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New and Emerging Biomarkers in Left Ventricular Systolic Dysfunction - Insight into Dilated Cardiomyopathy

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Abstract

Background—Dilated cardiomyopathy (DCM) is characterized by deteriorating cardiac performance and impaired contraction and dilation of the left (or both) ventricles. Blood markers – known as “biomarkers” allow insight into underlying pathophysiologic mechanisms and biologic pathways, while predicting outcomes and guiding heart failure management and/or therapies.

Content—In this review, we provide an alternative approach to conceptualize heart failure biomarkers: the cardiomyocyte, its surrounding microenvironment, and the macroenvironment with clear interaction between these entities which may impact cellular processes involved in the pathogenesis and/or propagation of DCM. Newer biomarkers of left ventricular systolic dysfunction can be categorized under: (a) myocyte stress and stretch, (b) myocyte apoptosis, (c) cardiac interstitium, (d) inflammation, (e) oxidative stress, (f) cardiac energetics, (g) neurohormones and (h) renal biomarkers.

Summary—Biomarkers provide insight into the pathogenesis of DCM while predicting and potentially providing prognostic information in these patients with heart failure.

Keywords

Biomarkers; dilated cardiomyopathy; heart failure

Cardiomyopathy is defined as an alteration in the structure and function of the myocardium, leading to deterioration of myocardial performance often resulting in the development of clinical heart failure. Dilated cardiomyopathy (DCM), a common cardiomyopathy leading to heart failure, has a prevalence of 1:2500 [1] and is characterized by enlargement of one or both of the ventricles with associated systolic dysfunction. Many diverse etiologies, either primary (solely or predominantly confined to the heart muscle) or secondary (myocardial involvement from a systemic disease process), may lead to the DCM phenotype. A diagnosis of DCM requires evidence of dilation and impaired contraction of the left ventricle or both ventricles (e.g., left ventricular ejection fraction (LVEF) < 40 percent) [2]. The disease is considered idiopathic if primary and secondary causes of heart disease are excluded. Of note, in the literature, the term DCM is usually an all-encompassing term for a non-ischemic cardiomyopathy with depressed left ventricular (LV) function.

Macroscopically, DCM consists of hearts that are heavy (increased LV mass) with geometric changes indicating eccentricity (defined as low relative wall thickness - normal or

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reduced wall thickness in relation to a dilated LV chamber size) [3]. Microscopically, cardiomyocytes in DCM often consist of a classic histological triad – myocyte hypertrophy, myocyte loss, and interstitial fibrosis [4]. However, these findings are imprecise in identifying underlying etiologies for cardiomyopathies. In addition, the natural course of DCM can be variable, contingent on multiple factors, including etiology and initial cardiac phenotype of the cardiomyopathy, on-going cardiac insults and genetic underpinnings of an individual's resistance to adverse cardiac remodeling.

Heart failure is a clinical syndrome that manifests as a consequence of the progression of the underlying cardiomyopathy. It is a complex process and features pressure and/or volume overload leading and ventricular remodeling. Diverse etiologies, presentations, and outcomes are seen thus, making the classification of cardiomyopathies challenging. Equally challenging is categorizing biomarkers of heart failure as they are often described according to their mechanism (e.g., neurohormonal, oxidative stress etc.). However, an alternative method to conceptualize biomarkers in heart failure is to approach the classification from three vantage points: the cardiomyocyte, its surrounding microenvironment, and the macroenvironment (Figure 1). In heart failure, the cardiac myocyte is subjected to many stressors – such as mechanical, oxidative and pro-inflammatory, resulting in structural and functional changes (i.e., hypertrophy, necrosis/ apoptosis, altered myocyte energetics, impaired contraction and relaxation). The myocyte "microenvironment", the environment immediately surrounding a myocyte, includes the cardiac interstitium, cardiac fibroblasts, and other factors that interact or cross-talk with cardiomyocytes. Lastly, the "macroenvironment" in heart failure refers to the interaction of the heart and other organ systems and the impact of those systems on the heart (e.g., insulin resistance, cardiac cachexia, obesity, cardiorenal syndrome and ventricular-vascular coupling). The intimate relationship between the micro- and macroenvironment with the cardiomyocyte may result in downstream cellular or signaling changes which may be important in the initiation and propagation of DCM or reflect changes that have already taken place in DCM.

