from May 2005 until May 2010, we invited 1208 former participants from a previously identified random population for a follow-up examination at the field centre, including echocardiography. However, 153 participants were unavailable for follow-up, because they had died (n = 26), because they had been institutionalised or were too ill (n = 27), or because they had moved out of the area (n = 100). Of the remaining 1055 former participants, 828 renewed their informed consent. The participation rate for the follow-up examination was therefore 78.5%. We excluded 15 subjects, because of atrial fibrillation (n = 8) or the presence of an artificial pacemaker (n = 3), or because diastolic function could not be reliably determined (n = 4). We discarded further 86 subjects from analysis because serum samples were not available (n = 44) or the amount of serum was insufficient (n = 42) for hs-cTnT measurements. Therefore, the number of participants statistically analysed totaled 727.

2.2. Echocardiography

The participants refrained from smoking, heavy exercise, and drinking alcohol or caffeine-containing beverages for at least 3 h before echocardiography. The blood pressure during echocardiography was the average of two readings, obtained with a validated OMRON 705IT device (Omron Corp., Tokyo, Japan) at the end of the echocardiographic examination.

A complete echocardiographic protocol and reproducibility study are provided in the Data Supplement. Briefly, one experienced physician (T.K.) did the ultrasound examination [8], using a Vivid7 Pro (GE Vingmed, Horten, Norway) interfaced with a 2.5- to 3.5-MHz phased-array probe, according to the recommendations of the American Society of Echocardiography [13]. All digitally stored images were analysed, averaging 3 heart cycles for statistical analysis, using a workstation running the EchoPac, version 4.0.4 software package (GE Vingmed, Horten, Norway). End-diastolic LV dimensions were used to calculate LV mass by an anatomically validated formula. LV mass index (LVMI) was LV mass divided by body surface area (BSA). LVH was a LV mass index exceeding 110 g/m^2 in women, and 125 g/m^2 in men [14]. We measured LA dimensions in 3 orthogonal planes: the parasternal long, lateral, and supero-inferior axes. LA volume was calculated using the prolate-ellipsoid method and was indexed to BSA. LA enlargement (LAE) was a LA volume index (LAVI) exceeding 29 ml/m^2 [15].

From the transmitral flow signal, we measured peak early diastolic velocity (E), peak late diastolic velocity (A), the E/A ratio, and A flow duration. From the PV flow signal, we measured the duration of PV reversal time during atrial systole (AR). From the TDI recordings, we measured peak early (e′) diastolic mitral annular velocity at the 4 acquisition sites (septal, lateral, inferior, and posterior). We combined the mitral inflow and TDI velocities to classify the stages of LVDD at baseline as previously described [8,16]. The first group included subjects with an abnormally low age-specific transmitral E/A ratio indicative of impaired relaxation, but without evidence of increased LV filling pressures (E/e′ ≤ 8.5). The second group had mildly-to-moderately elevated LV filling pressures (E/e′ > 8.5), and E/A ratio within the normal age-specific range. We also used the differences in durations between the mitral A flow and the reverse PV flow during atrial systole (Ad < ARd + 10) and/or LAVI (>29 ml/m^2) to confirm possible elevation of the LV filling pressures in group 2. Group 3 had an elevated E/e′ ratio and an abnormally low age-specific E/A ratio (combined dysfunction). Of notice, the prognostic significance of the considered LVDD classification in the current study has been proven in the general population [17].

2.3. Biochemical measurements

A complete description of the biochemical measurements is provided in the Data Supplement. Briefly, hs-cTnT levels were measured in serum using a highly sensitive assay (Troponin T hs STAT, Roche Diagnostics) optimized on the Cobas 8000 modular analyser series (Roche Diagnostics). PICP was quantified in serum by sandwich enzyme linked immunosorbent assay (ELISA) using the METRA EIA kit (Quidel Corporation, San Diego, CA), serum CITP was determined by a quantitative enzyme immunoassay (EIA) (Orion Diagnostica, Espoo, Finland), free TIMP-1 was determined in serum by the ELISA method (TIMP-1 Human Biotrak ELISA System from GE Healthcare, UK Limited) and PIIINP was assessed in serum as a marker of collagen type III turnover by ELISA (MyBioSource, San Diago, CA). NT-proBNP was measured in plasma by a competitive EIA for research use (Biomedica Gruppe, Vienna, Austria). From the considered 727 participants, plasma samples from 33 subjects were not

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