Hibernating Myocardium, Apoptosis, and a Simple Mathematical Task

We read with extreme interest the recent report by Elsasser et al. (1). Their study reliably shows that both apoptotic and autophagic cell death occur in hibernating myocardium and may be responsible for progressive clinical deterioration and lack of functional recovery.

However, we are afraid the investigators may have made an inaccurate estimate of apoptotic cell death rate. The researchers indeed report an incidence of apoptosis of 0.002% (i.e., 1 of 50,000 cells). These data would suggest that at least 50,000 cells were counted per patient in order to ascertain whether at least one was apoptotic. But the investigators fail to clarify this issue thoroughly.

This point is particularly relevant when considering the electron microscopy data. Considering the specific limitations of electron microscopy we would imagine that the investigators evaluated not more than 100 cells at electron microscopy per case. Yet assuming 100 cells examined per case and an apoptotic rate of 1 in 50,000, the chance of randomly finding an apoptotic cell at the electron microscope level in a single case would be 1 in 500. Accordingly, the probability of 3 positive cases at electron microscopy would be 1 in 125 million.

In conclusion, we find the message given by Elsasser et al. (1) extremely attractive and clinically relevant. However, we believe that they might have underestimated the incidence of apoptotic myocytes at confocal microscopy. We would greatly appreciate it if the investigators could clarify these apparent inconsistencies.

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REPLY

We thank Dr. Abbate and colleagues for their interest in our work (1). The major point of our recent publication is the fact that autophagic cell death as described previously in patients with dilated cardiomyopathy (2) is an important mechanism for killing myocytes in hibernating myocardium and that apoptosis seems to be of less importance. We are fully aware of the many technical problems that might occur when attempting a quantitative analysis of the rate of cell death, be it apoptosis, autophagic cell death, or necrosis (3). In our experience, electron microscopy is not a suitable method for determining the rate of cell death, which has been emphasized by others as well (4). Therefore, we use the confocal microscope. We analyze entire sections, and as many cells as are available from the patient’s material; we count the total number of nucleated myocytes per patient and we determine the number of specifically labeled cells. This information is then statistically analyzed on the basis of individual data from each patient and ultimately expressed as a percentage. In a final stage, results are summarized for an entire group of patients, and different groups are compared by employing appropriate statistical tests. Using this procedure each patient is weighted equally, even if there are no labeled cells present.

We read with interest Dr. Abbate and colleagues’ work on myocardial apoptosis in patients with unfavorable left ventricular remodeling and we noticed the unusually high rates of apoptosis reported for both infarcted myocardium and areas remote from the infarct (5). Unfortunately, a precise indication of the total number of myocytes examined is lacking from the description of methods, rendering difficult an interpretation of these results. It would have been more convincing had Dr. Abbate and colleagues used the same criteria in his own work that he requests from ours.

There is no doubt, however, that myocyte death is a major contributing factor to the deterioration of cardiac function in pathological situations in the human heart, either in postinfarction remodeling or in hibernating myocardium.

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