For the purpose of this review, emerging biomarkers in DCM will be the primary focus. Although 20-35% of DCM has been genetically correlated with greater than 20 loci and associated genes [1], genetic biomarkers are out of the scope of this review and will not be discussed. The biomarkers reviewed are not unique to DCM, and we do not provide an exhaustive list (Table 1) but provide insight into underlying pathophysiologic mechanisms and biologic pathways important in, but not specific to DCM. Some of these biomarkers may prognosticate outcomes, enable guidance in heart failure therapeutics and may be used for monitoring treatments in DCM.

THE CARDIOMYOCYTE

Myocyte stress/stretch

One of the most well-described and studied biomarkers in heart failure and ventricular stress is **B-type natriuretic peptide (BNP)** and its **amino terminal fragment (NT-pro-BNP)**. Activation of the BNP gene (natriuretic peptide B), in response to myocardial stress (predominantly via stretch) results in the production of both peptides. Both biomarkers diagnose acute heart failure syndromes [5, 6] but without predicting DCM or LV systolic dysfunction (LVSD). While NT-proBNP and BNP are both higher in patients with LVSD, in sub-studies modest correlations were seen predicting LVEF [7-9]. In a recent meta-analysis pooling biomarker-guided therapy trial data, a significant reduction in mortality was seen utilizing these natriuretic peptides in chronic heart failure management [10] but with varied baseline LVEF and with no specific analysis in DCM patients. Recently, however, the Use of NT-proBNP Testing to Guide Heart Failure Therapy in the Outpatient Setting study specifically looked at chronic LVSD (mean LVEF < 30%, of which a third had a non-

ischemic etiology) and found a statistically significant reduction in total cardiovascular event rates, improved quality of life, and reduction in LV chamber size as shown by LV end-systolic and -diastolic volume indexes, thus indicating improved cardiac remodeling with NT-proBNP guided therapy compared to standard of care [11]. Moreover, recent advances in BNP physiology have targeted the up-stream 108 amino acid prohormone of BNP and NT-pro-BNP, pro-BNP1-108 to identify asymptomatic LVSD in conjunction to known predictive abilities of BNP and NT-proBNP [12-14].

Atrial natriuretic peptide (ANP), is secreted predominantly from the atria during times of stretch, although can be released from ventricular myocytes in times of ventricular stress [15]. ANP has recently been evaluated in the context of the precursor pro-ANP peptide using a sandwich assay of the mid regional sequence of ANP (**MR-proANP**), which is more stable and less susceptible to enzymatic degradation compared to ANP [16]. Two recent studies in patients with lower LVEF showed that elevated MR-proANP was able to identify LVSD and to predict mortality [17, 18].

Soluble ST-2 (sST2) is a truncated soluble receptor of the interleukin-1 receptor family and is a biomarker of mechanical strain and fibrosis in conjunction with IL-33 (a ligand of ST2, synthesized by cardiac fibroblasts) [19, 20]. In a small cohort of DCM patients, sST2 (in addition to NT-proBNP) predicted sudden cardiac death [21]. In acutely decompensated heart failure patients with depressed LVEF (median 34%), sST2 levels predicted mortality risk [22]. In an echo sub-study for the pro-BNP investigation of Dyspnea in the Emergency Room, sST2 levels correlated with cardiac structure (LV end-diastolic and systolic dimensions) in addition to predicting mortality [23], indicating the poor prognosis of cardiac remodeling and potentially the utility of sST2.

Myocyte injury

We will not discuss cardiac troponin I and T in this review, but refer the reader to Table 2 where other biomarkers not discussed in this review are listed. Cardiac troponins are the most common markers of myocyte necrosis. Release of troponin in heart failure is due to myocyte injury, regardless of the mechanism involved and low circulating levels are present in chronic LVSD and DCM [24, 25].

