A review of indicators for heart failure in people with hypertension

[1]Dr. Jyoti Batra, [2]Dr. Juhi Aggarwal, [3]Dr Sanjukta Naik, [4]Shailja Yadav

[1]Professor, Department of Biochemistry, Santosh Medical College and Hospital, Santosh deemed to be University, Ghaziabad, Uttar Pradesh -201009.

[2]Professor & Head, Department of Biochemistry,Santosh Medical College and Hospital, Santosh deemed to be University, Ghaziabad, Uttar Pradesh -201009

[3]Assistant Professor**,** Department of Biochemistry, Santosh Medical College and Hospital, Santosh deemed to be University, Ghaziabad, Uttar Pradesh -201009

[4]MBBS Student, Batch 2021-22,Santosh Medical College and Hospital, Santosh deemed to be University, Ghaziabad, Uttar Pradesh-201009

ABSTRACT

High sensitivity, specificity, repeatability, cost-effectiveness, and incremental predictive or diagnostic efficacy over conventional risk factors or tests are required of biomarkers. Only a few biomarkers have been shown to accurately predict heart failure (HF) in hypertensive patients, despite several studies looking at these biomarkers. This article compiles information from a number of studies on potential biomarkers of HF in hypertensive patients, including serum uric acid (SUA), interleukins, monocyte chemoattractant protein one (MCP1), cardiotrophin-1 (CT-1), carboxy-terminal propeptide of procollagen type I (PICP), type I collagen telopeptide (CITP), and N-terminal propeptide of type III procollagen (PIIINP Early implementation of efficient preventive measures may arise from patient identification of elevated risk for hypertensive heart disease.In order to identify patients for whom earlier or more aggressive action can enhance clinical outcomes, it is necessary to develop newer biomarkers that can improve risk prediction.

Keywords: diagnosis, heartfailure, hypertension, biomarkers, blood pressure.

INTRODUCTION

Biomarkers are useful for both prognostic and diagnostic purposes. A biological marker (biomarker) should be an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention that can be objectively measured and evaluated, represent a feature or variable that measures how a patient feels, functions, or survives, and act as a stand-in for a clinical endpoint, according to the Biomarkers Definitions Working Group's (2001) recommendations [1,2]. As a result, the perfect biomarker would be highly sensitive, specific, and reproducible. Additionally, it would offer incremental clinical outcome prediction and better clinical value than demographic factors, commonly used clinical diagnostics, and risk factor evaluations. It should also be economical and practical from a technical standpoint [3]. Although new biomarkers are constantly being developed, their application may be restricted. In an effort to improve their predictive power, attempts have also been made to combine different biomarkers to create multiple biomarker indices.

Although there are many studies looking into biomarkers in heart failure (HF), there aren't many that link these markers to HF in people with high blood pressure. This is crucial because one of the key predictors

of HF is thought to be hypertension. Chronic heart failure (CHF), cardiac function changes, and left ventricular structural remodelling have all been linked to persistent hypertension [4-6].

The outlook for HF is quite grim. In patients with the most severe HF, the 1-year survival rate is only slightly better than 50%, and the average 4-year survival rate is only around 50% [4]. The prognosis for this condition is comparable to or worse than that of advanced cancer [3,4].

For individuals with uncomplicated essential hypertension, left ventricular hypertrophy (LVH), which has been established by echocardiography, is a potent, independent risk factor for future cardiovascular (CV) morbidity and mortality [11–13]. The best independent predictors of CV events or CV death in patients with hypertension, according to Koren et al. [8], are LVH and age. These findings highlight the significance of starting hypertension medication at its peak early and beginning symptomatic treatment for heart failure early in order to stop the development of severe disease. According to the most recent European Society of Hypertension (ESH) guidelines, searching for subclinical organ damage is an essential component of quantitative risk assessment in hypertension patients [14]. Patients with well-controlled hypertension may in clinical settings describe activity restriction and/or stenocardial pain, which are not captured by a typical conventional resting echocardiogram. On an electrocardiographic stress test and during a coronary angiography, there are frequently no indications of coronary artery disease (CAD) [14,15]. To enable the early detection of irregularities before the emergence of symptoms and, thus, to enable the adoption of the best treatment, it is crucial to construct a panel of diagnostic tests in patients with hypertension.

The biomarkers discussed in this article were chosen based on novelness and predictability, as well as the most recent data that suggests their potential utility in the diagnosis of left ventricular failure in patients with hypertension.

SEARCH STRATEGY

Electronic databases [MEDLINE (1966–December 2011), EMBASE and SCOPUS (1965–December 2011), and DARE (1966–December 2011)] were used for our search. In addition, abstracts from regional and global CV meetings were looked at. To get more information, the appropriate writers were contacted as needed. Biomarker(s), blood pressure (BP), diagnostic, heart failure (HF), hypertension, and marker were the primary data search terms (s).

