Biochemical markers of myocardial remodelling in hypertensive heart disease

Arantxa González1, Begoña López1, Susana Ravassa1, Javier Beaumont1, Teresa Arias1, Nerea Hermida1, Amaia Zudaire1, and Javier Díez1,2

1Division of Cardiovascular Sciences, Centre of Applied Medical Research, University of Navarra, Pamplona, Spain; and 2Department of Cardiology and Cardiovascular Surgery, University Clinic, University of Navarra, Pamplona, Spain

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The intricate mechanisms responsible for the structural remodelling of the myocardium that facilitates the evolution to heart failure in hypertensive patients, namely in those with left ventricular hypertrophy, requires from clinicians the utilization of a multibiomarker approach for short-term and long-term stratification as well as prognostication of patients. Biochemical markers may also help to identify patients with no clinical evidence of hypertensive heart disease, and provide information about the need for more aggressive therapy during different stages of the disease, and potentially provide valuable biochemical data for the specialist. Although there is a continuous and complex interplay between biochemical and imaging markers, perhaps their use will also have the potential to modify the medical management of patients with hypertensive heart disease and therapeutic decision-making by tailoring a targeted therapy according to the predominant mechanism of myocardial remodelling. This article will review in brief the most relevant information on a panel of circulating molecules that may accomplish the criteria required to be considered as biochemical markers of the cardiomyocyte and non-cardiomyocyte structural changes that occur in the hypertensive myocardium.

1. Introduction

Hypertensive heart disease (HHD), here defined by the presence of left ventricular hypertrophy (LVH) in the absence of a cause other than arterial hypertension, has been long considered as one of the most common aetiological conditions predisposing to heart failure (HF). In fact, although hypertension increases the risk for developing HF,1 LVH itself is an independent risk factor for HF.1,2 Furthermore, in spite of the continuous progress of antihypertensive strategies over the years, the incidence of HF in hypertensive patients with LVH remains high and comparable with that of major cardiovascular events, such as stroke.3

HHD is characterized by complex changes in myocardial structure (e.g. enhanced cardiomyocyte growth, excessive cardiomyocyte apoptosis, accumulation of interstitial and perivascular collagen fibres, disruption of endomyssial and perimysial collagen network) that induce the remodelling of the myocardium, and ultimately, deteriorate left ventricular function and facilitate the development of HF.4 Hypertensive myocardial remodelling is the consequence of a number of pathological processes mediated by mechanical, neurohormonal, and cytokine routes, occurring in the cardiomyocyte and the non-cardiomyocyte compartments of the myocardium.5

The identification of biomarkers of potential usefulness for the clinical handling of cardiac diseases evolving to HF has been a prolific field in the last years. Biomarkers either determined in the circulation as biochemical markers or detected in the heart by imaging technologies, can be defined as alterations in the constituents of tissues or body fluids that can be applicable in at least five clinical areas: screening, diagnosis, prognostication, prediction of disease recurrence, and therapeutic monitoring. The investigation of novel circulating biochemical markers of myocardial remodelling in HHD has been accelerating at a remarkable pace, but it has also deluged the clinical and research communities with candidate molecules, very few of which are likely to survive the test of time as useful clinical tools.6,7 In this regard, it is the opinion of the authors that for a circulating molecule to be considered a biochemical marker of myocardial remodelling it must fulfil several criteria. First of all, there must be a relationship between its expression in the myocardium and its blood concentration; secondly, there has to be a positive gradient from its concentration in coronary sinus blood towards its
concentration in peripheral vein blood, proving its main cardiac origin; thirdly, there must be an association of its concentration in blood with the cardiac structural and/or functional parameters reflecting the hallmarks of the myocardial changes under study; finally, its levels should vary in parallel with the changes in the above parameters induced by pharmacological treatment. On the other hand, its method of determination must be easy (i.e. ELISA), reproducible and low cost, and the biochemical marker must have a good sensitivity and specificity to detect the pathology under study.

In this conceptual framework, recent studies performed in our laboratory and by other groups with small populations of hypertensive patients in which other cardiac conditions different from HHD were carefully excluded, have allowed to identify a panel of circulating molecules that fulfil the above criteria. This paper reviews and summarizes recent literature on these biochemical markers.

