SELECTED PREDICTIVE FACTORS OF NEW-ONSET ATRIAL FIBRILLATION IN PATIENTS WITH HEART FAILURE

Wybrane czynniki predykcyjne migotania przedsionków u pacjentów z niewydolnością serca

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Abstract

Atrial fibrillation, which is one of the most commonly diagnosed arrhythmias in adults, is associated with high morbidity and mortality. Atrial fibrillation is also the most common arrhythmia in patients with heart failure, and it has been shown to increase the risk of death, heart failure-related hospitalization, and stroke or transient ischemic attack. Considering these clinical and therapeutic implications, it seems advisable to assess patients for risk factors of atrial fibrillation. The purpose of this study was to present the predictors of new-onset atrial fibrillation particularly in patients with heart failure.

Streszczenie

Migotanie przedsionków, będące jednym z najczęściej rozpoznawanych zaburzeń rytmu serca u osób dorosłych, wiąże się z wysoką zachorowalnością i śmiertelnością. Stanowi ono również najczęstszą arytmię u chorych z niewydolnością serca i wykazano, że zwiększa ryzyko zgonu, hospitalizacji związanej z niewydolnością serca oraz udaru mózgu i przemijającego ataku niedokrwiennego. Biorąc pod uwagę te implikacje kliniczne i terapeutyczne, wydaje się uzasadnionym, aby oceniać pacjentów pod kątem czynników ryzyka wystąpienia migotania przedsionków. Celem niniejszej pracy było przedstawienie czynników predykcyjnych wystąpienia migotania przedsionków u pacjentów z niewydolnością serca.

Keywords: heart failure, atrial fibrillation, new-onset atrial fibrillation

Słowa kluczowe: niewydolność serca, migotanie przedsionków, migotanie przedsionków de novo

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Introduction

Atrial fibrillation (AF), which is the most common arrhythmia in adults, is associated with high morbidity and mortality [1]. The prevalence of AF in the general population is 2–4%, with the proportion expected to rise two- to threefold [2]. Due to the close alignment of pathophysiology and risk factors of AF and heart failure (HF), those conditions coexist in a large percentage of patients [3, 4]. Regarding the increasing prevalence of AF and HF, both conditions generate significant costs to healthcare services globally [5, 6]. Moreover, patients presenting with concomitant AF and HF have a significantly worse prognosis [7]. New-onset AF (NOAF) in patients diagnosed with HF considerably affects their prognosis, as it indicates a more advanced condition, with worse cardiac function [8]. There is abundant evidence suggesting that AF increases the risk of death, HF-related hospitalization and stroke or transient ischemic attack [9–12]. These clinical and therapeutic implications make it advisable to search for novel factors that predispose to AF in patients with HF. The various hemodynamic, neuroendocrine, and inflammatory changes associated with HF result in both structural and functional changes to the left atrium, which contributes to the development of AF. Such changes, known as left atrial (LA) remodeling, alter LA cardiomyocytes and increase noncollagen deposits in the extracellular matrix, which leads to LA dilatation and fibrosis, and subsequent LA dysfunction and electrical conduction delay [13]. These remodeling processes are referred to as atrial cardiomyopathy; with risk factors including old age, obesity, diabetes mellitus, hypertension, and obstructive sleep apnea. Atrial cardiomyopathy not only precedes the development of AF but also, due to blood stasis and endothelial dysfunction, forms a prothrombotic milieu, which may lead to a stroke [14]. Figure shows a diagram illustrating the mechanism of atrial fibrillation development in heart failure.
Clinical risk factors and biochemical parameters