Myocyte apoptosis

Heart-type fatty acid binding protein (H-FABP) is a cytosolic, non-enzymatic protein, which transports long-chain fatty acids into cardiomyocytes and is released into the circulation when the myocardium is injured [26]. In heart failure patients, H-FABP levels together with cTnT, were more sensitive in detecting worse New York Heart Association (NYHA) functional class and identified a higher risk group when cTnT levels were normal but H-FABP levels were elevated [27]. Several studies showed that H-FABP levels were strongly predictive of cardiac mortality and heart failure re-hospitalizations in multivariate analyses [27-29]. Thus, its strength in prognosis is likely because this biomarker represents ongoing myocardial damage and identifies a higher risk subset and likely provides insights into ongoing adverse cardiac remodeling.

Similarly, soluble markers of apoptosis, specifically **soluble apoptosis stimulating fragment (sFAS)** may eventually allow earlier prognostication in patients with heart failure. In low LVEF patients, sFAS independently predicted the composite outcome of all-cause mortality and rehospitalization for worsening heart failure [30]. Inflammatory mediators, such as such as IL-6 and TNF-α (Table 2), appear to be important determinants of the FAS-FAS ligand pathway [31] – thus, the inflammatory milieu of heart failure contributes to the apoptotic process in patients with LVSD.

Myostatin (also known as growth differentiating factor-8, GDF-8), a member of the transforming growth factor-beta (TGF-β) superfamily, is a secreted factor that inhibits muscle differentiation and growth. Myostatin is produced predominantly in skeletal muscle and is a negative regulator of skeletal muscle mass [32]. However recent evidence now links myostatin to cardiomyocyte homeostasis, since myostatin is up-regulated in patients with severe heart failure and DCM. Increased myostatin levels are seen as a possible protective counter-regulator of cardiomyocyte hypertrophy in advanced heart failure [33, 34]. A recent study in patients with depressed LVEF and heart failure (mean LVEF 22.6%) showed increased myostatin levels correlated with worsening NYHA classification [35]. Whether myostatin serum levels correlates with the skeletal muscle wasting phenomenon in heart failure and cardiac cachexia, still remains to be studied.

THE MICROENVIRONMENT

Cardiac interstitium

In DCM, the myocardial interstitium is in a constant state of flux with increased extracellular matrix turnover and decreased collagen linking, leading to a distorted and defective matrix architecture [36, 37]. A loss of alignment of the cardiomyocyte fascicles contributes to LV dilation and a loss of the matrix-myocyte interface likely weakens the myocyte-shortening force transduction, leading to impaired myocardial force and systolic performance [38]. **Matrix metalloproteinases (MMPs)**, myocardial interstitium proteases that are pivotal in myocardial remodeling, are held in delicate balance by tissue-inhibitors of matrix metalloproteinases (TIMPs) [39]. The overall change in matrix proteins in DCM favors increased MMP-mediated matrix proteolysis with up-regulation noted in MMP-2, MMP-3, MMP-9, MMP-13 and MT1-MMP with decreases seen in MMP-1 and varied responses of TIMP-1, TIMP-2, and TIMP-3. However, these findings were measured by tissue samples and not by blood protein characterization [36, 37, 40]. Plasma MMP-9 levels in the Randomized Evaluation of Strategies for LV Dysfunction (RESOLVED) study were inversely related to LV systolic function – suggesting a role for monitoring ongoing cardiac remodeling [41]. Plasma TIMP-1 levels correlated with cardiovascular risk factors, LV mass and hypertrophy and were inversely associated with cardiac function (fractional shortening) in a community-based cohort [42] – suggesting these proteins may provide early predictive information in patients at greatest risk for developing heart failure.