2. Biochemical markers related to the cardiomyocyte

2.1 Cardiotrophin-1 and cardiomyocyte hypertrophy

2.1.1 Fundamental aspects
LVH is the first compensatory mechanism that the haemodynamically overloaded myocardium employs to maintain normal function of the left ventricle in conditions of systemic arterial hypertension. At the cellular level, the growth of cardiomyocytes is the main determinant of LVH, and it is accepted now that it represents the cell response to both mechanical stretch and activation of humoral growth factors due to pressure overload.8

Cardiotrophin-1 (CT-1) is a cytokine member of the interleukin-6 (IL-6) superfamily, produced by cardiomyocytes and cardiac fibroblasts in situations of biomechanical stress and under exposure to humoral factors such as angiotensin II (Figure 1).9,10 Once secreted, it interacts with its receptor, the heterodimer formed by gp130 and the leukaemia inhibitory factor receptor, activating different signalling pathways leading to cardiomyocyte growth and dysfunction.11 In vitro experiments have demonstrated that CT-1 induces an exaggerated growth response in cardiomyocytes from adult spontaneously hypertensive rats (SHR) when compared with those from adult Wistar rats.12 Recently, Zolk et al.13 reported in heart tissues reconstituted from rat cardiomyocytes that long-term exposure to CT-1 depressed basal force of contraction and the inotropic response to Ca2+ and isoprenaline. In addition, CT-1 down-regulated expression of calsequestrin, a protein involved in Ca2+ handling, and prevented the formation of longitudinally oriented bundles of cardiomyocytes, both changes might contribute to ineffective force generation.

In studies performed in vivo it has been reported that CT-1 expression is abnormally high in the hypertrophied left ventricle of SHR.12,14,15 In addition, it has been reported that the myocardial expression of CT-1 is higher in aged SHR with HF than in adult SHR without HF.16 Altogether, the experimental data support the notion that an excessive production of CT-1 by cardiac cells in response to biomechanical stress associated with increased blood pressure might, in turn, be involved in the hypertrophy and dysfunction of the cardiomyocyte in hypertension (Figure 1).

2.1.2 Plasma CT-1 in hypertensive patients
In studies performed in humans, it has been reported that plasma CT-1 concentration shows a positive gradient from coronary sinus blood towards aortic blood.17 On the other hand, it has been shown that plasma concentration of CT-1 is directly correlated with the myocardial expression of CT-1.18 Collectively, these findings suggest that, in the human the heart secretes CT-1 via the coronary sinus into the peripheral circulation, and that the concentration of circulating CT-1 is a reliable index of cardiac CT-1.

Plasma CT-1 concentration has been found to be increased in hypertensive patients as a whole group when compared with normotensive subjects.19,20 Additionally, it has been
reported that plasma CT-1 is higher in patients with LVH than in patients without LVH,19 and in patients with HF than in patients with LVH (Figure 2A).18 It is interesting to point out that 31% of hypertensive patients without LVH already exhibited concentrations of CT-1 abnormally elevated (above the upper normal limit measured in the normotensive control population),19 suggesting that CT-1 increases early during the evolution of arterial hypertension.

Plasma CT-1 concentration is correlated with left ventricular mass index (L VMI) in hypertensive patients (Figure 2B).18,19,21 Furthermore, an association has been found between antihypertensive treatment-induced decrease of plasma CT-1 and reduction of L VMI in patients with LVH.23 The lack of association of L VMI with plasma IL-6,21 another member of the IL-6 superfamily of cytokines, reinforces the specificity of the association of CT-1 with LVH and suggests that plasma CT-1 may be a potential biochemical marker for assessment of LVH in hypertension. This is supported by the finding that it presents an acceptable sensitivity (70%) and specificity (75%) to detect LVH, as assessed by echocardiography, in hypertensive patients.19

Plasma CT-1 concentration has been measured also in hypertensive patients in whom left ventricular mass exceeds individual needs to compensate haemodynamic load imposed by increased blood pressure and thus present inappropriate left ventricular mass, defined by a ratio of observed/predicted left ventricular mass >135%.22 Plasma CT-1 concentration has been found to be higher in patients with inappropriate left ventricular mass than in patients with appropriate left ventricular mass.23 In addition, plasma CT-1 is directly correlated with the ratio of observed/predicted left ventricular mass in all patients. After treatment, plasma CT-1 decreases and increases in patients in whom inappropriate left ventricular mass regresses and persists, respectively, despite a similar reduction of blood pressure in the two subgroups of patients. Interestingly, abnormally high plasma CT-1 concentration is associated with reduced fractional shortening and altered relaxation in patients with inappropriate left ventricular mass, suggesting that the cytokine can be one of the non-haemodynamic factors involved in both excessive growth and functional deterioration of the left ventricle in these patients.

