Cardiomyocyte Apoptotic Cell Death in Arterial Hypertension
Mechanisms and Potential Management

Maria Antonia Fortuño, Susana Ravassa, Ana Fortuño, Guillermo Zalba, Javier Díez

Abstract—Hypertensive heart disease is a progressive condition in which the compensatory left ventricular hypertrophy that maintains cardiac output leads to myocardial remodeling, characterized by fibrosis, insufficient vascularization, and alterations in cardiomyocytes, including contractile disturbances, changes in gene expression, and decrease in the number of cells. Structural abnormalities in the myocardial wall accelerate the development of diastolic and systolic dysfunction, resulting in heart failure. Many observations point to the apoptotic cell death of cardiomyocytes as a relevant factor in the transition from compensatory hypertrophy to pump failure in experimental and human hypertension. Potential inducers of cardiomyocyte apoptosis in overloaded hearts include extrinsic factors, such as mechanical forces, neurohormonal activation, oxidative stress, hypoxia, and cytokines. Some lines of evidence indicate that angiotensin II and the overstretching of cardiomyocytes are originally involved in the triggering of apoptosis in hypertension, whereas other factors are being investigated. Furthermore, intracellular changes, such as downregulation of survival proteins or activation of death proteins, seem to play an important role. The assumption that the apoptosis of cardiomyocytes worsens hypertensive heart disease prognosis brings forth new approaches to avoid or slow the transition to pump failure. In this respect, experimental data indicate that currently used antihypertensive drugs interfere with cardiomyocyte apoptosis. Moreover, the knowledge of intracellular apoptotic processes in cardiomyocytes provides novel therapeutic strategies to be added to the multimodal approach in the prevention of heart failure. (Hypertension. 2001;38:1406-1412.)

Key Words: angiotensin II ■ apoptosis ■ myocytes ■ hypertension, arterial ■ cardiomyopathies

Congestive heart failure is one of the most significant causes of morbidity and mortality in developed countries. It occurs as a late manifestation in diverse cardiovascular diseases characterized by the loss of contractile muscle mass and/or by volume or pressure overload. Most patients with heart failure have antecedents to arterial hypertension.1 The pathological time course of hypertensive heart disease includes 2 stages. Initially, concentric hypertrophy of the left ventricle compensates pressure overload and normalizes systolic wall stress, and thus cardiac function is maintained. However, this adaptive hypertrophy is accompanied by structural modifications of the cardiac muscle, including alterations in gene expression, loss of cardiomyocytes, defective vascular development, and fibrosis. Thus, the compensatory response is inexorably followed by a transition to cardiac failure (which is characterized by the onset of chamber dilatation with the failure of further concentric hypertrophic growth to normalize load) and progressive contractile dysfunction.2

Apoptosis is an energy-requiring physiological mechanism of cell death that regulates cell mass in many tissues. It is also called programmed cell death because it is a genetically directed process that takes place in response to internal or external stimuli. Apoptosis should be contrasted to necrosis, which is considered a nonregulated and nonphysiological form of cell death. In contrast to the classic swelling and membrane rupture associated with necrosis, apoptotic cells shrink, maintain their membrane integrity, and are rapidly cleared by neighboring cells or local macrophages.3 The demonstration of apoptosis may be difficult because it occurs quite rapidly, with disappearance of the cells within several hours. The introduction of terminal deoxynucleotidyl transferase–mediated dUTP nick end-labeling (TUNEL) methodology to localize the 3′ end of DNA in situ, and the detection of internucleosomal DNA fragments in agarose gels, has been proposed as useful tools in the identification of apoptosis. However, the distinction between apoptosis, necrosis, and DNA repairing may not be clear with these technologies, and their limitations are being reviewed.4,5

Because cardiomyocytes are terminally differentiated cells, it has been traditionally accepted that they are able neither to replicate nor to undergo apoptosis. However, recent abundant

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literature has demonstrated that apoptosis of cardiomyocytes can be induced by many pathological conditions in experimental models and in human cardiac disease.6

The purpose of the present article is to review the status of knowledge regarding the factors responsible for cardiomyocyte apoptosis in experimental and human hypertensive heart remodeling and the pathophysiological relevance of this phenomenon. Moreover, we will briefly examine the possibilities of pharmacological management of cardiomyocyte apoptosis.