SERUM URIC ACID

In both chronic and acute heart failure (AHF), hyperuricemia is an independent predictive factor for mortality and morbidity [16–18]. High SUA levels are present in 25–40% of patients with untreated hypertension and in more than 80% of patients with malignant hypertension [19,20]. Echocardiographic left ventricular mass and SUA levels were shown by Kurata et al. [11] to positively and significantly correlate in male hypertension patients. The patients with concentric hypertrophy had the greatest SUA levels, according to a classification of these patients made on the basis of their left ventricular geometry pattern [11]. Given that SUA is a potent antioxidant, epidemiological studies that found a link between SUA and CV risk [20,21] were somewhat unexpected.

SUA inhibits the generation of peroxynitrite and the inactivation of nitric oxide (NO) by superoxide anions while defending against the harm caused by free radicals [20]. According to some research, SUA, which functions as an antioxidant under physiologically normal circumstances, has negative effects on the atherosclerotic state, including endothelial dysfunction, vascular smooth muscle cell proliferation, increases in platelet adhesiveness, oxidation of low-density lipoprotein cholesterol (LDL-C), and lipid peroxidation [20,22]. SUA concentrations are also linked to increased superoxide dismutase activity and endothelium-dependent vasodilation in CHF patients [23]. In hypertensive patients, both LVH and increased SUA may be signs of preclinical CV illness, which may be reversible with efficient treatment measures [24,25]. SUA as a time-varying covariate was strongly related with an elevated risk of the composite endpoint in the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) study (P 0.0001) [25]. Even after accounting for additional CV risk variables in women, the baseline SUA concentration had a significant impact on the composite endpoint [25]. When recognised risk factors were taken into account independently, there was, however, only a minor connection in men [25].

Losartan significantly decreased the risk of the primary composite endpoint by 29% (P 0.004) by attenuating the rise in SUA [25]. The LIFE trial demonstrated for the first time that decreasing SUA has positive effects on the course of treatment for hypertension [25]. Another study that showed that hyperuricemia can predict HF in those with preexisting hypertension was the Samuelsson et al. [26] study. Ekundayo et al. [27] found that the link between hyperuricemia and concurrent HF was only significant in patients without hypertension [hazard ratio 1.31; 95% confidence interval (CI): 1.03-1.66; P 0.03].

The impact of SUA on CV risk has been attributed to a number of different mechanisms. SUA values have been proposed as a potential indicator of CV risk because they may reflect a reduced glomerular filtration rate (GFR) [25]. However, SUA continued to be a predictor of CV events in the LIFE trial after accounting for renal function indicators, pointing to a distinct mechanism [25]. High levels of SUA in people have a positive correlation with plasma renin activity in hypertensive patients [28], which raises the possibility that SUA's negative effects on the cardiovascular system may be mediated through activation of the renin-angiotensin-aldosterone (RAA) system [25,28].

Increased SUA production may also be linked to hyperuricemia-induced HF, which is most likely caused by elevated xanthine oxidase (XO) substrate levels as well as an upregulation and increase in XO activity [17,19]. Allopurinol's suppression of the XO enzyme has positive effects on peripheral vasodilator capacity, systemic blood flow, and clinical outcomes [29,30].

SUA can have extra negative effects on the cardiovascular system and can influence how the immune system reacts [17,19,31]. C-reactive protein (CRP), interleukin (IL)-6, and neutrophil count are serum markers of inflammation that are elevated in HF patients who also have hyperuricemia [32], as are markers of endothelial activation such as soluble intercellular adhesion molecule-1 (sICAM-1) and elevated inflammatory markers such as IL-6,

tumour necrosis factor (TNF)-a, and its receptors. [18,25,29,33–46]

INTERLEUKINS AND MONOCYTECHEMOATTRACTANT PROTEIN-1

Patients with acute and chronic HF can use a variety of inflammatory biomarkers as predictors of long-term prognosis [47]. When target organ damage is present, elevated inflammatory markers that are not seen in isolated hypertension become obvious [37,48,49]. Significantly raised IL-6, MCP-1, and IL-8 levels were seen in hypertensive individuals with symptoms of HF, according to Collier et al. [37]. The amount of IL-6 appeared to be linked to damage to target organs, significant unfavourable CV event rates, and cardiomyocyte hypoxic stress [37,50]. When MCP-1 is released, cardiac myocytes are invaded by macrophages, transforming growth factor (TGF)-b is induced, reactive fibrosis develops, and diastolic dysfunction occurs [37,51]. IL-4 has been proposed as an additional HF marker. It is an anti-inflammatory cytokine that stimulates the synthesis of collagen types I and III and inhibits the production of inflammatory cytokines [52]. In patients with hypertension cardiomyopathy, Rosello'-Llet' E et al. [52] found increased amounts of IL-4 and N-terminal propeptide of type III procollagen(PIIINP). Additionally, they found that patients with CHF, particularly those with hypertension cardiomyopathy, had a substantial positive correlation between IL-4 and PIIINP (r 14 0.7, P 0.01) [52]. This was most likely caused by these patients' elevated profibrotic activity [52,53].

In hypertensive individuals, elevated hsCRP and myeloperoxidase (MPO) levels have been proposed as indicators of HF [47]. The combined analysis of these two indicators showed a sixfold increased risk of HF (95% CI: 2.4-16.8; P 0.01) when both markers were elevated, despite the lack of a significant connection between log-transformed hsCRP and MPO [47]. The authors claim that individuals with persistent systolic HF may have separate and complementary prognostic value when concurrent hsCRP and MPO measures are taken [47,54].