In addition to the regulators of collagen matrix formation, serum procollagen peptides have been evaluated to characterize and understand extracellular matrix turnover. Circulating amino-terminal propeptide of type III procollagen (PIIINP) portend a higher risk of death and hospitalization, particularly in lower LVEF patients [41]. Reverse remodeling after LV assist device implantation supports an initial increase in serum **N-terminal pro-peptide for Type I collagen (PINP)** and PIIINP which may provide insight to adverse cardiac remodeling [43]. Additional studies in a specific DCM cohort with serum markers are needed to further elucidate their role in risk prediction and prognosis.

Galectin-3, a β-galactoside-binding protein secreted by immune cells, has been associated with myocardial fibrosis, ventricular remodeling, and left ventricular dysfunction [44, 45]. In two recent studies evaluating chronic heart failure patients, galectin-3 predicted mortality and heart failure hospitalization and correlated positively with LV end-systolic and end-diastolic volumes [46, 47]. Similarly, galectin-3 was associated with all-cause mortality and an increased risk of incident heart failure, thus implicating the predictive role of galectin-3 in detecting asymptomatic fibrosis and early adverse remodeling [48].

Inflammation

Many markers of inflammation have been implicated in the pathogenesis of heart failure with TNF-α being one of the most well studied [49, 50]. We will not be discussing TNF-α in this review (see Table 2 for references).

Tumor necrosis factor-like weak inducer of apoptosis (TWEAK), a member of the TNF factor family, is a trans-membrane protein that is released in a truncated, active form to bind to fibroblast growth factor inducible-14 (Fn14). Fn14 is a highly inducible cell-surface receptor that is involved in multiple signaling pathways, including the NF-κB pathway. TWEAK plays a role in cardiomyocyte proliferation, myocardial hypertrophy, and cardiac fibrosis during cardiac remodeling. However there is conflicting data about the use of TWEAK levels as a biomarker. On the one hand increased levels of TWEAK after myocardial infarction with cardiac remodeling has been shown to portend adverse outcomes [51]. Conversely lower levels of soluble TWEAK have been associated with increased mortality in heart failure patients [52, 53]. Thus the role of TWEAK in heart failure and LVSD require further clarification.

Osteoprotegerin (OPG), a member of the TNF receptor superfamily, binds to the receptor activator of NK-κB ligand (RANKL) and prevents the interaction between RANKL and its receptor. In a cohort of stable heart failure patients with LVSD (mean LVEF 32%) with both ischemic and non-ischemic etiologies, OPG levels were elevated in heart failure patients compared to controls and were positively correlated with worse NYHA functional class, degree of myocardial dysfunction (cardiac index), and neurohormonal activation (N-BNP) [54]. Additionally, in chronic heart failure patients, OPG levels are associated with mortality, independent of other risk factors of death. Thus OPG levels may assist in risk stratification in these patients [55].

Pentraxin-3 (PTX3), a member of the pentraxin superfamily (which includes C-reactive protein and serum-amyloid P), is an inflammatory marker that is part of the innate immunity system which is produced by endothelial cells, smooth muscle cells, and macrophages [56]. PTX3, not C-reactive protein, proved to be an independent predictor of adverse events – including all-cause mortality and hospitalization for worsening heart failure in several heart failure studies including GISSI-heart failure and CORONA cohorts [57, 58].

Cardiotrophin-1 (CT-1), is a cytokine and a member of the IL-6 family of cytokines. CT-1 mediates its effects by interacting with the glycoprotein 130 (gp130)/leukemia inhibitory factor receptor beta (LIFR) heterodimer. It has potent hypertrophic and survival effects on cardiac myocytes. CT-1 activates phosphatidylinositol 3-kinase in cardiac myocytes and enhances transcription factor NF-κB DNA-binding activities. CT-1 levels are increased in patients with DCM and are significantly correlated with the LV mass index, suggesting that CT-1 plays an important role in structural LV remodeling [59].