The main driving force behind the growing incidence of AF is population aging, with such conditions as hypertension, diabetes mellitus, HF, coronary artery disease, chronic kidney disease, obesity, and obstructive sleep apnea, also playing a role. The risk of developing AF is lower among women and non-Caucasians [15, 16]. Considering the aging population, the increasing co-occurrence of AF and HF has been highlighted, as these two conditions have similar underlying pathological mechanisms, which, combined, adversely affect the overall risk of cardiovascular events [17]. Based on a large, multinational, European Society of Cardiology registry of patients with HF, AF has been associated with older age, higher New York Heart Association (NYHA) class, history of HF-related hospitalizations, increased heart rate at rest, and more significant symptoms of congestion [18]. The prevalence of AF in the evaluated population was 27% in patients with HF with reduced ejection fraction (HFrEF), 29% in patients with HF with mildly reduced ejection fraction (HFrEFm), and 39% in patients with HF with preserved ejection fraction (HFrEPf). AF rates were associated with age, reaching 50% in over 80-year-olds. Patients with AF were more likely to have no-ischemic HF, history of stroke, and more advanced mitral regurgitation than individuals with sinus rhythm. Moreover, in comparison with sinus rhythm, AF was associated with higher N-terminal prohormone of brain natriuretic peptide (NTproBNP) levels in each HF phenotype subgroup. The mentioned study also showed higher cardiovascular risk and mortality in people with AF irrespective of their left ventricular ejection fraction (LVEF). Pellicori et al. [19] demonstrated that despite having higher LVEF, patients with HF and AF presented with more severe symptoms, higher NTproBNP levels, worse kidney function, and higher rates of loop diuretic treatment than people with sinus rhythm. The study had been conducted in a group of 3,570 patients with HF, 1,164 (33%) of whom had AF at baseline. In this group, HFrEF was more common than HFrEF (40% vs. 26%, p <0.001). Of patients in sinus rhythm, 1,372 had HFrEF and 1,034 had HFrEPf. The incidence of AF at one year was similar (3%) for each HF phenotype (p = 0.73). Age, male sex, history of paroxysmal AF, and higher NTproBNP levels were found to be independent predictors of incident AF during a median follow-up of 1,574 days.

Coronary artery disease, low systolic and diastolic blood pressure, and increased creatinine and bilirubin levels were other parameters associated with NOAF in the study mentioned above.

A 2018 Chinese study also assessing the association between AF and HF with different categories of ejection fraction showed age, coronary artery disease, heart rate, and both LA and left ventricular end-diastolic diameters to be associated with NOAF independently of LVEF [12]. The 405 patients with HF included in that study were stratified into three subgroups based on their LVEF: HFrEF (n = 109, 26.9%), HFrEFm (n = 94, 23.2%), and HFrEPf (n = 202, 49.8%). Patients with HFrEPf and HFrEFm were found to have a higher prevalence of AF than those with HFrEF. Moreover, AF was associated with a higher risk of death and HF-related hospitalization.

Electrolyte imbalance is usually linked to an increased risk of NOAF. Hypokalemia and hyponatremia are the most common electrolyte abnormalities encountered in clinical practice, especially in patients with HF. In their studies investigating the relationship between potassium concentration and the risk of atrial arrhythmias, Auer et al. [20] have shown that lower serum potassium concentrations increase the perioperative risk of AF. Krijthe et al. [21] have also reported a link between increased risk of AF and hypokalemia (<3.50 mmol/l).

A Turkish study demonstrated hyponatremia (apart from other well-known risk factors) to be significantly and independently associated with AF (odds ratio [OR] = 2.457; 95% confidence interval [CI] = 1.586–3.806, p <0.001) [22]. Lu et al. [23] revealed that low sodium and low potassium-induced slowing of sinoatrial node beating rate and increased pulmonary veins burst firing might contribute to the higher occurrence of AF during hyponatremia or hypokalemia.

Echocardiographic predictors of AF

LA enlargement and dysfunction may be treated as predictors of AF. Furthermore, AF itself additionally contrib-
utes to the worsening of these two parameters. Recent studies have assessed the use of novel echocardiographic techniques, such as speckle-tracking echocardiography, in predicting AF in patients with HF. Park et al. [24] evaluated the prognostic value of reduced peak atrial longitudinal strain (PALS) in patients with HF. The study subjects were stratified by quartiles of PALS, and then further subdivided by LVEF values and history of AF. The primary endpoints were overall mortality and HF-related hospitalization. The incidence of NOAF over a five-year follow-up was shown to be higher in patients with reduced PALS (≤18%) (18.2% vs. 12.7%; p < 0.001) across all HF phenotypes. Having adjusted for covariates, the authors identified five other predictors of NOAF: age >70 years, hypertension, LA volume index (LAVI) (>40 mL/m²), HFrEF, and no beta-blocker prescription at discharge. Another study on the topic was conducted by Malagoli et al. [25], who assessed the predictive value of PALS in a group of patients with HFrEF, with the study population stratified into HFrEF quartiles. First-quartile patients (with the lowest PALS values) were shown to have the highest risk of NOAF. This subgroup was also characterized by worse renal function, higher NYHA class, higher brain natriuretic peptide levels, greater LA volume, lower LVEF, and worse left ventricular diastolic function than fourth-quartile patients (with the highest PALS values). Additionally, PALS assessment via speckle-tracking echocardiography was shown to be an independent predictor of cardiovas-