CARDIOTROPHIN-1

A prolonged increase in CT-1 levels has been theorised to be linked to the development of HF in hypertensive patients [38]. IL-6 superfamily cytokine CT-1 was initially thought to have an impact on cardiomyocyte hypertrophy and survival [38,55,56].

The heterodimer made up of the glycoprotein 130 (gp130) and the leukaemia inhibitory factor receptor b (LIFR) is how it affects cells [57]. As shown by the correlation between ventricular CT-1 mRNA and LVH, CT-1 likely plays a significant role in the structural remodelling of the heart [58]. In systemic arterial hypertension, the hypertrophy of the left ventricle (LV) is a compensatory mechanism that aids the hemodynamically overloaded myocardium in maintaining normal left ventricular function [59,60].

The activation of pressure overload-induced humoral growth hormones and the cell response to mechanical strain both contribute to the adaptive expansion of cardiomyocytes in LVH [59,60].In spontaneously hypertensive rats (SHR), CT-1 may support cardiomyocyte hypertrophy and left ventricular expansion, according to experimental research [61]. However, other investigations have shown

that CT-1 is unlikely to have a mechanistic impact on the rat model of LVH formation and maintenance [57,62-64].

When it comes to identifying stage C HF in hypertensive patients, CT-1 is more sensitive than N-terminal pro-B-type natriuretic peptide (NT-proBNP) but has less specificity [38]. However, it appears that simultaneous measurement of plasma CT-1 and serum NT-proBNP may improve the capacity to identify hypertensive patients with stage C HF. Increased NT-proBNPwas linked to lower GFR, but increased CT-1 was linked to left ventricular hypertrophy and dysfunction as determined by echocardiography. [38,40]

FIBROSIS BIOMARKERS

Myocarditis and CHF-related inflammatory fibrosis are both characterised by excessive collagen synthesis and deposition by fibroblasts [50, 51]. According to a cross-sectional study [41], changes in the level of serological fibrosis markers were linked to the progressive decline in heart function in hypertensive individuals with HF.

In hypertensive patients with NYHA classes III and IV as well as the upper LVMI tertile, the amount of plasma PIIINP was considerably higher, indicating increased collagen production [41]. Additionally, it was found that the procollagen type I (PIP) / CITP ratio fell while the levels of type I collagen telopeptide (CITP) increased, both of which may indicate that collagen I catabolism was the major process [41]. However, NYHA classes I and II did not show a change in the levels of the serological indicators of collagen production and breakdown [41]. This may be accounted for by the overlapping effects of various extracellular matrix turnover-influencing agents, including metalloproteinases (MMPs) and their tissue inhibitors [41]. As a biomarker of collagen type 1 synthesis, the serum carboxy-terminal propeptide of procollagen type I (PICP) has been proposed [42]. In hypertensive individuals with HF with normal ejection fraction (HFNEF), altered levels of plasma tissue inhibitor of metalloproteinase-1 (TIMP-1) and serum PICP have been found [51,71,72,73].

METALLOPROTEINASES

TIMPs have been hypothesised to be elevated and MMPs to be diminished in hypertensive heart disease [78,79]. Reduced collagen breakdown and increased collagen buildup are related to this [6]. The increased fibrillar collagen quantity, changed fibrillar collagen shape, and elevated collagen I to III isotype ratio have all been linked to hypertensive heart disease in experimental and clinical studies [6,80,81]. In hypertensive heart disease, MMP-2 and MMP-9 expression is altered, indicating that their activation aids in myocardial remodelling [6, 82]. Data from multiple investigations indicate that MMP-2 levels steadily rise following the beginning of an acute myocardial infarction [83,84]. After an acute myocardial infarction, the serum content of MMP-9 drops for a few days before progressively increasing [84,85]. Reduced MMP-2 and elevated MMP-9 levels, according to research by Ahmed et al. [6], may be a factor in the structural and functional cardiac alterations associated with hypertensive heart disease.Collier et al. [37] similarly noted significant elevations of MMP2 and MMP9 levels in the context of HF symptoms.

BNPAND ITS DERIVATIVES

Natriuretic peptides [43,86,87] and tumour marker antigen carbohydrate 125 (CA125) [88,89] have both been proposed as biomarkers that may be helpful in assessing the severity of the disease and predicting clinical outcomes in AHF patients [90].

GLYCOPROTEIN CA125

Epithelial serosal cells produce glycoprotein CA125 in response to fluid buildup [97,98] and proinflammatory stimulation [99]. A greater NYHA class and symptoms of fluid congestion are linked to an elevated antigen carbohydrate 125 level [98,100,101]. Increased levels of glycoprotein CA125 have been demonstrated to negatively correlate with the deceleration time of early filling on transmitral Doppler [89,90] and to directly correlate with the pulmonary artery wedge and right atrial pressures [88,89,102]. According to Nu'nez et al. [90], a higher CA125 was linked to a higher 6-month mortality. It has been proposed that measuring both of their levels following initial treatment for AHF could provide a better tool for risk stratification because CA125 and BNP reflect different pathophysiological mechanisms for the progression of HF and because fluctuations of both biomarkers have been observed in response to treatment [90].

