However, an animal model would provide results that may help to understand pathophysiological mechanisms in AF.

In our study (3), we did not assert to use the immunological analysis for quantification. After finding clear histological differences (by visualization) between patients in sinus rhythm (SR) and AF, we quantified the expression of AT_1 and AT_2 by Western blot techniques. We could detect a significant increase in AF compared to SR in the AT_1 expression, but not in the AT_2 expression (Fig. 3A [3]). As shown in Figure 2, there was a higher level of AT_1 in patients with both lone AF and MVD + AF compared to a lower level in patients with SR. In contrast to the claim of Goette et al., there was no lack of expression of AT_1 in SR; however, a low level (Fig. 2 [3]).

We cannot exclude that other substrates or pathways may influence the expression of AT_1/AT_2 in patients with AF. However, a time-dependent expression of AT_1 has not yet been analyzed and is difficult to investigate in humans. In fact, differences exist in the expression of angiotensin II receptor subtypes between human left and right atrium. Furthermore, because AF depends from the left atrium (5), it is important to consider both atria to draw possible conclusions about pathophysiological influences of signaling pathways. Owing to our results, AF is associated with an upregulation of AT_1 in the left atrium, but not in the right atrium. This suggests a pathophysiological role of AT_1 in AF (3,6,7).

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From Controlled Trials to Clinical Practice: Monitoring Transmyocardial Revascularization Use and Outcomes

Considering the significant clinical experience with transmyocardial revascularization (TMR) in both the controlled trial and "real-world" setting, we felt compelled to comment on the recent retrospective registry report by Peterson et al. (1) culled from the Society of Thoracic Surgeons national cardiac database. Regarding sole-therapy TMR, the investigators confirm findings observed in five prospective randomized trials comparing TMR to medical therapy in "no option" class III/IV angina patients: like most new technologies, there is a learning curve, and surgical risk is increased in sicker patients (2–6). Their commentary, similarly, is not new. Allen et al. (2) reported reduced operative mortality rate from 5% overall to 2% in the last 100 randomized patients, attributable to surgical technique refinement and patient selection; Frazier et al. (3) reported unstable angina as a significant predictor of operative mortality. Others with clinical experience in treating unstable patients (2,7,8) confirm that such patients without conventional options represent a higher risk group for TMR.

Although not the intent of their retrospective study, Peterson et al. (1) fail to summarize adequately the clinical benefits of sole-therapy TMR. In prospective randomized trials at one year, TMR provided superior angina relief, decreased rehospitalizations, and improved exercise times compared to patients managed medically. A recent five-year follow-up of randomized patients demonstrated significantly increased Kaplan-Meier survival rates and sustained, significantly superior angina relief in patients randomized to TMR compared to medical therapy (9).

As reported by the investigators (1), TMR is increasingly being utilized adjunctively with coronary artery bypass grafting (CABG) in patients with diffuse coronary artery disease (CAD) who would be incompletely revascularized by CABG alone. In a prospective, randomized trial involving 263 such patients, CABG/TMR provided operative and one-year mortality benefits with a trend toward superior angina relief compared to CABG alone (10). The retrospective report by Peterson et al. (1) compares patients in the STS database who received CABG/TMR with a concocted control group consisting of CABG-only patients with triple-vessel disease who received <3 grafts. The appropriateness of this comparison is questionable, because it *assumes* that incomplete revascularization in the control group occurred in an area of ischemic viable myocardium supplied by a diffusely diseased, ungraftable coronary artery and that all participating centers accurately and consistently defined three-vessel disease. It is not possible to verify this by simply querying the STS database. It is important also to note that surgeons are increasingly operating on patients with diffuse-CAD, which has been shown to be a powerful independent predictor of operative mortality (11,12). Unfortunately, the presence of diffuse-CAD is not factored into the STS database or other national databases. Thus, such case-matched comparisons against CABG/TMR-treated patients with diffuse-CAD can be unreliable because control database sources fail to account for diffuse-CAD and therefore *underestimate* predicted operative mortality in this select patient group.

We applaud the investigators in supporting continued physician training and education regarding the judicious application of sole-therapy TMR or adjunctively in patients who would be incompletely revascularized by CABG alone. Long-term

follow-up of the latter group will further define the role of TMR in the treatment of an increasingly complex cardiac surgical patient.

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REPLY

The letter by Dr. Allen and colleagues raises a number of important issues. First, they point out that the operative risk factors for transmyocardial revascularization (TMR) identified in our study (1) were similar to those noted in earlier randomized studies. Although we agree that the preoperative risk factors identified were not unique, our study provided confirmatory evidence as to their generalizability in a broader clinical practice setting. More significantly, our national study demonstrated there is still a need to optimize appropriate patient selection for the procedure in contemporary care. Specifically, our study and others clearly demonstrate the risks of TMR in patients with unstable symptoms or recent myocardial infarction (MI). Despite this, we found more than half of TMR cases done in community practice were performed under these conditions. Thus, we believe it valuable to re-emphasize to clinicians these potentially modifiable operative risk factors as a means of encouraging safer use of TMR in community practice in the future.

Dr. Allen and colleague's second point was that we failed to acknowledge the efficacy data for TMR-only. In this regard, we would argue that our study did reference the six randomized clinical trials that support the effectiveness of TMR-only to reduce patient symptoms. The recent abstract on five-year results sited by Allen was not available before our study's publication, and we look forward to seeing this work in press soon.

The third point raised by Dr. Allen and colleagues concerns the role of TMR when used in conjunction with coronary artery bypass graft (TMR + CABG). Our study confirms that this combined procedure has become the dominant role for TMR in contemporary practice. There is less compelling evidence for the efficacy of TMR in this setting, however, than is found in TMR-only. The sole randomized trial of TMR + CABG failed to identify a significant reduction in angina symptoms, but it did report an unexpected reduction in perioperative event rates (2). Our observational study could not confirm these promising findings when comparing operative outcomes among patients with three-vessel disease who got TMR + CABG versus those receiving incomplete revascularization with CABG-only (i.e., one or two grafts only). We agree with Dr. Allen and colleagues that observational treatment comparisons, even when risk-adjusted, may still be challenged by unmeasured patient selection biases (a point we included in our report).

In conclusion, our study emphasized the importance and utility of clinical registry information in providing evidence to further refine the optimal application of technology after its introduction into clinical care. Its main goals were to describe contemporary practice patterns; to improve the safety of the procedure through appropriate patient selection; and to stimulate future research in areas requiring further clarification. We hope we have accomplished these goals and that Dr. Allen and colleagues continue to refine the optimal role for this procedure.

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