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REVIEW

Cardiotrophin-1 in hypertensive heart disease

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Abstract Hypertensive heart disease, here defined by the presence of pathologic left ventricular hypertrophy in the absence of a cause other than arterial hypertension, is characterized by complex changes in myocardial structure including enhanced cardiomyocyte growth and non-cardiomyocyte alterations that induce the remodeling of the myocardium, and ultimately, deteriorate left ventricular function and facilitate the development of heart failure. It is now accepted that a number of pathological processes mediated by mechanical, neurohormonal, and cytokine routes acting on the cardiomyocyte and the non-cardiomyocyte compartments are responsible for myocardial remodeling in the context of arterial hypertension. For instance, cardiotrophin-1 is a cytokine member of the interleukin-6 superfamily, produced by cardiomyocytes and non-cardiomyocytes in situations of biomechanical stress that once secreted interacts with its receptor, the heterodimer formed by gp130 and gp90 (also known as leukemia inhibitory factor receptor beta), activating different signaling pathways leading to cardiomyocyte hypertrophy, as well as myocardial fibrosis. Beyond its potential mechanistic contribution to the development of hypertensive heart disease, cardiotrophin-1 offers the opportunity for a new translational approach to this condition. In fact, recent evidence suggests that cardiotrophin-1 may serve as both a biomarker of left ventricular hypertrophy and dysfunction in hypertensive patients, and a potential target for therapies aimed to prevent and treat hypertensive heart disease beyond blood pressure control.

Keywords Arterial hypertension · Cardiotrophin-1 · Heart failure · Hypertensive heart disease · Left ventricular hypertrophy

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Introduction

Many cell types mount elaborate, compensatory responses to stress that can lead to the release of cytokines (i.e., cytokines from the interleukin-6 (IL-6) family), which can behave in an autocrine and paracrine manner to enhance survival. Cardiotrophin-1 (CT-1), a 201 amino acid protein member of the IL-6 family, mediates a pleiotropic set of survival effects through a unique receptor system, consisting of glycoprotein 90 or leukemia inhibitory factor receptor beta (LIFRβ) and a common signal transducer, the glycoprotein 130 (gp130) [1]. The signaling pathway downstream from gp130 is reported to consist of, at least, three distinct pathways: 1) the janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, 2) the p42/44 mitogen-activated protein kinase (p42/44 MAPK) pathway, which is also known as the extracellular receptor kinase-1/2 (ERK1/2) pathway, and 3) the phosphatidylinositol 3-OH kinase (PI3K)/Akt pathway. It is likely that CT-1 achieves its effects via a combination of these three signaling pathways. Although predominant actions of CT-1 are on the heart, it is now clear that CT-1 is also expressed in many other organs and exhibiting important roles there.

As previously mentioned, CT-1 is a stress-induced cytokine released by the cells in response against potentially harmful stresses. In this conceptual framework, it has been reported that at the cardiac level, CT-1 expression is up-regulated in cardiomyocytes and non-cardiomyocytes by a number of stressor factors, including mechanical (i.e., mechanical stretch [2, 3]), neurohumoral (i.e., angiotensin II [4], aldosterone [5], norepinephrine [6], urocortin [7], and fibroblast growth factor-2 [8]), and metabolic (i.e., glucose and insulin [9], and hypoxic stress [10]) factors. Although the underlying molecular mechanisms for each specific factor remain unclear, recent data show that hypoxia increased CT-1 levels in cardiac cells (in vitro and in vivo) through a direct regulation of *CTF1* promoter by a signaling pathway that involves Ca^{2+}, PI3K/Akt/mTOR, and HIF-1α [11].