Oxidative Stress

Increased oxidative stress is characterized by the excessive production of reactive oxygen species (ROS) which overwhelms the host's antioxidant defenses. Oxidative stress is present in many cardiovascular disorders, such as heart failure. Increased ROS in heart failure may mediate many pathways that play a role in adverse cardiac remodeling including the propagation of apoptosis, deleterious effects on endothelial function, activation of neurohormonal systems [60], as well as direct effects on cardiomyocytes that can impair cardiac performance (i.e. ROS-induced structural modifications of the sarcomere) [61]. Many methods exist to characterized levels of ROS, however, only recently have there been

human studies evaluating biomarkers that measure indirect markers of free radicals and assess their role in heart failure.

One biomarker of interest is **myeloperoxidase (MPO)**, a leukocyte-derived heme peroxidase that is associated with neutrophil activation and inflammation with direct effects on ventricular remodeling in the post-infarct setting [62, 63]. In patients with LVEF < 35%, MPO was associated with right ventricular dysfunction and a more restrictive diastolic dysfunction pattern, on echocardiography. MPO was also more predictive of increased future adverse clinical events even after multivariate adjustment [64]. In addition, combined with other markers of inflammation (like high-sensitivity C-reactive protein) MPO levels provided incremental risk prediction in chronic systolic heart failure patients [64]. Thus MPO levels may also provide a means of monitoring anti-inflammatory effects with heart failure therapy [65] and determining on-going risk in heart failure patients.

Another marker of oxidative stress, plasma **oxidized low-density lipoprotein (oxLDL)** levels, was shown to be elevated in the coronary sinus of the heart compare to aortic root samples in DCM patients demonstrating increased oxidative stress in heart failure patients [66]. This transcardiac gradient of oxLDL correlated inversely with LV systolic function with oxLDL levels have been shown to be an independent predictor of mortality and adverse cardiac events in heart failure patients [66-68].

THE MACROENVIRONMENT

Myocyte energetics

Alterations in cardiac metabolism and energy substrate utilization have been described as pathological consequences as well as therapeutic targets for heart failure [69, 70]. Adipokines are secreted by adipose tissue and are implicated as playing a role in the pathogenesis of heart failure [71, 72]. **Adiponectin**, an insulin-sensitizing hormone, is secreted not only by adipose tissue but also cardiomyocytes during cardiac stress. Adiponectin activates AMP activated protein kinase (AMPK) leading to downstream effects such as inhibiting LV hypertrophy as well optimizing energetics by preferentially supporting the major cardiomyocyte fuel, fatty acids, which is responsible for ~70% of the cardiac energy needs [73]. Recent studies have implicated changes in serum adipokine levels between compensated and decompensated heart failure as well as evidence of adiponectin resistance that is reversed in the setting of left ventricular assist device (LVAD) therapy [74, 75]. Adiponectin modulates cardiac dysfunction by its interaction with several intracellular signaling pathways [76]. Depressed levels of adiponectin reflect greater cardiovascular risk and inflammation, in conditions such as hypertension, coronary artery disease, obesity and insulin resistance [77-79]. On the contrary, in humans with LVSD and heart failure [33, 80, 81], adiponectin levels are elevated [71] and associated with the severity of heart failure symptoms, disease severity and mortality [80, 82, 83]. It has been proposed that elevated adiponectin in LVSD is a state of ‘adiponectin-resistance’ and reflects an attempt to mitigate pro-inflammatory or impaired metabolic states and demonstrates a balance between protective and harmful pathways in the failing heart.

Neurohormones

Neurohormones such as norepinephrine, renin, angiotensin II and aldosterone (see Table 2 for references) have been well described in prior reviews of biomarkers in heart failure [60]. Novel neurohormones including **adrenomedullin (ADM)**, a peptide which is released by many tissue types, including the kidney and adrenal medulla and is stimulated by pressure and volume overload. ADM belongs to the calcitonin gene-related peptide family and is implicated in vasodilation via nitric oxide with resultant cardioprotective effects such as

increasing cardiac output, decreasing afterload, and modulating cardiac fibroblast proliferation [84]. **Mid-region-proADM** is a stable prohormone fragment of ADM that is easier to measure. It independently predicted 2-year mortality, particularly in LVSD with non-ischemic etiology and NYHA Class II or worse functional class [85].

