Cardiovascular Remodeling, Apoptosis, and Drugs

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Apoptosis, a form of programmed cell death, mediates the controlled deletion of so-called “unwanted” cells. This review deals with the key features of this cell death program, showing that apoptosis is regulated by factors extrinsic and intrinsic to the dying cell.

The elucidation of the possible interactions between these factors may be of major interest in preventing the progression to cardiovascular remodeling in patients with hypertensive disease. New pathways of research are emerging for drugs, such as β-blockers, ACE inhibitors, the calcium-antagonists, and the receptor antagonist of angiotensin II, all of which have beneficial effects on cardiovascular remodeling. This may be due to the direct effect of these drugs on the cell proliferation/apoptosis balance.

KEY WORDS: Apoptosis, cardiovascular remodeling, antihypertensive drugs.

Arterial hypertension can reduce vessel and cardiac lumen size through hypertrophy, with wall thickening, and remodeling, with an increase in the thickness/radius of the arterioles, but with no increase in the parietal section surface. This occurs in humans because their cardiovascular apparatus is not passively affected by hemodynamic factors, but interacts with them and conditions them while also being influenced by them.

It was recently stressed that cardiovascular remodeling during hypertension expresses an imbalance between proliferative and cell death pathways (Figure 1). Death, a somewhat unpopular topic in our society, can play a positive role, at least as far as cells are concerned. It is crucial to normal tissue turnover. In adult humans, the number of cells making up tissue must be kept constant while guaranteeing cell renewal and regulating the delicate balance between cellular proliferation-differentiation and death. Although there is a close correlation between the survival of a cell and that of its host, we do not yet understand the connection between these two processes.

A cell can die from necrosis, death being due to external forces and occurring too rapidly to allow any activation of a protective mechanism. Whether damage is due to external or internal factors, the target is always the structure that produces energy for the cell itself, the mitochondrion, which swells up; deprived of their energy source, the cell pumps arrest their activity. The cells become impregnated with water and explode. Consequently, the molecules within the cell are expelled from it into an anomalous environment, in which an inflammatory response develops.

In nature there is another type of death: apoptosis, a condition in which cells shrink rather than swell, with a 30% loss in their volume in less than an hour. The mitochondria appear to remain normal; the nucleus becomes the target for changes, at least from the morphologic viewpoint. Cromatin condenses under the...
nuclear membrane and the cell fragments. Each fragment, enveloped in the cell membrane, contains cytoplasm and parts of the nucleus. The different cellular components are rapidly phagocytized, by cells that in normal conditions are aphagocytic. As the cell does not expel its contents, inflammatory phenomena are obviated. As of now, it is not known whether necrosis and apoptosis are on a continuum with each other or completely independent processes. This has recently been discussed in studies conducted on vascular smooth muscle cell cultures.

In apoptotic phenomena, a crucial role in this complex process of cell fragmentation is played by caspases, a family of proteolytic enzymes (Figure 2). All cells contain procaspases, which, with the opportune stimulus, rapidly trigger cell death. At present, pathways known to translate the so-called “death signal” are the mitochondrial-dependent pathway, by means of cytochrome c, Bcl-2, and Bax; the mitochondrial-independent pathway, with the caspase-3 activation, which may be dependent on caspase-6 activation via death receptors. Control may be inhibited by Bcl-2 family proteins; caspases may be inhibited by the synthetic peptides zVAD, yVAD, and DEVD, blocking their proteasic activity and competing with them. DELTAM, transmembrane potential mitochondrion; p53 and CrmA, caspases inhibiting viral proteins.

