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The impact of confounders on the test performance of natriuretic peptides for cardiac dysfunction in subjects aged 80 and older

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ABSTRACT

The hypothesis that natriuretic peptides could be used to identify 'pancardiac' damage has been proposed. However, multiple factors are known to influence circulating levels of natriuretic peptides, especially in the very old. Therefore, the impact of confounders on the association between natriuretic peptide levels and cardiac dysfunction was further explored in subjects aged 80 and older. A diagnostic cross-sectional study embedded within the BELFRAIL study ($n = 567$) was performed. Baseline BNP and NT-proBNP levels were measured and echocardiograms were performed at the subject's home. Cardiac dysfunction was defined as systolic dysfunction, valvular heart disease or isolated severe diastolic dysfunction. Several functional and structural echocardiographic parameters were independently related to circulating levels of natriuretic peptides. Cystatin C, BMI, β blockers, diabetes, heart frequency, usCRP, age and sex were identified as confounders. The prevalence of cardiac dysfunction was 17.1% in the subjects without and 30.8% in the subjects with chronic atrial fibrillation (CAF) or pacemaker (PM). Only in subjects with CAF or PM the C statistic for cardiac dysfunction improved after correcting for confounders. The post-test probability for a negative test (PTP−) ranged from 3.7% to 12.2% and the PTP+ ranged from 21.9% to 62.2% in different strata of confounders. According to these data adjusting for identified confounders does not improve the diagnostic accuracy of the natriuretic peptides for cardiac dysfunction, except in subjects with CAF or PM. Stratifying for individual confounders showed that different cut-off values could be used to optimize the diagnostic characteristics of natriuretic peptides.

1. Introduction

Aging populations and improved survival following acute cardiac events have led to an increased prevalence of cardiac dysfunction and heart failure, especially in the elderly [17]. Asymptomatic functional and structural abnormalities of the heart are considered to be precursors of symptomatic heart failure and are associated with high mortality [15,30]. Therefore, timely and adequate diagnoses of cardiac dysfunction are important because treatment can delay the progression to overt heart failure [26].

A cardiac dysfunction diagnosis is often challenging when multiple comorbidities are present. The accuracy of a clinical diagnosis based on signs and symptoms is often limited in elderly patients [16]. Echocardiography is currently the diagnostic test of choice for identifying functional and structural cardiac abnormalities. However, its availability to elderly patients can be limited, so there is the possibility of considerable over- and under-diagnosis of cardiac dysfunction [23,31]. This possibility emphasizes the need for a simple test to identify at risk patients. Measuring natriuretic peptides

Abbreviations: BNP, brain natriuretic peptide; NT-proBNP, amino-terminal pro-brain natriuretic peptide; BMI, body mass index; usCRP, ultra-sensitive C-reactive protein; CAF, chronic atrial fibrillation; PM, pacemaker; PTP+, post-test probabilities for positive test; PTP−, post-test probabilities for negative test; LV, left ventricular; GP, general practitioner; CRA, clinical research assistant; ECG, electrocardiogram; CV, coefficient of variation; EF, ejection fraction; VHD, valvular heart disease; IQR, inter-quartile range; ROC, receiver operating characteristic; AUC, area under the curve; LA, left atrial; LVIDs, left ventricular internal dimension at end systole; LVIDd, left ventricular internal dimension at end diastole; RWMA, regional wall motion abnormalities; E, early transmitral inflow wave peak velocity; A, atrial transmitral inflow wave peak velocity; E′, peak velocity of mitral annulus motion during early diastole; DT, deceleration time; IVRT, isovolumic relaxation time; Vp, flow propagation parameter of diastolic function.

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has been proposed as a screening method for left ventricular (LV) dysfunction in high-risk patients, such as the elderly [1,2].

Furthermore, natriuretic peptides have been shown to identify both increased intracardiac volume/pressure and any form of cardiac damage, such as silent ischemia, left ventricular hypertrophy and atrial fibrillation [3,12,20,32]. The hypothesis that natriuretic peptides could be used to identify 'pancardiac' damage, even when it is silent, has been proposed [25]. However, multiple factors are known to influence circulating levels of natriuretic peptides, especially in the elderly. The prevalence of possible influencing factors, such as renal dysfunction and diabetes, increases with age [2]. Understanding these factors is a prerequisite for optimally using these peptides to diagnose cardiac dysfunction in the community [10].

Therefore, a cross-sectional analysis within the BELFRAIL cohort (BF_{C80+}) was performed to determine the correlations between the natriuretic peptides and various echocardiographic abnormalities of the heart and to investigate the influence of possible confounders. In addition, the impact of identified confounders on the diagnostic accuracy of natriuretic peptides for cardiac dysfunction was further explored.

