Apoptosis in hypertensive heart disease
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Numerous hypotheses have been considered to explain the fundamental mechanism(s) for the development of systolic dysfunction and heart failure in animals and humans with arterial hypertension. Besides contractile disturbances of cardiomyocytes and interstitial and perivascular fibrosis, cardiomyocyte loss is now being considered as one of the determinants of the maladaptive processes implicated in the transition from compensated to decompensated left ventricular hypertrophy.

A number of experimental evidence suggest that exaggerated apoptosis may account for the loss of cardiomyocytes in the hypertensive left ventricle. Furthermore, some factors intrinsic and extrinsic to the cardiomyocyte emerge as potential candidates to trigger apoptosis. The elucidation of the possible interactions between these factors may be of major interest to prevent the progression to heart failure in patients with hypertensive heart disease.

Arterial hypertension alters the structure and compromises the function of the cardiac muscle. Besides affecting the myocardium directly, hypertension is also one of the risk factors for the development of atherosclerosis in the major coronary arteries, and this facilitates the development of myocardial ischemia and infarction. Because of this global involvement, morbidity and mortality caused by the cardiac consequences of hypertension are common. Thus, most patients with heart failure have antecedent hypertension [1].

From a pathophysiologic point of view, hypertension affects the myocardium at two different stages [2]. In both human and animal models, pressure overload is characterized by a period of compensation in which left ventricular concentric hypertrophy normalizes systolic wall stress, and contractile function is preserved. The period of adaptation, which may last for weeks in rodents and months to years in humans, is inexorably followed by a transition to cardiac failure. This transition is characterized by impaired survival, the onset of chamber dilatation with the failure of further concentric hypertrophic growth to normalize load, and progressive contractile dysfunction. Several observations suggest that the transition to failure relates mainly to cardiomyocyte loss caused by both apoptosis and necrosis [3], changes in the composition of motor unit and cytoskeleton of cardiomyocytes [4], and alterations in the metabolism of extracellular matrix [5].

The purpose of this article is to analyze evidence that suggests that apoptosis may have a role in the pathophysiology of hypertensive heart disease via cardiomyocyte loss. In addition, the available information on the factors that may contribute to the development of cardiomyocyte apoptosis in the hypertensive left ventricle is also discussed.

General aspects
Basic description of apoptosis
Apoptosis is a physiologic mechanism of deleting cells that regulates cell mass and architecture in many tissues. It is also called programmed cell death because it is an energy-requiring process that is genetically regulated. Thus, apoptosis should be compared with necrosis, which is considered a nonregulated and nonphysiologic form of cell death. In contrast to the classic swelling and membrane rupture associated with necrosis, apoptotic cells shrink and maintain their membrane integrity [6].

The process of apoptosis can be subdivided into several different phases: initiation, regulation, execution, and
degradation [7]. Although the initiation and regulation phases depend on apoptotic stimuli and are cell-type–specific, the execution and degradation phases are common to all apoptotic processes. Multiple initiating pathways have been proposed to trigger apoptosis, such as DNA damage, hypoxia, oxidative stress, the binding of apoptotic factors to specific receptors, or the absence of survival factors. The genes that participate in the regulation of the apoptotic process include those that primarily suppress apoptosis, those that act as facilitators of apoptosis, and intermediate genes [8]. The two best-known hallmarks of the execution phase are 1) the fragmentation of DNA by specific endonucleases that recognize internucleosomal sites and 2) the activation of a family of cystein-aspartate specific proteases (CASP3 or caspases), which have an important role in the execution of apoptosis by their proteolytic action on specific targets [9]. Apoptosis is followed almost inevitably by rapid uptake into adjacent phagocytic cells. Interestingly, macrophages that have ingested apoptotic cells have been shown to inhibit proinflammatory cytokine production and, thus, inflammation is avoided [10].

The detection of internucleosomal DNA fragments has been proposed as a useful tool to identify apoptosis [11]; however, the demonstration of apoptosis may be difficult because it occurs quite rapidly with disappearance of the cells within several hours. On the other hand, the distinction between apoptosis and necrosis may not be clear [12]. This may be the case for several cardiac conditions in which both phenomena may be present at the same time [13]. Therefore, the current tendency to confirm the existence of apoptosis is based on the combination of different analysis: histochemical detection of internucleosomal cleavage, DNA laddering to confirm DNA fragmentation biochemically, and structural definition of chromatin alterations.