Altogether, these findings support the notion that plasma CT-1 may be a potential biochemical marker of the development, progression, and regression of cardiomyocyte-dependent LVH in hypertensive patients.

2.2 Annexin A5 and cardiomyocyte apoptosis

2.2.1 Fundamental aspects

Exaggerated stimulation of cardiomyocyte apoptosis is one of the cellular characteristics of the hypertrophied left ventricle in arterial hypertension.24 Cardiomyocyte apoptosis may be involved in the deterioration of left ventricular function and development of HF through several mechanisms, including loss of cardiomyocytes due to cell death, compromise of oxidative phosphorylation and ATP production due to the loss of mitochondrial cytochrome c into the cytosol, and progressive contractile dysfunction of viable cardiomyocytes related to enzymes involved in the apoptotic process.24

Annexin A5 (AnxA5) is a 32–35 kDa Ca2+-binding protein that becomes upregulated in response to different apoptotic stimuli acting on cardiomyocytes and other cardiac cells (Figure 1).25–27 In addition, recent data suggest that an excess of intracellular AnxA5 will, in turn, contribute to apoptosis of cardiomyocytes, likely through alterations in cellular Ca2+-handling and mitochondrial metabolism.27,28 It is likely that AnxA5 released to the extracellular space will reach the blood via cardiac lymph and/or venous drainage.

An abnormal increase of myocardial AnxA5 protein has been reported in the heart of guinea pigs made hypertensive by stenosis of the abdominal aorta and in which LVH and left ventricular dysfunction developed.29 Although the immunohistochemical study showed intense staining for AnxA5 at the level of both cardiomyocytes and the interstitium in hypertensive animals, AnxA5 was seen just within cardiomyocytes in normotensive sham-operated animals. Of interest, annexins A2 and A6 did not show this pattern of interstitial accumulation in the left ventricle of hypertensive animals.

The expression of AnxA5 has been shown to be also abnormally increased in the myocardium of hypertensive patients with LVH exhibiting increased cardiomyocyte apoptosis, namely in those with HF.30 The excess of myocardial AnxA5 was associated with impairment of systolic function in HF patients.30 In comparison to normotensive subjects and patients without LVH, AnxA5 was highly expressed in cardiomyocytes and the interstitium of both patients with LVH and patients with HF. Upregulation and translocation from cardiomyocytes to interstitial tissue of AnxA5, but not of other annexin isoforms, has also been reported in the myocardium of patients with end-stage HF of non-hypertensive origin.31,32 Collectively, the available data suggest that

![Figure 2](https://example.com/figure2.png)

**Figure 2** (A) Changes in the circulating concentration of cardiotrophin-1 (CT-1) in hypertensive patients when compared with normotensive subjects. (B) Association between CT-1 and left ventricular mass index (L VMI) in normotensive subjects and hypertensive patients. NT, normotensive subjects; HT, hypertensive patients without left ventricular hypertrophy; LVH, hypertensive patients with left ventricular hypertrophy; HF, hypertensive patients with heart failure. Results are shown as mean ± SE. Adapted from González et al.,19 López et al.,19 and González et al.21
increased production of AnxA5 by the hypertensive myocardium might contribute to further cardiomyocyte apoptosis and dysfunction (Figure 1).