CYSTATIN C

The involvement of CysC in hypertensive patients is also significant since renal impairment, which may manifest very early in this group of patients, also indicates the severity of HF [103].A protein called CysC, which belongs to the class of cysteine proteinase inhibitors, has 120 amino acids [104]. All of the body's nucleated cells express the gene that gave rise to it. It quickly gets through glomerular filtration because of its low molecular weight and high isoelectric point [46].It is absorbed and then catabolized in the proximal tubule, preventing its return to circulation [46]. Urinary analysis cannot estimate CysC clearance because of the low content of CysC in urine. However, its plasma concentration and GFR are correlated [46,104].Age-related increases in CysC concentration are independent of sex, muscle mass, or BMI [46].

CONCLUSION

Early identification of individuals with a higher risk of developing hypertensive heart disease may make it easier to apply effective preventive measures sooner, like more vigilant blood pressure monitoring and other risk factor control [37,108,109]. Furthermore, high-risk individuals may be the best candidates for interventional trials evaluating innovative medications intended to prevent HF. There are currently just a few established indicators for HF in hypertensive patients. There is a need for a broad search for novel markers that are independent of demographic variables and have high sensitivity, specificity, repeatability, and biovariability.

REFERENCES

1. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. ClinPharmacolTher 2001; 69:89–95.
2. Bakhtiar R. Biomarkers in drug discovery and development. J PharmacolToxicol Methods 2008; 57:85–91.

3. Lainscak M, von Haehling S, Anker SD. Natriuretic peptides and other biomarkers in chronic heart failure: from BNP, NT-proBNP, and MRproANP to routine biochemical markers. Int J Cardiol 2009; 132:303–311.
4. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KKL. The progression from hypertension to congestive heart failure. JAMA 1996; 275:1557– 1562.
5. Kenchaiah S, Pfeffer MA. Cardiac remodeling in systemic hypertension. Med Clin North Am 2004; 88:115–130.
6. Ahmed SH, Clark LL, Pennington WR, Webb CS, Bonnema DD, Leonardi FH, et al. Matrix metalloproteinases/tissue inhibitors of metalloproteinases: relationship between changes in proteolytic determinants of matrix composition and structural, functional, and clinical manifestations of hypertensive heart disease. Circulation 2006; 113:2089–2096.
7. Casale PN, Devereux RB, Milner M, Zullo G, Harshfield GA, Pickering TG, Laragh JH. Value of echocardiographic measurement of left ventricular mass in predicting cardiovascular morbid events in hypertensive men. Ann Intern Med 1986; 105:173–178.
8. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. Ann Intern Med 1991; 114:345–352.
9. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Left ventricular mass and incidence of coronary heart disease in an elderly cohort: the Framingham Heart Study. Ann Intern Med 1989; 110:101– 107.
10. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med 1990; 322:1561–1566.
11. Kurata A, Shigematsu Y, Higaki J. Sex-related differences in relations of uric acid to left ventricular hypertrophy and remodeling in Japanese hypertensive patients. Hypertens Res 2005; 28:133–139.
12. Banach M, Bhatia V, Feller MA, et al. Relation of baseline systolic blood pressure and long-term outcomes in ambulatory patients with chronic mild to moderate heart failure. Am J Cardiol 2011; 107:1208– 1214.
13. Bielecka-Dabrowa A, Rysz J, Mikhailidis DP, Banach M. What is the risk of hyperkalaemia in heart failure? Expert OpinPharmacother 2011; 12:2329–2338.
14. Mancia G, Laurent S, Agabiti-Rosei E, Ambrosoni E, Burnier M, Caulfield MJ, et al. European Society of Hypertension. Reappraisal of european guidelines on hypertension management: a european society of hypertension task force document. J Hypertens 2009; 27:2121–2158.
15. Karasek D, Sinkiewicz W, Blazejewski J. Relationship between Btype natriuretic peptide serum level, echocardiographic TEI index and the degree of diastolic dysfunction in patients with heart failure with preserved systolic function. Arch Med Sci 2011; 7:449– 456.
16. Anker SD, Coats AJS. Metabolic, functional, and hemodynamic staging for CHF? Lancet 1996; 348:1530.