Copeptin, the C-terminal portion of the precursor peptide of the neurohormone **arginine vasopressin (AVP or antidiuretic hormone)**, is a surrogate biomarker for AVP, which exerts its primary effects in the hypothalamus by stimulating adrenocorticotrophic hormone, on vascular tissue causing vasoconstriction, and in the kidneys resulting in water retention. Increased copeptin levels in LVSD populations is linked to decreased survival rates, particularly in symptomatic NYHA class II-IV heart failure patients [86]. In the OPTIMAAL (Optimal Trial In Myocardial Infarction with Angiotensin II Antagonist Losartan) neurohormonal substudy which included a mixed population of acute heart failure syndrome plus LVSD patients, copeptin levels were a predictor of mortality post-myocardial infarction and performed better than BNP and NT-proBNP levels [87].

Renal markers

The relationship between renal dysfunction and heart failure is tightly intertwined with activation of neurohormones and release of stress biomarkers that are associated with adverse cardiac outcomes [88]. **Neutrophil gelatinase-associated lipocalin (NGAL)** is secreted by many cell types including renal tubule cells, hepatocytes, endothelial, and smooth muscle cells in response to cellular stress, inflammation and ischemia [89]. NGAL, in patients with acutely decompensated heart failure at the time of discharge, was a strong predictor of 30-day heart failure readmissions and all-cause mortality [90]. In addition, NGAL predicted acute kidney injury in heart failure patient with LVSD [91] and correlated strongly with markers of anemia even after multivariate adjustment, such as renal function and markers of inflammation [92], suggesting that NGAL initially produced as a compensatory response may not simply be a risk marker but an active player in the heart failure syndrome.

Beta-trace protein (BTP), a glycoprotein produced in all tissues (except the ovaries) converts prostaglandin H2 to prostaglandin D2 and **cystatin C**, a competitive inhibitor of cysteine proteases is produced by all nucleated cells. Both have been purported to be novel markers of glomerular filtration [93]. In acutely decompensated heart failure patients, both BTP and cystatin C predicted risk of death/and or heart failure hospitalizations and were superior to creatinine, estimated glomerular filtration rate, and blood urea nitrogen [93]. However, characterization of these biomarkers specifically in DCM has not been evaluated and merits further investigation.

Kidney injury molecule-1 (KIM-1) is also a glycoprotein that is expressed in the proximal tubule in renal injury. Both KIM-1 and NGAL levels were increased in patients with LVSD and may provide prognostic information in LVSD patients with mild renal insufficiency. These findings suggest an important role for biomarkers in cardiorenal interactions in heart failure [94].

Increasing evidence shows that the heart secretes factors to maintain its performance and coordinate cellular activities in response to cardiac stress as outlined above. However, newer proteins secreted from cardiac tissue have been identified. These cardiac-secreted factors are termed cardiokines.

Growth differentiation factor-15 (GDF-15) is a stress-responsive cytokine induced by cardiac stress. GDF-15 in conjunction with other biomarkers may add prognostic value for predicting death, overall cardiovascular events, and heart failure in community based studies

[95]. Importantly elevated circulating levels of GDF-15 are evident in end-stage DCM patients at the time of LVAD implantation and levels decrease after mechanical unloading. GDF-15 correlates with myocardial fibrosis and kidney function [96].

Follistatin-like 1 (Fstl1), also referred to as TSC36 (TGFβ stimulating clone 36), is a divergent member of the Follistatin family of extracellular glycoproteins, and it functions in a non-canonical manner relative to other family members. Fstl1 is poorly understood with regard to its function, but has been shown to suppress cell growth and invasion. Fstl1 has both anti-inflammatory [97, 98] and pro-inflammatory [99] actions. Fstl1 is also regulated in human heart failure. In a collaborative effort between the Sam and Eschenhagen labs, we examined protein expression of Fstl1 in failing explanted human myocardium. Circulating Fstl1 levels were measured in a well-characterized cohort of chronic heart failure patients with LVSD. Fstl1 levels were significantly elevated and significantly associated with LVH and circulating levels of BNP [100]. Other groups have shown that myocardial Fstl1 mRNA levels are elevated in severe systolic heart failure that return to normal when LV function recovers after LVAD explantation [101].