2.2.2 Plasma AnxA5 in hypertensive patients
Several findings support the potential usefulness of measurement of plasma AnxA5 concentration to assess myocardial AnxA5 abundance in humans. First, the finding that there is a gradient of the plasma concentration of AnxA5 from the coronary blood to the peripheral blood suggests that this protein is released from the heart through the coronary sinus. Secondly, the highly significant correlation observed between plasma concentration of AnxA5 in antecubital vein blood and coronary sinus blood suggests that the heart is, among other organs, an important source of circulating AnxA5. Thirdly, the direct correlations found between plasma and myocardial AnxA5 suggest that circulating AnxA5 may be a representative index of myocardial AnxA5 in these patients. It is important to mention that the above findings were reported in hypertensive patients free of coronary artery disease after angiographic examination, thus the potential origin of AnxA5 from coronary atherosclerotic plaques was excluded.

It has been reported that although plasma concentration of AnxA5 was normal in patients without LVH, it was abnormally high in patients with LVH (Figure 3A). In addition, plasma AnxA5 concentration was higher in patients with HF than in patients with LVH (Figure 3A). Interestingly, plasma AnxA5 was directly correlated with left ventricular end-diastolic diameter and inversely correlated with ejection fraction in the whole group of patients (Figure 3B).

Therefore, these clinical findings support the notion that plasma AnxA5 may be useful as a biochemical marker of apoptosis-related cardiomyocyte dysfunction in hypertensive patients.

3. Biochemical markers related to the collagen matrix

3.1 Carboxy-terminal propeptide of procollagen type I and myocardial fibrosis

3.1.1 Fundamental aspects
An exaggerated accumulation of collagen fibres, namely of type I, within the myocardial interstitium and surrounding intramural coronary arteries and arterioles has been consistently found in a number of studies performed in post-mortem human hearts and endomyocardial human biopsies in patients with HHD. Myocardial fibrosis increases progressively in HHD, being higher in patients with LVH than in patients without LVH and normotensive subjects, and higher in patients with HF than in patients with LVH. Hypertensive myocardial fibrosis is related to the predominance of an exaggerated synthesis over an unchanged degradation of collagen molecules, as a consequence of a number of processes, mediated by mechanical and humoral mechanisms. The increase in collagen content increases myocardial stiffness and promotes the onset of abnormalities in diastolic function, as well as in the regulation of coronary reserve and electrical activity in the hypertensive heart.

An emerging experimental and clinical experience holds promise for the determination of various serum peptides derived from the metabolism of collagen type I in arterial hypertension. More specifically, the serum concentration of the carboxy-terminal propeptide of procollagen type I or PICP (a peptide that is cleaved from procollagen type I during the extracellular synthesis of fibril-forming collagen type I by the enzyme procollagen type I carboxy-terminal proteinase or PCPase, and which is released into the blood stream with a stoichiometric ratio of 1:1) (Figure 4) has been shown to be associated with the volume of myocardial tissue occupied by collagen fibres in both SHR with LVH and hypertensive patients with LVH. In addition, serum PICP concentration has been found to be associated with the activation of the enzyme PCPase in the myocardium of patients with HHD.

3.1.2 Serum carboxy-terminal propeptide of procollagen type I in hypertensive patients
Recently, we reported that the concentration of PICP was significantly higher in blood from the coronary sinus than in blood from the antecubital vein in patients with HHD, but not in normotensive subjects. In addition, PICP measured in blood from the antecubital vein was associated with PICP measured in blood from the coronary sinus and with the amount of collagen fibres present in the myocardium. It is important to remark that none of these findings has been reported for other collagen-derived peptides than can also be measured in blood (i.e. the amino-terminal propeptide of procollagen type I, and the carboxy-terminal and the amino-terminal propeptides of

![Figure 3](https://academic.oup.com/cardiovascres/article-abstract/81/3/509/403742/182x72/A. Gonzalez et al.)

Figure 3 (A) Changes in the circulating concentration of annexin A5 (AnxA5) in hypertensive patients when compared with normotensive subjects. (B) Association between AnxA5 and left ventricular ejection fraction (LVEF) in normotensive subjects and hypertensive patients. NT, normotensive subjects; HT, hypertensive patients without left ventricular hypertrophy; LVH, hypertensive patients with left ventricular hypertrophy; HF, hypertensive patients with heart failure. Results are shown as mean ± SE. Adapted from Ravassa et al.
procollagen type III). Therefore, the available findings suggest that just circulating PICP is a reliable index of the extent and severity of fibrosis in the human hypertensive myocardium.