Apoptosis in hypertension
Apoptosis maintains tissue integrity by counterbalancing cellular proliferation [7]. As hypertrophy or hyperplasia develops in organs exposed to hypertension, it is not surprising that a higher level of apoptosis has been found in the hearts, kidneys, and brains of adult spontaneously hypertensive rats (SHRs) [14] and in the hearts of rats with renal hypertension [15]. Furthermore, increased responses to apoptotic stimuli [14] and alterations in the regulatory phase of apoptosis have been also described in vascular cells from rats with genetic hypertension [16]. Thus, hypertension may represent a process in which increased cell growth and its correspondent increase in cell death contribute to the remodeling of target organs [17]. Interestingly, antihypertensive agents have been shown to modify vascular apoptosis during vascular regression in SHRs [18]. Therefore, the pharmacologic modulation of apoptosis has been proposed as a new potential approach to deal with cardiovascular remodeling and, ultimately, with hypertension-induced target organ damage [19].

Apoptosis and cardiomyocytes
It has been classically accepted that adult cardiomyocytes are not capable of proliferation and, thus, are resistant to develop apoptosis. Thus, the existence of a balance between apoptotic cell death and cell regeneration in aging or pathologic states of the heart has been denied until recently. In fact, in the past few years, observations have been made showing that cardiomyocyte apoptosis occurs in diverse conditions (Fig. 1 and Table 1) and that cardiomyocyte apoptosis and proliferation are simultaneously present in several situations [3]. Therefore, apoptosis in cardiac cells is recognized, increasingly, as a contributing cause of cardiomyocyte loss with important pathophysiologic consequences [20,21].

Apoptosis and cardiomyocyte loss in hypertensive heart disease
Experimental findings
The SHR is a genetic model of hypertension in which early hypertrophic adaptation to hypertension and subsequent transition to severe heart failure and premature death occur [22,23]. The transition from compensated hypertrophy to heart failure in SHRs is accompanied by numerous structural and functional changes in cardiomyocytes and the extracellular matrix. Quantitative histologic measurements have demonstrated a reduction in the relative cardiomyocyte mass and an increase in fibrous tissue in this model [24]. On the other hand, hemodynamic studies have shown that impaired heart function in the aging SHRs is also caused by changes in the intrinsic properties of the myocardium [25].

Increased apoptosis has been demonstrated recently in the hypertrophied left ventricle of SHRs compared with the normotensive Wistar-Kyoto control rats [14,26,27].

Fig. 1. In situ detection of apoptosis using a system that identifies cells with internucleosomal fragmentation of DNA. The photomicrograph corresponds to an infarcted human myocardium and apoptotic cardiomyocytes can be identified in the infarct center by their brown nuclei (magnification, × 480).
Furthermore, an increased occurrence of cardiomyocyte apoptosis has been demonstrated in the heart from failing SHRs compared with nonfailing SHRs [27••]. Thus, apoptosis may be a mechanism involved in cardiomyocyte loss that accompanies the transition from stable compensation to heart failure in this model.

**Clinical findings**

Side-to-side slippage of cardiomyocytes was identified by Linzbach [28] almost 4 decades ago as a critical factor of ventricular dilation in the decompensated hypertrophied human heart. The importance of this observation is that when this mechanism of wall restructuring was identified [29], single cardiomyocyte death was postulated to occur to allow side-by-side translocation of cells within the wall.

More recently, Olivetti et al. [30] showed that hypertension-induced cardiac hypertrophy in middle-aged patients with no clinical history of heart dysfunction or failure, and no anatomic evidence of coronary atherosclerosis or myocardial infarction was characterized by an increase in size of cardiomyocytes, 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.

Although the lack of hemodynamic measurements does not rule out that some impairment in ventricular function was present in hypertensive patients, cardiomyocyte loss seems to accompany the evolution of cardiac hypertrophy and seems to precede the impairment in ventricular pump function.

