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Biomarkers in electrophysiology: role in arrhythmias and resynchronization therapy

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Abstract

Circulating biomarkers related to inflammation, neurohormones, myocardial stress, and necrosis have been associated with commonly encountered arrhythmic disorders such as atrial fibrillation (AF) and more malignant processes including ventricular arrhythmias (VA) and sudden cardiac death (SCD). Both direct and indirect biomarkers implicated in the heart failure cascade have potential prognostic value in patients undergoing cardiac resynchronization therapy (CRT). This review will focus on the role of biomarkers in AF, history of SCD, and CRT with an emphasis to improve clinical risk assessment for arrhythmias and patient selection for device therapy. Notably, information obtained from biomarkers may supplement traditional diagnostic and imaging techniques, thus providing an additional benefit in the management of patients.

Keywords

Biomarkers; Arrhythmias; Cardiac resynchronization therapy

1 Introduction

Heart failure (HF) and cardiac arrhythmias are a leading cause of cardiovascular morbidity and mortality. While developments in device therapy, pharmacology, and ablation techniques have been the focus of recent scientific research in the field of electrophysiology,

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the role of biologic markers (biomarkers) in this arena is still in its infancy. This review will focus on the diagnostic as well as prognostic information provided by biomarkers in atrial fibrillation (AF), sudden cardiac death (SCD), and cardiac resynchronization therapy (CRT). In 2001, a National Institute of Health committee defined a biomarker as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” [1]. This could be a variety of clinical tests involving blood or urine, imaging studies, genetic variants, or tissue biopsies. For the purpose of our review, we will refer to biomarkers as substances measured in the blood, plasma, or urine. Notably, a biomarker can be useful in clinical practice only if it satisfies certain criteria. It has to be accurate and reproducible with a high specificity and sensitivity. It should also aid in clinical decision making by standardizing the measured level [2–4]. Although no formal classification for biomarkers exists they can be broadly divided into the following categories (Table 1).

2 Biomarkers in atrial fibrillation

Atrial arrhythmias constitute a major burden of cardiovascular morbidity and mortality. AF is a common arrhythmia in clinical practice affecting 0.4–1 % of the general population [5]. The incidence of AF increases with age, and it confers a 4- to 5-fold increase in the risk of stroke [6] and is an independent predictor of mortality [7]. Recurrence rates are high despite recent advances in antiarrhythmic drug therapy and ablation techniques [8]. The high morbidity and mortality associated with these conditions make it imperative to identify individuals at risk of developing these arrhythmias and their complications. Biomarkers may serve as a useful tool for risk stratification and early diagnosis.

2.1 Inflammatory biomarkers

There has been a substantial interest in the role of inflammation in AF. Several mechanisms have been proposed, inclusive of inciting the focal triggers, as well as structural changes that may promote reentry and consequently AF. Previous experimental work to support this [9] has demonstrated lymphocytic infiltrates with myocyte necrosis and fibrosis in atrial biopsies of patients with lone AF (defined as AF without the presence of underlying organic heart disease or hyperthyroidism). Among the biopsy specimens taken from the interatrial septum, 66 % had evidence of acute myocarditis, 17 % had a noninflammatory cardiomyopathic process, and the remainder 17 % had evidence of patchy fibrosis. Likewise, histology from atrial biopsies in animal models with AF and mitral regurgitation (MR) has shown the presence of chronic inflammation [10]. Several clinical studies have confirmed this relation between proinflammatory markers and AF, especially via inflammatory responses that are exacerbated in postoperative cardiac patients who frequently develop AF [11, 12]. In addition, increased levels of C-reactive protein (CRP) and interleukin 6 (IL-6) are seen in patients with paroxysmal or chronic AF [13, 14]. Other inflammatory cytokines such as IL-1, IL-2, IL-8, tumor necrosis factor- α (TNF- α), monocyte chemoattractant protein-1 (MCP-1), and serum amyloid protein A (SAA) activate the immune system by stimulating production of similar cytokines and recruiting lymphocytes and neutrophils [15]. A study by Cheng et al. [16] established that, among the inflammatory biomarkers, IL-6, high sensitivity CRP (hs-CRP), TNF- α , and SAA were significantly elevated in the presence

of AF. The clinical and therapeutic implications of these biomarkers are fairly limited. The presence of inflammation may impact outcome, as elevated CRP levels negatively correlate to the success of cardioversion (CV) in patients with paroxysmal or persistent AF [17, 18]. There is, however, a paucity of information regarding the potential value of treating inflammation guided by these markers to lower the AF burden [15].

Myocardial oxidative stress is also associated with inflammation, thereby playing a role in AF [19]. Higher levels of derivatives of reactive oxygen metabolites (DROM) were seen in persistent AF when compared to paroxysmal AF and noted to be predictive of AF recurrence following catheter ablation [20]. Myeloperoxidase (MPO), a heme peroxidase stored in neutrophils and released during their activation, reacts with various oxidizable molecules resulting in the production of reactive oxygen species. The profibrotic properties of MPO and its role in the pathogenesis of AF have been demonstrated [21]. This study reported elevated plasma levels of MPO along with its increased deposition in atrial tissue in patients with paroxysmal AF. Increased plasma levels of MPO were similarly associated with early recurrence of AF following AF ablation [22].