We and others have reported that serum PICP concentration is elevated in hypertensive patients when compared with normotensive subjects. Interestingly, higher serum PICP concentrations have been found in patients with HF when compared with hypertensives patients without heart failure compared with hypertensives patients without heart failure. NT, normotensive subjects; HT, hypertensive patients without left ventricular hypertrophy; LVH, hypertensive patients with left ventricular hypertrophy; HF, hypertensive patients with heart failure. Results are shown as mean ± SE. Adapted from Querejeta et al., Diez et al., López et al., and Müller-Brunotte et al.

It has also been shown that the variation in serum PICP concentration induced by treatment is associated with parallel changes in the amount of myocardial fibrosis in treated hypertensive patients. In fact, the values of PICP and the volume of myocardial tissue occupied by collagen fibres decrease in parallel in patients with LVH treated with losartan, and in patients with HF treated with torsemide. On the contrary, no changes in either serum PICP concentration or myocardial collagen content were observed in patients with LVH treated with amlodipine, and patients with HF treated with furosemide.

An association has been reported between the serum concentrations of PICP and transforming growth factor-beta (TGF-β) in patients with HHD before and after antihypertensive treatment. Because TGF-β has been shown to upregulate PCPase expression and to stimulate its activity, it is tempting to speculate that serum PICP may reflect the metabolic and functional changes occurring in the myocardium of patients with HHD.
myocardial profibrotic activity of the cytokine in patients with HHD.

On the other hand, serum PICP concentration has been found to be directly correlated with LVMi in hypertensive patients.\(^{42,46}\) In addition, the increase of serum PICP parallels the increase of left ventricular stiffness constant in patients developing HF (Figure 5B).\(^{41}\) suggesting that the compromise of diastolic function, likely secondary to an exaggerated accumulation of collagen type I fibres within the myocardium, may play a determinant role in the development of HF in patients with HHD.

Collectively, these findings suggest that PICP provides indirect diagnostic and therapeutic information regarding the extent of collagen type I-dependent myocardial fibrosis and the ability of pharmacological therapy to reduce it in hypertensive patients.

### 3.2 Matrix metalloproteinase-1/tissue inhibitor of metalloproteinases-1 balance and collagen network disruption

#### 3.2.1 Fundamental aspects
The collagen network (collagen associated with groups of cardiomyocytes or perimysium, and collagen which surrounds and interconnects individual cardiomyocytes or endomysium) is responsible for providing the supportive scaffolding for cardiomyocytes, but also serves to integrate the individual contractions of these cells and provide a coordinated delivery of force (pressure) to the left ventricular chamber for expulsion of blood.\(^{50}\) Therefore, the loss or disruption of this collagen network may compromise systolic function by three mechanisms.\(^{51,52}\) The first implies discontinuities in the myosal matrix that provides support, geometric alignment, and coordination of adjacent cardiomyocyte fascicle contraction. The second involves the loss of the normal collagen matrix-basement membrane-integrin connections that contribute to the synchrony and synergy of sarcomeres during the contractile process. The third is related to sliding displacements (slippage) of cardiomyocytes leading to a decrease in the number of muscular layers in the ventricular wall and left ventricular dilatation, which in turn impairs the working conditions of the left ventricular myocardium.

The interaction between the enzyme matrix metalloproteinase-1 (MMP-1) or collagenase that initiates the degradation of collagen fibres within the heart, and its inhibitor tissue inhibitor of metalloproteinases-1 (TIMP-1) is of critical relevance in the maintenance of the integrity of the collagen network (Figure 4). A clear cause-and-effect relationship between excessive myocardial MMP-1 activity, increased myosal collagen degradation, and progression to systolic HF has been shown experimentally through the use of transgenic models and the use of pharmacological MMP activators.\(^{53,54}\) In addition, experimental evidence has been provided showing that following chronic neurohormonal activation, increased synthesis and release of MMPs into the local extracellular matrix of the cardiomyocyte occurs,\(^{55}\) which in turn could contribute to endomysial and perimysial collagen degradation and disruption.