**Emerging hypothesis**

Recent experimental information has shown that increased apoptosis of cardiomyocytes occurs in the heart during genetic hypertension; however, because the diagnosis is still based primarily on histologic assessment and a cardiac-based biopsy protocol is not manageable in hypertensive patients, its occurrence in the human hypertensive heart remains to be determined. Furthermore, because of several technical limitations, estimation of the rate of apoptosis in the myocardium has not been established with certainty.

Although the effects of high blood pressure in SHRs have been considered to be similar in many respects to hypertension in humans [31], the transition to the failure state in this rodent model may not necessarily involve the same pathophysiology as seen in other mammalian hearts. Because rat myocardium differs in several respects from other mammalian species, including man, such as excitation-contraction coupling and myosin isoform profiles, extrapolation of findings to human pathophysiology clearly must be done with caution.

With these limitations borne in mind, it could be hypothesized that cardiomyocyte loss seen in the hypertrophied left ventricle of patients with arterial hypertension may be caused by enhanced cardiomyocyte apoptosis. An ongoing process of cardiomyocyte apoptosis may lead to a progressive deterioration in myocardial function, culminating in end-stage heart failure. In support of this possibility are recent findings showing that loss of cardiomyocytes caused by apoptosis is present in patients with end-stage cardiac diseases [32,33].

**Pathophysiologic significance**

**Quantification of cardiomyocyte apoptosis**

The time course of cardiomyocyte apoptosis is relatively rapid [34]. In the case of SHRs with heart failure, the number of apoptotic cardiomyocytes was estimated at 0.04% [27••]. If the average time course of cardiomyocyte apoptosis is estimated at 6 hours, 0.16% of cardiomyocytes may undergo apoptosis/day, and approximately 50% of cardiomyocytes would be lost in 10 months. Cardiomyocyte loss observed in experimental studies [22–25] may be consistent with apoptosis as explaining the gradual course of cardiac decompensation in the SHR with failure appearing at an average age of 18 to 24 months.

The 30% loss of cardiomyocytes documented by Olivetti et al. [30] in the left ventricle of hypertensive patients did not seem to have reached a critical value for the development of severe ventricular dysfunction and failure. At present, no information is available concerning the magnitude of cell loss required to depress cardiac performance in the hypertrophied human heart when cell death occurs. Studies in humans [35,36] and animals [37,38] have indicated that occlusion of a major coronary artery, resulting in acute myocardial infarction and a segmental loss of cardiomyocytes, leads to overt failure when destruction in muscle mass involves 40% to 50% of the cardiomyocyte population of the left ventricle. Whether cardiomyocyte apoptosis must result in loss of nearly 40% to 50% of the
cells before ventricular failure ensues in man remains an
important unanswered question.

**Hypertrophy and apoptosis of cardiomyocytes**

With hypertrophy following aortic constriction in rats,
expression of the oncogenes *c-fos* and *c-jun* was found to
be markedly decreased in 18-month-old relative to 9-
month-old animals [39]. The effect of a stimulus such as
pressure load on oncogene expression apparently
depends on a number of factors, including the develop-
ment stage of the animal. Factors such as mechanical
load and angiotensin II, which have been shown to
result in immediate-early gene expression and hypertro-
phy of cardiomyocytes, may induce apoptosis in the
aging, chronically overloaded heart. Therefore, as
suggested by Bing [40], cardiomyocyte apoptosis may
develop after the loss of intracellular signals that
normally suppress the development of the apoptotic
program in these cells.

In support of this possibility is the observation that the
intensity of cardiomyocyte apoptosis parallels the time of
exposure to hypertension and not the degree of elevation
of blood pressure in SHR studied at different ages [26••].

**Cardiomyocyte apoptosis and interstitial fibrosis**

It has been recently suggested that alterations of the
collagen framework in the myocardium may have an
important role in the genesis of ventricular dysfunction
of hypertensive origin [5•]. This has been supported by
the finding that fibrillar collagen deposition in the
cardiac interstitium contributes critically to a depression
in myocardial and ventricular function in SHRs [25].
The problem concerns whether this type of interstitial
alteration occurs through activation of fibroblasts via
humoral or mechanical factors in the absence of
cardiomyocyte loss [41] or whether cell death is
required for the stimulation of the growth response of
the noncardiomyocyte compartment of the myocardium.
The observation by Olivetti *et al.* [30] that fibrosis is
associated with cell loss in the hypertensive left ventri-
acle raises questions about the mechanism responsible
for the modification of the interstitium with accumu-
lation of fibrillar collagen. As proposed by Anversa *et al.*
[42], death of individual cardiomyocytes may be more
common than generally believed, and this phenomenon
may stimulate discrete healing processes contributing to
the expansion of the interstitium.