2.2 Renin–angiotensin–aldosterone system and others

The role of the renin–angiotensin–aldosterone system (RAAS) and its association to cardiac arrhythmias has been well investigated. The mechanisms postulated is an increase in cardiac fibrosis, hypertrophy, and collagen synthesis in cardiac tissue [23] leading to a disruption in the conduction pathways along with repolarization abnormalities. It has also been hypothesized that the RAAS system can induce oxidative stress and modulate membrane ion channels leading to proarrhythmic effects [24]. On comparing atrial tissue biopsies (from patient undergoing surgery) of patients in AF to patients in normal sinus rhythm (NSR), there was an up-regulation of angiotensin II receptors [25] and angiotensin-converting enzyme (ACE) levels [26]. The angiotensin II type 2 receptor was upregulated during chronic AF by 246 % ($P=NS$) and during paroxysmal AF by 505 % ($P<0.01$), while ACE levels were increased by 3-fold when compared to matched controls in sinus rhythm. Clinical studies have also suggested that RAAS blockade with ACE inhibitors (ACE-I) or ARB may reduce the recurrence of AF. Yin and colleagues [27] demonstrated that the addition of an ACE-I ($P=0.04$, log rank test) or ARB ($P=0.006$, log rank test) to Amiodarone resulted in a decreased recurrence of AF when compared to Amiodarone only. This clinically significant effect of ACE-I and ARB could be attributed to the reversal of the AF-induced structural and electrical remodeling of the atrium. The Trandolapril Cardiac Evaluation (TRACE) study also showed a clinically significant reduction in the incidence of atrial fibrillation in patients with left ventricular dysfunction treated with Trandolapril (long acting ACE inhibitor) after an acute myocardial infarction (MI) (RR, 0.45; 95 % CI, 0.26–0.76; $P<0.01$) [28]. Furthermore, the Losartan Intervention for Endpoint Reduction (LIFE) study randomized 8851 hypertensive patients with no history of AF and evidence of left ventricular (LV) hypertrophy on ECG to Losartan only or Atenolol only arm. Development of new onset AF was assessed over a period of 4.8 ± 1 years. Patients in the Losartan arm compared to the Atenolol arm were less likely to develop AF (6.8 vs. 10.1 per 1000 person-years; relative risk, 0.67; 95 % CI, 0.55–0.83; $p<0.001$) along with the trend for longer maintenance of NSR (1809 vs. 1709 days, $P=0.057$). Among the patients who developed

new onset AF, the risk of development of stroke was lower in the Losartan arm compared to the Atenolol arm ($n=19$ vs. 38 ; HR, 0.49 ; 95 % CI, $0.29-0.86$; $P=0.01$) [29].

Copeptin is another neurohormone that is synthesized along with Vasopressin. It is the C-terminal portion of provasopressin derived from pre-provasopressin. It is a measure of plasma levels of vasopressin and is increased in any condition that results in decreased renal perfusion [30]. Copeptin levels are elevated in decompensated HF and acute MI [30], but recent studies did not show a predictive value for new onset AF [31] or a first recurrence of AF [32].

2.3 Biomarkers of myocardial wall stress

There are several biomarkers that are released as a result of atrial or ventricular myocardial wall stress. The most widely studied among this group of biomarkers is the natriuretic peptide system. These are several neurohormones that play an important role in the regulation of the cardiovascular, renal, and central nervous systems [33]. B-type natriuretic peptide (BNP) has been extensively studied in HF [34], but the understanding of its role in AF is still evolving. AF can lead to atrial wall stress by inducing fast heart rates and diastolic dysfunction, thereby causing increased levels of natriuretic peptides.

BNP is synthesized primarily in the ventricular myocardium with additional production in the brain and the atrial myocardium. Its release from the ventricles is modulated by the myocardial stretch receptors. The precursor protein pro-BNP is cleaved to form BNP and an amino terminal fragment called N-terminal pro-BNP (NT pro-BNP). Both these molecules circulate in the plasma and are measured by a number of commercially available assays [35].

BNP levels are typically elevated in patients with HF. However, multiple studies have demonstrated elevation of BNP in patients with AF without underlying HF or structural abnormalities of the heart [36, 37]. In a community-based sample of the Framingham Heart Study, a 1 standard deviation (SD) increase in BNP was associated with a 66 % increase in the risk of AF ($P<0.001$) [38]. Data from the Cardiovascular Health Study following 5445 elderly patients in the community over a median follow-up period of 10 years revealed that NT pro-BNP was highly predictive of incident AF with a multivariate adjusted HR of 4.0 (95 % confidence interval (CI) $3.2-5.0$; $P<0.001$) [39]. Thus, elevated levels of biomarkers of myocardial wall stress can serve as independent predictors for the risk of development of AF in patients with or without HF.

