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Letters to the Editor

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 probabilty of 3 positive cases at electron microscopy would be only 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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The Year in Congenital Heart Disease

The review by Graham (1) is an excellent and welcome summary of surgical, interventional, and medical progress in congenital heart disease. There are sufficient data to allow the reader to form an opinion, backed up by specific references, as well as useful critical remarks of consensus.

I was particularly interested in his comments about postoperative pulmonic insufficiency in patients with tetralogy who are now being recognized as a significant problem in a growing population of postoperative adults. Initially, we all had hoped that pulmonic insufficiency would not be a problem, and surgeons were urged to abolish completely any gradient across the right ventricular (RV) outflow tract because of concerns that if the RV pressure was still elevated it would create a risk for arrhythmias, and even sudden death. As these youngsters lived with their insufficiency, they developed large right ventricles, but were generally asymptomatic. This tolerance of volume overload is also characteristic of the left ventricle, but in their teens and twenties those young patients are beginning to need valve replacements. Unfortunately, we do not have the same reliable guidelines (ejection fraction) for the right ventricle as we have for the left.

Although we will have to face difficult decisions for our current generation of postoperative tetralogy patients with severe pulmonic insufficiency—considering the limited half-life for biological valve replacements, as Graham (1) mentioned—shouldn't we revisit the degree of insufficiency being created in today's infants and children? Many years ago one of the pioneers of surgical correction of tetralogies anticipated the problem: Frank Gerbode (personal communication, June 1965) warned that it would be better physiologically to leave a moderate degree of pulmonic stenosis rather than create severe pulmonic insufficiency. He reasoned that the less compliant right ventricle associated with moderate stenosis would resist the insufficiency, and that moderate stenosis would be better tolerated.

As a minimum, we should review the evidence as to whether we have unnecessarily accepted all the problems of severe pulmonic replacement absent a test of the alternate approach of moderation in disabling the valve at surgery.

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REPLY

It is a pleasure to respond to Dr. Guntheroth's comments regarding my paper (1) and the current state of affairs for patients with tetralogy of Fallot and significant postoperative pulmonary insufficiency. As he clearly states, many of these adult patients have an enlarged right ventricle that can show a progressive decrease in ventricular function, which at some point becomes partially or completely irreversible. In addition, patients with a marked degree of right ventricular (RV) enlargement and decreased function appear to be potentially more susceptible to significant arrhythmias, which, on rare occasions, can be life-threatening. The optimal treatment for these patients is theoretically available with pulmonary valve replacement, which can be performed with low mortality and morbidity. When this procedure is done early enough in the course of the inexorable decrease of RV function, there is a decrease in RV size (usually modest) and improvement in RV function and exercise ability. Unfortunately, valves that have been used in the pulmonary position have, under most circumstances, shown a half-life of only 10 to 12 years. The newer, larger bio-prosthetic pericardial valves have shown some promise for holding on longer, but the data are not complete on these valves to make that a clear-cut alternative with promise for a longer interval between reoperations.

The search for an optimal bio-prosthetic valve (one that can be grown from one's blood cells outside the body and then re-implanted and possibly delivered with a catheter-interventional technique) is the hope of the future.

In the interim, I agree with Dr. Guntheroth that we should continue to revisit the issue of leaving mild pulmonary stenosis rather than create severe pulmonary insufficiency. This can be a difficult management decision in the operating room as the more severe tetralogy patients with severe outflow obstruction and small main pulmonary arteries are not amenable to successful repair without leaving them with significant pulmonary insufficiency. Moreover, when one has to do a significant ventriculotomy and leave moderate stenosis, right ventricle dysfunction can occur early in the postoperative period and be even more severe than that associated with moderate/severe pulmonary insufficiency.

During follow-up visits, postoperative tetralogy patients, most of whom have had an excellent overall outcome long term, continue to need attention to their RV size and function and to the potential for rhythm disorder; this should be done by physicians with expertise in both adult cardiology and congenital heart disease. Magnetic resonance imaging of the right ventricle with quantification of RV volumes and ejection fraction as well as exercise testing with maximum Vo_2 measurement can be quite useful in terms of serial assessment and consideration for intervention. There is a growing need for training the next generation of physicians who can provide optimal care for this burgeoning group of adults with congenital heart disease.

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