Journal of Clinical & Experimental Cardiology

Berezin, J Clin Exp Cardiolog 2016, 7:4
DOI: 10.4172/2155-9880.1000436

Mini Review Open Access

# The Role of Circulating Myeloid-Related Protein Complex Calprotectin in Prediction of Heart Failure with Preserved Ejection Fraction

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**Received date:** February 17, 2016; **Accepted date:** April 11, 2016; **Published date:** April 21, 2016



## Abstract

Both phenotypes of heart failure (HF) with preserved (HFpEF) and reduced (HFrEF) ejection fraction associate with various co-morbidities. The role of specific mediators in certain pathological conditions related to HFpEF and reduced HFrEF is not completely investigated. In this context, the discovery of novel biomarkers that might predict the development of HFpEF is attractive. The objective of the mini review: to investigate the potential role of calprotectin in identifying patients at higher risk of HFpEF phenotype development. Calprotectin (known as Myeloid-Related Protein complex 8/14, S100A8/A9) is calcium and zinc binding heterocomplex protein that was found in elevated level in several conditions associated with infections, inflammation, autoimmunity, allografts' rejection, malignancy, obesity/metabolic disorders. In HF individuals calprotectin contributes to maintenance of contractile cardiac function and relaxing ability of ventricles, as well as it might reverse negative force-frequency interrelationship, improve sarcoplasmic reticulum $Ca^{2+}$ uptake and protect against arrhythmia. There is a large spectrum of evidence regarding the role of exaggerated level of calprotectin in prediction adverse clinical outcomes in patients with HFpEF exhibits considerable clinical value and requires more investigations.

**Keywords:** Heart failure; Calprotectin; Stratification; Prediction

## Introduction

Prevalence of heart failure (HF) with preserved left ventricular (LV) ejection fraction (HFpEF) consequently rises for last two decades in development countries and currently nearly half of all novel incidences of HF are defined as HFpEF [1,2]. Development of HFpEF closely associates with several co-morbidities frequently appear to be in age-related manner [3]. Recent epidemiological and observation studies have elucidated that patients with HFpEF compared to those with declined LVEF are not only older, but they are more likely to be women [3,4]. Therefore, HFpEF individuals are referred less likely to have asymptomatic atherosclerosis and coronary artery disease, and more likely to have hypertension, diabetes, LV hypertrophy and atrial fibrillation [3-5]. Nevertheless, patients with HFrEF and HFpEF exhibit a similar risk of mortality rate and risk of re-admission, while the prevalence of sudden death was lower, and that of non-cardiovascular death higher, in HFpEF compared with HFrEF [6,7]. However, for more accurate and earlier diagnosis, exact risk stratification of the patients with HFpEF novel diagnostic algorithms based on imaging, invasive assessment of left ventricular function, and biomarker identification of biomechanical stress are required [7].

In this context, the biomarkers that contribute in development and progression of underlying co-morbidities might be useful to predict of HFpEF manifestation (Figure 1). It has been suggested that some of the specific cardiac structural abnormalities represented in HFpEF phenotype may tightly relate to cardiac myocyte hypertrophy, ventricular interstitial fibrosis, myocardial inflammation, exaggerated oxidative stress, and atherosclerosis.

However, it is so difficult to present distinguished biomarkers for HFpEF and HFrEF, whereas the attempts to propose a signature of biomarkers in this context have been performed [8]. Apart from higher age some circulating biomarkers (i.e. N-terminal pro-B-type natriuretic peptide [NT-proBNP]) have exhibited a prediction of the risk for development of both HFpEF and HFrEF [9]. Contrary, increased NT-proBNP was stronger associated with HFrEF risk, whereas age was more likely related to HFpEF [10,11]. Elevated circulating level of highly sensitive cardiac troponins, previous myocardial infarction, dilated cardiomyopathy, and current smoking status are sufficient predictors for increased risk for HFrEF development, whereas they did not exhibit a discriminative value for HFpEF manifestation [10,12]. Conversely, LV hypertrophy, atrial fibrillation, ST2, cystatin C, growth differentiation factor 15, increased urinary albumin excretion, cardiotrophin-1, and probably soluble endoglin and signature of micro RNA were significantly more associated with HFpEF risk [12-15]. In this context, the discovery of novel biomarkers that might predict the development of HFpEF is attractive.

Based on currently available evidence regarding the role of low-grading inflammation in development and progression of HF phenotypes, several biomarkers that reflect various faces of pathogenesis of inflammation-related cardiac remodeling are widely investigated [16].