Designed primarily to function rapidly and acutely as a cardiomyocyte survival factor, chronic and excessive activation of CT-1 signaling has been postulated to be harmful to normal cardiac biophysiology, paradoxically by exacerbating the underlying stress that it is intended to mollify [12] (Fig. 1). In this conceptual framework, emerging experimental and clinical evidences suggest that chronic exposure of the myocardium to excessive levels of CT-1, as those occurring in conditions of pressure overload, may induce cardiomyocyte hypertrophy (and likely dysfunction), thus contributing to the development of pathologic left ventricular hypertrophy (LVH) [13] (Fig. 1). This review is aimed to provide some insights into the mechanistic role of CT-1 in the development of pathologic LVH in arterial hypertension (i.e., hypertensive heart disease or HHD). In addition, the potential role of CT-1 as a biomarker and a therapeutic target for HHD will be also considered.

CT-1 and the myocardium

As demonstrated by several experimental conditions, performed both in vivo and in vitro, CT-1 plays a dual role in the biophysiology of the myocardium, providing myocardial protection on the one hand, but predisposing the heart to pathological conditions on the other hand.

Cardioprotective actions

Cardiac muscle cell survival plays a critical role in maintaining the normal function of the heart and possibly in cardiac development. Adult cardiomyocytes are thought to be terminally differentiated. Therefore, they have lost their proliferative capacity, and an irreversible heart injury might result in scarring and an eventual decrease in global cardiac function. Importantly, CT-1 has been shown to be capable of promoting both the proliferation and the survival of either embryonic or neonatal cardiomyocytes [14]. Moreover, Stephanou et al. [15] showed that pre-treatment with CT-1 was able to protect cultured neonatal cardiomyocytes

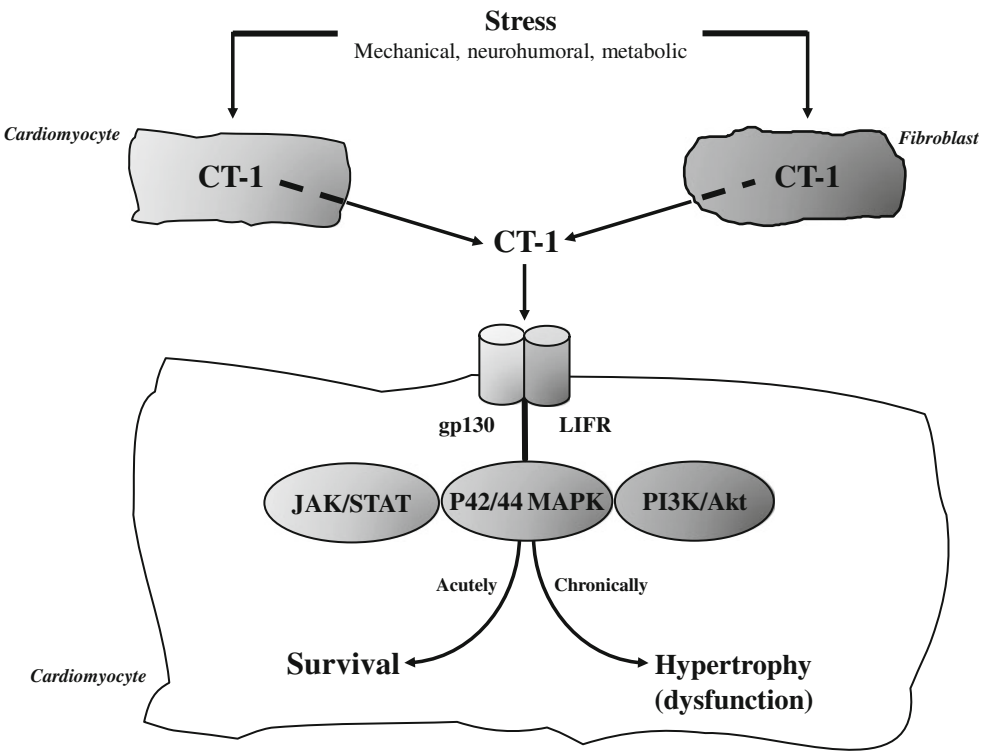

Fig. 1 Schematic representation of the production and actions of cardiotrophin-1 (CT-1) in the myocardium. (See text for abbreviations)