Table. Proposed predictors of NOAF in patients with heart failure

<table>
<thead>
<tr>
<th>Publication</th>
<th>Study population</th>
<th>Evaluated clinical parameters</th>
<th>Evaluated biochemical parameters</th>
<th>Evaluated echocardiographic parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xu et al. [12]</td>
<td>HFrEF HFrEF HFrEF</td>
<td>Age: 77 ± 8 in HFrEF; 71 ± 10 in HFrEF; 69 ± 9 in HFrEF</td>
<td>BNP Cholesterol Triglycerides</td>
<td>LA diameter LVEDd</td>
</tr>
<tr>
<td>Zafrir et al. [18]</td>
<td>HFrEF HFrEF HFrEF</td>
<td>Age: 74.3 ± 11.5 in HFrEF; 70.4 ± 12.2 in HFrEF; 68.5 ± 11.2 in HFrEF</td>
<td>NTproBNP: 2,500 pg/mL in HFrEF; 2,615 pg/mL in HFrEF; 3,320 pg/mL in HFrEF</td>
<td>Moderate-to-severe mitral regurgitation</td>
</tr>
<tr>
<td>Pellicori et al. [19]</td>
<td>LVEF &gt;45% vs. LVEF &lt;45%</td>
<td>Age 76 years (70–82); Male sex; History of paroxysmal AF; Ischemic heart disease</td>
<td>NTproBNP 1.936 (1.057–3.607) ng/L; Creatinine 104 (86–130) Umol/L; Bilirubin 16 (13–21) Umol/L</td>
<td>LA diameter 4.7 cm</td>
</tr>
<tr>
<td>Cavusoglu et al. [22]</td>
<td>HFrEF</td>
<td>(-)</td>
<td>Sodium &lt;135 mmol/L</td>
<td>(-)</td>
</tr>
<tr>
<td>Park et al. [24]</td>
<td>HFrEF HFrEF HFrEF</td>
<td>Age &gt;70 years</td>
<td>(-)</td>
<td>↓PALS &lt; 18% ↓LAVI &gt; 40 mL/m²</td>
</tr>
<tr>
<td>Malagoli et al. [25]</td>
<td>HFrEF</td>
<td>(-)</td>
<td>(-)</td>
<td>↑PALS LAVI</td>
</tr>
<tr>
<td>Choi et al. [26]</td>
<td>Dual-chamber pacemaker or ICD</td>
<td>(-)</td>
<td>(-)</td>
<td>GLAS &lt; 37.4%</td>
</tr>
<tr>
<td>Kosmala et al. [27]</td>
<td>Dual-chamber pacemaker</td>
<td>(-)</td>
<td>(-)</td>
<td>↓LA strain ↓LA volume ↓LVED</td>
</tr>
</tbody>
</table>

Abbreviations: BNP – brain natriuretic peptide; GLAS – global left atrial strain; HF – heart failure; HFrEF – heart failure with mildly reduced ejection fraction; HFrEF – heart failure with preserved ejection fraction; HFrEF – heart failure with reduced ejection fraction; ICD – implantable cardioverter-defibrillator; LA – left atrial; LAVI – left atrial volume index; LVEDD – left ventricular end-diastolic diameter; LVEF – left ventricular ejection fraction; NTproBNP – N-terminal prohormone of brain natriuretic peptide; NYHA – New York Heart Association; PALS – peak atrial longitudinal strain; SBP – systolic blood pressure.
cular events. The lowest PALS values were associated with shorter cardiovascular event-free survival than the highest PALS values. A South Korean study [26] assessed whether local LA strain (GLAS) might be a predictor of AF. The retrospective study included 127 patients with a cardiac implantable electronic device (either a dual-chamber pacemaker or implantable cardioverter-defibrillator). The development of silent AF (SAF) was adopted as the primary endpoint, while death, stroke, and HF-related hospitalization constituted the composite secondary endpoints. The main endpoint was reached in 13.4% of the study population (n = 17). Patients with SAF had significantly higher LAVI and lower GLAS values. After adjusting for age, LVEF and LAVI, GLAS values of <37.4% were shown to be a single predictor of SAF (HR 7.382; 95% CI 1.64–33.27; p = 0.009). GLAS values of <37.4% were also independently associated with the composite secondary endpoint after adjustment for the CHA2DS2-VASc score (HR 5.43; 95% CI 1.14–25.87; p = 0.034). A study by Kosmala et al. [27] also demonstrated that, in addition to LA volume and other clinical parameters, speckle-tracking echocardiography might help assess the risk of NOAF. A total of 146 patients with negative AF history who were treated with dual-chamber pacing were included. Over a two-year follow-up, NOAF was observed in 29 patients (20%), two of whom developed permanent AF. NOAF was associated with higher systolic blood pressure (p = 0.01), lower LVEF (p = 0.03), lower LA strain during atrial contraction (p <0.001), and higher LA volume (p <0.003). A study conducted at a Warsaw center showed that lower LA reservoir strain in patients with AF undergoing radiofrequency catheter ablation was associated with older age, female sex, LA enlargement, and worse left ventricular diastolic function [28]. Moreover, lower LA reservoir strain and lower LA strain during atrial contraction were linked to higher LA pressure values (measured directly), which indicates that these novel echocardiographic parameters may be useful in assessing LA dysfunction.