17. Patel PD, Arora RR. Uric acid and xanthine oxidase: perspectives in chronic heart failure. Arch Med Sci 2008; 4:219–225.
18. Anker SD, Doehner W, Rauchhaus M, et al. Uric acid and survival in chronic heart failure: validation and application in metabolic, functional, and hemodynamic staging. Circulation 2003; 107:1991–1997.
19. Feig DI, Kang DH, Johnson RG. Uric acid and cardiovascular risk. N Engl J Med 2008; 359:1811–1821.
20. Iliesiu A, Campeanu A, Dusceac D. Serum uric acid and cardiovascular disease. J Clin Med 2010; 5:186–192.
21. Fang J, Alderman MH. The NHANES I Epidemiologic Follow-up Study, 1971–1992. JAMA 2000; 283:2404–2410.
22. Nieto FJ, Iribarren C, Gross MD, et al. UA and serum antioxidant capacity: a reaction to atherosclerosis? Atherosclerosis 2000; 148:131– 139.
23. Alcaino H, Greig D, Chiong M, Verdejo H, Miranda R, Concepcion R, et al. Serum uric acid correlates with extracellular superoxide dismutase activity in patients with chronic heart failure. Eur J Heart Fail 2008; 10:646–651.
24. Verdecchia P, Reboldi G, Schillaci G, Borgioni C, Ciucci A, Telera MP, et al. Circulating insulin and insulin-like growth factor-1 are independent determinants of left ventricular mass and geometry in essential hypertension. Circulation 1999; 100:1802–1807.
25. Høieggen A, Alderman MH, Kjeldsen SE, Julius S, Devereux RB, De Faire U, et al. The impact of serum uric acid on cardiovascular outcomes in the LIFE study. Kidney Int 2004; 65:1041–1049.
26. Samuelsson O, Wilhelmsen L, Pennert K, Berglund G. Angina pectoris, intermittent claudication and congestive heart failure in middleaged male hypertensives. Development and predictive factors during long-term antihypertensive care. The Primary Preventive Trial, Go¨teborg, Sweden. Acta Med Scand 1987; 221:23–32.
27. Ekundayo OJ, Dell'Italia LJ, Sanders PW, Arnett D, Aban I, Love TE, et al. Association between hyperuricemia and incident heart failure among older adults: a propensity-matched study. Int J Cardiol 2010; 142:279–287.
28. Saito I, Saruta T, Kondo K, et al. Serum uric acid and the reninangiotensin system in hypertension. J Am GeriatrSoc 1978; 26:241– 247.
29. Krishnan E. Hyperuricemia and incident heart failure. Circulation 2009; 2:556–562.
30. Doehner W, Schoene N, Rauchhaus M, Leyva-Leon F, Pavitt DV, Reaveley DA, et al. Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricemic patients with chronic heart failure: results from 2 placebo-controlled studies. Circulation 2002; 105:2619–2624.
31. Lippi G, Mantagna M, Franchini M, Favaloro EJ, Targher G. The paradoxical relationship between serum acid uric and cardiovascular disease. ClinChimActa 2008; 392:1–7.
32. Kanellis J, Kang DH. Uric acid as a mediator of endothelial dysfunction, inflammation, and vascular disease. SeminNephrol 2005; 25:39– 42.

33. Leyva F, Anker SD, Godsland IF, Teixeira M, Hellewell PG, Kox WJ, et al. Uric acid in chronic heart failure: a marker of chronic inflammation. Eur Heart J 1998; 19:1814–1822.
34. Bielecka-Dabrowa A, Goch JH, Mikhailidis DP, Rysz J, Maciejewski M, Banach M. The influence of atorvastatin on parameters of inflammation and function of the left ventricle in patients with dilated cardiomyopathy. Med SciMonit 2009; 15:MS12–MS23.
35. Athyros VG, Karagiannis A, Ganotakis ES, Paletas K, Nicolaou V, Bacharoudis G, et al. Assessing The Treatment Effect in Metabolic syndrome without Perceptible diabeTes (ATTEMPT) Collaborative Group. Association between the changes in renal function and serum uric acid levels during multifactorial intervention and clinical outcome in patients with metabolic syndrome. A post hoc analysis of the ATTEMPT study. Curr Med Res Opin 2011; 27:1659–1668.
36. Karagiannis A, Mikhailidis DP, Tziomalos K, Sileli M, Savvatianos S, Kakafika A, et al. Serum uric acid as an independent predictor of early death after acute stroke. Circ J 2007; 71:1120–1127.
37. Tang WH, Shrestha K, Troughton RW, Borowski AG, Klein AL. Integrating plasma high-sensitivity C-reactive protein and myeloperoxidase for risk prediction in chronic systolic heart failure. Congest Heart Fail 2011; 17:105–109.
38. Navarro-Gonzalez JF, Mora C, Muros M, Jarque A, Herrera H, Garcia J. Association of tumor necrosis factor-alpha with early target organ damage in newly diagnosed patients with essential hypertension. J Hypertens 2008; 26:2168–2175.
39. Mujib M, Desai R, Levitan EB, Howard V, Howard G, McGwin G, Mujib M. Prospective population studies of incident heart failure without data on baseline left ventricular ejection fraction. Arch Med Sci 2010; 6:686–688.
40. Collier P, Watson CJ, Voon V, Phelan D, Jan A, Mak G, et al. Can emerging biomarkers of myocardial remodelling identify asymptomatic hypertensive patients at risk for diastolic dysfunction and diastolic heart failure? Eur J Heart Fail 2011; 13:1087–1095.
41. Melendez GC, McLarty JL, Levick SP, Du Y, Janicki JS, Brower GL. Interleukin 6 mediates myocardial fibrosis, concentric hypertrophy, and diastolic dysfunction in rats. Hypertension 2010; 56: 225–231.
42. Kuwahara F, Kai H, Tokuda K, Takeya M, Takeshita A, Egashira K, Imaizumi T. Hypertensive myocardial fibrosis and diastolic dysfunction: another model of inflammation? Hypertension 2004; 43:739– 745.
43. Rosello´-Lletı´ E, Rivera M, Bertomeu V, Corte´s R, Jorda´n A, Gonza´lezMolinad A. Interleukin-4 and cardiac fibrosis in patients with heart failure. Rev EspCardiol 2007; 60:777–780.
44. Lo´pez B, Gonza´lez A, Querejeta R, Larman M, Dı´ez J. Alterations in the pattern of collagen deposition may contribute to the deterioration of systolic function in hypertensive patients with heart failure. J Am CollCardiol 2006; 48:89–96.
45. Malyszko J, Zbroch E, Malyszko J, Mysliwiec M, Iaina A. The