Some less commonly measured biomarkers of increased atrial wall stress and neurohormonal activation can also be potentially useful. Among them, midregional proatrial natriuretic peptide (MR pro-ANP), a cleavage product of the prohormone N-terminal pro-ANP (NT pro-ANP), stimulates vasodilatation, natriuresis, and diuresis [33]. In a recent analysis from the Malmo Diet and Cancer Study, baseline MR pro-ANP levels independently predicted development of AF (HR= 1.62 ; 95 % CI, $1.42-1.84$; $P<0.001$) [31]. Among the 5187 patients, AF was prevalent in 47 (0.9 %) patients. During a mean follow-up period of 13.8 years, new onset AF was diagnosed in 284 individuals. In multivariable regression models with backward elimination including all significant biomarkers and conventional risk factors, MR-pro-ANP and CRP remained significant. The GISSI-AF trial

revealed that changes over time of MR pro-ANP also tended to predict subsequent recurrence of AF [32]. Another biomarker from this group is midregional proadrenomedullin (MR pro-ADM) produced by cleavage of the precursor hormone proadrenomedullin into adrenomedullin (ADM) and the mid-regional portion. ADM is synthesized by multiple tissues and is released by cardiomyocytes in response to wall stress [40] causing natriuresis and vasodilatation [41]. It is difficult to measure ADM due to a binding protein; therefore, MR pro-ADM serves as a surrogate marker. At this time, further studies are necessary to evaluate the potential role of MR pro-ADM in AF.

2.4 Biomarkers of cardiomyocyte damage

The most commonly measured marker of cardiomyocyte damage is troponin. It is a complex of three different subunits—troponin C (TnC), troponin T (TnT), and troponin I (TnI) with TnT and TnI being specific for cardiac tissue. It regulates the calcium-mediated binding of myosin to actin filaments leading to muscular contraction. Myocardial ischemia and infarction resulting in cardiomyocyte necrosis is the commonest mechanism for release of troponin into the circulation [42]. Troponin elevations can be present during AF, too, which is possibly mediated by a “supply–demand ischemia” in the setting of a fast heart rate. Alterations in coronary vascular resistance during AF [43] and left ventricular wall strain due to the AF itself can also result in a troponin leak. The significance of TnI elevations in AF was recently demonstrated in a study by van den Bos et al. [44] where even minor TnI elevations were independently associated with cardiovascular mortality. A substudy of the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial established that rates of stroke in AF were independently related to TnI levels [45].

2.5 Biomarkers for myocardial remodeling

Cardiac extracellular remodeling involves a complex interaction between collagen synthesis and degradation. Amino (PINP and PIIINP) and carboxyterminal (PICP and PIIICP) propeptides of type I and III procollagen (PCI and PCIII) serve as biomarkers of collagen synthesis. Increased collagen production resulting in excessive fibrosis can distort atrial architecture leading to AF [46]. Furthermore, the composition of the extracellular matrix is regulated by matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs). These groups of proteolytic enzymes are responsible for the degradation of matrix components between cells [47]. Alterations in the extracellular matrix resulting from an imbalance between MMPs and their TIMPs can lead to atrial structural remodeling, thereby creating a nidus for AF development and propagation [48]. Homocysteine, an important mediator of MMP activity, can serve as a predictor of AF recurrence [49]. In a recent prospectively conducted study [50], in patients with essential HTN and normal LVEF, those with AF had higher levels of MMP and lower levels of TIMP compared to patients with sinus rhythm. In addition, lower levels of TIMP-1 had a strong association with AF incidence. Similarly, elevated serum MMP-2 levels have been correlated to postablation AF recurrence [51] and cardiovascular mortality [52]. Hence, an imbalance resulting from elevated levels of TIMPs and lower levels of MMPs can predict AF incidence and recurrence.

2.6 Biomarkers for renal insufficiency

Cystatin C (Cys-C), a newer biomarker, appears to be a more sensitive indicator of glomerular filtration rate (GFR) than creatinine [53]. It is a protease inhibitor synthesized by all nucleated cells and filtered by the glomerulus. Urinary albumin excretion is similarly an indicator of chronic kidney disease. In the Atherosclerosis Risk in Communities (ARIC) study, decreased estimated GFR (e-GFR) measurements based on Cys-C filtration and albuminuria were strongly associated with AF incidence [54]. This study followed 10,328 patients free of AF for a median period of 10.1 years, and 788 cases of incident AF were identified. On comparing individuals with low e-GFR (15–29 ml/min/1.73 m²) to individuals with normal e-GFR (>90 ml/min/1.73 m²), the risk of developing AF was approximately three times higher (HR, 3.2; 95 % CI, 2.0–5.0) after adjusting for potential confounders and history of cardiovascular disease. Albumin/creatinine (ACR) ratio determined the presence of microalbuminuria (ACR of 30–299 mg/ g) and macroalbuminuria (ACR>300 mg/g). Patients with both microalbuminuria (HR, 2.0; 95 % CI, 1.6–2.4) and macroalbuminuria (HR, 3.2; 95 % CI, 2.3–4.5) were at a higher risk of developing AF when compared to those with ACR<30 mg/g. The risk of developing AF in patients with low e-GFR and macroalbuminuria was cumulative (HR, 13.1; 95 % CI, 6.0–28.6) when comparing to patients with normal e-GFR and ACR<30 mg/g. Similar findings were reported in the study by McManus et al. [55] where lower e-GFR calculated by Cys-C clearance and a higher albumin/creatinine ratio were significantly associated with prevalent AF. Thus, Cys-C can serve as a useful adjunct to the more commonly used biomarkers to help predict the risk of developing AF.