against subsequent exposure to either elevated temperature (heat shock) or simulated ischemia/hypoxia. These effects were associated with the ability of CT-1 to induce enhanced levels of the heat shock proteins hsp70 and hsp90 [15], over-expression of which has been shown to protect cardiomyocytes against both thermal and ischemic stress [16–18]. Recent studies [19, 20] have demonstrated, both in neonatal and in adult cardiomyocytes, the cytoprotective effects of CT-1 against ischemia, when added both before and after the hypoxic stimulus. In addition, CT-1 protects cardiac cells from non-ischemic death stimuli. For instance, it has been reported that CT-1 blunts angiotensin II- and hydrogen peroxide-induced apoptosis in adult cardiomyocytes by means of the PI3K/Akt and the p42/44 MAPK intracellular cascades [21].

Detrimental actions

Although CT-1 is expressed in the normal developing and adult heart, it was first isolated as a factor capable of inducing cardiomyocyte hypertrophy that is one of the most important adaptive responses of the heart and a central feature of many cardiac diseases in man. The original report [22] showed that CT-1 was a dose-dependent potent inducer of hypertrophy, and that it was more potent than other members of the IL-6 family in terms of inducing hypertrophy. In subsequent in vitro studies [23], it was observed that the hypertrophy induced by CT-1 was distinct from that induced, for example, by α-adrenergic stimulation, both in terms of cell morphology and gene expression pattern. Thus, stimulation with CT-1 leads to an increase in cardiac cell size that is caused by an increase in cell length without a significant change in cell width. Similarly, CT-1-stimulated cells show the assembly of sarcomeric units in series (eccentric hypertrophy) rather than in parallel (concentric hypertrophy), as it is observed with α-adrenergic stimulation. However, these studies indicate that CT-1 does not affect skeletal α-actin or myosin light chain–2v expression.

Recent findings suggest that the phenotype of cardiomyocytes may influence the responses to CT-1. In fact, López et al. [24] reported that whereas in cardiomyocytes from normotensive Wistar cells, CT-1 augmented cell length but did not modify either the transverse diameter or cell depth, CT-1 increased cell length, cell width, and cell depth, augmented the expression of myosin light chain-2v and skeletal alpha-actin, and enhanced MLC-2v phosphorylation in cells from adult spontaneously hypertensive rats (SHR) with LVH (Fig. 2). These differential hypertrophic effects of CT-1 might be mediated by the induction of the intracellular renin-angiotensin system in hypertensive cells, but not in normotensive cells [24]. On the other hand, it has been found that in cardiomyocytes isolated from SHR with normal cardiac function, CT-1 inhibited apoptotic and non-apoptotic cell death induced by angiotensin II or hydrogen peroxide, whereas cardiomyocytes isolated from SHR with heart failure (HF) were resistant to