**Apoptotic Factors in Experimental Hypertension**

The loss of cardiomyocytes by apoptosis has emerged as an important factor contributing to myocardial remodeling in response to hemodynamic overload. In the context of hypertension, the local factors that may trigger the apoptotic program of cardiomyocytes include mechanical forces, oxidative stress, hypoxia, and an unbalanced presence of growth factors and cytokines (eg, angiotensin II) or neurotransmitters (eg, norepinephrine). Importantly, the apoptotic signals are those that have largely been demonstrated to produce an enlargement of cardiomyocytes. In this respect, it has been proposed that when growth signals persist chronically in terminally differentiated cells, they produce a contradictory genetic demand and trigger the apoptotic response.7,8 A molecular explanation for this double response may be that persistent growth stimuli can drive hypertrophied cardiomyocytes to lose intracellular survival signals that normally suppress the development of the apoptotic process; as a consequence, growth factors turn into apoptotic factors (Figure, panel A). Another possibility is that intrinsic genetic predisposition directly determines whether cardiomyocytes enter apoptosis or develop hypertrophy in response to local environmental conditions. The recent description of cardiomyocyte survival pathways may be of special interest in understanding the mechanisms underlying the responses of this cell type.

**Mechanical Stress**

Mechanical forces that are present in the pressure-overloaded heart are one of the main forms of cellular injury that may cause apoptotic cell death. In this respect, it has been established that overstretching of either papillary muscles or cardiomyocytes isolated from adult rats produces an increment in the cardiomyocyte apoptotic index.10,11 Similar results have been obtained from animal models subjected to overloading maneuvers. Increased cardiomyocyte apoptosis has been demonstrated after aortic binding in rats,12 ascending aortic stenosis in mice,13 and 2-kidney, 1-clip hypertension in hamsters.14 In contrast, in genetic models of hypertension, mechanical stress is not the most important inducer of apoptosis since cardiomyocyte apoptosis has been shown to be a phenomenon independent of blood pressure values.15–18 Alterations of cardiac apoptosis have been reported in newborn, young, adult, and aged spontaneously hypertensive rats (SHR) with and without heart failure. Compared with aged-matched normotensive Wistar-Kyoto rats (WKY),
the cardiac DNA fragmentation index is decreased in newborn SHR\textsuperscript{15}; it is augmented from 8 to 16 weeks, and again falls under control values at 24 weeks,\textsuperscript{16,19} indicating that changes in cardiac apoptosis are independent of blood pressure values. Previous results from our laboratory showed that cardiomyocyte apoptosis is higher in the hypertrophied left ventricle of SHR at 30 weeks than at 16 weeks of age, although systolic and diastolic blood pressure values were similar at the 2 ages.\textsuperscript{17} Similar findings analyzing the time course of cardiomyocyte apoptosis in SHR\textsuperscript{18} and comparing aged SHR with and without heart failure\textsuperscript{20} have recently been reported. All these data demonstrate that no clear association exists between cardiomyocyte apoptosis and blood pressure values in genetic hypertension.

Angiotensin II

Observations outlined above suggest that nonhemodynamic factors must be involved in cardiomyocyte injury that results in apoptotic cell death in genetic hypertension. Candidates include (among others) growth factors that result from neurohormonal activation. We have previously reported that the increment of cardiomyocyte apoptosis in the hypertrophied left ventricle of adult SHR is associated in a temporal way with cardiac ACE activity and that a direct correlation exists between the 2 parameters in hypertensive animals.\textsuperscript{17} Moreover, chronic treatment with either an ACE inhibitor or an angiotensin type 1 receptor (AT\textsubscript{1}) antagonist prevents cardiomyocyte apoptosis in this model,\textsuperscript{17,21,22} suggesting that the local renin-angiotensin system activation may be involved in the triggering of cardiomyocyte apoptosis. In this respect, it has been demonstrated that binding of angiotensin II to its AT\textsubscript{1} receptor induces apoptosis of cardiomyocytes isolated from neonatal\textsuperscript{23} and adult\textsuperscript{24} normotensive rats. Results recently reported from our laboratory demonstrate that compared with cardiomyocytes isolated from normotensive WKY rats, cardiomyocytes isolated from SHR exhibit increased susceptibility to the apoptotic effects of angiotensin II.\textsuperscript{25} This observation is compatible with the possibility that, besides other conditioning factors, such as a genetic predisposition, the octapeptide may cause the excess of cardiomyocyte apoptotic death observed in this experimental model. It is interesting to note that angiotensin II promotes hypertrophy and apoptosis, interacting with the AT\textsubscript{1} receptor in cardiomyocytes, whereas in other cell lines, the octapeptide has been shown to promote apoptosis via the AT\textsubscript{2} receptor.\textsuperscript{26} These observations confirm that apoptosis is triggered and regulated in a cell type–specific manner.