2.7 Summary

A multitude of biomarkers are now available to help risk stratify patients with AF for developing cardiovascular events, stroke, heart failure hospitalizations, and mortality. Biomarkers for inflammation are commonly used in clinical practice to help guide management for a wide variety of medical conditions. Proinflammatory states may predispose patients to developing AF. Similarly, biomarkers for myocardial wall stress and cardiomyocyte damage are commonly measured for patients presenting with HF and MI, respectively. Their routine measurement can also help diagnose patients at risk of developing AF and identifying those at risk of developing cardiovascular and cerebrovascular complications. Furthermore, there is evidence to suggest that RAAS blockade may reduce the recurrence and development of AF. Among the newer biomarkers, MMPs and their TIMPs and Cys-C appear to be promising yet lack substantive clinical evidence for them to be incorporated into routine practice.

3 Biomarkers in sudden cardiac death

SCD is responsible for approximately 213,000 deaths per year in the USA [56]. VA contributes to the majority of SCDs [57] with survival rates being only 5 % despite improvements in resuscitation techniques and availability [58]. Left ventricular ejection fraction (LVEF) has historically been the most frequently used clinical predictor for SCD with implantable cardioverter-defibrillators (ICD) being advised for individuals with an

LVEF<35 % [59]. However, the majority of patients (>65 %) presenting with SCD do not meet this criteria [60].

3.1 Inflammatory biomarkers

Inflammation appears to play an important role in the development of atherosclerosis and coronary artery disease (CAD). Stable atherosclerotic plaques in the setting of inflammation and thrombosis can transform into vulnerable plaques [61] with acute plaque rupture commonly associated with VA and SCD [62]. Inflammatory biomarkers are thus an area of significant research for CAD and SCD.

CRP is the most commonly studied marker that was first evaluated as part of the analyses of the Physician's Health Study comprising of 22,071 male subjects [63]. Baseline CRP values were significantly associated with risk for SCD over a 17-year follow-up ($p=0.001$).

However, in a recent study [64], in 300 patients with EF <30 % and ICDs, there was no significant difference for CRP values <3 versus >3 mg/l in predicting SCD or fast VT/VF ($p=0.76$). Nonetheless, CRP levels >3 mg/l were strongly associated with mortality due to HF. Another biomarker of interest in inflammatory pathways is IL-6. This has been extensively studied in CAD with higher values predicting fatal events [65]. So far, there has only been one prospective study that has looked at the association of IL-6 and SCD [66]. In 9771 healthy European men followed over a period of 10 years, there was a 3-fold increase in risk of SCD for the upper tertile compared to the lower tertile of IL-6 levels after adjusting for baseline confounders. These studies prove that SCD has a significant association with inflammatory mechanisms.

Chronic myocardial inflammation is associated with pathologies such as cardiac sarcoidosis, chronic Chagas cardiomyopathy (CCC), and HIV cardiomyopathy. Conduction system abnormalities in cardiac sarcoidosis can result from direct involvement of the conduction system or ventricular wall from granulomatous infiltration and scar tissue [67]. The prevalence of SCD in cardiac sarcoidosis is reported between 12 and 65 % [68] and primary prevention via ICD implantation is a grade IIA recommendation (level C) [69]. Similarly CCC is associated with chronic inflammation resulting from *Trypanosoma cruzi* infection. CCC causes a highly arrhythmogenic cardiomyopathy with a high incidence of VA and SCD [70]. It is estimated that more than 50 % of the deaths in CCC is due to SCD [70]. The current guidelines recommend ICD implantation for both primary and secondary prevention of SCD [69]. HIV-associated cardiomyopathy is associated with a 4.5 times higher rate of SCD compared to the general population [71]. The exact inflammatory mechanism responsible for these individual conditions is beyond the scope of this article, but specific biomarkers of inflammation predicting SCD are yet to be established for any of these pathologies.

