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

Alexander E Berezin

Consultant of Cardiology Unit, Internal Medicine Department, State Medical University, Ukraine

*Corresponding author: Alexander E Berezin, Consultant of Cardiology Unit, Internal Medicine Department, State Medical University, 26, Mayakovsky av, Zaporozhye, Ukraine, Tel: +380612894585; E-mail: dr_berezin@mail.ru

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

Copyright: © 2016 Berezin AE. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

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 interrelationship, improve sarcoplasmic reticulum Ca²⁺ 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 observational 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 HFpEF and HFrEF 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 HFrEF and HFpEF [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, cardi trophin-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 non-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.
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-xB (NF-xB) 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, calprotectin expression was reported in the myocardium, up-regulated after myocardial infarction and closely

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

**References**

1. Tsutsui H, Tsuchihashi-Makaya M, Kinugawa S (2010) Clinical characteristics and outcomes of heart failure with preserved ejection fraction: lessons from epidemiological studies. J Cardiol 55:13-22.
2. Tsuchihashi-Makaya M, Hamaguchi S, Kinugawa S, Yokota T, Goto D, et al. (2009) Characteristics and outcomes of hospitalized patients with heart failure and reduced vs preserved ejection fraction. Report from the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). Circ J 73: 1893-1900.
3. Zacharias M, Joffe S, Konadu E, Meyer T, Kiernan M, et al. (2016) Clinical epidemiology of heart failure with preserved ejection fraction (HFpEF) in comparatively young hospitalized patients. Int J Cardiol 202: 918-921.
4. Quiror R, Doros G, Shaw P, Liang CS, Gauthier DF, et al. (2014) Comparison of characteristics and outcomes of patients with heart failure preserved ejection fraction versus reduced left ventricular ejection fraction in an urban cohort. Am J Cardiol 113: 691-696.
5. Kenchaiah S, Vasan RS (2015) Heart Failure in Women--Insights from the Framingham Heart Study. Cardiovasc Drugs Ther 29: 377-390.
6. Hamaguchi S, Kinugawa S, Sobirin MA, Goto D, Tsuchihashi-Makaya M, et al. (2012) Mode of death in patients with heart failure and reduced vs. preserved ejection fraction: report from the registry of hospitalized heart failure patients. Circ J 76: 1662-1669.
7. Borlaug RA, Paulus WJ (2011) Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. Eur Heart J 32: 670-679.
8. Berezin AE (2015) Predicting Heart Failure Phenotypes using Cardiac Biomarkers: Hype and Hope. J Dis Markers. 2: 1035-1041.
9. Sanders-van Wijk S, van Empel V, Davarzani N, Maeder MT, Handschin R, et al. (2015) Circulating biomarkers of distinct pathophysiological pathways in heart failure with preserved vs. reduced left ventricular ejection fraction. Eur J Heart Fail 17: 1006-1014.
10. Brouwers FP, de Boer RA, van der Harst P, Voors AA, Gansevoort RT, et al. (2013) Incidence and epidemiology of new onset heart failure with preserved vs. reduced ejection fraction in a community-based cohort: 11-year follow-up of PREVEND. Eur Heart J 34: 1424-1431.
11. Brunner-La Rocca HP, Kurlings L, Richards AM, Januzzi JL, Pfisterer ME, et al. (2015) Which heart failure patients profit from natriuretic peptide guided therapy? A meta-analysis from individual patient data of randomized trials. Eur J Heart Fail 17: 1252-1261.
12. D’Elia E, Vadugananathan M, Gori M, Gavazzi A, Butler J, et al. (2015) Role of biomarkers in cardiac structure phenotyping in heart failure with preserved ejection fraction: critical appraisal and practical use. Eur J Heart Fail 17: 1231-1239.
13. Huerta A, Lopez B, Ravassa S, San Jose G, Querejeta R, et al. (2016) Association of cystatin C with heart failure with preserved ejection fraction in elderly hypertensive patients: potential role of altered collagen metabolism. J Hypertens 34:130-138.
14. Berezin AE (2016) The Biomarker Utility in Risk Stratification in an Ambulatory Heart Failure: ST2 or Galectin-3? J Cardiology and Therapy 3: 456-458.
15. Berezin AE (2015) The risk stratification in heart failure patients: The controversial role of high-sensitive ST2. J Integr Cardiol 1: 216-217.
16. Berezin AE (2016) Prognostication in different heart failure phenotypes: the role of circulating biomarkers. Journal of Circulating Biomarkers 1-8.
17. Nijhuis J, Rensen SS, Sluots Y, van Dielen FM, Buurman WA, et al. (2009) Neutrophil activation in morbid obesity, chronic activation of acute inflammation. Obesity (Silver Spring) 17: 2014-2018.
18. Schaefer BW, Heizmann CW (1996) The S100 family of EF-hand calcium-binding proteins: functions and pathology. Trends Biochem Sci 21: 134-140.
19. Most P, Rempiss A, Pleger ST, Katus HA, Koch WJ (2007) S100A1: a novel inotropic regulator of cardiac performance. Transition from molecular physiology to pathophysiological relevance. Am J Physiol Regul Integr Comp Physiol 293: 568-577.
20. Lood C, Tydén H, Gullstrand B, Jönsson A, Källberg E, et al. (2016) Platelet-derived S100A8/A9 and cardiovascular disease in systemic lupus erythematosus. Rheumat Res.