There is a large body of evidence that the cardiac remodeling is regulated through epigenetic modifications affected synthesis and secretion of wide spectrum of pro-inflammatory mediators, i.e. interferon-β, matrix metalloproteinases (MMPs), interleukins [13-16]. Calprotectin (a member of the EF-hand proteins) was found as inflammatory marker closely related to inflammatory (Crohn's disease and ulcerative colitis) and none-inflammatory (non-steroidal anti-inflammatory drugs-induced enteropathy) bowel diseases, rheumatic diseases (rheumatoid arthritis and psoriatic arthritis), and cardiovascular events, while its role in HF-related morbidity and

mortality is not completely clear. The aim of the mini review: to investigate the role of circulating calprotectin in identifying patients at higher risk of HFpEF phenotype development.

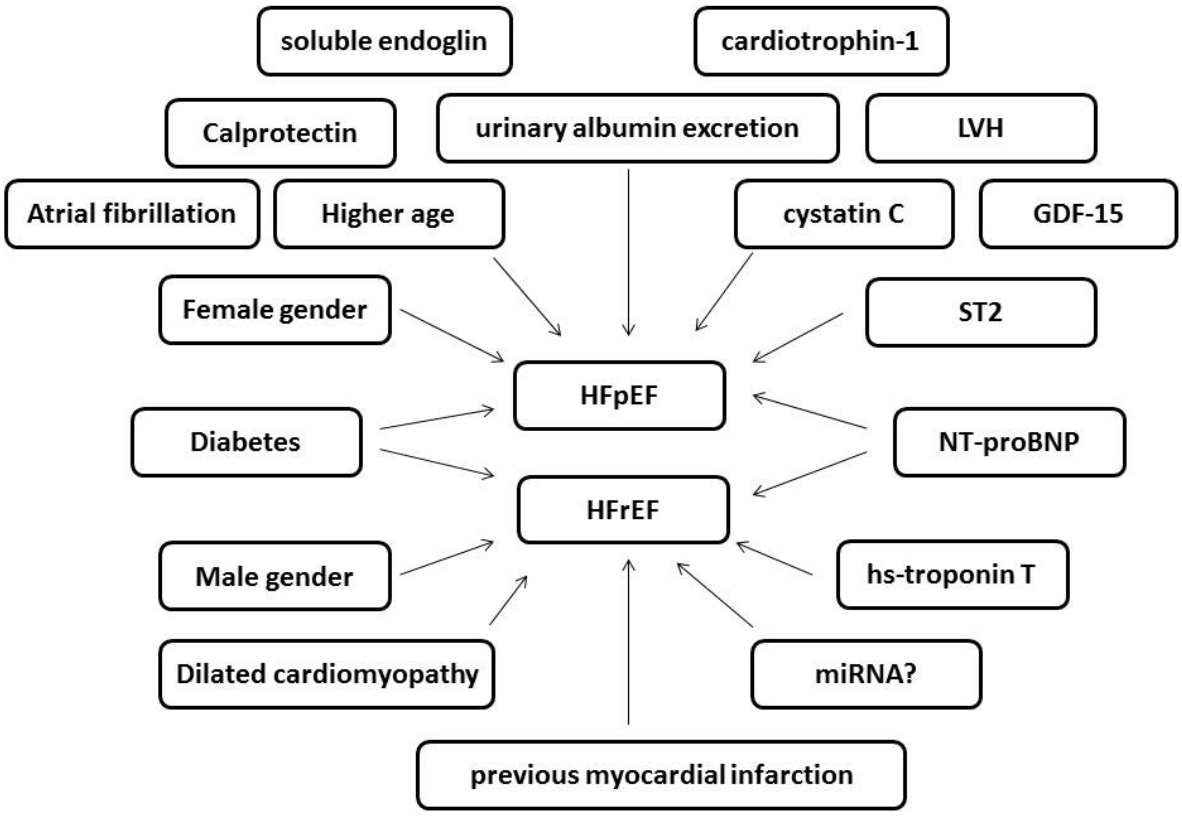


**Figure 1:** Basic biomarkers contributing in HFpEF and HFrEF phenotypes development. LVH: Left Ventricular Hypertrophy; NT-proBNP: N-terminal pro-B-type Natriuretic Peptide; GDF-15: Growth Differentiation Factor 15.

## Calprotectin: The main biological role and function

Calprotectin (known as Myeloid-Related Protein [MRP] complex 8/14, S100A8/A9) is calcium and zinc binding hetero complex protein consisted of two intracellular calcium-binding subunits: S100A8 (MRP8), and S100A9 (also referred to as S100A8/A9 MRP14) [17,18].