In this context, we have reported recently that the volume of myocardial tissue occupied by perimysial and endomysial collagen was lower in hypertensive patients with HF and depressed ejection fraction (systolic HF), than in hypertensive patients with HF and preserved ejection fraction (diastolic HF) and normotensive subjects.\(^{56}\) Of interest, the interstitial and perivascular accumulation of collagen fibres was abnormally high in the two groups of patients. Thus, myocardial fibrosis may coexist with disruption of the myosal collagen network in hypertensive patients with systolic HF. The MMP-1 expression was increased in the myocardium of systolic HF patients compared with diastolic HF patients and normotensive subjects. In particular, cardiomyocyte MMP-1 expression was higher in systolic HF patients than in the other two groups of subjects. No differences in myocardial expression of TIMP-1 were observed among the three groups of subjects. These findings suggest that excessive MMP-1 dependent degradation of myosal collagen may be related to the compromise of systolic function in HF hypertensive patients.

#### 3.2.2 Serum matrix metalloproteinase-1 and tissue inhibitor of metalloproteinases-1 ratio in hypertensive patients
The higher concentrations of MMP-1 and TIMP-1 in blood from the coronary sinus blood vs. blood from the antecubital vein blood, found in hypertensive patients but not in normotensive subjects, and the correlations between their antecubital vein and coronary sinus concentrations,\(^{56}\) suggest that circulating MMP-1 and TIMP-1 detected in HF hypertensive patients may be of cardiac origin and that the serum MMP-1:TIMP-1 ratio detected in HF hypertensive patients may be useful as an index of the MMP-1:TIMP-1 balance within the myocardium.

![Figure 6](https://academic.oup.com/cardiovascres/article-abstract/81/3/509/403742)

**Figure 6** (A) Changes in the values of the serum ratio of matrix metalloproteinase-1 to tissue inhibitor of matrix metalloproteinases-1 (MMP-1: TIMP-1) in hypertensive patients when compared with normotensive subjects. (B) Parallel increases in the values of serum MMP-1: TIMP-1 and left ventricular end-diastolic volume (LVEDV) in hypertensive patients with systolic heart failure compared with hypertensive patients with diastolic heart failure. NT, normotensive subjects; HT, hypertensive patients without left ventricular hypertrophy; LVH, hypertensive patients with left ventricular hypertrophy; HF, hypertensive patients with heart failure. Results are shown as mean ± SE. Adapted from López et al.\(^{56}\) and Lavdies et al.\(^{57}\)
Biochemical markers in hypertension

4. Future directions

4.1 Clinical integration

The pivotal criterion with regards to the potential clinical value of a candidate biochemical marker for a given disease is the consistency and strength of the association between the biochemical marker and the outcome of the disease, and the extent to which it is an improvement on (either adding to or replacing) established tools [e.g. brain natriuretic peptides (BNPs)].

In this conceptual framework, the studies here reviewed have set the stage for larger on-going trials wherein biochemical markers of myocardial remodelling could prove to be definitively useful per se and when compared with BNPs for the following aspects. First, early detection of hypertensive patients at risk of developing LVH (e.g. patients with high plasma levels of CT-1); secondly, identification of hypertensive patients with LVH prone to evolve to HF (e.g. patients with increased serum levels of PICP); and thirdly, identification of hypertensive patients with HF that will exhibit progressive deterioration of cardiac pump performance (e.g. patients with enhanced plasma AnxA5 and/or serum MMP-1:TIMP-1 ratio). Some of these trials are currently ongoing. For instance, preliminary data show that plasma CT-1 measurement provides additional prognostic information to that of BNP and that combined levels of CT-1 and BNP are more accurate at predicting mortality in patients with CHF than either marker alone.86

Similarly, the potential usefulness of these biochemical markers in other cardiac conditions different from HHD needs also to be investigated. Up to now, several promising findings have been reported (Table 1).

4.2 Combination of biochemical and imaging markers

Although circulating biochemical markers may offer the advantage of availability, relative easy of collection and storage, and lower cost, they may not prove as sensitive as imaging markers in the detection or assessment of disease. On the other hand, imaging technologies can assess disease in human clinical trials with a high degree of sensitivity and specificity but may be limited by technical difficulty, availability, and cost. In this context, the combination of some of the biochemical markers here considered and imaging markers have inherent advantages.