This proposal is further supported by the recent finding
by Bing *et al.* [43••] that failing hearts from the SHRs
present colocalization of collagen α1, type I gene expres-
sion to areas of focal cardiomyocyte degeneration,
suggesting that cardiomyocyte loss is associated with
collagen type I production and focal scar formation in the
SHRs during the transition from compensated hypertro-
phy to failure.

**Potential causes of cardiomyocyte apoptosis in hypertensive heart disease**

Apoptosis may occur as a result of an imbalance between
those factors known or suspected to be present in the
hypertrophied myocardium, which, acting on the
cardiomyocyte, induce or prevent apoptosis (Table 2).
Alternatively, apoptosis may reflect some intrinsic abnor-
malities in factors that, acting within the cardiomyocyte,
determine the resistance or the susceptibility of the cell
to apoptosis (Table 2).

**Myocardial factors acting on the cardiomyocyte**

**Mechanical overload**

Hemodynamic stimulation secondary to aortic banding
has been shown to induce cardiomyocyte apoptosis in the
rat [44]. Overstretching of isolated papillary muscles *in vitro*,
which mimics an elevation of diastolic stress *in vivo*,
resulted in an increase in cardiomyocyte apoptosis [45].
Interestingly, augmented superoxide formation and
expression of the cell surface molecule involved in apop-
totic death, Fas, were observed in this condition.
The addition of the nitric oxide-releasing drug C87-3754
prevented apoptosis and superoxide anion formation,
which points to the induction of superoxide as a relevant
factor in overstretching-induced cardiomyocyte apoptosis.
Therefore, the physical forces may facilitate cardiomy-
ocyte apoptosis in conditions of pressure overload of the
heart. This might explain the enhanced occurrence of
apoptosis in the hypertrophied left ventricle of SHRs
exposed to elevated blood pressure [14,26••,27••].

**Ischemia**

Hypoxia of cultured neonatal cardiomyocytes has been
shown to cause apoptosis and upregulation of Fas receptor
[46]. Recent studies have shown that exposure of rat
cardiomyocytes to hypoxia resulted in apoptosis and was
accompanied by increased p53 transactivating activity and
protein accumulation [47•]. These results suggest that the
intracellular signalling pathways activated by p53 might

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**Table 2**

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<th>Mechanisms potentially involved in apoptosis of cardiomyocytes in arterial hypertension</th>
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<tbody>
<tr>
<td>Stimulation by proapoptotic factors</td>
</tr>
<tr>
<td>Mechanical overload</td>
</tr>
<tr>
<td>Ischemia</td>
</tr>
<tr>
<td>Angiotensin II</td>
</tr>
<tr>
<td>p53</td>
</tr>
<tr>
<td>Bax</td>
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<td>Loss of efficacy of survival factors</td>
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<tr>
<td>Insulin-like growth factor-1</td>
</tr>
<tr>
<td>Cardiotrophin</td>
</tr>
<tr>
<td>Bcl-2</td>
</tr>
<tr>
<td>WAF-1</td>
</tr>
<tr>
<td>Other abnormalities that may facilitate the apoptotic response</td>
</tr>
<tr>
<td>Oxidative stress</td>
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<tr>
<td>Calcium overload</td>
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<td>Mitochondrial defects</td>
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<tr>
<td>Altersations of caspases</td>
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have a critical role in the regulation of hypoxia-induced apoptosis of cardiomyocytes.

Detrimental effects of sustained arterial hypertension on functional and morphologic characteristics of coronary vasculature and microvasculature have been described in hypertensive patients and SHRs [48,49]. Possibly, these alterations affect the oxygenation potential of the left ventricular hypertrophied myocardium. Whether hypoxia is a contributing factor to cardiomyocyte apoptosis in hypertension and whether this is mediated through p53 stimulation require further examination.