cardiorenal-anaemia syndrome predicts survival in peritoneally dialyzed patients. Arch Med Sci 2010; 6:539–544.

46. Lo´pez B, Gonza´lez A, Querejeta R, Barbac J, Dı´ez J. Association of plasma cardiotrophin-1 with stage C heart failure in hypertensive patients: potential diagnostic implications. J Hypertens 2009; 27:418– 424.
47. Pennica D, King KL, Shaw KJ, Luis E, Rullamas J, Luoh SM, et al. Expression cloning of cardiotrophin-1, a cytokine that induces cardiac myocyte hypertrophy. ProcNatlAcadSci USA 1995; 92:1142–1146.
48. Sheng Z, Pennica D, Wood WI, Chien KR. Cardiotrophin-1 displays early expression in the murine heart tube and promotes cardiac myocyte survival. Development 1996; 122:419–428.
49. Lo´pez N, Dı´ez J, Fortun˜o MA. Characterization of the protective effects of cardiotrophin-1 against nonischemic death stimuli in adult cardiomyocytes. Cytokine 2005;30:282–292.
50. Jougasaki M, Tachibana I, Luchner A, Leskinen H, Redfield MM, Burnett JC Jr. Augmented cardiac cardiotrophin-1 in experimental congestive heart failure. Circulation 2000; 101:14–17.
51. Sadoshima J, Izumo S. The cellular and molecular response of cardiac myocytes to mechanical stress. Annu Rev Physiol 1997; 59:551–571.
52. Gonza´lez A, Lo´pez B, Ravassa S, Beaumont J, Arias T, Hermida N, et al. Biochemical markers of myocardial remodeling in hypertensive heart disease. Cardiovasc Res 2009; 81:509–518.
53. Lo´pez N, Dı´ez J, Fortun˜ MA. Differential hypertrophic effects ofcardiotrophin-1 on adult cardiomyocytes from normotensive and spontaneously hypertensive rats. J Mol Cell Cardiol 2006; 41:902–913.
54. Ishikawa M, Saito Y, Miyamoto Y, Harada M, Kuwahara K, Ogawa E, et al. A heart-specific increase in cardiotrophin-1 gene expression precedes the establishment of ventricular hypertrophy in genetically hypertensive rats. J Hypertens 1999; 17:807–816.
55. Ishikawa M, Saito Y, Miyamoto Y, Kuwahara K, Ogawa E, Nakagawa O, Nakao K. cDNA cloning of rat cardiotrophin-1 (CT-1): augmented expression of CT-1 gene in ventricle of genetically hypertensive rats. BiochemBiophys Res Commun 1996; 219:377–381.
56. Lo´pez N, Varo N, Dı´ez J, Fortun´o MA. Loss of myocardial LIF receptor in experimental heart failure reduces cardiotrophin-1 cytoprotection. A role for neurohumoral agonists? Cardiovasc Res 2007; 75:536–545.
57. Banach M, Kjeldsen SE, Narkiewicz K. Controversies in hypertension treatment. CurrVascPharmacol 2010; 8:731–732.
58. Lo´pez B, Castellano JM, Gonza´lez A, Barba J, Dı´ez J. Association of increased plasma cardiotrophin-1 with inappropriate left ventricular mass in essential hypertension. Hypertension 2007; 50:977–983.
59. Gonza´lez A, Ravassa S, Loperena I, Lo´pez B, Beaumont J, Querejeta R, et al. Association of depressed cardiac gp130-mediated antiapoptotic pathways with stimulated cardiomyocyte apoptosis in