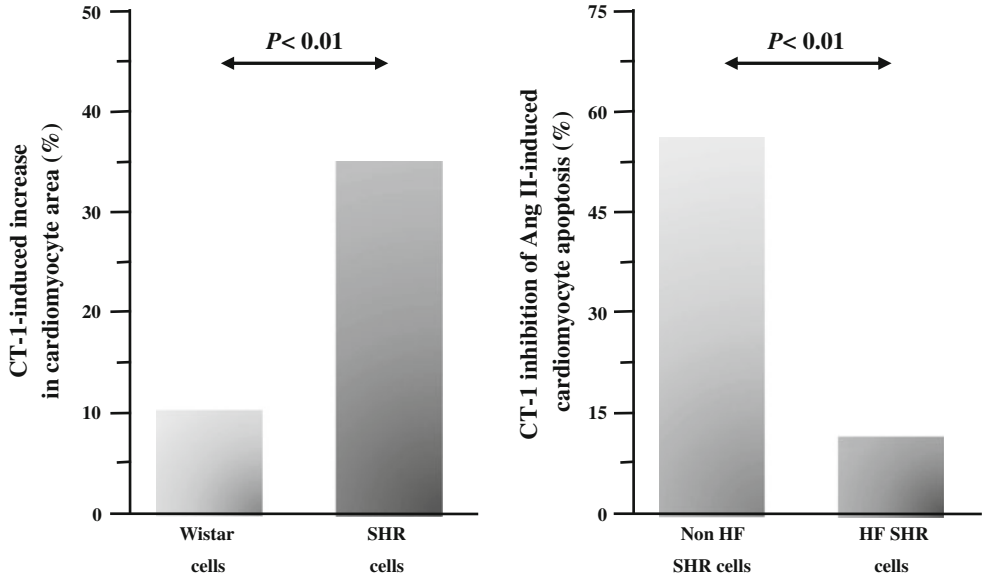

Fig. 2 *Left panel*. Hypertrophic effect (as assayed by planimetry in an image analysis system) of cardiotrophin-1 (CT-1, 10^{-9} M for 48 h) on primary culture of cardiomyocytes obtained from the left ventricle of adult normotensive Wistar rats and spontaneously hypertensive rats (SHR). (Adapted from reference 24). *Right panel*. Antiapoptotic effect (as assayed by the TUNEL methodology) of cardiotrophin-1 (CT-1, 10^{-9} M for 48 h) on primary culture of cardiomyocytes obtained from the left ventricle of adult spontaneously hypertensive rats (SHR) without or with heart failure (non HF SHR cells and HF SHR cells, respectively) and previously incubated with angiotensin II (Ang II, 10^{-7} M for 24 h). (Adapted from reference 25)

the cytoprotective effects of CT-1 [25] (Fig. 2). Although the causes of the loss of cytoprotection by CT-1 in cardiomyocytes from failing SHR are unclear, it is interesting to point out that these cells exhibited a marked reduction in LIFR expression [25].

Zolk et al. [26] reported in heart tissues reconstituted from rat cardiomyocytes that long-term exposure to CT-1, at concentrations comparable to CT-1 blood levels found in patients with chronic HF, depressed basal force of contraction and the inotropic response to Ca^{2+} and isoprenaline in a dose-dependent manner. In addition, CT-1 downregulated the expression of calsequestrin, a protein involved in Ca^{2+} handling, and prevented the formation of longitudinally oriented bundles of cardiomyocytes. Since both changes might contribute to ineffective force generation, the possibility emerges that long-term exposure to high concentrations of CT-1 impairs cardiac systolic performance.

More recently, it has been reported that in cultured HL-1 cardiomyocytes long-term incubation with a high concentration of CT-1 was accompanied by decreased gp130:phosphorylated gp130 (at Ser782) ratio and increased gp130 ubiquitination [27], thus suggesting that chronic exposure to a chronic excess of CT-1 may result in gp130 downregulation and the compromise of cytoprotective mechanisms mediated by gp130 ligands.

Finally, it has been reported that CT-1 receptor is also present in cardiac fibroblasts, and that the cytokine, dose dependently, stimulates DNA and collagen synthesis in these cells [28, 29]. While this finding appears to be contradictory to other published data [30], recent in vivo data support a role for CT-1 in mediating the fibrotic actions of aldosterone in the rat heart [31]. In addition, CT-1 exerts chemotactic effects in rat ventricular myofibroblasts via changes in membrane potential, alterations in intracellular Ca^{2+}, and activation of a number of intracellular signaling pathways (including JAK and myosin light chain kinase) [32]. Therefore, the role of CT-1 in myocardial fibrosis deserves to be considered.

Myocardial CT-1 in HHD

At the structural level, HHD is characterized by cardiomyocyte hypertrophy and interstitial and perivascular fibrosis that induce the remodeling of the LV myocardium and facilitate the development of HF [33]. Some experimental and clinical evidence suggests that CT-1 may contribute to hypertensive myocardial remodeling.

Animal data

In studies performed in vivo, it has been reported that CT-1 expression is abnormally high at the mRNA and protein levels in the hypertrophied left ventricle of SHR [24, 34–36] and heterozygous transgenic TGR (mREN2) rats [36]. Of interest, whereas increased myocardial CT-1 expression preceded the development of LVH in SHR, its level in other organs, including kidney and lung, was normal [35].