3.2 Biomarkers of myocardial wall stress

Elevated BNP levels can serve as independent predictors of SCD in patients following an acute MI [72] and in those with decreased LVEF with heart failure [73]. However, these studies involved patients with preexisting CAD and heart failure. A couple of studies have looked at SCD as the primary endpoint in a healthy patient population. In a prospective

cohort of 121,700 patients from the Nurses' Health Study, NT-pro BNP was an independent risk factor associated with a 1.5-fold increased risk for SCD [74]. Another recent analysis from the Cardiovascular Health Study followed 5447 patients over a median time period of 12.5 years. For this cohort, NT-pro BNP was strongly associated with SCD with an adjusted HR of 2.5 for the fifth versus the first quintile (95 % CI, 1.6–3.8; $P<0.001$) [75]. BNP may therefore be an important predictor of SCD even in healthy individuals with no prior history of CAD or HF.

3.3 Biomarkers of cardiomyocyte damage and myocardial remodeling

Myocardial ischemia and infarction resulting in ACS can be a potential trigger for VA and SCD during and immediately following the event. Troponin elevation is expected during ACS with VA and SCD being possible complications. A small single center study looked at the role of TnI elevations in patients with underlying chronic HF [76]. The frequency of developing nonsustained ventricular tachycardia was 2-fold higher in patients with detectable TnI levels. Further studies are necessary to understand the significance of troponin elevation in patients presenting with VA and SCD with no history of underlying CAD.

Serum levels of the propeptide of PCI and PCIII can serve to quantify collagen formation after an acute MI [77]. In hypertensive individuals, increased serum levels of PICP correlated with ventricular fibrosis on cardiac biopsies [78]. The excessive fibrosis can eventually result in VA [79]. Likewise, disproportionate MMP activity can lead to ventricular dilatation from collagen breakdown. Flevari et al. [80] reported a significant relation between the frequency of ventricular tachyarrhythmia episodes to the ratio of MMP-9/TMP-1 and PICP/PIIINP. This study suggested that excessive ventricular dilatation and increased ventricular fibrosis can both lead to a higher risk of VA. Multiple studies have also linked an elevated homocysteine level to SCD in the setting of acute MI [81, 82]. To date, numerous MMPs and TIMPs have been discovered. However, further studies are necessary to determine which among these are best suited for routine use in clinical practice.

3.4 Other biomarkers

A few miscellaneous biomarkers have also been studied in relation to SCD. Cys-C levels were analyzed in the Cardiovascular Health Study, and a 3-fold increased risk of SCD was seen among patients in the highest tertile when compared to the lowest tertile of levels [83]. Nonesterified free fatty acids (NEFA) are known to be proarrhythmic [84]. The Paris Prospective Study I followed 5250 men aged between 42 and 53 for an average duration of 22 years. After adjusting for covariates, NEFA concentration was an independent risk factor for SCD [85]. This was confirmed by another large study [86] in which NEFA levels were measured in 3315 patients scheduled for coronary angiography.

3.5 Summary

Identifying patients at risk of developing SCD still remains a challenge. Inflammation appears to play a role in the development of SCD, and recognizing patients with proinflammatory states may help target therapy towards these individuals. Among the established biomarkers, elevated levels of natriuretic peptides are associated with a higher

risk of developing SCD in a healthy patient population. Newer biomarkers for myocardial remodeling and renal insufficiency will require further studies to establish their clinical significance. Notably, elevated NEFA levels appear to show some potential value as an independent risk factor for SCD.

4 Biomarkers in cardiac resynchronization therapy

Cardiac resynchronization therapy (CRT) is an effective treatment modality for patients with drug-refractory advanced HF [87, 88]. Using the standard selection criteria of depressed LVEF<35 %, QRS duration >120 ms, and advanced heart failure, about 30 % of patients continue to be nonresponders [89]. Multiple biomarkers are associated with congestive HF (Fig. 1) and could have value in selecting patients and predicting response in this patient subgroup.

4.1 Inflammatory biomarkers

Heart failure (HF) has a known association with systemic inflammation involving the interplay of proinflammatory and inhibitory cytokines [90]. However, the influence of pre-implantation inflammatory status on CRT response remains unclear. It is speculated that CRT reduces inflammation, which could be one of the many factors responsible for an improvement in HF symptoms. A few small studies have looked at the effect of CRT on inflammation [91–93], but they have been limited by either a small sample size or a short follow-up period. One of the larger studies [94] that followed 140 patients undergoing CRT over a median duration of 9 months showed that CRT-induced reverse remodeling (RR*) led to a decrease in inflammatory markers resulting in a reduction in adverse events. The routine use of these inflammatory markers in predicting response is, however, questionable and requires further validation.

4.2 Biomarkers of myocardial wall stress

Biomarkers of the natriuretic peptide system are extensively used in the diagnosis and management of HF. Their release is typically modulated by atrial or ventricular wall stress. Trials such as the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) study [95] and Breathing Not Properly study [96] established the role of natriuretic peptides in diagnosing acute HF in patients presenting to the emergency department with dyspnea. Studies have also suggested that BNP-guided treatment of chronic HF was associated with a superior event free survival [97, 98].