For example, an association between alterations in echocardiographic indices, namely diminution in the cyclic variation of backscatter signal, and increase in fibrous tissue was shown in the heart of hypertensive patients.77,78 Interestingly, an association has been found between diminished cyclic variation of backscatter and increased serum concentration of PICP in hypertensive patients.47,79 In magnetic resonance imaging studies, it has been shown that late gadolinium enhancement has strong correlation with histologically assessed myocardial fibrosis in patients with arrhythmogenic right ventricular cardiomyopathy80 and hypertrophic cardiomyopathy.81 On the other hand, (99m)Tc-labelled AnxA5 has been successfully used for the non-invasive detection of myocardial apoptosis in patients with HF of non-hypertensive origin.82

4.3 Targeted therapy

A role might exist for biochemical markers in the monitoring of therapy and tailoring of management for individuals. In particular, the combination of biomarkers with clinical phenotypes and genetic information can lead to a more precise diagnosis and therapy on an individual basis. For instance, based on various lines of evidence suggesting that systemically and/or locally produced angiotensin II may participate in the development of myocardial fibrosis in HHD via activation of AT1 receptors, we investigated the potential interaction of the A1166C polymorphism of the AT1 receptor gene with PICP in patients with the clinical phenotype of HHD.83 In the study, patients were studied before and 1 year after treatment with either the AT1 receptor blocker losartan or the beta-blocker atenolol. Baseline PICP and LV chamber stiffness were significantly increased in AA hypertensives compared with AC/CC hypertensives.

<table>
<thead>
<tr>
<th>Cardiac disease</th>
<th>Increase in plasma CT-1</th>
<th>Increase in plasma AnxA5</th>
<th>Increase in serum PICP</th>
<th>Increase in serum MMP-1:TIMP-1 ratio</th>
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<tr>
<td>Aortic stenosis</td>
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CT-1, cardiotrophin-1; AnxA5, annexin A5; PICP, carboxy-terminal propeptide of procollagen type I; MMP-1:TIMP-1, ratio of matrix metalloproteinase-1 to tissue inhibitor of metalloproteinases-1.
Confounding factors were similar in the two subgroups of hypertensives. Administration of losartan was associated with significant reduction in PICP and left ventricular chamber stiffness in AA hypertensives but not AC/CC hypertensives. Treatment with atenolol did not change these two parameters in either subgroup of hypertensives. Blood pressure was reduced to the same extent in the four subgroups with treatment. If these results were confirmed by larger, prospective, double-blind studies, the combination of the genotype of the A1166C polymorphism of the AT₁ receptor gene with serum PICP levels could be a useful indicator for antihypertensive drug strategy aimed to reduce cardiac fibrosis and stiffness in patients with HHD.

4.4 Search of new biochemical markers of interest

The development of new biochemical markers of myocardial remodelling can be thought of as consisting of two complementary approaches: the ‘knowledge-based’ and the ‘unbiased’. The knowledge-based approach relies on a direct understanding of the biological mechanisms that underlie the process of myocardial remodelling and its evolution to HF. It may comprise designing assays for attractive new candidate molecules informed by the biology of the remodelling process. In this regard, a number of candidates currently under clinical investigation are presented in Table 2.

Proteomic analysis provides a unique opportunity to perform the unbiased approach to identify new candidate biomarkers for the diagnosis, staging, and tracking of HF. Analysis of ventricular proteomic changes during the initial inception, development, and progression to HF revealed large-scale pattern differences. In terms of plasma, the protein candidates are also consistent with the efforts of the Human Proteomic Organisation (HUPO) to analyse the human plasma subproteome systematically. Initial analysis identified families of proteins involved in inflammation, signalling, growth and differentiation, cytoskeletal, channel/receptors, and extracellular matrix turnover processes.

5. Conclusions

Large epidemiological and clinical studies will be required to assess the cost-effectiveness of biochemical markers of hypertensive myocardial remodelling here reviewed. Those biochemical markers that perform well and cost-effectively in the testing of rapid ‘rule out’ or ‘rule in’ strategies and those that help to triage patients into low- and high-risk treatment strategies will be integrated into clinical decision-making protocols for hypertensive patients. In addition, those biochemical markers of myocardial remodelling that facilitate choice of the most appropriate drug and that enable titration of drug dose to maximize therapeutic anti-remodelling effects are likely to be attractive to clinicians attending hypertensive patients.

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