In addition, it has been reported that CT-1 mRNA and protein levels are higher in both aged SHR [25] and Dahl salt-sensitive (DS) rats which were fed with a high-salt diet [37, 38] presenting with LVH and HF than in their counterpart strains with normal cardiac function. Interestingly, CT-1 was associated with cardiomyocyte apoptosis in failing SHR [25] and with left ventricular end-diastolic dimension in failing DS rats [38]. Albeit descriptive, these data point to a pathogenetic role of CT-1 in the transition from LVH to HF in hypertensive rats. However, it is to note that transplantation of CT-1-expressing skeletal myoblasts to the left ventricular wall attenuated left ventricular dilatation and retarded the transition to HF in DS rats which were fed with a high-salt diet [39].

Human data

Although no information is available comparing the expression of CT-1 in the myocardium of patients with HHD and matched normotensive controls, it has been reported that CT-1 was increased at both the mRNA and protein levels in HF hypertensive patients with LVH compared with non-HF hypertensive patients with LVH [27]. In addition, gp130 protein expression, and p42/44 MAPK and PI3K/Akt activation were decreased, and cardiomyocyte apoptosis was increased in patients with HF compared with patients without HF [27]. Interestingly, inverse correlations occurred between cardiomyocyte apoptosis and p42/44 MAPK and PI3K/Akt activation on one hand, and between CT-1 and gp130 on the other hand, in all hypertensive patients [27]. Since an inverse association between increased CT-1 and decreased gp130 has been reported also in the myocardium of patients with end-stage HF due to ischemic and dilated cardiomyopathy [40], the notion emerges that gp130 receptor downregulation balances enhanced CT-1 expression in human HF, and thereby inhibits activation of the gp130 signaling cytoprotective pathway, thus contributing to the transition from LVH to HF (Fig. 3).

Translational approach to CT-1 in hypertension

A number of clinical findings support the notion that circulating CT-1, measured in either serum or plasma, may be a potential biochemical marker of the development, progression, and regression of HHD. In addition, recent

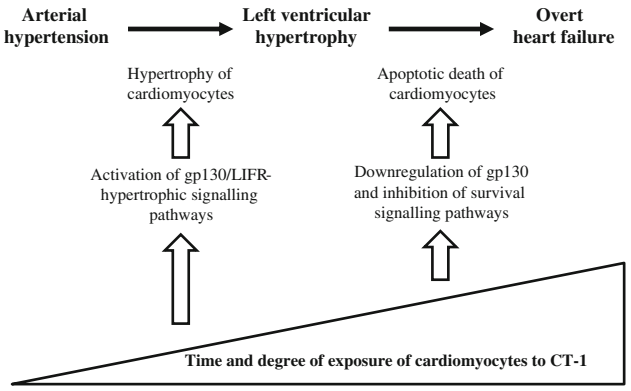

Fig. 3 Schematic representation of the mechanisms involved in the contribution of cardiotrophin-1 (CT-1) to the clinical evolution of hypertensive heart disease

evidence suggests that CT-1-mediated detrimental cardiac actions may be a therapeutic target in HHD.

CT-1 as a diagnostic biomarker

In studies performed in humans, it has been reported that CT-1 concentration shows a positive gradient from coronary sinus blood toward aortic blood [41]. On the other hand, it has been shown that the concentration of CT-1 in blood is directly correlated with the myocardial expression of CT-1 [27]. Collectively, these findings suggest that, in humans, 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.