21. Sekimoto R, Kishida K, Nakatsuji H, Nakagawa T, Funahashi T, et al. (2012) High circulating levels of S100A8/A9 complex (calprotectin) in male Japanese with abdominal adiposity and dysregulated expression of S100A8 and S100A9 in adipose tissues of obese mice. Biochem Biophys Res Commun 419: 782-789.

22. Sorg C (1992) The calcium binding proteins MRP8 and MRP14 in acute and chronic inflammation. Behring Inst Mitt: 126-137.

23. Goebeler M, Roth J, Burwinkel F, Vollmer E, Böcker W, et al. (1994) Expression and complex formation of S100-like proteins MRP8 and MRP14 by macrophages during renal allograft rejection. Transplantation 58: 355-361.

24. Kerkhoff C, Klemp M, Sorg C (1998) Novel insights into structure and function of MRP8 (S100A8) and MRP14 (S100A9). Biochim Biophys Acta 1448: 200-211.

25. Foell D, Wittkowski H, Vogl T, Roth J (2007) S100 proteins expressed in phagocytes: a novel group of damage-associated molecular pattern molecules. J Leukoc Biol 81: 28-37.

26. Berezin AE (2015) The Myeloid-Related Protein Complex Calprotectin as Biomarker of Cardiovascular Risk in Diabetes Mellitus Patients. Diabetes Res Treat Open Access 2: 129-136.

27. Faust A, Völler T, Busch F, Schafer M, Roth J, et al. (2015) Development and evaluation of a non-peptidic ligand for the molecular imaging of inflammatory processes using S100A9 (MRP14) as a novel target. Chem Commun (Camb) 51: 15637-15640.

28. Berezin AE (2016) The Cardiovascular Risk Prognostication in Diabetes Mellitus: The Role of Myeloid-related Protein Complex Calprotectin. Int J Pathol Clin Res 2: 26-30.

29. Frosch M, Vogl T, Wäldherr R, Sorg C, Sunderkötter C, et al. (2004) Expression of MRP8 and MRP14 by macrophages is a marker for severe forms of glomerulonephritis. J Leukoc Biol 75: 198-206.

30. Sunderkötter CH, Tomimori-Yamashita J, Nix V, Maeda SM, Sindrelaru A, et al. (2004) High expression of myeloid-related proteins 8 and 14 characterizes an inflammmatory active but ineffective response of macrophages during leprosy. Immunology 111: 472-480.

31. Ehren JM, Sunderkötter C, Foell D, Vogl T, Roth J (2009) The endogenous Toll-like receptor 4 agonist S100A8/S100A9 (calprotectin) as innate amplifier of infection, autoimmunity, and cancer. J Leukoc Biol 86: 557-566.