Other Extrinsic Factors

An altered regulation of cell volume and ionic transport systems has been largely described in human and experimental hypertension. Interestingly, osmotic stress may exert an apoptotic effect on cardiomyocytes.\textsuperscript{27} In adult SHR, acute osmotic stress induction by the administration of mannitol activates renal and cardiac apoptosis.\textsuperscript{28} The precise involvement of osmotic stress in pathological conditions in this model and its potential role in human hypertension require more investigation.

Sympathetic activation may also be present in hypertension since it is an early mechanism that maintains cardiac output; however, it can also exert growth and/or apoptotic effects. Norepinephrine promotes apoptosis in isolated cardiomyocytes via β\textsubscript{-} but not α-adrenergic receptor activation.\textsuperscript{29} Moreover, β\textsubscript{-}adrenergic activation exerts apoptotic effects, whereas β\textsubscript{2}-adrenergic receptor activation may participate in both survival and the death response of cardiomyocytes, depending on the G protein that is associated, ie, G\textsubscript{i} or G\textsubscript{s}.\textsuperscript{30,31} On the other hand, continuous β-adrenergic stimulation has been demonstrated to induce cardiomyocyte apoptosis in normotensive Wistar rats, this effect being independent of increased heart rate, systolic load, and left ventricular hypertrophy.\textsuperscript{32} To our knowledge, there is no direct evidence indicating the participation of adrenergic activation of cardiomyocyte apoptosis in hypertension. Thus, more studies are needed to clarify this possibility.

Many in vitro and in vivo studies have demonstrated that hypoxia and oxidative stress may activate the apoptotic cell death of cardiomyocytes.\textsuperscript{6} Because overloaded cardiac tissue is exposed to hypoxic conditions and reactive oxygen species, it is tempting to speculate that these chronic nonextreme environmental conditions may cause scarce apoptotic death of cardiomyocytes, in contrast with the massive apoptotic and necrotic cell death observed after an acute ischemic injury.

Intrinsic Factors

It is important to point out that besides environmental factors, abnormalities in death and survival proteins may be determinant in the apoptotic response of cardiomyocyte. As we previously reported, the increased amount of the proapoptotic protein Bax-α in hearts from adult SHR and its normalization after long-term AT\textsubscript{1} blockade suggest that alterations in this protein regulation underlie the enhanced apoptotic process observed in SHR.\textsuperscript{21} Interestingly, angiotensin II increases Bax-α protein expression in isolated cardiomyocytes, and this effect is higher in cells from SHR compared with cells from normotensive WKY rats.\textsuperscript{21,25} Anomalies in other proapoptotic proteins have been reported in this genetic model of hypertension,\textsuperscript{20} indicating that besides extrinsic factors, an intracellular predisposition to develop apoptosis exists in SHR cardiomyocytes.

Recently, the transmembrane signal transducer gp130 molecule has been proposed to exert a survival effect in cardiomyocytes, mediating hypertrophic signals triggered by the interleukin-6–related cytokines (ie, cardiotrophin-1).\textsuperscript{33,34} Specific left ventricular gp130 knockout mice exhibit normal cardiac phenotype but develop a rapid dilated cardiomyopathy with massive cardiomyocyte apoptosis in response to mechanical stress. These findings indicate that gp130 is a dispensable protein for normal cardiac growth, but it is critical in the compensatory hypertrophic response, in mediating cardiomyocyte survival, and in avoiding apoptosis.\textsuperscript{35} It is possible that the downregulation of this protein in genetic hypertension decreases the survival capability of cardiomyocytes and makes them more susceptible to all-around apoptotic factors.