hypertensive patients with heart failure. J Hypertens 2007; 25:2148–2157.
60. Gonza´lez A, Lo´pez B, Martı´n-Raymondi D, Lozano E, Varo N, Barba J, et al. Usefulness of plasma cardiotrophin-1 in assessment of left ventricular hypertrophy regression in hypertensive patients. J Hypertens 2005; 23:2297–2304.
61. Lo´pez-Andre´s N, In˜igo C, Gallego I, Dı´ez J, Fortun˜o MA. Aldosterone induces n-1 expression in HL-1 adult cardiomyocytes. Endocrinology 2008; 149:4970–4978.
62. Yasukawa H, Hoshijima M, Gu Y, Nakamura T, Pradervand S, Hanada T, et al. Suppressor of cytokine signaling-3 is a biomechanical stressinducible gene that suppresses gp130-mediated cardiac myocyte hypertrophy and survival pathways. J Clin Invest 2001; 108:1459– 1467.
63. Liao Z, Brar BK, Cai Q, Stephanou A, O'Leary RM, Pennica D, et al. Cardiotrophin-1 (CT-1) can protect the adult heart from injury when added both prior to ischaemia and a reperfusion. Cardiovasc Res2002; 53:902–910.
64. Monserrat L, Lo´pez B, Gonza´lez A, Hermida M, Ferna´ndez X, Ortiz M, et al. Cardiotrophin-1 plasma levels are associated with the severity of hypertrophy in hypertrophic cardiomyopathy. Eur Heart J 2011; 32:177–183.
65. Plaksej R, Kosmala W, Frantz S, Hermann S, Niemann M, Sto¨rk S, et al. Relation of circulating markers of fibrosis and progression of left and right ventricular dysfunction in hypertensive patients with heart failure. J Hypertens 2009; 27:2483–2491.
66. Querejeta R, Varo N, Lo´pez B, Larman M, Artin˜ano E, Etayo JC, et al. Serum carboxy-terminal propeptide of procollagentype I is a marker of myocardial fibrosis in hypertensive heart disease. Circulation 2000; 101:1729–1735.
67. Gonza´lez A, Lo´pez B, Querejeta R, Zubillaga E, Echeverrı´a T, Dı´ez J. Filling Pressures and Collagen Metabolism in Hypertensive Patients With Heart Failure and Normal Ejection Fraction. Hypertension 2010; 55:1418–1424.
68. Alagiakrishnan K, Banach M, Jones LG, Ahmed A, Datta S, Aronow WS. Update on diastolic heart failure or heart failure with normal ejection fraction in the elderly. Ann Med 2012; doi:10.3109/ 07853890.2012.660493 (in press).
69. Querejeta R, Lo´pez B, Gonza´lez A, Sa´nchez E, Larman M, MarftinezUbago JL, Dı´ez J. Increased collagen type I synthesis in patients with heart failure of hypertensive origin: relation to myocardial fibrosis. Circulation 2004; 110:1263–1268.
70. Baker KM, Chernin MI, Wixson SK, Aceto JF. Renin-angiotensin system involment in pressure overload cardiac hypertrophy in rats. Am J Physiol 1980; 259:H324–H332.
71. Komuro M, Kurabyashi M, Takuku F, Yazaki Y. Expression cellular oncogenes in the myocardium during the developmental stage and pressure overload hypertrophy of the rat heart. Circ Res 1988; 62:1075–1079.
72. Berk BC, Fujiwara K, Lehoux S. ECM remodeling in hypertensive heart

disease. J Clin Invest 2007; 117:568–575.
73. Piotrowski G, Banach M, Gerdts E, Mikhailidis DP, Hannam S, Gawor R, et al. Left atrial size in hypertension and stroke. J Hypertens 2011; 29:1988–1993.
74. Mieczkowska J, Mosiewicz J, Barud W, Kwasniewski W. Changes in the activity of connective tissue matrix enzymes in the metabolic syndrome. Arch Med Sci 2011; 7:634–641.
75. Rysz J, Banach M, Stolarek RA, Mikhailidis DP, Cialkowska-Rysz A, Pokoca L, et al. Serum metalloproteinases MMP-2, MMP-9 and metalloproteinase tissue inhibitors TIMP-1 and TIMP-2 in patients on hemodialysis. IntUrolNephrol 2011; 43:491–498.
76. Weber KT, Sun Y, Guarda E. Structural remodeling in hypertensive heart disease and the role of hormones. Hypertension 1994; 23:869– 877.
77. Lopez B, Gonzalez A, Varo N, Laviades C, Querejeta R, Diez J. Biochemical assessment of myocardial fibrosis in hypertensive heart disease. Hypertension 2001; 38:1222–1226.
78. Shirakabe A, Asai K, Hata N, Yokoyama S, Shinada T, Kobayashi N, Mizuno K. Clinical significance of matrix metalloproteinase (MMP)-2 in patients with acute heart failure. Int Heart J 2010; 51:404–410.
79. Hojo Y, Ikeda U, Ueno S, Arakawa H, Shimada K. Expression of matrix metalloproteinases in patients with acute myocardial infarction. JpnCirc J 2001; 65:71–75.
80. Squire IB, Evans J, Ng LL, Loftus IM, Thompson MM. Plasma MMP-9 and MMP-2 following acute myocardial infarction in man: correlation with echocardiographic and neurohumoral parameters of left ventricular dysfunction. J Card Fail 2004; 10:328–333.
81. Inokubo Y, Hanada H, Ishizaka H, Fukushi T, Kamada T, Okumura K. Plasma levels of matrix metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 are increased in the coronary circulation in patients with acute coronary syndrome. Am Heart J 2001; 141:211– 217.
82. Lacchini R, Jacob-Ferreira ALB, Luizon MR, Gasparini S, Ferreira-Sae MCS, Schreiber R, et al. Common matrix metalloproteinase 2 gene haplotypes may modulate left ventricular remodelling in hypertensive patients. J Hum Hypertens 2012; 26:171–177.
83. Nu´n˜ez J, Nu´n˜ez E, Robles R, Bodı´ V, Sanchis J, Carratala´ A, et al. Prognostic value of brain natriuretic peptide in acute heart failure: mortality and hospital readmission. Rev EspCardiol 2008; 61:1332– 1337.
84. Fonarow GC, Peacock WF, Phillips CO, Givertz MM, Lopatin M, ADHERE Scientific Advisory Committee, Investigators. Admission B-type natriuretic peptide levels and in-hospital mortality in acute decompensated heart failure. J Am CollCardiol 2007; 49:1943– 1950.
85. Nu´n˜ez J, Nu´n˜ez E, Consuegra L, Sanchis J, Bodı´V, Martı´nez-Brotons A, et al. Carbohydrate antigen 125: an emerging prognostic risk factor in acute heart failure? Heart 2007; 93:716–721.
86. D'Aloia A, Faggiano P, Aurigemma G, Bontempi L, Ruggeri G, Metra M, et al. Serum levels of carbohydrate antigen 125 in patients with chronic