**Angiotensin II**

Angiotensin II has been shown to induce apoptosis of neonatal [50••] and adult [51••] rat ventricular myocytes in vitro. Binding of angiotensin II type 1 receptor (AT₁) triggers apoptosis by a mechanism involving protein kinase C-mediated increases in cytosolic calcium and the stimulation of calcium-dependent DNase I, which results in internucleosomal DNA fragmentation (Fig. 2) [50••, 51••].

Cardiomyocytes possess the various molecular components of the renin-angiotensin system, and they are capable of synthesizing and releasing angiotensin II [52]. Stretching of cardiomyocytes in vitro leads to the autocrine formation of angiotensin II [52] and the increase in the number of AT₁ receptors [53]. Although unequivocal evidence remains to be obtained, it is tempting to speculate that the interaction between stretch and angiotensin II may be a significant component of stretch-dependent cardiomyocyte apoptosis in vitro (Fig. 2) [45].

Recent findings suggest that increased cardiomyocyte apoptosis may be related to exaggerated angiotensin-converting enzyme (ACE) activity in the left ventricle of adult SHRs (Fig. 3) [26••]. In addition, it has been shown that long-term treatment with an ACE inhibitor blocks apoptosis of cardiomyocytes in adult [26••] and aged [27••] SHRs. Furthermore, chronic blockade of AT₁ receptor with losartan has been found to prevent apoptosis in the left ventricle of SHRs independently of its hemodynamic effect [54••]. These observations may be consistent with the possibility that the renin-angiotensin system may mediate cardiomyocyte apoptosis in this model of genetic hypertension.

**Insulin-like growth factor 1**

Insulin-like growth factor 1 (IGF-1) is now considered a survival factor that protects from apoptosis in a variety of cell types. For instance, its administration attenuates cardiomyocyte apoptosis in ischemia reperfusion injury [55]. Furthermore, results have shown that overexpression of human IGF-1 in transgenic mice protects from cardiomyocyte apoptosis after infarction [56•]. The mechanisms by which IGF-1 protects from apoptosis are unknown. The interaction of the factor with its receptor

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**Fig. 2. Schema showing the potential involvement of angiotensin II-dependent pathways in apoptosis of cardiomyocytes in conditions of mechanical overload or myocardial ischemia. BP=blood pressure; RAS=renin-angiotensin system.**

**Fig. 3. Time-course of changes in cardiomyocyte apoptosis and angiotensin-converting enzyme (ACE) activity in the left ventricle of normotensive Wistar-Kyoto rats (WKY) (open circles) and spontaneously hypertensive rats (SHR, closed circles). ACEI=ACE inhibitor; α=P<0.05 when comparing 30-week-old SHR with 30-week-old WKY; b=P<0.05 when comparing 30-week-old SHR with 15-week-old SHR and ACEI-treated 30-week-old SHR. (Adapted from Diez et al [26••]; with permission.)**
has been shown to mediate the formation of some apoptosis-inhibitory oncoproteins of the Bcl-2 family [57]. In addition, IGF-1 reportedly blocks the activation of some members of the interleukin-converting enzyme family that act as effectors of apoptosis [58].

IGF-1 mRNA expression is increased in the hypertrophied myocardium of pressure-overloaded animals [59] and SHRs [60]. Thus, the cardiomyocyte may be resistant to the cytotoxic action of IGF-1 in these models.

**Interleukin-6-related cytokines**

Besides the induction of cardiomyocyte hypertrophy [61], interleukin-6-related cytokines (eg, cardiotoxin 1) prevent apoptosis in cardiomyocytes [62]. Recently, this effect has been shown to be mediated through the stimulation of a Bcl-2–related gene that prevents apoptosis [63•]. Interleukin-6-related cytokines were reported to be produced by cardiomyocytes upon stimulation with hypoxia, interleukin-1, or epinephrine [64]. Therefore, these cytokines may provide a cytoprotective effect in cardiomyocytes submitted to these types of stimulation. Further studies are necessary to ascertain whether alterations in the actions of these cytokines have some role in cardiomyocyte apoptosis in hypertension.

