cells into native myocardial fibers: anatomic basis for functional improvements. *J Thorac Cardiovasc Surg.* 2002;124:584-90.

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Reply to the Editor:

Dr Taheri made an important point in his comment, which we probably should have discussed in our article. However, first I, on behalf of my coauthors, wish to clarify that we did not inject "isogenic myofibril grafts," which would represent a differentiated anatomic unit of a muscle tissue. Instead, we transplanted either skeletal myoblasts, which are immature progenitor cells, or marrow stromal cells, which contain a pluripotent cell population. Such immature cells are able to migrate and self-assemble with preexisting supracellular structure, as we reported.

The hypothesis we postulated to explain the mechanism of this phenomenon should indeed predict that those donor cells, if implanted as an isolated island within a scar tissue, would lack the microenvironment to allow them to integrate into the preexisting native myocardial syncytium. We and others have pointed out that how such cells surrounded by scar contribute to the myocardial function, as has been reported experimentally and in some early clinical trials, remains unclear at present.¹ It is of some interest to recall how the strategy of implanting cells into scar started. In our studies in the early 1990s,^{2,3} which were the first attempts to use cell therapy for myocardial regeneration, we lacked the tools for cell labeling and thus created a homogeneous scar induced by cryoinjury. By implanting myoblasts within such a scar, we were able to show that the new myofibers surrounded by the scar tissue originated from our donor cells. Because turning noncontractile scar tissue into potentially contractile muscle tissue is an intuitively appealing idea, many investigators in the subsequent studies, both experimental and clinical, have continued to use the model of implanting cells within the scar tissue, even though there has been no convincing evidence that these isolated muscle fibers can actually contribute to the synchronized contractile function of the myocardium.

In studying the pathophysiologic roles of marrow stromal cells, it has been shown that tissue injuries, such as myocardial in-

farcion, can send a signal to recruit marrow stromal cells from the bone marrow, which traffic through the bloodstream to target the infarcted segment of the myocardium. There they undergo milieu-dependent differentiation, expressing a number of phenotypes.⁴ We have suggested that some of these cells that reached the peri-infarct zone became endothelial and vascular smooth muscle cells to participate in vasculogenesis and enhance collateral circulation. Some cells, which reached the scar tissue through patent collateral vessels, may express a myofibroblastic phenotype and participate in scar maturation to reduce scar expansion and rupture. The marrow cells in the peri-infarct zone that are in contact with viable and contracting host myofibers may differentiate into cardiomyocytes and integrate into the existing myofibers as we reported¹, and this may play a role in modulating the postinfarct remodeling process of the ventricle. Yet other mechanisms are possible. The neocardiomyocytes, which have received phenotypic signals from native cardiomyocytes at the peri-infarct zone, may then migrate toward the myocardial scar to reduce infarct size. Various transforming growth factors and cytokines coming from the surrounding cells and extracellular matrix may also play important roles, as suggested by Dr Taheri. Clearly, much needs to be learned, and from such understanding better clinical strategies to use cell therapy for myocardial injury may yet evolve in the future.

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Asymptomatic mitral valve incompetence: Is there evidence for surgery?

To the Editor:

The article by David and colleagues¹ in the May 2003 issue of the Journal, "Late Outcomes of Mitral Valve Repair for Floppy Valves: Implications for Asymptomatic Patients," stirs important unanswered questions and concerns. The conclusion that patients with asymptomatic mitral valve incompetence are candidates for surgery might be extrapolative yet beneficial—if it had stemmed from a different study design. In statistical terms, significance for operating was clearly established; however, this was more rhetorical than useful in clinical practice. The following issues were not mentioned in the discussion or among the discussants.

First, asymptomatic simply means no symptoms. Mitral valve surgery is feasible, but its benefits to the individual patient cannot be observed here because of the confounding variables in the methodology and results. To the reader, the concept of cause and effect is paramount to executing successful cardiovascular epidemiology. Whereas the scientific sequence of cause and effect is clear, the application of such a valid concept in this article leans to the reverse order. In other words, because surgery in patients without symptoms had a low morbidity and mortality (cause), it is recommended to operate for asymptomatic mitral incompetence (effect). Lowering the threshold to operate must stem from convincing data, and even if statistically significant the clinical indication is neither relative nor absolute. The patient's physiologic status must be the underlying cause for an operation, and the outcome of the operation (effect) must treat that cause. In this article despite the effect being feasible, the cause is far from a true clinical indication. The practicing surgeon can be confused with the paradigm of cause and effect that appears to argue that the mortality is higher among patients with symptoms. Drawing feasibility from such a statistic may introduce a new "fuzzy logic" dimension that has no order and no cause followed by effect features.² This logic results from many decision-making and problem-solving tasks that are too complex to be understood quantitatively; however, people succeed by using knowledge that is imprecise rather than precise.