In arterial hypertension, cell growth increases and the corresponding increase in cell death contributes to the remodeling of target organs, ie, the heart, blood vessels, kidney, and brain. The factors determining or inducing apoptosis of the cardiovascular apparatus during arterial hypertension have not yet been well defined. In experiments conducted on culture media from smooth muscle fiber cells from spontaneously hypertensive rats (SHR) in the presence of TGF-β and TNF it has been suggested that genetic factors are spontaneous inductors, as has been found for cardiomyocytes in rats with hypertension. Ventricular remodeling in response to pressure overload involves hypertrophy of muscle cells and proliferation of nonmuscle cells. Cardiac cell loss has been observed, but attributed to necrosis. However, recent studies conducted both on rat cardiomyocytes and on arterial vessels have demonstrated that overstretching induces cell apoptosis. These findings have been confirmed in humans after both the cold pressor test and percutaneous transluminal coronary angioplasty. Different protooncogenes (Bcl-2 family members, Fas, c-myc) have been considered mediators of apoptosis. Physical forces may therefore facilitate cellular apoptosis in conditions of cardiovascular pressure overload, and this might explain the enhanced occurrence of apoptosis in the vascular and hypertrophic left ver-
tricles of patients with high blood pressure\textsuperscript{21,22} (Table 1).

Under experimental conditions, it has been demonstrated that cardiomyocytes can undergo apoptosis during hypoxia, myocardial infarction, and heart failure\textsuperscript{23,24} Sustained arterial hypertension has been found to have an adverse effect on the functional and morphologic characteristics of the coronary vasculature and microvasculature in patients with hypertension. These alterations may affect the oxygenation potential of the hypertrophic left ventricular myocardium. Experimental studies in patients with patent infarct-related arteries have shown that, as well as becoming overtly necrotic, a subset of myocytes undergoes apoptosis after myocardial infarction\textsuperscript{25} Apoptosis precedes necrosis and apoptotic nuclei, identified at 2 and 3 h, peaked at 4.5 h after infarct. Factors known to be associated with both ischemia-reperfusion injury and apoptosis include oxygen-derived free radicals,\textsuperscript{26} inflammatory reaction, increased p53, tumor suppressor protein,\textsuperscript{27} and an abnormally increased Bcl-2/Bax ratio.\textsuperscript{28}

In cardiovascular remodeling in hypertensive subjects, a particularly significant role is played by vasoconstrictive humoral factors, such as epinephrine, the renin-angiotensin system, and endothelin. These factors have a direct mitogenic action and inhibit apoptosis, independent of the hypertensive effect.\textsuperscript{29,30} This growth is accompanied by the induction of the expression of growth-related protooncogenes (c-fos, c-jun, and c-myc), as well as the synthesis of autocrine growth factors, such as PDGF-A and TGF-\(\beta\).\textsuperscript{31} These data have also been confirmed in humans. Several drugs, such as \(\beta\)-blockers, ACE inhibitors, and angiotensin II antagonists, can have a favorable effect on the processes of cardiovascular remodeling induced by hypertension and ischemic disease.\textsuperscript{32–34} Elsewhere, Buemi et al\textsuperscript{35} demonstrated that captopril has a pro-apoptotic effect, and confirmed the findings made by other authors with different ACE inhibitors (Figure 3). In fact, Diez et al\textsuperscript{36} have demonstrated that quinapril can stimulate apoptosis by increasing bax and diminishing bcl-2 concentrations, and others have shown that enalapril can reduce neointima formation after balloon-arterial injury by inducing apoptosis in the cells of the neointima itself.\textsuperscript{37} The long-term administration of quinapril is associated with the normalization of ACE activity and apoptosis in treated SHR.\textsuperscript{38} This suggests that cell death dysregulation may be a novel target for antihypertensive agents that interfere with the renin-angiotensin system in hypertension. The incubation of the serum of patients with hypertension in antihypertensive treatment using losartan, a receptor antagonist of AII, has a significant capacity to induce apoptosis in myocyte culture (Table 2).