In this review, newer and perhaps mechanistically more important biomarkers in DCM (and likely other cardiomyopathies) were selected, that have shown to confer predictive and prognostic abilities in symptomatic and asymptomatic heart failure patients. Importantly several of these biomarkers have been evaluated in other cardiomyopathies that have mechanistic overlap (e.g., increased fibrosis in heart failure with preserved ejection fraction (HFpEF), amyloidosis, hypertrophic cardiomyopathy etc). Of the aforementioned biomarkers, NT-proBNP, BNP, PTX-3, GDF-15, galectin-3 and ST-2 have been implicated in both the prediction of incident heart failure and also cardiovascular outcomes in HFpEF phenotypes [102-109]. Osteoprotegerin levels predict cardiovascular outcomes and incident heart failure events in patients with ischemia as well as in chronic ischemic heart failure [110, 111]. Mid-region pro-ADM levels have been shown to predict mortality in light chain cardiac amyloidosis [112]. KIM-1 levels have been implicated not only in LVSD but also in the prediction of incident HF [113]. Biomarkers, such as sFas, MPO, and follistatin-like 1 have been measured in patients with LVSD (and non-ischemic etiologies), but not specifically in DCM.

Thus, biomarkers in heart failure provide insight into the pathobiology of the cardiomyopathy and into mechanisms at the myocyte level, the micro- and macro-environment. Importantly, they provide diagnostic, predictive and prognostic information while offering opportunities for potential targets for emerging therapies for heart failure. Measurements of biomarkers, even those that are not independent risk predictors or specific to DCM, remain clinically important as they provide mechanistic information about the pathogenesis of heart failure. Although biomarkers have been studied and validated individually, recent studies have utilize multiple biomarker panels to help augment risk prediction, integrate multiple biologic pathways, and potentially increase specificity in heart failure groups. Ky and colleagues found that a score derived from multiple biomarkers (which encompassed diverse biologic pathways) improved the prediction of adverse events beyond current measures in heart failure patients with LVSD [114]. Similarly recent work from our group in patients with cardiac amyloidosis with LVSD, we showed that biomarkers in aggregate (MMP-2/TIMP-2 in combination with BNP and cTnI) had a potential discriminative ability for distinguishing between the different types of cardiac amyloidosis prompting more invasive diagnostic interventions and presumably therapies in these patients [115]. Furthermore assessment of these aggregate biomarkers suggests that therapeutic intervention that reduces collagen deposition should be studied in these patients [115]. Thus a greater focus and emphasis on multiple biomarker panels may be more important and clinically relevant, in terms of detection, prediction, diagnosis specificity, prognosis and

therapeutic response. Combined with clinical assessments, biomarkers may lead to a better understanding of the various types of heart failure, allowing use of a more personalized approach in identifying and treating patients with LVSD and cardiomyopathy.