**Genetic factors acting within the cardiomyocyte**

p53

The protein product of the p53 gene affects the resistance of cells to counteract apoptotic stimuli, enhancing their sensitivity to multiple death signals: increases in p53 protein activity potentiate the effects of DNA-damaging agents on the magnitude of apoptosis but cannot per se trigger the apoptotic program of cells [65].

The ability of this tumor suppressor protein to enhance apoptosis seems to be mediated through the upregulation of Bcl-2 oncoproteins that induce apoptosis and the downregulation of Bcl-2 oncoproteins that inhibit apoptosis in the cells [66].

Transfection experiments in rat ventricular cardiomyocytes with recombinant adenovirus containing p53 resulted in increased apoptotic death of the cells [67••]. Interestingly, angiotensinogen and AT₁ mRNAs increased in transfected adult cardiomyocytes, and this phenomenon was associated with increased secretion of angiotensin II [67••]. Furthermore, the AT₁ receptor antagonist losartan and angiotensin II antibody prevented p53-induced apoptosis [67••]. Thus, p53 enhances the cardiomyocyte renin-angiotensin system in cells that develop apoptosis (see Fig. 2).

p53 transcripts detectable in the myocardium do not seem to increase with cardiac hypertrophy [68]. In addition, no documentation of elevated p53 labeling by immunohistochemistry of heart muscle has been obtained thus far following stretch-induced cardiomyocyte cell death [43••]. Therefore, whether p53-dependent cardiomyocyte apoptosis develops only when cells are simultaneously exposed to both mechanical load and ischemia is unclear.

**Bcl-2 family**

The Bcl-2 proto-oncogene family is critical for the regulation of apoptosis [69,70•]. As previously mentioned, Bcl-2 family oncoproteins come in two functional categories: those that stimulate apoptosis (eg, Bax) and those that block apoptosis (eg, Bcl-2). The relative abundance of these proapoptotic and antiapoptotic proteins determines the susceptibility to cell death. Thus, it has been proposed that cell viability after an apoptotic stimulus may depend on the ratio of the level of Bcl-2 to that of Bax [71]. For instance, apoptosis develops in rat cardiomyocytes when the Bcl-2–Bax ratio decreases after transfection with the p53 gene [67••].

No changes in the expression of Bcl-2 protein were observed in the hearts of adult [54••] and aged [27••] SHRs with increased cardiomyocyte apoptosis. Because Bcl-2 has been found to protect ventricular cardiomyocytes from apoptosis [72••], these findings suggest that the induction of apoptosis in the SHR heart might not be accompanied by compensatory changes in Bcl-2 in an attempt to maintain survival of cardiomyocytes and, thus, apoptosis might develop.

Recently, Bax overexpression was reported in the left ventricle of adult SHRs with increased cardiomyocyte apoptosis [54••]. In addition, the Bcl-2–Bax ratio was abnormally decreased in these rats, suggesting that cardiomyocytes of the left ventricle are highly susceptible to apoptosis in SHRs. Interestingly, the expression of Bax protein was normalized in SHRs chronically treated with losartan. Thus, angiotensin II may facilitate cardiomyocyte apoptosis in SHRs via stimulation of the proapoptotic protein Bax (see Fig. 2).

**WAF-1**

The WAF-1 gene encodes a protein that inhibits the function of cyclin-dependent complexes and prevents cell cycle progression [73]. Expression of WAF-1 seems to be regulated by p53-dependent [74] and p53-independent [75] mechanisms. Recent studies suggest that, under some circumstances, WAF-1 overexpression blocks apoptosis [76,77].

Increased expression of WAF-1 has been found in cardiomyocytes exposed to hypoxia [47•] and in the heart of aged SHRs [27••]. Because in both situations apoptosis was also stimulated, the precise role of WAF-1 in the process of apoptosis in cardiomyocytes requires further study.

**Conclusions**

Necrosis has been generally believed to be the exclusive mechanism of cardiomyocyte death in the myocardium;
however, recent information has shown that apoptosis of cardiomyocytes may be activated in the heart in a disease-dependent way. For instance, cardiomyocyte apoptosis has been found to be abnormally activated in SHRs, especially in animals that develop heart failure. One major challenge for future research should be to determine whether increased apoptosis may also account for the exaggerated loss of cardiomyocytes described in humans with hypertensive heart disease. Furthermore, whether apoptotic death is also activated in other cell populations of the hypertensive myocardium (eg, interstitial fibroblasts and vascular cells) remains to be determined.