### TABLE 1. BLOOD Bcl-2 CONCENTRATIONS (U/mL) BEFORE AND AFTER CPT

<table>
<thead>
<tr>
<th></th>
<th>–5 Min</th>
<th>0 Min</th>
<th>4 Min</th>
<th>10 Min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive subjects</td>
<td>53 ± 7</td>
<td>56 ± 9</td>
<td>66 ± 15*</td>
<td>60 ± 17</td>
</tr>
<tr>
<td>Hypertensive subjects</td>
<td>90 ± 13</td>
<td>87 ± 15</td>
<td>103 ± 18†</td>
<td>98 ± 15</td>
</tr>
</tbody>
</table>

*Results are given as mean ± SD.
* \(P = .0001\) v basal; † \(P = .002\) v basal.

### TABLE 2. SYSTOLIC (SBP) AND DIASTOLIC (DBP) BLOOD PRESSURE AFTER THERAPY WITH PROPRANOLOL, LOSARTAN, AND LOSARTAN + PROPRANOLOL

<table>
<thead>
<tr>
<th></th>
<th>Wash-Out</th>
<th>Propranolol</th>
<th>Losartan</th>
<th>Losartan + Propranolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mm Hg)</td>
<td>161 ± 5.2</td>
<td>160 ± 5.2</td>
<td>146 ± 6.2*</td>
<td>144 ± 6.1*</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>96 ± 3.1</td>
<td>95.7 ± 2.4</td>
<td>83.1 ± 2.6*</td>
<td>81 ± 2.6*</td>
</tr>
<tr>
<td>Apoptosis (%)</td>
<td>3.8 ± 0.5</td>
<td>16.3 ± 1.2*</td>
<td>8.8 ± 1.5*</td>
<td>6.4 ± 1.2*</td>
</tr>
<tr>
<td>(r = −0.7)</td>
<td>(P = 0.8)</td>
<td>(r = 0.30), (P = 0.3)</td>
<td>(r = 0.25), (P = 0.4)</td>
<td>(r = 0.03), (P = 0.9)</td>
</tr>
<tr>
<td>(r = 0.13)</td>
<td>(P = 0.7)</td>
<td>(r = −0.10), (P = 0.7)</td>
<td>(r = 0.00), (P = 1.0)</td>
<td>(r = 0.09), (P = 0.8)</td>
</tr>
</tbody>
</table>

* \(P < 0.001\) v wash-out.
that the apoptotic action occurs secondary to the receptor antagonism of angiotensin II, even though the indolic group present in the chemical structure of losartan may play a fundamental and direct role through oxidative stimuli.40 The apoptotic action expressed in the sera of hypertensive subjects taking propranolol, a β-receptor antagonist, occurs independent of receptor antagonism mechanisms. There is experimental evidence that this drug has similar intrinsic anesthetic capacities, and can also stimulate the turnover of membrane phospholipids. Nifedipine, a dihydropyrrinnic calcium antagonist, also stimulates smooth muscle cell apoptosis, in vitro, before reducing blood pressure.39 In humans, in vivo, increased pressure from the cold pressor test caused a further increase in blood Bcl-2 concentrations, both in hypertensive and in normotensive subjects. Treatment of hypertensive patients with nifedipine was found to cause a reduction in Bcl-2.21 The reduction in Bcl-2 concentrations caused by hypotensive drugs may thus be partly independent of the hypotensive effect itself (Table 2). Similar to Diez et al26 in rats, we found no correlation between modifications in pressure and Bcl-2 concentrations. Previous studies showed that drugs such as hydralazine, which effectively modify pressure, cannot change apoptotic phenomena. Other drugs that can regulate the activation of cellular caspases are now under investigation and new molecules are being tested in relation to vascular remodeling, with the prospect of promising trends in future treatment.41

In conclusion, arterial remodeling is now known to be a key concept in the pathophysiology of arterial hypertension. Improvements in our understanding of the cellular processes involved in growth-apoptosis, have modified the therapeutic approach, offering new pharmacologic possibilities. In fact, antihypertensive therapy now calls for the capacity not only to diminish hyperreactivity in the target arteriole, but also to achieve a structural modification in the peripheral arterial resistance.

REFERENCES