To date, there have been multiple studies that have investigated the role of BNP in the treatment and prognosis of patients on CRT (Table 2). Delgado et al. [99] demonstrated a decrease in BNP levels in CRT responders and an increase in nonresponders. BNP values at baseline and 3 months were followed in 70 patients undergoing CRT. A rise in the levels was indicative of poor cardiovascular outcomes and death. Others [100] have also confirmed that preimplantation BNP levels can serve as an independent predictor of CRT response. Studies have also suggested that CRT induces favorable changes in the neurohormonal system leading to a decrease in NT pro-BNP levels [101].

The subanalysis from the Cardiac Resynchronization-Heart Failure (CARE-HF) study was the first randomized control trial confirming that CRT exerts an early (3 months) and sustained (18 months) reduction in NT pro-BNP levels possibly due to an improvement in LV systolic function and a reduction in mitral regurgitation [102]. In a subsequent analysis from the CARE-HF study, baseline log-transformed NT pro-BNP was an independent predictor of all-cause mortality, sudden death, and death from pump failure [103]. In a recent study by Smit et al. [104], atrial natriuretic peptide (ANP) predicted response to CRT while NT pro-BNP was associated with increased all-cause mortality. These studies prove that BNP levels at the time of initiation of therapy and subsequently during CRT serve as predictors of CRT response.

Adrenomedullin (ADM), a member of the natriuretic peptide family, has natriuretic and vasodilating properties [41]. It appears to have prognostic value in patients with chronic HF [40]. Morales et al. [105] showed that elevated levels of ADM at baseline were indicative of RR* after CRT. Larger studies are necessary to fully evaluate the prognostic potential of this biomarker.

4.3 Biomarkers of cardiomyocyte damage

Troponin is the most frequently used marker for cardiomyocyte damage and is usually released into the circulation in the setting of cardiomyocyte necrosis [42]. It is routinely used in the diagnosis and management of ACS, though detectable levels of TnI and TnT have been reported in patients with HF without any evidence of myocardial ischemia [106]. Furthermore, they appear to be predictive of increased risk of mortality. Studies have demonstrated [107] that measurement of TnT by high-sensitivity assays (hs-TnT) was predictive of cardiovascular death and HF in patients with stable CAD. To date, there has been only one study [108] that assessed the role of hs-TnT in relation to CRT. This study revealed that elevated levels of hs-TnT were present in the majority of HF patients and were predictive of response to CRT and incidence of severe cardiovascular events.

4.4 Biomarkers for myocardial remodeling

MMPs are proteolytic enzymes responsible for remodeling the extracellular matrix of cardiac tissue. A balance usually exists between the MMPs and their TIMPs, which prevents excessive ventricular dilatation and remodeling. These enzymes are implicated in the pathophysiology of advanced HF [109] with elevated levels being associated with a higher likelihood of cardiovascular events [110]. A recent work has suggested that a significant decrease in MMP-9 levels correlates with CRT-associated RR* over a 6-month follow-up period [111]. Furthermore, higher TIMP-1 levels have been shown to be an independent predictor of nonresponse to CRT [112]. Increased collagen production resulting in excessive fibrosis can exert a deleterious effect on ventricular function. This can eventually result in LV dilatation with impaired systolic and diastolic function [113, 114]. PINP, PIIINP, PICP, and PIIICP serve as biomarkers of collagen synthesis while a degradation product of type I procollagen, the carboxyterminal telopeptide (ICTP), serves as a biomarker of collagen breakdown. A few studies have investigated the relationship between collagen propeptides and CRT. Garcia-Bolao et al. [115] demonstrated that high baseline PICP levels were associated with a favorable long-term response to CRT. These favorable effects were linked

to a normalization of PICP levels during CRT, while further elevation of PICP levels during treatment correlated with a lack of response. This study suggested that a decrease in collagen production resulted in favorable CRT outcomes. In another study published by the same author at a later date, the PICP/ICTP ratio had a direct correlation to CRT response with higher baseline values predicting better outcomes [116]. A decline in this ratio as a result of decreasing collagen production correlated with a positive CRT response.

Galectin-3 (Gal-3), a β -Galactosidase binding lectin, is an emerging biomarker implicated in the development of fibrosis in the heart [117] and appears to have a prognostic value in chronic HF patients [118]. A recent substudy of the CARE-HF trial demonstrated that Gal-3 values >30 ng/ml were associated with a 3-fold increase in death or HF hospitalization on multivariate analysis [119]. However, this association was no longer significant when e-GFR was included in the multivariate model, suggesting the role of cardio-renal interactions in the setting of chronic HF.

4.5 Biomarkers for renal insufficiency and CRT response

Renal failure (RF) has been established as an independent risk factor for morbidity and mortality in HF patients [120]. The MADIT-CRT trial showed that the benefits of CRT-defibrillator (CRT-D) to ICD alone were related inversely to S-Cr and directly to BUN levels [121]. To date, there has been only one single center study that has evaluated the role of Cys-C in CRT. Yamamoto et al. [122] showed that elevated baseline levels of Cys-C were predictive of cardiovascular morbidity and mortality. To establish its role in CRT, larger randomized controlled trials will be necessary. There is still strong evidence to consider renal insufficiency as a negative predictor for CRT success.