The proposed selected predictive factors of NOAF in patients with heart failure are summarized in table.

**Carotid artery atherosclerosis**

An interesting parameter studied in the context of the risk of developing NOAF, though not assessed directly in heart failure patients, is carotid intima-media thickness (cIMT). Atherosclerosis is an important etiologic factor predisposing to the development of HF, mainly located in the intima of many medium-sized arteries. Non-invasive imaging techniques for assessing anatomic or functional manifestations of atherosclerosis include carotid artery ultrasonography. Carotid intima-media thickness is a less recognized parameter considered to be a predictor of AF (to a similar extent as hypertension and HF). The parameter has been associated with subclinical atherosclerosis, and its increase helps predict the risk of cardiovascular events. Studies have shown increased cIMT to be an independent predictor of AF. Three studies (Rotterdam [29], Bruneck [30], and Malmö [31]) demonstrated that ultrasound-measured cIMT predicted the risk of NOAF. Willett et al. [30] reported that detectable carotid artery atherosclerosis preceded the development of AF in 8 out of 10 patients, and conversely, atherosclerosis-free individuals were unlikely to develop AF. A recent study on lone AF (i.e., AF in non-elderly patients without underyling heart disease or other risk factors) showed this arhythmia to be significantly associated with increased cIMT and increased arterial stiffness [32]. The study population comprised euthyroid, <60-year-olds without diabetes mellitus, hypertension, coronary artery disease, HF, valvular disease, or cardiomyopathy. Increased cIMT and increased arterial stiffness were also associated with sustained (persistent or permanent) AF. The authors proposed that early structural and functional arterial changes might contribute to AF development. A 2015 Italian study showed a strong pathophysiological link between atherosclerosis and the development of AF. The cut-off value for increased cIMT was adopted at 0.9 mm, with values above 1.5 mm defined as atherosclerotic plaque. Out of the 673 patients with AF (paroxysmal [38%], persistent [18%], or permanent [44%]) included in the study, 71% had a cIMT of >0.9 mm. In comparison with individuals with normal cIMT values, patients with increased cIMT were older; had higher rates of previous hypertension, diabetes mellitus, or stroke; presented with persistent or permanent AF; and had CHA2DS2-VASc scores of >2. Increased cIMT predicts not only NOAF but also the progression of paroxysmal AF to persistent/permanent AF [33]. The results of the clinical studies mentioned above seem to indicate that carotid artery atherosclerosis and cIMT are closely associated with coronary artery atherosclerosis and microvascular injury, which may lead to impaired LA perfusion and ischemia and, consequently, fibrosis and AF. Moreover, aortic and cardiac remodeling may be a common denominator linking the potentially adverse effects of age, hypertension, and carotid atherosclerosis. Therefore, it seems that cIMT assessment should be considered in predicting AF, irrespective of the established indicators of AF risk.

**Conclusions**

In summary, there are many factors that may increase the risk of NOAF in patients with HF, which aggravates the underlying disease in a population whose survival rates are already significantly lower than in the general population. Early intervention and control of modifiable risk factors seem to decrease the incidence of NOAF, thus improving the prognosis in patients with HF. Measurement of the AF predictors discussed in this paper in patients with HF may help identify those at the highest risk of NOAF and improve already known tools for risk assessment. The relative paucity of data on the predictors of NOAF discussed in this paper and the considerable effect of AF on the prognosis in patients with HF warrant a continued search for novel NOAF predictors and validation of the already proposed ones. More accurate prediction of NOAF would most likely help in earlier diagnosis and more effective preventive measures in this population.

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