Cardiomyocyte loss has been shown to be a critical factor in the onset and progression of ventricular dysfunction in several cardiac conditions. Loss of cardiomyocytes decreases the functional capacity of the myocardium, resulting in an increased workload on the remaining cells and facilitating the transition from compensated to decompensated cardiac hypertrophy and failure. A challenging question is whether the exaggerated fibrillar collagen deposition in the hypertensive myocardium is a primary event or the consequence of apoptotic cell loss in the ventricular wall. Such an acute accumulation of collagen also impairs the contractile behavior of the myocardium. The understanding of the interactions between factors that trigger cardiomyocyte apoptosis and factors that block it, and the knowledge of the gene regulation of the final response of cardiomyocytes to these factors is a major challenge for future research in hypertensive heart disease. This is of particular relevance when considering the subtle mechanisms by which a given stimulus (eg, mechanical loading or angiotensin II) may cause either hypertrophy or apoptosis of cardiomyocytes.

Recognition that several factors can lead to cardiomyocyte apoptosis in patients with hypertension and that they can be modulated by current antihypertensive therapy is important for the development of new therapeutic strategies. These strategies should be addressed to interfere with this process of cell loss and, consequently, with the development of ventricular remodeling and, ultimately, with hypertension-induced heart failure. In this regard, a new pathway of research is emerging for drugs such as ACE inhibitors and AT1-receptor antagonists, which have demonstrated experimentally to possess the ability to inhibit myocardial apoptosis and clinically have demonstrated beneficial effects in patients with heart failure.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
- Of special interest
- Of outstanding interest

10. Fadok VA, Bratton DL, Konowal A, Freed PW, Westcott JY, Henson PM: Macrophages that have ingested apoptotic cells in vitro inhibit proinflammatory cytokine production through autocrine/paracrine mechanisms involving TGF-β, PGE2, and PAF. J Clin Invest 1998, 101:890–898. This article investigated some of the mechanisms through which binding or phagocytosis of apoptotic cells induces active anti-inflammatory or suppressive properties in human macrophages.


This article showed that the timing and mechanisms responsible for apoptosis and hypertrophy of cardiomyocytes are different in spontaneously hypertensive rats. Whereas hypertrophy seems to be an earlier alteration that develops in parallel with hypertension, apoptosis develops later in association with overactivity of the local ACE.


This is an interesting report showing that increased numbers of apoptotic cells are present in failing SHR hearts. Administration of the ACE inhibitor captopril, which ameliorates heart failure in this model, is associated with a reduction in the exaggerated apoptosis that accompanies heart failure.


40. Bing OHL: Hypothesis: apoptosis may be a mechanism for the transition to heart failure with chronic pressure overload. J Mol Cell Cardiol 1994, 26:943–948.


The authors showed that failing hearts from the spontaneously hypertensive rat exhibit focal α1(I) collagen mRNA accumulation in the endocardium and at sites of degenerating single myocardial cells.


This study showed that exposure of cardiomyocytes to prolonged hypoxia resulted in apoptosis and was accompanied by increased p53 activity and expression.


This article demonstrated that angiotensin II induced apoptosis in neonatal cardiomyocytes through the stimulation of calcium-dependent DNase I, via the activation of AT1 receptor subtype.


This article can be considered complementary to Cigola et al. [50], because it demonstrated that angiotensin II also induced apoptosis in adult ventricular cardiomyocytes.


The main finding of this paper is that left ventricular cardiomyocytes of SHR$_{pat}$ overexpress the proapoptotic protein Bax and that this alteration is prevented by chronic AT1 blockade with losartan.


57. An investigation of the ability of insulin-like growth factor 1 to oppose cardiomyocyte apoptosis after experimentally induced myocardial infarction.


This study provided the first demonstration that p53 leads to apoptosis of cardiomyocytes via the activation of the cellular renin-angiotensin system.


Concise overview of the role of Bcl-2 gene products in the regulation of apoptosis.


This interesting report provided the first indication for the operation of Bcl-2 gene in ventricular myocytes as an antiapoptotic factor.