4.6 Other biomarkers

Growth differentiation factor-15 (GDF-15), a member of the transforming growth factor- β cytokine superfamily, appears to have prognostic value in patients with chronic HF [123]. Previous work [124] has demonstrated that preimplant GDF-15 was a predictor of mortality and morbidity post-CRT, independent of NT pro-BNP levels. The predictive value was superior when combining preimplant levels of GDF-15 and NT pro-BNP. Annexin A5 (AnxA5), a plasma protein playing a role in cardiomyocyte apoptosis [125], has also been studied with elevated levels being reported in systolic HF [126]. Ravassa et al. [127] observed reduced levels of AnxA5 in patients with CRT induced RR*. Another alternative biomarker that has been investigated is osteopontin (OPN), a matrix glycoprotein that regulates inflammation at multiple levels [128]. Elevated levels of OPN in HF patients are linked to mortality [129]. Early work [130] has revealed an inverse correlation between plasma OPN levels and CRT induced RR*. These novel biomarkers are exciting prospects for future investigations, but their role in prognosis of HF and CRT is yet to be determined (Table 3).

4.7 Role of biomarker-guided CRT therapy in reversible cardiomyopathy

Potentially reversible causes of cardiomyopathy (CM) such as peri-partum, alcoholic, drug related, and tachycardia induced could be considered for potential CRT if they met the standard inclusion criteria. However, since they are potentially reversible, an attempt to

correct the etiology should always be attempted. If the condition continues to be persistent despite eliminating the reversible cause, CRT is always a viable option. This is a completely novel area, and further studies incorporating the various classes of biomarkers are necessary for risk stratifying and monitoring patients with reversible cardiomyopathy.

4.8 Summary

Biomarkers in HF have been extensively studied. However, there are limited studies for HF patients undergoing CRT. Inflammation has a known association with HF, and a few small single center studies have attempted to examine its role in CRT patients. These studies suggest that CRT exerts an anti-inflammatory effect and may help decrease adverse events by CRT-induced RR*. BNP levels may help predict response to CRT with elevated levels being linked to increased mortality. A number of small studies have looked at the role of biomarkers of myocardial remodeling in CRT. At this time, larger randomized control studies will be necessary to establish their significance in CRT patients. Renal insufficiency is a known risk factor for increased morbidity and mortality in HF patients, and these findings also translate to patients undergoing CRT. Finally, a number of novel biomarkers are being studied, but their role as meaningful predictors during CRT is yet to be established.

5 Limitations

Given the magnitude of the subject matter involved, we have tried to incorporate the most pertinent information to present this review. It was not possible to analyze and incorporate all studies available from the different classes of biomarkers. As per our observation, studies involving biomarkers of inflammation, myocardial wall stress, and RAAS have been more extensively studied in population trials compared to the other classes. Currently, most studies involving the other classes are limited by their nonrandomized design, small sample size, or limited follow-up. Larger population-based studies incorporating multiple classes of biomarkers will be necessary to derive more concrete information.

6 Conclusion

Biomarkers are an exciting and constantly evolving field in the arena of electrophysiology and HF. Their role in the pathophysiology of arrhythmias and HF, along with the molecular mechanisms involved, is being extensively investigated. They have the potential to provide valuable information for disease prognosis, risk stratification, and patient selection. As the field of genomics and proteomics continues to evolve, newer biomarker molecules will continue to emerge. As can be seen, much of this arena of biomarkers in arrhythmias and CRT is investigational. In our practice, biomarkers serve as a useful adjunct to traditionally established methods of diagnosis and management of arrhythmias and CRT patients. There is significant potential to develop and incorporate single and multimarker strategies to better risk stratify and treat patients with arrhythmias and resynchronization. Our recent work [131] on multimarker strategies has begun influencing our practice, but much of it still needs validation in prospective randomized studies.

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Fig. 1.
A diagram showing the interaction of the different biomarker pathways in congestive heart failure

Table 1**Classes of biomarkers**

Inflammation
C-reactive protein
Interleukin-6
Neurohormones
Renin
Aldosterone
Angiotensin II
Atrial wall stress
Brain natriuretic peptide
N-terminal pro-brain natriuretic peptide
Midregional pro-adrenomedullin
Atrial natriuretic peptide
Myocyte damage
Troponin I and T
Myocardial remodeling
Matrix metalloproteinases
Propeptides of procollagen type I and type III
Galectin-3
Renal insufficiency
Cystatin-C
Albumin
Creatinine
Other biomarkers
Myeloperoxidase
Non-esterified free fatty acids
Growth differentiation factor-15
Annexin A5
Osteopontin