Second, it is interesting that absolute risk reduction in mortality from 23% to 6% is 17% in those symptom-free patients who were operated on. However, all variables in a scientific study must be controlled except the single variable that is being studied. Thus, when David and colleagues¹ attempted to modify a successful operative procedure, underlying background pathologies in the control and study groups needed to be similar. This was lacking.

Third, the demographic data (Table 1 in the original article¹) reveal an important cause with regard to the population sample. Atrial fibrillation (AF) was more prevalent in the symptomatic than asymptomatic group ($P = .0001$). Chronic AF carries greater risk than intermittent AF, doubling the risk of cardiovascular mortality. In other words, implications for symptom-free patients are only indirectly related, as opposed to a direct cause-effect relationship with AF.³ Moreover, diabetes mellitus in the symptomatic group approached a statistically significant difference ($P = .07$). More recently, it has been shown that all the patients with insulin-dependent diabetes mellitus with left diastolic dysfunction have evidence of definitive autonomic neuropathy. Such isolated diastolic dysfunction may be the principal physiologic mechanism in these patients. The annual mortality from diastolic heart failure varies widely, from 9% to 28%.⁴ This variable should be addressed in the context of patient cohort by reviewing echocardiographic evidence of diastolic dysfunction. The mortality rate among patients with diastolic heart failure is 4 times that among persons without heart failure but half that among patients with systolic heart failure.

Third, apart from the semantics of asymptomatic, of more interest at mean follow-up 93% of patients in the asymptomatic group were in New York Heart Association (NYHA) functional class I or II, which was not statistically significant from the symptomatic group (88%). This result argues that mitral valve surgery repair on symptom-free patients does not confer any further clinical benefit. This statistic is consistent with others and follows classic teachings. Also, the discrepancy between the reoperation rate and the incidence of significant mitral valve regurgitation indicates that not all patients having important valve incompetence late after repair undergo surgery again within the time

frame. This repeated observation creates a new argument that recurrent mitral incompetence lacks substance as an indication for operation and argues against the primary hypothesis and conclusion of David and colleagues.¹

Fourth, David and colleagues¹ did not mention the well-known limitations to the simple NYHA scale for cardiovascular disability. NYHA has a tendency to oversimplify an issue or a problem by ignoring complexities or complications. The criteria committee of the NYHA has provided a widely used classification that relates symptoms to "ordinary" activity. The term *ordinary* is subject to various interpretations, as are terms such as *undue fatigue*. Such terms have limited the accuracy and reproducibility of the NYHA classification.⁵

In the end, it is desirable to seek patients who need an operation. Offering such surgery to symptom-free patients on the basis of effect rather than cause, however, is simplistic and fuzzy. Better data analytic methodology and study design are needed to qualify for a new indication.

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Reply to the Editor:

Dr Shuhaiber makes some valid points about our study,¹ but many of his comments are irrelevant. He ignored the fact that ours was an observational study and did not establish causation but rather an association between functional class and

late mortality after mitral valve repair for mitral regurgitation caused by prolapse. The objectives of the study were clearly defined, and in addition to showing the late outcomes of mitral valve repair for floppy valves it also showed associations between certain preoperative variables and late mortality by multivariable analysis with bootstrap validation. Our study was not a prospective randomized trial, and consequently we could not control the variables before the operation as he suggested. This is, of course, a major limitation of all retrospective studies. One can only adjust for those factors that were measured. Residual confounding by unmeasured variables may potentially distort results. However, numerous studies have shown that careful, multivariable analysis of observational data produces treatment effects very similar to those of randomized controlled trials.²⁻⁴

Atrial fibrillation and diabetes were included in all multivariable models. Dr Shuhaiber's concerns regarding chronic atrial fibrillation may in fact provide further argument to operate on symptom-free patients. Atrial fibrillation may be a consequence of deterioration in ventricular function in patients with mitral regurgitation, and by the time it first occurs irreversible changes may already be present.

His remarks regarding postoperative functional class and the probability of recurrent mitral regurgitation in our patients are incorrect. One would not expect symptom-free patients to have lessened symptoms after the operation simply because they were already in functional classes 1 and 2 (ceiling effect). The analysis at follow-up was designed to demonstrate the improvement in the patients with symptoms. The mechanism of mitral valve prolapse was similar in both groups of patients, and recurrent mitral regurgitation after mitral valve repair is more dependent on the pathology of the mitral valve than on presence or absence of preoperative symptoms. That is reason why recurrent mitral regurgitation and reoperation rates were similar in the two groups.

We agree that functional class is a soft, subjective variable, especially between classes 2 and 3, but certainly not between classes 1 and 3 or 2 and 4. Moreover, symptoms are usually the reason a patient seeks medical advice. What our study showed is that postponing surgery until symptoms are more obvious (functional