Both S100 proteins are abundant in cytosol of phagocytes and exert diverse effects with respect to its intracellular versus extracellular actions, as well as its expressions in various cell types. By now, family of S100 proteins has known as key regulator of cellular function, which has been affected transcriptional activity, intracellular molecular danger signal systems, enzyme activity, NO homeostasis, as well as cell proliferation, differentiation, and survival [19]. The main biological function of calprotectin is referred in the Figure 2.

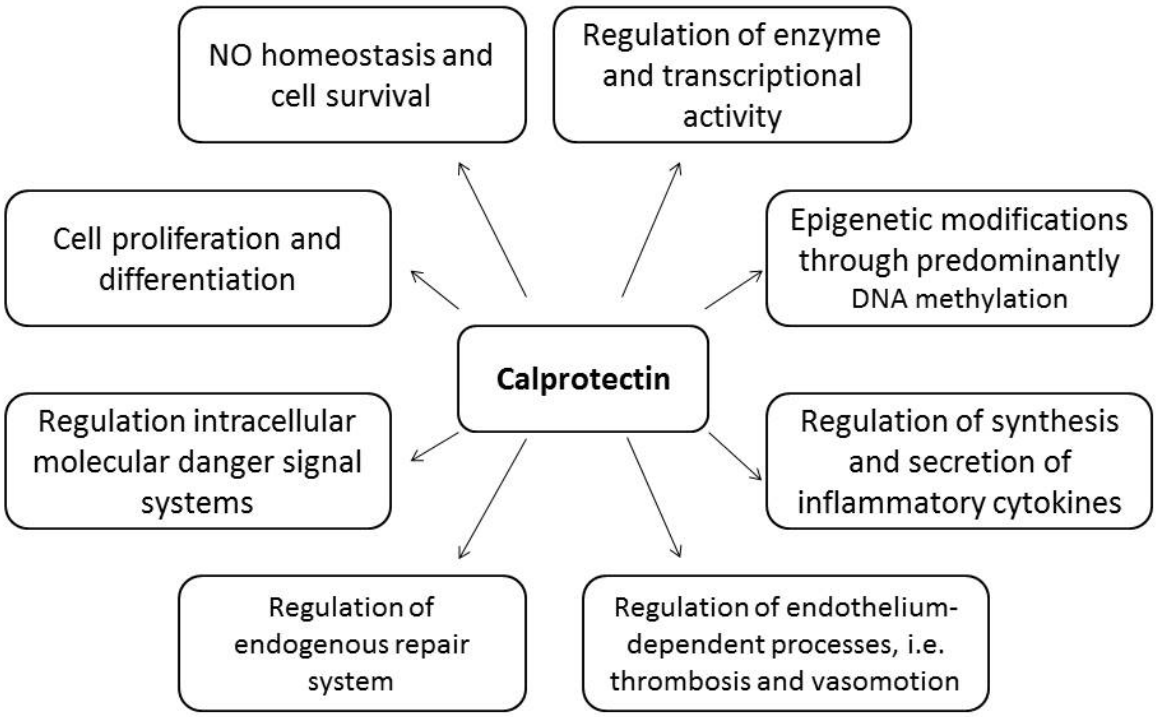


**Figure 2:** The main biological function of calprotectin.

Initially, S100A8/A9 was considered a pro-inflammatory and pro-thrombotic protein complex that was involved in the pathogenesis of infective and rheumatic diseases. Recently the increased circulating levels of S100A8/A9 and over-expressed S100A8/A9 at the surface of the blood cells including platelets and mononuclears were found in several diseases including vasculitis, connective tissue disease, CV disease, dysmetabolic states (e.g. diabetes, metabolic syndrome), allografts' rejection, and malignancy [20], whereas in cytosol of lymphocytes and monocytes received from peripheral blood in healthy volunteers calprotectin is usually not detected [21,22].

The abundant down-regulated expression of calprotectin in activated human innate immunity cells, mononuclears, adipocytes, indicate an exclusive role in immunity [21-23]. Indeed, S100A8/A9 was enriched at sites of membrane interactions, indicating a role of S100A8/A9 in cell-cell communications. S100A8/A9 levels were highly regulated by interferon alpha, both *in vivo* and *in vitro* [20,24,25]. Moreover, S100A8/A9 may acts synergistically with MMP-8 and MMP-10 on tissue remodeling and inflammation regulating cell cycle via increased DNA methylation [22].