Table 2

Studies investigating the role of biomarkers of atrial wall stress in the treatment and prognosis of patients undergoing CRT

Author	Study design	Comments
Delgado et al. [99]	<i>N</i> =70, baseline BNP and follow-up levels at 3 months	BNP levels decreased in responders and increased in nonresponders; rise in the BNP levels was indicative of poor cardiovascular outcomes and death
Lellouche et al. [100]	<i>N</i> =164, baseline BNP and follow-up levels at 6 months	Preimplantation BNP was an independent predictor of CRT response
Braun et al. [101]	<i>N</i> =124 (total); <i>N</i> =65 (CRT), undergoing CRT for 24 months; neurohormones measured at baseline, 1, 12, and 24 months	Short-term decrease in neurohormonal activation with reduced levels of NT pro-BNP at 1 and 12 month follow-up
Fruhwald et al. [102]	<i>N</i> =732 (total); <i>N</i> =362 (CRT), baseline NT pro-BNP with follow-up levels at 3 and 18 months	CRT exerts an early and sustained reduction in NT pro-BNP levels
Berger et al. [103]	<i>N</i> =813 (total); <i>N</i> =409 (CRT), median follow-up 37.6 months, NT pro-BNP levels at baseline and 3 months	Baseline log transformed NT pro-BNP was an independent predictor of all-cause mortality, sudden death and death from pump failure
Smit et al. [104]	<i>N</i> =338, ANP and NT pro-BNP levels at baseline with follow-up at 6 months	Lower ANP at baseline was an independent predictor of response to CRT while baseline NT pro-BNP predicted all-cause mortality
Morales et al. [105]	<i>N</i> =50, follow-up 16±6 months, ADM measured preimplantation	Elevated preimplantation ADM levels were associated with CRT-induced reverse remodeling

CRT cardiac resynchronization therapy, *BNP* brain natriuretic peptide, *NT pro-BNP* N terminal pro-BNP, *ANP* atrial natriuretic peptide, *ADM* adrenomedullin

Table 3**Novel biomarkers and their role in electrophysiology**

Biomarker	Mechanism of action	Probable therapeutic role
Copeptin	C-terminal portion of provasopressin synthesized along with vasopressin and serves as a stable plasma surrogate for vasopressin Vasopressin mediates water reabsorption from kidneys and increases peripheral vascular resistance	Serves as an accurate prognostic indicator of mortality in decompensated HF Role in AF, VA, and CRT patients is yet to be established
MR pro-ANP	Cleavage product of the prohormone NT pro-ANP released in response to myocardial wall stress Stimulates vasodilatation, natriuresis and diuresis	Baseline levels independently predicted development of AF with changes over time correlating with recurrence of AF Role in SCD and CRT requires further investigation
MR pro-ADM	Cleavage product of pro-ADM into ADM and mid regional portion Stable surrogate plasma marker for ADM ADM synthesized by multiple tissues and released by cardiomyocytes in response to wall stress causing natriuresis and vasodilatation	Elevated levels are independently associated with adverse outcomes in chronic HF Role in AF, SCD, and CRT requires further investigation
Cystatin-C	Cysteine protease inhibitor synthesized by all nucleated cells and filtered by the glomerulus More sensitive and specific indicator for GFR than creatinine	Decreased e-GFR based on cystatin-C filtration can predict increased AF incidence and prevalence Elevated baseline levels associated with increased risk of SCD Elevated baseline levels predict cardiac mortality and morbidity in CRT patients
Galectin-3	B-Galactosidase binding lectin produced in several tissues Promotes fibrogenesis in cardiac tissue	Elevated levels predict increased mortality in HF patients Role in AF, SCD, and CRT requires further investigation
GDF-15	Protein belonging to transforming growth factor- β superfamily expressed in multiple organs Expressed in cardiac myocytes in response to oxidative stress, proinflammatory cytokines and ischemia	Elevated baseline and follow-up levels indicate worse prognosis in chronic HF Preimplant GDF-15 levels can predict morbidity and mortality post-CRT Role in AF and SCD requires further investigation
Annexin A5	Plasma protein that regulates cardiomyocyte apoptosis	Upregulation of myocardial levels seen in systolic HF Reduction in plasma levels seen in CRT-associated RR
Osteopontin	Matrix glycoprotein that regulates biomineralization and inflammation at multiple levels and inhibits vascular calcification	Elevated levels predict mortality in HF Decreased plasma levels seen in CRT induced RR Role in AF and SCD requires further investigation

HF heart failure, *AF* atrial fibrillation, *VA* ventricular arrhythmias, *SCD* sudden cardiac death, *CRT* cardiac resynchronization therapy, *MR pro-ANP* midregional proatrial natriuretic peptide, *NT pro-ANP* N terminal pro-ANP, *MR pro-ADM* midregional pro-adrenomedullin, *ADM* adrenomedullin, *GFR* glomerular filtration rate, *e-GFR* estimated GFR, *GDF-15* growth differentiation factor-15, *RR* reverse remodeling