EDITORIAL COMMENT

Types of Cardiomyocyte Death and Clinical Outcomes in Patients With Heart Failure*

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Despite all efforts in pharmaceutical treatment, heart failure is still a major cause of morbidity and mortality worldwide (1). The fundamental mechanism that underlies the progressive nature of myocardial dysfunction leading to heart failure has been termed remodeling. As defined by Cohn et al. (2), this process consists of a complex of molecular and cellular events that lead to important changes in the structure, function, and phenotype of the myocardium.

Until recently, single myocyte cell loss scattered diffusely throughout the ventricle was largely ignored as a potential pathogenetic factor in failing myocardium. However, it has now widely been recognized, and there is general consensus that replacement fibrosis is the consequence of the reparative process following myocyte cell loss (3–5). The lack of knowledge of myocyte cell death as a pathogenetic factor of heart failure was due to the general belief that cell necrosis following acute myocardial ischemia was the exclusive mechanism of myocyte death in the myocardium (6), because of a lack of evidence and of methodological approaches to detect the occurrence of single cell death.

During the past decade, a number of different methods, including electron microscopy, as well as molecular and immunohistochemical approaches, have demonstrated that myocyte cell death can be identified, and this has generated the consensus that the magnitude of its occurrence is a quantifiable parameter in the normal and pathological heart (Table 1). Majno and Joris (7) distinctly defined the different types of cell death. Following their nomenclature, the Society of Toxicologic Pathology recommends that the term necrosis be reserved for the changes that occur after cell death, regardless of the pathway by which the cells die (8). The modifiers “apoptotic” and “oncotic” should be used to specify the predominant cell death pathway. This opinion is increasingly shared by many researchers (7,9–11). In addition to apoptosis (programmed cell death type I) and oncosis, accumulating evidence indicates the occurrence of a third mode of cell death (programmed cell death type II), namely, autophagic cell death (7,12–20). Thus, the recognition that cardiac myocytes die by multiple mechanisms and therefore substantially affect ventricular remodeling in diseased human hearts supports the concept of ongoing myocyte death in the progression of heart failure (3,15,21–23). It is worthy to note that the nomenclature of the 3 major types of cell death, namely, apoptotic, oncotic, and autophagic cell death, is the one most frequently used in the literature.

Autophagic cell death is a morphologic term derived from electron microscopic observations that denotes a form of cell death in which abundant autophagic vacuoles are present in the cytoplasm. Autophagy is referred to as an intracellular lysosome-mediated catabolic metabolism that is responsible for the bulk degradation and recycling of damaged or dysfunctional cytoplasmic components and intracellular organelles (24). Although autophagy plays an important role in cellular homeostasis, excessive autophagy might be expected to cause cellular destruction if the process is carried beyond a certain threshold. As a consequence, the cell “cannibalizes itself” from inside. Over time, this would mean that a significant percent of cytoplasm is being removed in an indiscriminate manner, resulting in negative effects on cell survival. Autophagy is associated with a growing number of pathological conditions, including cancer, neurodegenerative disorders, myopathies, and cardiomyopathies (9). Numerous studies have demonstrated that the proteasomal, autophagic, and lysosomal proteolytic pathways share cross-talk communication, and the impairment of each of these systems may lead to cellular degeneration and cell death (9,15).

It should be mentioned that a mixed type of myocyte cell death may also occur, namely, “autophagic necrosis,” which refers to a mode of cell death that combines morphological features of autophagy and necrosis, which is a result of the failure of the compensatory, prosurvival autophagic response (19). Similarly, the degree of adenosine triphosphate depletion (25) and the rate of mitochondrial permeability transition pore formation (26) could drive a cell toward apoptosis or necrosis or even change 1 morphology to another (i.e., “necroptosis”) (27).

From previous studies in patients with heart failure due to dilated cardiomyopathy, severe aortic valve stenosis, or hibernating myocardium, a total annual loss of more than 20% of cardiomyocytes is predicted (Table 2). What has
remained unclear is whether such a loss of cardiomyocyte dropout correlates with clinical outcomes.

In this issue of the Journal, Vigliano et al. (28) elegantly demonstrate for the first time that cardiomyocyte hypertrophy and cell damage by autophagic degeneration and death, especially when associated with oncosis, are independent predictors of death in patients with dilated cardiomyopathy and advanced heart failure. The investigators used most of the well-established markers for cell death (Table 1).

From this study (28) and previous studies (15,22,29), albeit indirectly, it is suggested that another variable of the progression of contractile dysfunction to terminal heart failure is the imbalance between myocyte cell death and myocyte renewal. For this reason, preventing myocyte cell death and an increasing generation of new myocytes may represent attractive targets in the treatment of human heart failure. Tremendous work to study the biology of either resident or circulating stem or pluripotent cells in myocardial regeneration still remains (30–32). Prospective clues to enhance myocardial regeneration are the newly discovered cells termed telocytes (33,34), formerly called myocardial interstitial Cajal-like cells (35), which are believed to nurse or “guide” the endogenous and exogenous stem cells for activation and commitment, but they also act as supporting cells for progenitor cells migration toward injured myocardium (36).

In conclusion, many more studies are needed to understand the delicate balance between cardiomyocyte death and cardiomyocyte renewal, thereby improving clinical outcomes in patients with heart failure, irrespective of its etiology.

**Table 1**

<table>
<thead>
<tr>
<th>Type of Cell Death</th>
<th>Detection Rate</th>
<th>Completion Time for Cell Removal</th>
<th>Annual Rate of Myocyte Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apoptotic necrosis</td>
<td>0.002%</td>
<td>Several hours</td>
<td>2%–4%</td>
</tr>
<tr>
<td>Oncotic necrosis</td>
<td>0.06%</td>
<td>48 h</td>
<td>~11%</td>
</tr>
<tr>
<td>Autophagic cell death</td>
<td>0.08%</td>
<td>Unknown</td>
<td>~10%</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>~20%–25%</td>
</tr>
</tbody>
</table>

*Invitrogen Corporation (Carlsbad, California). Reprinted, with permission, from Kostin et al. (15). DNA = deoxyribonucleic acid; EM = electron microscopy; IgG = immunoglobulin G; LC3 = microtubule-associated protein 1; light chain 3; MDC = monodansylcadaverine; TUNEL = terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick end labeling.

**Table 2**

<table>
<thead>
<tr>
<th>Type of Cell Death</th>
<th>Detection</th>
<th>Completion Time</th>
<th>Annual Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncotic necrosis</td>
<td>TUNEL, EM-TUNEL</td>
<td>DNA laddering detection</td>
<td>MDC staining</td>
</tr>
<tr>
<td>Myocyte enzymes release</td>
<td>Nuclear lamina fragmentation (lamin labeling)</td>
<td>LC3 intracellular localization and detection of LC3 electrophoretic mobility</td>
<td></td>
</tr>
</tbody>
</table>

**REFERENCES**


Key Words: cardiomyocyte death ■ dilated cardiomyopathy ■ heart failure ■ outcome.