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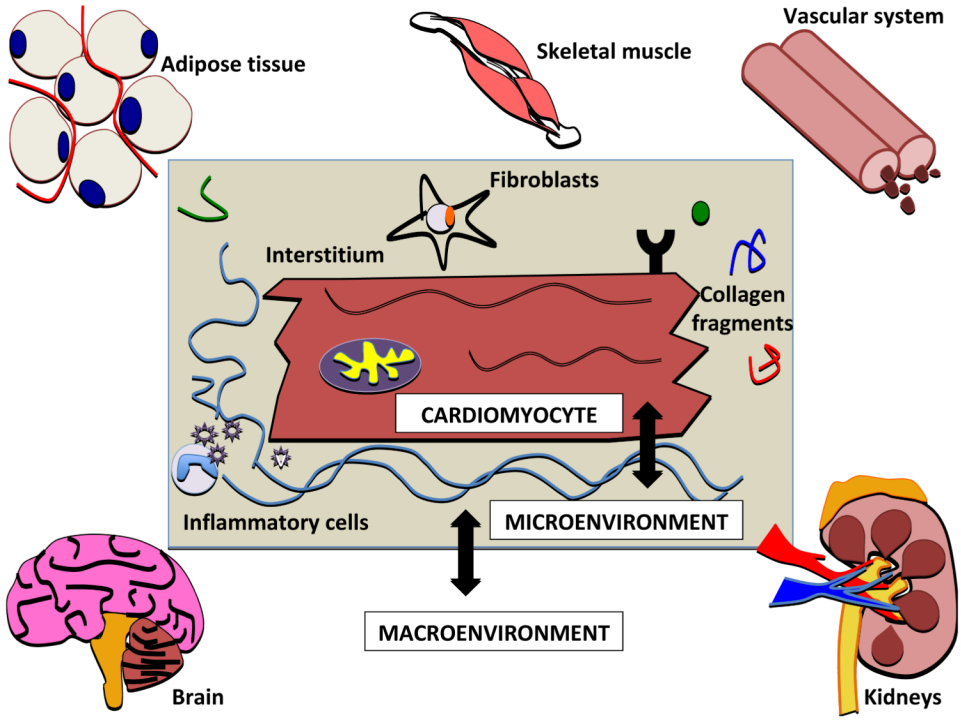

Fig 1. Interaction of heart failure biomarkers between the cardiomyocyte, the microenvironment, and the macroenvironment

Stressors on the cardiac myocyte lead to structural and functional changes (hypertrophy, apoptosis, altered myocyte energetics, and contraction apparatus modifications). Microenvironment refers to the immediate environment of the myocyte – the interstitium, cardiac fibroblasts, and inflammatory mediators. Lastly, the macroenvironment includes other organ systems and their impact on the heart in heart failure (e.g. adipose tissue, cardiac cachexia, cardiorenal syndrome, neurohormones, and ventricular-vascular coupling). Clear overlap exists between these domains contributing to the development and propagation of heart failure.

Table 1

Biomarkers in Dilated Cardiomyopathy (DCM)

CARDIOMYOCYTE	MICROENVIRONMENT	MACROENVIRONMENT
-Brain natriuretic peptide *	-Matrix metalloproteinases *	-Adipocytokines (adiponectin) *
-N-terminal brain natriuretic peptide *	-Tissue inhibitors of metalloproteinases *	-Neutrophil gelatinase-associated lipocalin (NGAL) *
-Atrial natriuretic peptide *	-Collagen propeptides *	-Beta-trace protein *
-Soluble ST2 *	-Galectin-3 *	-Cystatin-C *
-Heart-type fatty acid binding protein *	-Tumor necrosis factor-like weak inhibitory of apoptosis	-Kidney injury molecule-1
-Soluble apoptosis stimulating fragment *	-Osteoprotegerin *	-Endothelin
-Myostatin	-Pentraxin-3 *	-Adrenomedullin
	-Cardiotrophin-1	-MR-proADM *
	-Myeloperoxidase *	-Copeptin *
	-Oxidized-low density lipoprotein	-Growth differentiation factor-15 *
		-Follistatin-like 1

* Biomarker shown to have predictive abilities in cardiovascular outcomes

Table 2

Additional Biomarkers in Dilated Cardiomyopathy (DCM)

Inflammatory markers

- TNF-α[116-118]
- C-reactive protein[119,120]
- Interleukin (IL) 6[117,120] , IL 10[117,121,122], IL 18[123-125]
- TNF-related apoptosis inducing ligand (TRAIL)[30,126]

Neurohormones

- Norepinephrine[127,128]
- Renin[127-129]
- Aldosterone[130,131]
- Angiotensin II[132]
- Arginine vasopressin[127,133,134]