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Biomarkers in atrial fibrillation

The most common arrhythmias are atrial fibrillations with a high impact on patient's quality of life and the risk of adverse events. The goal is to better identify patients at risk for atrial fibrillation. With increasing knowledge concerning the genesis of the disease new and established biomarkers are in the focus for risk prediction models and, simultaneously, new therapy targets emerge.

Introduction

Among all arrhythmias atrial fibrillation (AF) is by far the most commonly seen by clinicians. The prevalence in western countries is around 2% and will double the next two decades [1]. AF is associated with reduced quality of life and an increased risk of stroke and death [2]. The pathophysiology of arrhythmias is still not fully elucidated and treatment success rates are limited [3, 4]. It was shown that sustained atrial fibrillation itself leads to electrical remodeling with fibrosis in atria due to fibroblast activation [3]. Predisposing factors for atrial fibrillation are heart failure, hypertension, history of myocardial infarction, diabetes mellitus, obesity [5], chronic kidney disease [6] and older age [7, 8, 9, 10] (Table 1). Over the last ten years, patient management strategies remained very similar, but catheter ablation use and oral anticoagulant medications increased and reduced thromboembolic events, while all-cause and cardiovascular mortality did not improve [10]. To identify patients at risk for arrhythmias ECG and imaging techniques are available, but resource-intensive. Thus, biomarkers are under investigation to support diagnosis and risk stratification and to better clarify the underlying pathomechanism, giving the potential to find targeted therapy strategies.

Pathophysiology of arrhythmias

AF has a multifactorial etiology with many different stressors that may lead to atrial hemodynamic stress, thus increasing various mediators promoting metabolic, electrical and structural remodeling, which predispose to AF [9, 11]. This is a longer process with different stages from early undetectable states over preclinical to manifest states. Inflammatory mechanisms and oxidant stress may have an important role in disease progression, and an association was shown between higher interleukin-6 (IL-6) or C-reactive protein (CRP) levels and increased left atrial diameters [12]. Also atrial stretch and remodeling promote the occurrence of AF [13].

Biomarkers

Classical cardiac biomarkers

In the Black Country Atrial Fibrillation Registry (BBC-AF; UK) more than 700 patients without known AF were screened by a seven-days ambulatory ECG monitoring [7]. Among forty investigated biomarkers and clinical parameters such as male sex, older age and higher body mass index, B-type natriuretic peptide (BNP) with an odds ratio of 1.293 and fibroblast growth factor 23 (FGF-23) with an odds ratio of 1.667 were the most significant ones associated with AF. BNP is the established heart failure biomarker synthesized by cardiomyocytes upon increased pressure and stretch. On the other hand, FGF-23 is a paracrine hormone promoting remodeling and cardiac hypertrophy [14]. BNP predicted incident AF during longtime follow-up and improved risk stratification based on established clinical risk markers, whereas CRP achieved only small improvements [15]. N-terminal proBNP (NT-proBNP) was the most powerful predictor of incident AF among other markers such as high-sensitivity cardiac troponin (hs-cTn), growth differentiation factor-15 (GDF-15), cystatin C and CRP in two large community-based cohorts with a follow-up period of more than ten years [16]. However, a combined biomarker approach including BNP, CRP and estimated glomerular filtration rate was incrementally additive to clinical risk factors for the prediction of arrhythmia recurrence after catheter ablation in patients with AF [17].

In healthy subjects without apparent cardiovascular diseases hs-cTnT concentrations higher than 11 ng/L during a health checkup revealed a 4.8-fold higher risk of AF after adjusting for confounding factors [18]. Similarly, elevated hs-cTnT levels above the cut-off of 14 ng/L were associated with a 1.78-fold higher risk for AF than undetectable levels in the Atherosclerosis Risk in Communities (ARIC) study [19]. Moreover, in the long term follow-up of 11.2 years minor hs-cTnT elevations at baseline were significant predictors of AF beyond traditional risk factors and biomarkers of inflammation or hemodynamic strain in the large cohort of the Cardiovascular Health Study (CHS) [20]. Furthermore, elevated hs-cTnT concentrations had a 13.4-fold higher risk of mortality in patients with AF [21]. Interestingly, a recent meta-analysis found a significant association of cTnT with incident AF occurrence and AF recurrence risk after radio-frequency ablation as well as stroke or major bleeding [22]. However, this was not observed for cTnI.

Inflammatory biomarkers

Persistent inflammation with increased interleukin 6 (IL-6) concentrations were linked to supraventricular arrhythmias [6]. In more than 3900 patients participating in the Chronic Renal Insufficiency Cohort (CRIC) Study IL-6, but not CRP, was significantly associated with AF, which was confirmed by ECG. Further, patients with IL-6 in the highest tertile showed a 2-fold higher risk of new-onset AF compared to those within the lowest tertile [6]. Concerning CRP, a single high CRP concentration at baseline was not useful to predict new-onset AF after adjustment for confounding factors in a population-based cohort of nearly 4500 patients [23]. However, persistent elevations of CRP above 1 mg/L during the 140 months follow-up were associated with a 2-fold risk of AF, suggesting a link between chronic inflammation and AF.

