amine infusion before the decrease. By contrast, the observations of Cladellas et al. concern patients who failed to achieve an adequate heart rate response; it is not clear whether heart rate decrease occurred in any patient. As we reported, only 1 of 14 patients with paradoxical sinus deceleration was taking beta-blockers. We mentioned in our report that all our patients fasted for at least 3 h before dobutamine stress echocardiography; mild hypovolemia may have facilitated the occurrence of the vasodepressor response.

In our conclusions, we reported that paradoxical sinus deceleration was most often seen in patients with coronary artery disease, but in 14% of our patients with heart rate decrease, there were no angiographic, echocardiographic, electrocardiographic or clinical signs of coronary artery disease. Sinus deceleration was often accompanied by a decrease in blood pressure, nausea and chest pain. We believe that sinus deceleration during dobutamine stress echocardiography is typically mediated by the Bezold-Jarisch reflex and is most commonly seen in the presence of ischemia but may occur in its absence.

The echocardiographic signs of myocardial ischemia may be subtle if heart rate is not increased and can be best appreciated by continuous echocardiographic surveillance. Atropine is effective in increasing heart rate in patients with paradoxical bradycardia and is recommended in those with no manifestations of ischemia.

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F-18 FDG Uptake in Transplanted Heart

In their recent report, Rechavia et al. (1) concluded that a threefold increase in the uptake of the glucose tracer analogue fluorine-18 2-deoxy-2-fluoroglucose (F-18 FDG) in transplanted hearts reflects a preference for glucose as a substrate. The authors further concluded that this preference for glucose may be due either to inefficient utilization of glucose by the transplanted heart or to the influence of circulating catecholamines.

This observation can be explained entirely by a change in the relation between F-18 FDG and glucose. The latter is commonly referred to as the "lumped constant" (LC) (2). This ratio between tracer (F-18 FDG) and tracee (glucose) reflects the kinetic differences between glucose and deoxyglucose transport and phosphorylation. Most studies have used a fixed value of 0.67 to quantitate glucose uptake from the F-18 FDG tracings (3–5), but we (6,7) and others (8) have recently observed in the isolated working heart that the LC is subject to significant variability, depending on the metabolic environment. Insulin and competing substrates to glucose cause a decrease in the LC (6–8), whereas epinephrine and ischemia can cause an increase in the LC (unpublished observations). An increase in the LC causes an overestimation of glucose uptake, whereas a decrease in the LC results in an underestimation of glucose uptake.

Thus, considering the results of Rechavia et al. (1) in light of the experimental findings (6–8), the concept of an increased LC in the transplanted hearts is in order. Such an increase would lead to the overestimation of glucose uptake. This effect may artificially introduce and accentuate otherwise minor differences in glucose uptake. The possibility of increased catecholamine sensitivity and the possible presence of chronic "demand ischemia" in transplanted hearts would argue in favor of this hypothesis.

A practical solution to this problem would be to determine the LC individually for every study from the time-activity curves of F-18 FDG accumulation (9). The results presented by Rechavia et al. (1) are undoubtedly interesting, but we caution against drawing any conclusions regarding the quantitation of glucose uptake or metabolism in transplanted human heart.

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Reply

In their comment on the report by Rechavia et al. (1), Doenst and Taegtmeyer make several important statements about the lumped constant (LC) for fluorine-18 2-fluoro-2-deoxy-D-glucose (F-18 FDG) and how changes in this variable would reflect on the quantitative assessment of myocardial glucose utilization with this method. They also surmize how the LC may differ between fasting conditions in normal subjects and in transplant recipients.

We agree with the view that it is important to develop an understanding of how the kinetics of F-18 FDG and glucose differ under varying pathophysiologic conditions in humans, but the absence of appropriate and unequivocal data means that predictions of how the LC might change clinically are still clearly speculative.

The results of various studies performed in isolated hearts support the notion that the potential range of changes in the value of the LC in humans may be substantial, although in the recent paper by Bøtker et al. (2), a reanalysis of data previously presented by Krivokapich et al. (3), shows a less than twofold variation in the LC for various physiologic changes (with values ranging between 0.45 and 0.85). In the same report (2), estimations of the LC are made for two subjects in the fasting state by means of the kinetics of F-18 FDG (the K_1:K_1 ratio). Although this approach looks very promising, there are no reliable data presented for the magnitude and range of values for the LC in fasting humans.