Other intracellular signaling factors involved in cardiomyocyte death/survival balance are the mitogen-activated...
protein kinase p38 subfamily and the p300 transcription coactivator family. Briefly, recent works indicate that the p38α isoform facilitates apoptosis, whereas the p38β isoform mediates a hypertrophic response, and the p300-related proteins are involved in cardiomyocyte specific survival. The precise role of these and other molecular pathways in the development of cardiomyocyte apoptosis present in hypertensive remodeling requires further investigation.

**Cardiomyocyte Apoptosis in Human Hypertension**

Side-to-side slippage of cardiomyocytes, a phenomenon identified for the first time 4 decades ago, is a critical factor in ventricular dilation in the decompensated hypertrophied human heart. Although the origin of this alteration is not well understood, it has been proposed that single cardiomyocyte death would allow side-to-side translocation of cells within the left ventricle wall. Importantly, the analysis of cardiac remodeling in a population of middle-aged hypertensive patients, with no clinical history of heart dysfunction and no anatomic evidence of ischemic cardiomyopathy, demonstrated an increase in the size of cardiomyocytes accompanied by cardiomyocyte cell loss and multiple foci of fibrosis. These changes were present in both ventricles but involved the left ventricle more extensively than the right ventricle. The lack of hemodynamic measurements does not rule out the possibility that some impairment in ventricular function was present in hypertensive patients. More recently, loss of cardiomyocytes due to apoptosis has been demonstrated in patients with end-stage heart failure. These data, along with the observations in experimental hypertension, lead to the hypothesis that cardiomyocyte loss seen in the hypertrophied left ventricle of patients with arterial hypertension may be due to enhanced cardiomyocyte apoptosis. An ongoing process of cardiomyocyte apoptosis will progressively deteriorate myocardial function, leading to the so-called early failure that characterizes hypertensive cardiomyopathy and facilitating the progression to end-stage heart failure.

The nature of cardiomyocyte cell death in hypertrophied human myocardium has recently been analyzed. Cytoplasmic and nuclear apoptotic events were studied in chronically overloaded human hearts. From their results, the authors postulate that cytoplasmic proteolysis is an early self-controlled process that leads to the delayed apoptotic nuclei elimination in cardiomyocytes. Interestingly, apoptotic nuclei were more abundant in hearts with eccentric hypertrophy than in hearts with concentric hypertrophy, probably reflecting different myocardial conditions and anticipating a worse prognosis when more cardiomyocytes are lost.

We are currently ending a study that was designed to deepen hypertensive cardiac remodeling. Among other topics, we wanted to check the hypothesis that hypertensive patients with very early cardiac affection exhibit an excess of apoptotic cardiomyocytes. Included in the study were middle-aged mildly to moderately hypertensive patients exhibiting left ventricular hypertrophy or diastolic dysfunction, without signals of ischemic cardiomyopathy or/and ventricular dysfunction. A cardiac biopsy–based protocol was used to analyze different aspects of cardiac remodeling, including the quantification of collagen content and the assessment of cardiomyocyte apoptosis. Preliminary data from our study show that besides the augmentation in myocardial collagen content, human overloaded hearts exhibit increased cardiomyocyte and noncardiomyocyte apoptotic indexes compared with those from myocardial necropsies obtained from normotensive subjects with no clinical or anatomic signals of cardiovascular disease. These findings support the possibility that apoptosis is present in human hypertensive heart disease.

**Pathophysiological Significance**

The pathological consequences of cardiomyocyte loss during hypertension are not fully established, although some lines of evidence indicate that the phenomenon is detrimental for cardiac function. The decrease in the number of contractile cells will result in an increased workload on the remaining cells, thus depressing ventricular function. Cell death involving individual cardiomyocytes was recognized to be a critical factor in the chronic evolution of ischemic cardiomyopathy; similarly, the scattered distribution of individual apoptotic events across the myocardial wall described in experimental hypertension may facilitate the impairment of cardiac function in overloaded hearts. Moreover, the apoptotic death of contractile cells and expansion of the interstitial component are related alterations in hypertensive cardiac remodeling. Clinical findings support the possibility that the interstitial fibrosis present in overloaded hearts reflects a process of myocardial scarring as a result of individual cardiomyocyte death. Recently, this possibility has been confirmed in hypertrophied human hearts by Yamamoto et al and by us (A. González, J. Díez, M.A. Fortuño, unpublished data, 2001).