Blood CT-1 concentration has been found to be increased in hypertensive patients as a whole group when compared with normotensive subjects [42, 43]. In addition, it has been reported that circulating CT-1 is higher in hypertensive patients with echocardiographically detected LVH than in patients without LVH [42], and in hypertensive patients with LVH and HF than in patients with LVH and no clinically overt HF [27]. In addition, blood CT-1 concentration is directly correlated with left ventricular mass index (LVMI) in hypertensive patients with and without clinically overt HF [42–44]. Of interest, blood CT-1 concentration has been found to be normal in normotensive athletes with LVH [45]. Furthermore, no association was found between circulating CT-1 and LVMI in these subjects [45]. Therefore, although these findings come from cross-sectional studies, it can be hypothesized that circulating CT-1 can be a potential biomarker of left ventricular growth in patients with HHD.

Some recent findings add further support to the above possibility. First, the functional 1742(C/G) polymorphism of the human CT-1 gene was found to be a significant determinant of both LVMI and circulating CT-1 in a general population sample, after adjusting for confounding factors [46]. In addition, the 1742(C/G) polymorphism was associated with LVH in hypertension and CT-1 was found to be one of the mediators of this association [46]. Second, López et al. [47] reported that blood CT-1 concentration was higher in patients with inappropriate left ventricular mass than in patients with appropriate left ventricular mass (as defined by a ratio of observed/predicted left ventricular mass >135 % [48]). In addition, circulating CT-1 was directly correlated with the ratio of observed/predicted left ventricular mass in all patients [47], suggesting that the cytokine can be one of the factors involved in the growth of left ventricle beyond pressure overload imposed by arterial hypertension.

It has been found that circulating CT-1 progressively increased, along with progression of HF stages, in patients with HHD [43] (Fig. 4). In particular, an inverse correlation between circulating CT-1 and left ventricular ejection fraction has been reported in patients with HHD and chronic HF [43]. On the other hand, abnormally high blood CT-1 concentration was found to be associated with reduced fractional shortening and altered diastolic relaxation in patients with inappropriate left ventricular mass [47]. More recently, direct correlations between circulating CT-1 and estimated left ventricular filling pressure and pulmonary capillary wedge pressure were reported in patients with chronic diastolic HF of hypertensive and non-hypertensive origin [49]. All these findings support the notion that CT-1 is associated not only with LVH but also with left ventricular dysfunction in HHD.

The above information comes from cross-sectional studies and no data are available on the prognostic role of

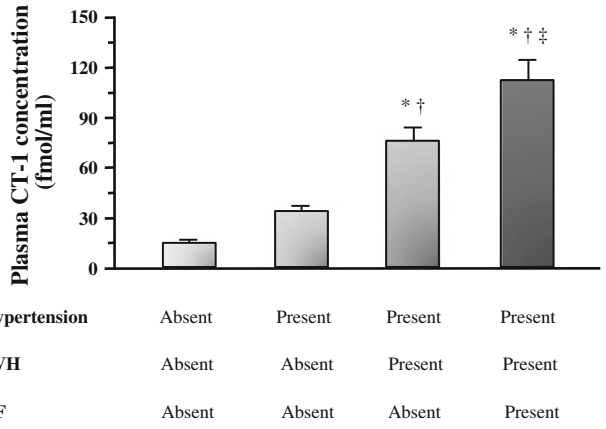

Fig. 4 Concentration of cardiotrophin-1 (CT-1) measured in plasma from normotensive subjects without cardiac disease (*first column*), hypertensive patients without hypertensive heart disease (HHD) (*second column*), hypertensive patients with HHD (*third column*), and hypertensive patients with HHD and heart failure (*fourth column*). * $P < 0.001$ versus normotensive subjects, † $P < 0.001$ versus hypertensive patients without HHD, ‡ $P < 0.001$ versus hypertensive patients with HHD. (Adapted from reference 43)

CT-1 in patients with HHD. However, Tsutamoto et al. [50] have reported that a high blood concentration of CT-1 is an independent predictor of mortality in patients with chronic HF of hypertensive and non-hypertensive origin. Although the reason why circulating CT-1 is an independent prognostic predictor remains unknown, factors such as left ventricular wall stress and other local neurohumoral factors that stimulate CT-1 may become maladaptive with the progression of chronic HF.