Therefore, there is evidence that calprotectin expressed at surface of membranes of neutrophils and monocytes interacts with the advanced glycation end products receptor (RAGE) [26,27]. Calprotectin activates RAGE-mediated inflammatory pathways and increases the expression of adhesion molecules and inflammatory cytokines [28]. Interestingly, that calprotectin contained in the cytosol fraction of mononuclear cells may release immediately after host-pathogen interaction and cytokine stimulation [27] that is essential to discriminate between intracellular and extracellular interaction of these partners [28-32].

The biological effect affecting antimicrobial, cytostatic, and chemotactic modalities of calprotectin could be realized through activation of Toll-like receptor 4 (TLR) and nuclear factor-κB (NF-κB) via nuclear translocation of p65 in target cells [33,34]. All these factors mediate synthesis and secretion of inflammatory cytokines, i.e. interleukin (IL)-6, IL-8, and tumor necrosis factor (TNF)-alpha in inflammasome-dependent manner [35]. There is evidence that calprotectin directly activates NADPH oxidase that is discussed as key tool for inducting apoptotic cascade through activation of both caspase-9 and caspase-3. As result, calprotectin may induce DNA fragmentation that leads to apoptosis and necrosis [36]. In contrast, calprotectin might interplay with IL-1β receptor on bone marrow myeloid progenitor cells and stimulate the production of monocytes/neutrophils that is considered as a clue in response of endogenous repair system affected endothelium and probably endothelium-dependent processes, i.e. thrombosis, vasomotion, inflammation [37].

Additionally, calpotectin expression was reported in the myocardium, up-regulated after myocardial infarction and closely

associated with infarct zine size in the animal model [37-39]. Furthermore, calprotectin contributes to maintenance of contractile cardiac function and relaxing ability of ventricles, as well as it might reverse negative force-frequency interrelationship, improve sarcoplasmic reticulum $Ca^{2+}$ uptake and protect against arrhythmia [40,41]. Finally, there is evidence regarding presence of both protective ability and tissue damage capacity in calprotectin.

## Calprotectin in HFpEF

Although it is well known that increased level of circulating calprotectin is common for HFpEF, the evidence regarding predictive value of calprotectin is limited. However, the role of calprotectin in prognosis of chronic HF is not fully understood. It has been suggested that calprotectin has been related to cardiovascular (CV) disease such as atherosclerosis and it might attenuate the risk for myocardial infarction, stroke, or CV adverse outcomes including death. Raphael et al. [42] reported that increased circulating calprotectin level has identified in HFpEF and may be an associated finding or causal to the disease progression. Imbalzano et al. [43] have also confirmed that increased circulating calprotectin levels were related to an unfavorable clinical outcome in chronic HF attested re-admission and death. Ma et al. [44] reported that elevated calprotectin level exhibited powerful predictive value in mortality for both 6 and 12 months in elderly adults with severe HF. Authors have found a significant positive correlation between calprotectin and IL-6 and IL-8 respectively in this patient population. Moreover, combination IL-6 with calprotectin is able to provide additive prognostic information in this vulnerable HF population especially in the elderly adults.

## Future Perspectives

Taken into consideration, that circulating calprotectin has been proven to play a critical role both in cardiac contractility/relaxation function, endothelium-dependent regulation of vasomotion and probably skeletal muscle function that could be important for understanding of innate mechanisms affected survival of HF individuals. Because the up-regulation of calprotectin is essential for pathological myocardial hypertrophy that contributes to the eventual progression to HFpEF, it has been suggested that this biomarker might be used as molecular target in therapy of HFpEF [45]. However, the direct comparisons of predictive value between calprotectin, natriuretic peptides, galectin-3, ST-2 have still not performed and this is challenging for further investigations in clinical setting for both HFpEF and HFrEF. Nevertheless, practical use of calprotectin as biomarker of HF evolution is challenging, because some reports are available wherein use of non-steroidal anti-inflammatory drugs also increases the fecal and tissue expressed levels of calprotectin through altering of the microbiota [46]. This is a limitation that should be taken into consideration, although the role of non-steroidal anti-inflammatory drugs in changing of circulating levels of calprotectin is not clear.

## Conclusion

The circulating level and tissue expression of calprotectin in various phenotypes of HF could help to stratify the patients at higher risk of disease development and progression. The ability of elevated level of calprotectin to predict clinical outcomes in patients with HFpEF exhibits considerable clinical interest and requires more investigations.

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