As previously noticed, some signals that produce the enlargement of cardiomyocytes and lead to compensatory left ventricular hypertrophy may also induce apoptosis. Although the origin and the time course of this switch in cardiomyocyte response remain unknown, it is plausible to think that if the early cardiomyocyte hypertrophy is followed by the apoptotic response because of the persistence of growth stimuli, the morphological expression of cardiac tissue remodeling will be the development of concentric compensatory hypertrophy, followed by chamber dilation. Alternatively, direct development of eccentric hypertrophy with its intrinsically worse prognosis could indicate a predominant apoptotic response in cardiomyocytes. This possibility is further supported by a recently reported finding of a higher number of apoptotic nuclei in hearts with eccentric hypertrophy than in hearts with concentric hypertrophy. The functional consequence of these structural changes that occur in the myocardial wall is a progressive deterioration in myocardial function, culminating in end-stage heart failure. However, many important issues remain unanswered. For instance, it is not known which degree of cardiomyocyte apoptosis determines the transition to heart failure and the onset of pump failure. Studies in humans and animals indicate that acute ischemia leads to overt failure when 40% to 50% of...
The occurrence of cardiomyocyte apoptosis in cardiac remodeling may contribute to worsen the prognosis of hypertensive heart disease, facilitating the transition from adaptive hypertrophy to heart failure. The possibility that blocking this process could prevent or slow cardiac failure progression opens new strategies in the treatment of cardiac disease. Cardiomyocyte apoptosis may be prevented by regulating the local factors that trigger the process or by directly blunting the intracellular apoptotic pathways. Although antihypertensive drugs will modulate environmental signals that cause apoptosis, the knowledge of the precise intracellular apoptotic mechanisms in these terminally differentiated cells is necessary to block them.

Effects of Antihypertensive Drugs

Whether currently used antihypertensive therapies are able to modulate the apoptotic death of cardiomyocytes is presently being investigated (Table). Experimental data indicate that many of the tested substances are able to interfere cardiomyocyte apoptosis induced by different stimuli. Of special interest for this review are data obtained from SHR. Previous results from our laboratory have shown that long-term pharmacological interference of the renin-angiotensin system prevents the increment of cardiomyocyte apoptosis in adult SHR. Other groups have confirmed these effects in adult SHR and failing aged SHR. In the same experimental model, Tea et al. recently analyzed the effects that a 4-week administration of different antihypertensive drugs had on cardiac hypertrophy regression and on the DNA fragmentation index. Basically, they showed that renin-angiotensin system intervention and β-adrenergic blockade produced an increment of apoptosis in parallel to cardiac hypertrophy regression; calcium channel antagonists produced a time window of apoptosis after the first week of administration, whereas hydralazine and hydrochlorothiazide did not modify either cardiac hypertrophy or DNA fragmentation. Thus, other tools beyond TUNEL should be applied for the evaluation of cardiomyocyte apoptosis.

### Pharmacological Aspects

### Table: Effects of Antihypertensive Drugs on Cardiomyocyte Apoptosis in Experimental Models of Hypertensive and Aging-Related Heart Failure Cardiomyopathies

