Relation of Contractile Reserve of Hibernating Myocardium to Myocardial Structure in Humans

To the Editor:

Nagueh and colleagues investigated the relationship between myocardial ultrastructure and the inotropic contractile reserve of the hibernating myocardium. They suggested that the amount of interstitial fibrosis in a dysfunctional myocardial segment is an important determinant of both inotropic contractile reserve during dobutamine stimulation and of the recovery of function after revascularization. The authors showed that myocardium with \( \geq 30\% \) interstitial fibrosis does not respond to dobutamine and that its function does not improve after revascularization. This is in agreement with earlier reports, which also demonstrated that the presence of this magnitude of interstitial fibrosis is associated with irreversible myocardial dysfunction. We suggest, therefore, that myocardial segments with these characteristics be removed from the analysis because they represent irreversibly damaged scar tissue rather than hibernating myocardium.

Nagueh et al conclude that the contractile response to dobutamine inversely correlates with the extent of interstitial fibrosis. However, close analysis of their data does not support this conclusion. Two groups of hibernating segments are reported. Group 3 consisted of segments with near-normal ultrastructure and minimal fibrosis (1%) that exhibited inotropic contractile reserve and recovered function after revascularization; in group 2, despite the modest amount of fibrosis (9%), 50% of the segments that had improved function after revascularization (ie, hibernating) did not exhibit inotropic contractile reserve. No continuous relationship between fibrosis and inotropic contractile reserve can be demonstrated in these segments. Thus, in hibernating myocardium, which is defined by the occurrence of improved systolic function after revascularization, the amount of interstitial fibrosis is low and seems unlikely to impair the response to adrenergic stimulation.

A number of studies, including our own, have also reported the lack of inotropic contractile reserve in a substantial number of hibernating myocardial segments, particularly in those from patients with severe left ventricular dysfunction. Our work indicated that hibernating myocardial segments (defined by contractile improvement after revascularization) without inotropic contractile reserve have an amount of fibrosis (\( \approx 14\% \)) similar to that in segments that exhibit a response to dobutamine but a greater number of myocytes with marked myofibrillar loss (26% versus 11%). This known ultrastructural “adaptation” of hibernating myocardium provides a plausible explanation for the lack of response to adrenergic stimulation. We suggest that the lack of inotropic contractile reserve found in many hibernating myocardial segments, which can be identified as viable by PET scanning and as hibernating by postoperative recovery of function, is due to the abundance of myocytes depleted of contractile units rather than the presence of fibrosis.

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Response

Drs Pagano and Camici question the relation of interstitial fibrosis to contractile reserve and systolic function after revascularization in patients with dysfunctional myocardium. We believe that our data strongly show that there is indeed a significant, inverse relationship between fibrosis and segmental function in response to dobutamine (see Figure 4 in our article) and postoperative thickening (see Figure 5 of our article). They further suggest excluding segments with \( \geq 30\% \) fibrosis from the analysis. Although it is easy to exclude such segments after the biopsies have been acquired, it was not possible to ascertain the extent of fibrosis beforehand.

Segments were biopsied if they met all of the following criteria: (1) abnormal function, (2) end-diastolic thickness \( \geq 0.9 \) cm, and (3) lack of a bright, reflective appearance indicative of scar tissue. These were all reasonable measures taken to avoid including predominantly scar segments. Furthermore, these inclusion criteria assured the inclusion of segments that resemble, to a great extent, the majority of segments in which myocardial viability is to be determined. As such, our “sampled segments” are very similar to the “general population of segments” and, therefore, we believe that our results are generalizable. We also disagree with the principle of changing inclusion criteria after they have been determined and the study has been conducted.

As stated clearly, our objective was to evaluate the relationship between the extent of viable myocardium by histopathology, resting perfusion as determined by rest-redistribution thallium-201, and the different contractile responses exhibited during dobutamine echocardiography. We determined our objectives a priori, and we reported what we set out to do. Excluding certain segments from the analysis to support a certain hypothesis and deviating from the purpose of the study is not appropriate.

Drs Pagano and Camici then examine data from \(< 50\% \) of the biopsied segments (16 of 37). They looked at the following 2 groups (see Figure 3). Group 2 included a total of 8 segments, of which 6 recovered and 3 had contractile reserve (fibrosis, 9%). Group 3 had a total of 8 segments, all of which recovered and had a contractile reserve during dobutamine (fibrosis, 1%). Even then and contrary to what is stated in their letter, it remained true that when the extent of fibrosis was higher (group 2 versus 3), both contractile reserve and recovery were less frequent. It is unclear to us where the assertion regarding the lack of a relationship between fibrosis and contractile reserve came from. In fact, when limiting the analysis to segments with \(< 30\% \) fibrosis, significant relationships were still present between interstitial fibrosis and thickening at low-dose dobutamine (\( r = -0.73; P < 0.05 \)) and...
with postoperative systolic function \( (r= -0.62; \ P<0.05) \). Finally, we believe that fibrosis alone accounted for the majority (69%) of the contractile reserve variance observed in our study but, as stated in our discussion, other parameters undoubtedly play a role; these include cellular function, coronary flow reserve, energy stores, and adrenergic receptors.3

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