Regarding the possible differences in the LC between the normal and the transplanted heart, Doenst and Taegtmeyer suggest the likelihood of an increase in the LC under conditions of increased epinephrine or ischemia (unpublished observations). In the report by Rechavia et al. (1), the possibility is raised that F-18 FDG uptake (and therefore glucose utilization) may be increased because of a state of chronic "demand ischemia." This state is proposed in the context of a substrate modifier, and in view of the modest increase in baseline workload of the hearts in these patients (53%—with a proportionate 41% increase in flow relative to that in normal control subjects), it is unrealistic to equate the status of the transplanted heart with full-blown acute myocardial ischemia.

In their letter, Doenst and Taegtmeyer suggest that they have evidence (unpublished observations) for an increase in the value of the LC with epinephrine; yet (as an illustration of the variability in the findings on this subject) they have themselves published data (4) suggesting a constant relation between the kinetic behavior of F-18 FDG and glucose during the administration of epinephrine (i.e., a constant value for the LC). Of equal importance, no indication for changes in the value of the LC were noted in the same studies during conditions of acute increase in workload. The additional finding that F-18 FDG uptake was not increased during the administration of insulin in those studies, contrary to the result of extensive experiment in humans and documented in Bøtka et al. (2), highlights the problem of extrapolating results from experimental animal models to humans.

Taken together, these findings do not support the notion that a significant difference in the value of the LC exists for the transplanted heart. It is therefore not unreasonable to interpret the finding of a threefold increase in F-18 FDG uptake in the heart transplant recipients (1) as an increase in the rate of glucose utilization. However, we do agree that there is a need for a simple and quantitative in vivo assessment of the LC, such as that proposed by Bøtker et al. (2).

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QT Dispersion as a Marker of Risk in Patients Awaiting Heart Transplantation?

We read with interest the report by Pinsky et al. (1) in a recent issue of the Journal on a possible new application of QT dispersion from the 12-lead surface electrocardiogram (ECG). The question of whether QT dispersion is a useful risk marker in patients with congestive heart failure is still under dispute (1–7). Pinsky et al. (1) reported that QT dispersion predicts death in patients awaiting list heart transplantation. In their conclusion, the authors claim that the index "may help to establish priority on a heart transplant waiting list." Obviously, such priority decisions may mean "life or death" in a given patient. The validity and objectivity of a risk stratification test in this setting are therefore of utmost importance.

Concerning the use of QT dispersion as a marker of arrhythmic events or death in patients with congestive heart failure, the contrasting results of available studies (1,4–7) indicate that the role and methodology of QT dispersion is far from settled and remains sensitive to methodologic discrepancies. We and others (2,8) have devoted research efforts to the methodology of QT dispersion that have led to entirely negative results for patients with congestive heart failure (5–7). The report by Pinsky et al. (1) raises a number of important methodologic questions.

1. QT dispersion cutoffs were determined post hoc, identifying a high risk patient group of six patients with QT dispersion >140 ms. Instead of calculating an odds ratio for such a small group, receiver operator characteristic curves could have yielded more valid statistical information. The average QT dispersion for both the event and nonevent groups was found to be significantly higher than that in published reports (4,6) and our own data (5,7). In our view, such extreme QT dispersion values must raise the suspicion of measurement errors.

2. An exact description of U wave identification was given; however, the incidence of U waves, which may have contributed to an increased QT dispersion, is not mentioned in the results section.

3. The reader is unable to discern whether measurements were taken by hand, by digitizing pad or with or without magnifying glasses. Notably, only six measurable ECG leads were required. Apparently, a 4×3 lead ECG display was used, which does not give simultaneous information for all 12 leads. This method is susceptible to errors caused by transient changes in the RR interval and associated QT intervals and may have increased the overall QT dispersion.

4. Patients with atrial fibrillation (n = 13) were included in the analysis. Again, changing RR and QT intervals between different beats prohibits accurate determination of QT dispersion.

5. No information on the reproducibility of the measurements was provided. Accurate measurement of QT intervals and QT dispersion, which is prone to subjective operator errors, requires stringent controls by comparing data from at least two independent blinded operators.

The discussion of the report, in our view, does not adequately consider methodologic considerations or limitations. In conclusion, we