heart failure: relation to clinical severity, hemodynamic and Doppler echocardiographic abnormalities, and short-term prognosis. J Am CollCardiol 2003; 41:1805–1811.

87. Nu´n˜ez J, Sanchis J, Bodı´ V, Fonarow GC, Nu´n˜ez E, Bertomeu-Gonza´lez V, et al. Improvement in risk stratification with the combination of the tumour marker antigen carbohydrate 125 and brain natriuretic peptide in patients with acute heart failure. Eur Heart J 2010; 31:1752–1763.
88. Levin ER, Gardner DG, Samson WK. Natriuretic peptides. N Engl J Med 1998; 339:321–328.
89. Trojnarska O, Gwizdala A, Katarzynski S, Katarzynska A, Oko-Sarnowska Z, Bre¸borowicz Z, Grajek S. Evaluation of exercise capacity with cardiopulmonary exercise testing and BNP levels in adult patients with single or systemic right ventricles. Arch Med Sci 2010; 6:192–197.
90. Suzuki M, Hamada M, Yamamoto K, Kazatani Y, Hiwada K. Brain natriuretic peptide as a risk marker for incident hypertensive cardiovascular events. Hypertens Res 2002; 25:669–676.
91. Freitag MH, Larson MG, Levy D, Benjamin EJ, Wang TJ, Leip EP, et al. Framingham Heart Study. Plasma brain natriuretic peptide levels and blood pressure tracking in the Framingham Heart Study. Hypertension 2003; 41:978–983.
92. Melander O, Newton-Cheh C, Almgren P, Hedblad B, Berglund G, Engstro¨m G, et al. Novel and conventional biomarkers for prediction of incident cardiovascular events in the community. JAMA 2009; 302:49–57.
93. Fradley MG, Larson MG, Cheng S, McCabe E, Coglianese E, Shah RV, et al. Reference limits for N-terminal-pro-B-type natriuretic peptide in healthy individuals (from the Framingham Heart Study). Am J Cardiol 2011; 108:1341–1345.
94. Suzuki M, Yamamoto K, Watanabe S, Iwata T, Hamada M, Hiwada K. Association between elevated brain natriuretic peptide levels and the development of hypertrophy in patients with hypertension. Am J Med 2000; 108:627–633.
95. Coutinho T, Al-Omari M, Mosley TH Jr, Kullo IJ. Biomarkers of left ventricular hypertrophy and remodeling in blacks. Hypertension 2011; 58:920–925.
96. Varol E, Ozaydin M, Dogan A, Kosar F. Tumour marker levels in patients with chronic heart failure. Eur J Heart Fail 2005; 7:840–843.
97. Turk HM, Pekdemir H, Buyukberber S, Sevinc A, Camci C, Kocabas R, et al. Serum CA 125 levels in patients with chronic heart failure and accompanying pleural fluid. Tumour Biol 2003; 24:172–175.
98. Kosar F, Aksoy Y, Ozguntekin G, Ozerol I, Varol E. Relationship between cytokines and tumour markers in patients with chronic heart failure. Eur J Heart Fail 2006; 8:270–274.
99. Kouris NT, Zacharos ID, Kontogianni DD, Goranitou GS, Sifaki MD, Grassos HE, et al. The significance of CA125 levels in patients with chronic congestive heart failure. Correlation with clinical and echocardiographic parameters. Eur J Heart Fail 2005; 7:199–203.
100. Chen YX, Wang XQ, Fang CF, Wang JF, Tang LJ. Value of BNP and tumour

marker CA125 in patients with heart failure. ActaCardiol 2008; 63:501–506.
101. Na¨gele H, Bahlo M, Klapdor R, Ro¨diger W. Fluctuations of tumor markers in heart failure patients pre and post heart transplantation. Anticancer Res 1999; 19:2531–2534.
102. Banach M, Rysz J. Current problems in hypertension and nephrology. Expert OpinPharmacother 2010; 11:2575–2578.