2. Methods

2.1. Study population

The BF_{C80+} study is a prospective, observational, population-based cohort study of subjects aged 80 years and older in three well-circumscribed areas of Belgium. The study design and characteristics of the cohort have been described in detail [28]. In brief, 29 general practitioner (GP) centers were asked to enroll patients aged 80 and older. Only three exclusion criteria were used: severe known dementia (mini-mental state examination score < 15), undergoing palliative care and experiencing medical emergencies. A total of 567 subjects were included in the BF_{C80+} study between November 2, 2008 and September 15, 2009. Each study participant was invited to attend four study visits. The GP recorded the background variables and a medical history and gathered a detailed anamnesis. A clinical research assistant (CRA) performed an extensive examination, including an electrocardiogram (ECG). The echocardiography was performed at the subject's home by a cardiologist. A blood sample was collected in the morning. All of the participants in the study gave informed consent and the Biomedical Ethics Committee of the Medical School of the Université Catholique de Louvain (UCL) of Brussels approved the study. All clinical and laboratory tests were performed in accordance with the Declaration of Helsinki.

2.2. Clinical characteristics

The dyspnea symptoms (according to the Medical Research Council [MRC] dyspnea scale [6]), fatigue and ankle swelling were registered.

Indicators of the cardiovascular risk profile were presence of hypertension and diabetes mellitus, as determined by the GP. The patient's smoking status was registered, and the body mass index (BMI) was calculated by the CRA based on a standardized measurement of weight and height.

Cardiac morbidities were defined by positive responses to a history of angina pectoris or myocardial infarction, decompensated heart failure, chronic atrial fibrillation (CAF), pacemaker (PM) implantation and important cardiac interventions or surgery (percutaneous transluminal coronary angioplasty or stenting and coronary or valvular surgery). A 12-lead ECG was recorded on a QRS Universal ECG device (QRS Diagnostic, Plymouth, Minnesota, USA, www.qrsdiagnostic.com) [28]. Prior histories of myocardial infarction (Minnesota Code 1-1 or 1-2, excluding 1-2-8), atrial fibrillation (Minnesota Code 8-3-1), an artificial PM (Minnesota Code 6-8), LV hypertrophy (Minnesota Code 3-1, 3-2 or 3-3) or a left bundle branch block (Minnesota Code 7-1-1) were noted. Myocardial infarction, CAF or PM were defined as reported by the GP or identified by the ECG.

The other cardiovascular morbidities were defined as positive responses to a history of transient ischemic attack, cerebrovascular accident, peripheral arterial disease or arterial surgery.

Data on the relevant cardiovascular medications including diuretics, potassium-sparing agents, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium antagonists and cardiac glycosides were also registered.

2.3. Laboratory tests

The plasma (EDTA) and serum samples were stored at −80 °C until the analysis. The hemoglobin concentrations were measured from whole blood using a Sysmex XE-2100 automated hematology analyzer (Milton Keynes, UK). Anemia was defined as a hemoglobin level of <12 g/dL for women or <13 g/dL for men [22]. The serum creatinine (IDMS Jaffé method), cystatin C and ultra-sensitive C-reactive protein (usCRP) were measured using a UniCel® DxC 800 Synchron (Beckman-Coulter, Brea, USA). The plasma BNP levels were measured using the Biosite® kit on a UniCel® DxI 800 Immunoassay System (Beckman-Coulter, Brea, USA). The coefficient of variation (CV) ranged from 5.4 to 6.7%. The serum NT-proBNP levels were measured using a Dade-Dimension® Xpand (Siemens, Deerfield, USA). The CV ranged from 3.9 to 4.3%.

2.4. Echocardiography

The echocardiograms were performed using a commercially available portable system (CX50, Philips, Andover, Massachusetts, USA) with M-mode, 2-dimensional and pulsed, continuous-wave and color-flow Doppler capabilities. The echocardiograms were performed by a single cardiologist who was blinded to the clinical characteristics and laboratory test results. All of the patients were examined in left lateral decubitus position. A complete examination, consisting of standard parasternal short- and long-axis, apical and subcostal 2D views, was performed according to the recommendations of the American Society of Echocardiography and the European Society of Echocardiography [11]. Still frames for the M-mode, continuous and pulsed Doppler and cineloops for assessing left ventricular (LV) function were digitally stored on a DVD and later transferred to a workstation. All of the measurements were performed off-line using the Xcelera software (Philips, Andover, Massachusetts, USA).

The LV function was calculated using the Simpson biplane method [11]. The echo image quality was semiquantitatively assessed on a 5-point scale [9]. In subjects with poor-quality images, the LV function was independently re-evaluated by a second cardiologist [29]. The subjects were determined to have poor LV function if both cardiologists visually estimated the ejection fraction (EF) to be ≤50% [29]. The left atrial (LA) volume was measured using the biplane area-length formula [11].

The mitral, aortic and tricuspid valves were evaluated with color Doppler echocardiography after optimizing the gain and Nyquist limit. Standard, continuous and pulsed-wave Doppler recordings were acquired. Stenotic and regurgitant valve diseases were evaluated, according to the semiquantitative and quantitative methods recommended by the American Society of Echocardiography [19,34]. Clinically relevant valvular heart disease (VHD) was defined as mitral stenosis of any severity, severe aortic stenosis (aortic valve area <1 cm^2), moderate or severe mitral