associated with an increased risk of death from sepsis. They further conclude that TEE is frequently needed to make the diagnosis of infective endocarditis and should be considered in all patients with *S. aureus* bacteremia. We agree that bacteremia is a serious condition and is associated with morbidity and mortality, and we commend the authors on their efforts to identify patients with infective endocarditis among this group. However, we believe that their conclusions are not justified on the basis of their study.

1. It is unclear exactly what hypothesis the authors were trying to test and how they designed the study to test it. They appear to want to evaluate the use of TEE in the diagnosis of infective endocarditis and to demonstrate that it is better than transthoracic echocardiography (TTE) for this purpose. This approach is problematic because the authors used TEE as part of the reference standard (along with the Duke criteria) for the diagnosis of infective endocarditis. They had no way of addressing specificity, and the sensitivity of TEE is naturally better than TTE because they considered TEE the reference standard. Thus, their study is not appropriately designed to determine whether TEE is better than TTE in this setting.

2. The authors evaluated only 59% of eligible patients with *S. aureus* bacteremia. The remaining patients were not evaluated because of either patient or physician refusal. Thus, their sample may not be representative of the intended study population. Furthermore, although the authors present the demographic and clinical characteristics of both the study and excluded groups, they did not report any statistical comparisons. When we made calculations based on the present data, there appeared to be significant differences between included and excluded patients. The proportion of patients with an unknown source of bacteremia in each group is significantly different ($p = 0.001$), as is the proportion of patients with catheter-related sepsis ($p = 0.001$). These baseline differences are significant even after adjustment for multiple comparisons and strengthens the premise that their sample may not be representative of all patients with *S. aureus* bacteremia. Specifically, the excluded group had a higher percentage of unknown infection source and a lower percentage of a catheter source. How these exclusions affect the authors' conclusion is unclear; however, the direction of any bias inherent in the selection of cases should be addressed.

3. The authors analyzed multiple outcomes between subjects with and without infective endocarditis. They claim that death due to *Staphylococcus* sepsis was significantly more likely in patients with infective endocarditis. The p value by Fisher exact test for this comparison is 0.034. Not only is this misreported twice as 0.003 in the report, but no mention of multiple comparisons is made. With four outcome measures being compared, the risk of a type I error is 0.20 (if alpha is 0.05). Using the Bonferroni correction, the alpha value for a significant difference should have been set at 0.0125. Thus, statistical significance was not achieved. Hence, there may not be a difference between the groups with and without infective endocarditis as far as death due to *S. aureus* bacteremia.

4. No information was provided concerning the specific treatment regimens administered during the prospective evaluation. Differences in treatment regimen in either group would either enhance or dilute any outcome relation.

In conclusion, the unclear hypothesis, sampling procedure, differences between included and excluded patients, statistically weak conclusions and lack of standardized treatment protocols make it difficult to accept the generalizability of their conclusions. We feel that this study does not establish routine TEE in patients with *S. aureus* bacteremia as the basis for future evaluation of clinical therapies.

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Reply

We thank Guzzo and Simpson for their interest in our report and for the questions that they raise regarding various aspects of it. We would like to clarify several points that address these misunderstandings.

Our colleagues suggested that we were using transesophageal echocardiographic (TEE) findings as our reference standard for the diagnosis of endocarditis. This suggestion is incorrect. We used the Duke criteria as the reference standard measure by which the diagnosis of endocarditis was made (see Table 2). This diagnostic schema is both sensitive (1–4) and specific (1,5) for the diagnosis of endocarditis and has been validated at Duke and elsewhere. TEE findings merely fulfilled a portion of these diagnostic criteria, which also include clinical and microbiologic criteria. Thus, the diagnosis of endocarditis in our report rested upon a validated diagnostic schema.

Guzzo and Simpson suggested that the group of patients undergoing TEE might not be representative of the intended study population because excluded patients who were significantly more likely to have no identifiable focus of infection and were significantly less likely to have an intravascular catheter source of infection. Indeed, these facts would make excluded patients more likely to have endocarditis, thus supporting our findings. The absence of an identifiable focus of infection among patients with *Staphylococcus aureus* bacteremia is a powerful risk factor for endocarditis (6), and patients with an intravascular device are at low risk for endocarditis when the catheter is promptly removed (7–9). Thus, the effect of the excluded patients would be underestimation of our findings. In other words, had fewer patients with a nonidentifiable focus of infection been excluded, an even higher rate of endocarditis might have occurred.