Receiver operating characteristic (ROC) curves analysis showed that circulating CT-1 presents an acceptable sensitivity (70 %) and specificity (75 %) to detect LVH, as assessed by echocardiography, in hypertensive patients without HF [42]. Of interest, the sensitivity of circulating CT-1 to detect asymptomatic LVH in these patients is clearly superior to that of the electrocardiogram (50 %). In addition, ROC curves analysis also showed that circulating CT-1 exhibits higher sensitivity but lower specificity for diagnosing clinically overt HF than amino-terminal pro-brain natriuretic peptide (NT-proBNP) in hypertensive patients, the simultaneous assessment of the two parameters resulted in an increase in the sensitivity of NT-proBNP to detect HF in these patients (from 72 to 78 %) [43]. Therefore, circulating CT-1 exhibits an acceptable performance to diagnose asymptomatic HHD and in combination with NT-proBNP increases the ability to diagnose HF among hypertensive patients.

CT-1 as a therapeutic target

An association has been found between antihypertensive treatment-induced decrease of blood CT-1 and reduction of LVMI in patients with LVH, this association being independent of changes in blood pressure [44]. Of interest, no association was found between changes in LVMI and changes in circulating IL-6, the master cytokine of the family to which CT-1 belongs, in treated hypertensive patients [44]. In addition, circulating CT-1 has been reported to decrease and to increase 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 [47]. Collectively, these findings suggest that circulating CT-1 may be useful for monitoring the effects of therapy on left ventricular mass in hypertension.

The mechanisms by which circulating CT-1 changes in response to antihypertensive treatment cannot be fully assessed from the above studies. One possibility is that different antihypertensive drugs may have distinct influences on the synthesis and secretion of CT-1. This possibility arises from the observation that most hypertensive patients in which LVH regressed and circulating CT-1 decreased simultaneously were treated with the AT_1 receptor blocker losartan [44, 47] (Fig. 5). In contrast, most hypertensive patients in whom LVH persisted and circulating CT-1 remained unchanged with treatment were receiving the beta adrenergic receptor blocker atenolol [44, 47] (Fig. 5). In this regard, whereas it has been shown that angiotensin II stimulates CT-1 in cardiac cells through the AT_1 receptor [4], the possibility remains that norepinephrine induces CT-1 in cardiomyocytes likely via stimulation of alpha 1 receptors [6]. Clearly, additional studies are required to explore the effects of antihypertensive drugs on CT-1 regulation.

Recent data expand to non-antihypertensive drugs (i.e., 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors and peroxisome proliferator-activated receptor gamma ligands) the potential to interfere with the cardiac detrimental actions of CT-1. In fact, simvastatin was proved, in a dose-independent manner, to decrease cardiomyocytes size as well as protein synthesis, and inhibit atrial natriuretic peptide (ANP) mRNA synthesis induced by CT-1 in