32. Decembrino L, De Amici M, Pozzi M, De Silvestri A, Stronati M (2015) Serum Calprotectin: A Potential Biomarker for Neonatal Sepsis. J Immunol Res 2015: 147973.

33. Catalán V, Gómez-Ambrosi J, Rodríguez A, Ramírez B, Rotellar F, et al. (2011) Increased levels of calprotectin in obesity are related to macrophage content: impact on inflammation and effect of weight loss. Mol Med 17: 1157-1167.

34. Rammes A, Roth J, Goebeler M, Klempt M, Hartmann M, et al. (1997) Myeloid-related protein (MRP) 8 and MRP1, calcium-binding proteins of the S100 family, are secreted by activated monocytes via a novel, tubulin-dependent pathway. J Biol Chem 272: 9496-9502.

35. Kraus C, Rohde D, Weidenhammer C, Qiu G, Pleger ST, et al. (2009) S100A1 in cardiovascular health and disease: closing the gap between basic science and clinical therapy. J Mol Cell Cardiol 47: 445-455.

36. Yui S, Nakatani Y, Mikami M (2003) Calprotectin (S100A8/S100A9), an inflammatory protein complex from neutrophils with a broad apoptosis-inducing activity. Biol Pharm Bull 26: 753–760.

37. Tsoporis JN, Marks A, Haddad A, Dawood F, Liu PP, et al. (2005) S100B expression modulates left ventricular remodeling after myocardial infarction in mice. Circulation 111: 598-606.

38. Cai XY, Xu L, Wang YN, Jin C, Zhang RX, et al. (2011) Association of increased S100B, S100A6 and S100P in serum levels with acute coronary syndrome and also with the severity of myocardial infarction in cardiac tissue of rat models with ischemia-reperfusion injury. Atherosclerosis 217: 536-542.

39. Nagareddy PR, Kraakman M, Masters SL, Stizraker RA, Gorman DJ, et al. (2014) Adipose tissue macrophages promote myelopoesis and monocytosis in obesity. Cell Metab 19: 821-835.

40. Wei X, Wu B, Zhao J, Zeng Z, Xuan W, Cao S, et al. (2015) Myocardial Hypertrophic Preconditioning Attenuates Cardiomyocyte Hypertrophy and Slows Progression to Heart Failure Through Upregulation of S100A8/A9. Circulation 131: 1506-1517.

41. Volz HC, Lahochewin D, Seidl C, Lasitschka F, Keibach K, et al. (2012) S100A8/A9 aggravates post-ischemic heart failure through activation of RAGE-dependent NF-Î³B signaling. Basic Res Cardiol 107: 250.

42. Raphael R, Purushotham D, Gagotungy C, Chesnik MA, Kowk WM, et al. (2016) Combining patient proteomics and in vitro cardiomyocyte phenotype testing to identify potential mediators of heart failure with preserved ejection fraction. J Transl Med 14: 18.

43. Imbalzano E, Mandrannino G, Casciaro M, Quartuccio S, Saitta A, et al. (2016) Pathophysiological mechanism and therapeutic role of S100 proteins in cardiac failure: a systematic review. Heart Fail Rev.

44. Ma JP, Haugen E, Ikemoto M, Fujita M, Terasaki F, et al. (2012) S100A8/A9 complex as a new biomarker in prediction of mortality in elderly patients with severe heart failure. Int J Cardiol 155: 26-32.

45. Berezin AE (2015) Biological markers of cardiovascular diseases. Part 4. Diagnostic and prognostic value of biological markers at risk stratification among patients with heart failure. LAMBERT Academic Publishing GmbH, Moscow: 329.

46. Whitfield-Cargile CM, Cohen ND, Chapkin RS, Weeks BR, Davidson LA, et al. (2016) The microbiota-derived metabolite indole decreases mucosal inflammation and injury in a murine model of NSAID enteropathy. Gut Microbes 23: 1-16.