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ORIGINAL ARTICLE

Serial Assessment of Natriuretic Peptides in Patients Undergoing Interventional Closure of the Left Atrial Appendage

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Background Closure of the left atrial appendage (LAA) to prevent cardioembolic events is an alternative therapy to oral anticoagulation in patients with non-valvular atrial fibrillation. The LAA is an important source of natriuretic peptides and its exclusion from the circulation may alter the blood level of these hormones, thereby influencing their diagnostic value and clinical effects.

Methods We aimed to prospectively assess potential changes in mid-regional pro A-type natriuretic peptide (MR-proANP) and N-terminal pro B-type natriuretic peptide (NT-proBNP) levels six weeks and six months after interventional LAA closure using the Watchman device.

Results In 29 consecutive patients with successful LAA closure baseline MR-proANP level was 274 ± 208 pmol/l and decreased by −24.5 ± 68 (p = 0.07) and −15.0 ± 44 pmol/l (p = 0.10) after six weeks and six months, respectively. The drop in the MR-proANP level after six weeks and six months was significant in patients with elevated (≥214 pmol/l) baseline MR-proANP level (n = 15: −54.3 ± 78.0, $p < 0.01$ and −31.8 ± 45.4 pmol/l, p = 0.03, respectively) and those with reduced left ventricular ejection fraction (LVEF < 45%, n = 7: −87.4 ± 97.3, p = 0.02 and −60.3 ± 42.6 pmol/l, p = 0.01, respectively). Baseline NT-proBNP level (median 1054 pg/ml; IQR 621–1977 pg/ml), sodium, potassium, mean systolic or diastolic blood pressure did not change significantly in the mentioned patient groups.

Conclusions After LAA closure, MR-proANP level decreased significantly in patients with elevated baseline MR-proANP level or reduced LVEF, whereas NT-proBNP level remained unchanged, thereby altering the correlation coefficient between the two biomarkers. Our findings should be considered when using these biomarkers for diagnostic or prognostic evaluation in patients with interventional LAA closure.

Keywords LAA closure • Watchman device • MR proANP • NT proBNP • Natriuretic peptides

Introduction

The rates of stroke and mortality are increased in patients with atrial fibrillation [1]. The embolism of intracardiac thrombi is assumed to be the pathomechanism of the added risk for cerebrovascular events in these patients. A meta-analysis of 34 studies reported the left atrial appendage (LAA) as the location of the atrial thrombi in 90% of patients

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with non-valvular atrial fibrillation [2]. The interventional closure of LAA to prevent cardioembolic cerebrovascular events or peripheral embolism has become an alternative therapy strategy to oral anticoagulation in patients with non-valvular atrial fibrillation [3–5].

The contribution of the LAA contraction to the cardiac pump function is low or negligible, especially in the setting of atrial fibrillation. Instead, the LAA is thought to allow a neurohumoral response to haemodynamic overload. An increase in haemodynamic load results in enhanced secretion of both A-type natriuretic peptide (ANP) and B-type natriuretic peptide (BNP), known as ''stretch-secretion coupling" [6]. ANP is stored in small granules [7] and is secreted from both the left atrium and the left ventricle [8]. In contrast to ANP, regulation of BNP secretion occurs mainly at the level of gene expression [9]. The prohormones of ANP and BNP are cleaved upon secretion into the active molecules and their amino-terminal counterparts NT-proANP and NT-proBNP, respectively [10,11]. Assays using antibodies directed to the mid-regional portion of NT-proANP (MR-proANP) showed the most robust and reliable quantitative results [12]. Determination of BNP or NT-proBNP is widely used for the diagnosis and therapy control of heart failure [13–15]. Previous studies found that the addition of MR-proANP to NT-proBNP measurements improves the diagnostic accuracy in patients with acute heart failure [16,17]. Furthermore, it was demonstrated that MR-proANP is an independent predictor of prognosis in patients with chronic heart failure [18,19] and patients suffering from myocardial infarction [20] or an acute ischaemic stroke [21].

It has also been demonstrated that ANP plasma concentrations increase with distention of the LAA wall [22] and both MR-proANP and NT-proBNP levels correlate with left atrial dimensions and left atrial function indices [23,24]. Accordingly, the exclusion of the LAA from the blood circulation (as an important source of production and storage of natriuretic peptides) may lead to altered levels of MR-proANP and NT-proBNP.

We aimed to prospectively assess potential changes in MR-proANP and NT-proBNP levels and their clinical significance six weeks and six months after interventional closure of LAA.

Methods

Consecutive patients with non-valvular atrial fibrillation and indication for interventional LAA closure, who gave their informed consent, were enrolled in our study prior to the implantation procedure. All patients underwent a diagnostic evaluation on the day before, as well as six weeks and six months after a successful implantation procedure. The evaluation included blood sampling for routine laboratory tests and determination of MR-proANP, NT-proBNP, 12-lead and Holter electrocardiography (ECG), 24-hour blood pressure monitoring, a six-minute walk test, transthoracic and transoesophageal echocardiography (TTE and TEE), the assessment of bleeding or cerebrovascular events and drug history.

Natriuretic Peptides

The prohormone of ANP is a polypeptide of 126 amino acids and is cleaved upon secretion into the biologically active peptide ANP (aminoacids 99-126) and its N-terminal counterpart (NT-proANP, aminoacids 1-98) [9]. MR-proANP concentrations were quantified in serum samples (frozen immediately after centrifugation at −80 °C) using time-resolved amplified cryptate emission (MR-proANP, Brahms GmbH, Germany) on a fully automated immune analyzer (Kryptor, Brahms GmbH, Germany) with an intra-assay coefficient of variation (CV) below 3.5%, inter-assay CV below 6.5% and a lower limit of detection of 2.1 pmol/l, as described by the manufacturer. All measurements were performed using reagents of the same lot number to minimise assay variation.

Similarly, the precursor of BNP contains 108 aminoacids and processing releases an active 32-aminoacid molecule and its amino-terminal counterpart (NT-proBNP) [11]. A standard assay for measurement of NT-proBNP was used, as well (ECLIA, Elecsys proBNP II STAT, Roche Diagnostics, Germany).

WATCHMAN Occluder

The WATCHMAN™ Left Atrial Appendage Closure (LAAC) device (Boston Scientific, Marlborough, USA) is a self-expandable third generation device made of a nitinol alloy with a permeable polyethylene terephthalate (PET) membrane mounted on the atrial facing surface of the frame to prevent thromboembolism and support device endothelialisation. The WATCHMAN™ LAAC device is available in diameters of 21, 24, 27, 30 and 33 mm. The WATCHMAN LAAC devices were implanted in the catheterisation laboratory as described elsewhere [26]. All patients received a dual antiplatelet therapy, which was limited to acetylsalicylic acid monotherapy 100 mg per day after exclusion of device thrombi at the scheduled TEE control after six months, according to our institutional routine practice.

The study was approved by the ethics committee of the Otto-von-Guericke University Magdeburg on 4 May, 2015 (approval number 10/15).

Statistical Analysis

Categorical parameters are presented as counts and percentages and were compared by chi-square test. Continuous variables are presented as mean values ± SD and were compared using the matched-pairs t-test after controlling for normal distribution of the original variables and their differences. Analysis of normality was performed with the Kolmogorov–Smirnov test. Non-normally distributed data were compared using the non-parametric Mann–Whitney U-test. A multivariable analysis was performed to assess

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