Our colleagues took issue with the statistical evidence surrounding the mortality of patients with and without endocarditis. We acknowledge that the correct p value for patients dying of *S. aureus* endocarditis is 0.03, as we reported in the abstract section. Furthermore, as demonstrated by the fact that our colleagues performed the calculation, we have provided the discerning reader with the means of calculating Bonferroni corrections should it be considered necessary. However, we interpret our finding as significant, because it makes numerical (15.4% mortality rate among endocarditis patients versus 2.6% among patients without endocarditis) and clinical sense (patients with endocarditis are more likely to die than patients without endocarditis), as well as being statistically valid.

Finally, Guzzo and Simpson suggested that differences in treatment regimen would have an impact on patient outcome. Although we agree

with this point, the primary focus of our report was the incremental benefit of TEE in the evaluation of patients with *S. aureus* bacteremia rather than the management of patients with endocarditis.

In conclusion, we respect the points raised by Guzzo and Simpson; however, we feel that the use of a validated diagnostic reference standard, the probable underestimation of endocarditis among excluded patients and the clinically logical conclusions in our study emphasize the need to consider TEE early in the evaluation of patients with *S. aureus* bacteremia.

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Propagation Velocity of Left Ventricular Filling Flow Measured by Color M-Mode Doppler Echocardiography

I read with great interest the report by Duval-Moulin et al. (1) regarding to the application of color M-mode Doppler to assessing left ventricular diastolic function. The report indicated that left ventricular diastolic dysfunction during coronary angioplasty could be assessed by the propagation velocity of left ventricular early filling flow using color M-mode Doppler technique and that this index showed good correlation with an invasive variable, tau. Their method was very similar to, but not the same as, our method, which was reported in the Journal in 1996 (2). In their discussion, they introduced our method as follows: "Takatsuji et al. used a derived technique by measuring the interval between the maximal rate of increase of action potential upstroke (Vmax) at the mitral level and 70% Vmax in the apical region." There are several inappropriate notations in this sentence. In our report, the propagation velocity was defined as follows:

> By changing the first aliasing limit sequentially at intervals of 2 cm/s with the use of the baseline shift, a flow velocity higher than the aliasing velocity could be displayed in blue within red filling flow signals. First, we located the point of maximal velocity around the mitral orifice in early diastole, which was obtained at the center of the minimized aliasing area. Next, we changed the first aliasing limit to 70% of the maximal velocity and located the point nearest to the apex on the aliasing boundary (which is usually obtained in the mid-left ventricle). The distance/time ratio, that is, the upward slope of the line connecting these two points, was measured and defined as the rate of propagation of peak early filling flow velocity.

First, the authors used the terms "action potential" and "Vmax," which were not used in our report, and this terminology might mislead the readers and prevent appropriate understanding of our method. Second, we did not measure the "interval" but the "distance/time ratio"; and third, the second measurement point is not "in the apical region" but "in the mid-left ventricle." We have some evidence that the propagation velocity measured by our method is more accurate than that measured at the wavefront of filling flow, which was used in their report. Therefore, if they carefully traced our protocol, I believe that they would obtain better correlation between propagation velocity and tau. Nevertheless, we appreciate the authors' results because their study enhances the usefulness of color M-mode Doppler for evaluating diastolic function in many clinical settings.

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Reply

We have taken into account the different points emphasized by Kitabatake about the report by Takatsuji et al. (1). As Kitabatake described, color M-mode Doppler allows remarkably effective observation of diastolic flow as a function of time and of space.

The color M-mode Doppler method has been developed by several groups, including Takatsuji et al. (1), Stugaard et al. (2) and ourselves (3,4). The technique shows correlation of the propagation of early diastolic flows in the left ventricle with hemodynamic data of relaxation, especially the index tau.

With regard to the report of Takatsuji et al. (1) we were naturally interested in their methods and results, which analyze the rate of propagation of peak early filling flow. However, their study was published in the Journal during the review process of our study. Consequently, we added this new information in the revised version of our manuscript, which may explain why we did not discuss all the aspects of the interesting report of Takatsuji et al.

Nevertheless, we would like to point out that in contrast to Takatsuji et al. (1) and Stugaard et al. (2), we preferred to analyze the flow front wave at the beginning of filling rather than the later events of the propagation of peak early filling flow to better evaluate the relaxation process.