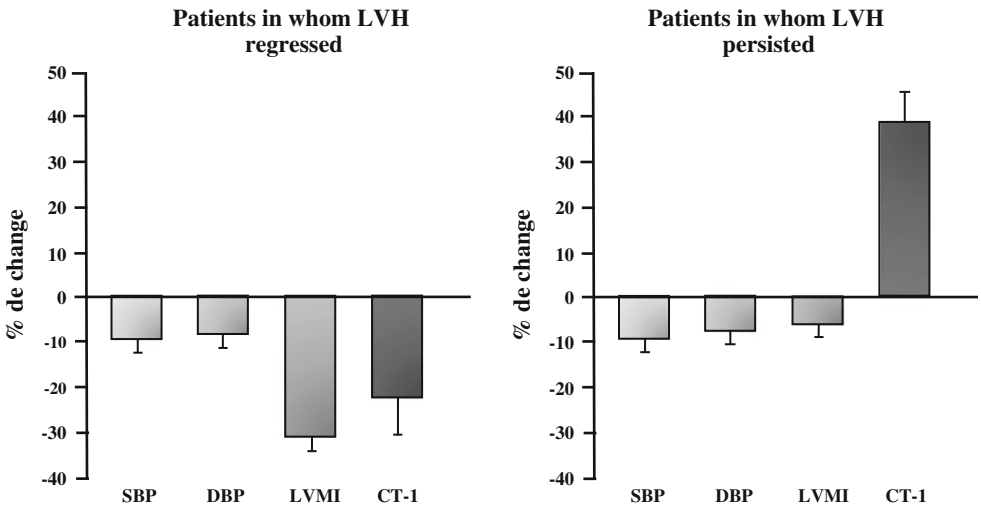

Fig. 5 Changes in systolic and diastolic blood pressure (SBP and DBP, respectively), left ventricular mass index (LVMI) and plasma cardiotrophin-1 (CT-1) concentration in hypertensive patients with hypertensive heart disease in whom left ventricular hypertrophy (LVH) regressed (*left panel*) or persisted (*right panel*). (Adapted from reference 44)

primary cultured rat cardiomyocytes [51, 52]. In addition, simvastatin attenuated cardiac hypertrophy in rats with pressure overload due to abdominal aortic constriction as assessed by reductions in the ratio of heart weight to body weight, the ratio of left ventricular weight to body weight, and the cross-sectional area of cardiomyocytes [51]. Molecular analysis indicated that the JAK/STAT pathway was involved in the mechanisms underlying the in vitro and in vivo inhibitory effects of simvastatin on cardiac hypertrophy [51, 52]. On the other hand, it has been reported that pioglitazone inhibited hypertrophy (as assessed by the increase in cellular surface area and ANP mRNA expression) and CT-1 mRNA overexpression induced by high glucose and insulin in primary cultured rat cardiomyocytes [9].

The effects of simvastatin and pioglitazone illustrate well the emerging notion that unbridled activation of JAK-STAT signaling by IL-6 –type cytokines (i.e., CT-1) would seem to be detrimental for the heart (i.e., the cardiomyocyte), and thus a therapeutic strategy targeting both excessive JAK or STAT activity may be of benefit in protecting a heart under chronic stress (i.e., the hypertensive heart) [12].

Future perspectives

CT-1 has a great number of functions that sometimes have opposite results. In fact, it can promote cardiac cell survival but can also cause pathologic LVH. Thus, we cannot say that CT-1 is a beneficial or a detrimental molecule. The different activities of CT-1 reflect the different signaling pathways activated by this cytokine. Further studies are needed to explain how many other signaling pathways downstream of gp130 in the cardiomyocytes or in the heart are stimulated by CT-1, and the functions of which are mediated by each of them. It is interesting to note that at least some of the effects exerted by CT-1, both in vitro and in vivo, are dose- and time-dependent and this could explain, partly, the opposite activities of CT-1. Another interesting observation is the shortage of experiments on adult cardiomyocytes, since CT-1 is involved in diseases of typical adult age. Neonatal cardiac cells have several and important differences from adult cardiac cells. In fact, neonatal cardiac cells are not terminally differentiated and mitochondrial, and sarcomere structure are also different from adult cells. Therefore, both the energy metabolism and contractile properties of the myocardium can be different. Understanding the role of CT-1 in HHD will allow researchers to characterize better its potential diagnostic and prognostic usefulness as a biomarker, as well as its potential value as a therapeutic target. Regarding the role of CT-1 as a cardiac biomarker, although several works have shown that circulating CT-1 concentrations correlate with the severity of LV morphological and functional abnormalities, we still do not have a value of reference. CT-1 levels reported in the literature cannot be compared for several methodological reasons [13]. Thus, technical developments to provide a single, valid, reproducible, and cheap method to asses CT-1 in serum or plasma samples are required. In addition, investigations aimed to develop a drug against CT-1 or to identify among the clinically available drugs those that can hinder the negative effects of CT-1 on the heart are also necessary. From these perspectives, it is clear that besides basic and pharmacologically oriented research, further longitudinal clinical studies are needed to ascertain the true usefulness of this molecule in the clinical handling of HHD.

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Conflict of interest None.

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