<table>
<thead>
<tr>
<th>Model</th>
<th>Treatment</th>
<th>Effect of Treatment</th>
<th>First Author (Year)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHR</td>
<td>Hydrochlorothiazide</td>
<td>No effect</td>
<td>Tea (1999)</td>
<td>47</td>
</tr>
<tr>
<td>Transgenic (Gαs) mice</td>
<td>Propanol</td>
<td>↓ CM apoptosis</td>
<td>Asai (1999)</td>
<td>50</td>
</tr>
<tr>
<td>SHR</td>
<td>Propanol</td>
<td>↑ Apoptosis of nonspecific cardiac cell type</td>
<td>Tea (1999)</td>
<td>47</td>
</tr>
<tr>
<td>SHR</td>
<td>Hydralazine</td>
<td>No effect</td>
<td>Tea (1999)</td>
<td>47</td>
</tr>
<tr>
<td>SHR</td>
<td>Doxazosin</td>
<td>↓ Apoptosis of nonspecific cardiac cell type</td>
<td>Rodriguez-Feo (2000)</td>
<td>48</td>
</tr>
<tr>
<td>SHR</td>
<td>Nifedipine</td>
<td>↑ Apoptosis of nonspecific cardiac cell type</td>
<td>Tea (1999)</td>
<td>47</td>
</tr>
<tr>
<td>SHR</td>
<td>Lercanidipine</td>
<td>↓ CM apoptosis</td>
<td>Ravassa* (2001)</td>
<td>...</td>
</tr>
<tr>
<td>Failing dogs</td>
<td>Enalapril</td>
<td>↓ CM apoptosis</td>
<td>Gaussev (1998)</td>
<td>51</td>
</tr>
<tr>
<td>Failing aged mice</td>
<td>Enalapril</td>
<td>↓ CM apoptosis</td>
<td>Ferder (1998)</td>
<td>52</td>
</tr>
<tr>
<td>SHR</td>
<td>Quinapril</td>
<td>↓ CM apoptosis</td>
<td>Diez (1997)</td>
<td>17</td>
</tr>
<tr>
<td>Failing SHR</td>
<td>Enalapril</td>
<td>↓ CM apoptosis</td>
<td>Liu (1997)</td>
<td>20</td>
</tr>
<tr>
<td>SHR</td>
<td>Ramipril</td>
<td>↓ CM apoptosis</td>
<td>Liu (2000)</td>
<td>18</td>
</tr>
<tr>
<td>SHR</td>
<td>Enalapril</td>
<td>↑ Apoptosis of nonspecific cardiac cell type</td>
<td>Tea (1999)</td>
<td>47</td>
</tr>
<tr>
<td>SHR</td>
<td>Losartan</td>
<td>↓ CM apoptosis</td>
<td>Fortuño (1998)</td>
<td>21</td>
</tr>
<tr>
<td>SHR</td>
<td>Losartan</td>
<td>↑ Apoptosis of nonspecific cardiac cell type</td>
<td>Tea (1999)</td>
<td>47</td>
</tr>
</tbody>
</table>

CM indicates cardiomyocyte.

*Unpublished.
New Therapeutic Strategies Targeting Apoptotic Pathways

Direct pharmacological manipulation of the intracellular apoptotic pathways has been evidenced to decrease cardiomyocyte apoptosis in experimental studies recently reviewed.\(^9\)

Basically, low molecular weight inhibitors of caspases, c-Jun N-terminal, and p38 kinases inhibit cardiomyocyte apoptosis either in isolated cells and or in animal models of ischemia/reperfusion. The role of these compounds in hypertensive cardiomyocyte apoptosis requires further investigation.

Conclusions

The involvement of cardiomyocyte apoptosis in hypertensive cardiac remodeling and its determinant role in the transition to heart failure is being confirmed in experimental and human hypertension. Experimental data indicate that mechanical forces, angiotensin II, and osmotic stress trigger cardiomyocyte apoptosis in genetic hypertension. Other factors present in overloaded hearts, such as norepinephrine, hypoxia, and oxidative stress, promote cardiomyocyte apoptosis in vitro, and their role in experimental and human hypertension remain to be investigated. Moreover, intracellular regulators of death and survival pathways seem to be determinant in the cardiomyocyte response to hypertensive local injury and require further study.

The knowledge that cardiomyocyte apoptosis promotes a worsening of prognosis in hypertensive cardiomyopathy raises 2 different strategies to achieve the prevention of heart failure: the inhibition of apoptotic signals that trigger the process and the direct blockade of the intracellular apoptotic mechanisms. Several currently used antihypertensive drugs have demonstrated antiapoptotic effects on cardiomyocytes, especially those that counteract neurohormonal systems. Alternatively, molecules that blunt executor/regulator mechanisms of cardiomyocyte apoptosis should be assayed as new targets in the multimodal prevention of hypertension-induced heart failure.

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