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Biomarker bei Vorhofflimmern

Vorhofflimmern ist die häufigste Erkrankung unter den Arrhythmien und bedeutet für Patienten eine beträchtliche Einbusse der Lebensqualität mit dem Risiko eines Hirninfarkts oder erhöhter Sterblichkeit. Mehrere prädisponierende Umstände, darunter auch Herzinsuffizienz oder Herzinfarkt, tragen zur Entstehung des Vorhofflimmerns bei. Um Patienten mit erhöhtem Risiko frühzeitig zu erkennen, wird vermehrt nach geeigneten Biomarkern gesucht. Die etablierten Herzinsuffizienz- und Herzinfarktmarker BNP/NT-proBNP und kardiale Troponine konnten in grösseren Studien das Risiko eines neu auftretenden Vorhofflimmerns besser abschätzen als klinische Parameter oder andere Biomarker. Entzündungsvorgänge und Fibrose scheinen bei der Genese des Vorhofflimmerns eine Rolle zu spielen. Entzündungsmarker wie Interleukin-6 sowie die neueren Fibrosemarker zeigten vielversprechende Ergebnisse. Ein bedeutender Stellenwert wird auch die Integration der Biomarker in die Berechnungen von Risikoscores erlangen. Darüber hinaus erlaubt die bessere Kenntnis der Pathophysiologie neue Therapiekonzepte zu entwickeln mit Angriffspunkten in Entzündung- und Fibroseprozessen.

Fibrosis biomarkers Gal-3, GDF-15 and sST2

The pro-fibrotic protein galectin-3 (Gal-3), a-galactoside-binding lectin, was shown to be activated by rapid electrical stimulation in experimental cell culture or animal models [24]. Such profibrotic processes were attenuated by a Gal-3 inhibitor in different studies, which underlines the role of Gal-3 in fibrosis and might serve as a new potential therapeutic target [24, 25, 26]. Furthermore, Gal-3 concentrations were higher in coronary sinus blood samples and left atrial tissues of patients with AF undergoing mitral valve surgery than of patients without AF [24]. Gal-3 concentrations increased stepwise from control subjects to patients with paroxysmal and persistent AF [27, 28, 29]. Nevertheless, the relation between Gal-3 and AF was diminished after the adjustment for traditional risk factors in the Framingham Offspring cohort [28]. Recently, Tang et al. demonstrated that patients with persistent or permanent AF had significantly worse left atrial appendage morphology and function as assessed by transesophageal echocardiography than patients with paroxysmal AF (29). These patients also showed significantly higher Gal-3 levels and were more likely to suffer from left atrial appendage thrombi. Moreover, Gal-3 was a significant independent predictor of the presence of thrombi beside the CHA2DS2VASc score.

Growth differentiation factor 15 (GDF-15) is a member of the transforming growth factor-cytokine superfamily that is activated upon cellular ischemia and mechanical or oxidative stress. Baseline GDF-15 concentrations were significantly higher in patients with paroxysmal AF compared with controls and displayed an independent association with the disease [30]. The strength of GDF-15 seems to be in the risk assessment of major bleedings in patients with AF [31, 32] or acute coronary syndrome [33]. GDF-15 was shown to be of prognostic value for mortality and major bleedings in anticoagulated patients with AF [32]. This finding was independent from clinical characteristics and biomarkers such as hs-cTnI and NT-proBNP [31] or inflammation (CRP, IL-6) and coagulation markers (D-dimer). Additionally, GDF-15 improved the value of risk scores like HAS-BLED, CHA2DS2VASc [31] and ORBIT [32].

A further fibrosis marker is soluble suppression of tumorigenicity (sST2), which was shown to prevent the binding of interleukin-33 to cardiomyocytes, so that cardioprotective effects cannot be exerted anymore [34, 35]. High concentrations of sST2 were demonstrated to be useful for risk stratification in patients after acute myocardial infarction to identify those who are at high risk to develop adverse cardiovascular events including death. The value as a predictor for new-onset AF was studied in more than 1,700 patients with coronary artery disease of whom approximately 8% developed AF within 5.7 years. Although hs-cTnT, BNP, hs-CRP and sST2 were all significantly associated with the occurrence of AF, only hs-CRP and sST2 remained their significant predictive power in a multivariate model [36]. However, these biomarkers did not markedly improve the risk model including all clinical risk markers, suggesting a limited clinical applicability in coronary artery disease patients. Further, in the Framingham Heart Study only hs-cTnI was significantly associated with AF. Nevertheless, none of the evaluated biomarkers including sST2, GDF-15 or hs-cTnI improved the risk prediction of incident AF beyond the known AF risk factors [37].

Table 1: Potential risk factors for atrial fibrillation

- Heart Failure
- Hypertension
- History of myocardial infarction
- Type 2 diabetes mellitus
- Metabolic syndrome
- Obesity
- Dyslipidemia
- Chronic kidney disease
- Obstructive sleep apnea
- Older age
- Alcohol consumption
- Excessive exercise or physical activity

Conclusion

Since AF has a high morbidity and mortality risk and is often only recognized after a complication such as stroke, a biomarker that could identify patients at high risk in an early disease state would be of great value. There are promising results for different biomarkers, but the overall improvement of risk prediction models has to be investigated further. Nevertheless, the integration of biomarkers into risk prediction scores may probably play an increasingly important role and help to better stratify therapies. Due to the better understanding of the pathophysiology of AF, which is associated with inflammatory and fibrotic processes, new therapeutic options may arise and target these specific pathways.

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References

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