Reply

We appreciate the keen interest of Broka et al. in our work on the hemodynamic effects of oxygen. They raised two concerns. The first relates to the importance and mechanism of our observation demonstrating a diminished cardiac output in response to supplemental oxygen. The second relates to the calculated oxygen consumption values in our study and the fact that oxygen consumption decreased as supplemental oxygen was added.

With regard to the first concern, the majority of subjects did not become symptomatic as we gave supplemental oxygen. However, one subject became short of breath and diaphoretic in response to this intervention. Another subject who was studied after completing this project also became diaphoretic as oxygen was delivered. We did not include these data in the original report because we did not systematically examine symptoms and considered these data to be too anecdotal. However, as we emphasized in our report, pulmonary capillary wedge pressure increased, confirming the finding that oxygen had a detrimental hemodynamic effect. We agree that measurements of plasma lactate would have been useful. Unfortunately, at the time of these studies, we did not think of performing these measurements.

What is the mechanism for the decrease in cardiac output? We would expect a change in cardiac output to be associated with either a change in loading conditions or a change in inotropy. As mentioned above, pulmonary capillary wedge pressure increased in response to oxygen, providing evidence that preload increased. This would suggest that cardiac output diminished at a time when Starling forces would dictate that cardiac output should increase. Therefore, one could only conclude that there must be a change in either inotropy or systemic resistance. Although we did not measure inotropy directly, a decrease in inotropy is typically accompanied by evidence of reflex sympathoexcitation. We found no changes in heart rate or peroneal nerve muscle sympathetic nervous system activity. Thus, we would surmise that inotropy did not decrease. We did calculate system vascular resistance and found it to increase fairly dramatically. Therefore, our data support the contention that oxygen acted as a direct vasoconstrictor, thereby increasing peripheral vascular resistance.

We have further pursued the issue of changes in systemic resistance in our experiments in patients with a left ventricular assist device. We have performed studies in six such patients and found a consistent relation between increased systemic resistance and the administration of oxygen (unpublished observations). Further, in normal subjects, we have performed experiments on forearm blood flow in response to 10 min of forearm ischemia. We have observed that peak vasodilation is reduced with the administration of supplemental oxygen (1). The exact mechanism for this change in systemic resistance is currently unknown.

In terms of the insightful discussion on oxygen delivery of Broca et al., we completely agree that the change in calculated oxygen consumption in our data would bring into question the dependency of oxygen consumption on oxygen delivery. Ideally, one would measure oxygen consumption during such experiments. Measuring oxygen consumption during oxygen delivery is fraught with a number of inaccuracies and, accordingly, we did not pursue these measurements. The work cited in their letter was performed in anesthetized patients with coronary disease (2). These subjects differed considerably from those in our study in that they were anesthetized, and there is no comment on the presence or absence of congestive heart failure. These are important considerations because spontaneous ventilation in the presence of increased filling pressures would substantially increase the work of breathing and total oxygen consumption. This could substantially alter the relation between oxygen consumption and oxygen delivery so aptly described in your letter.

With regard to the estimated oxygen consumption values in the letter of Broca et al., there were some assumptions made that would overestimate the calculated oxygen delivery. In reviewing the data in experiment 2, we found that oxygen delivery ranged from 333 ml/min on room air to 270 ml/min with 100% oxygen. Accordingly, we were in the previously described range where there is a dependency of oxygen consumption on oxygen delivery. Additionally, from the data that Broca et al. referenced, one would predict a 21% decrease in oxygen consumption. Based on our patients, a 29% change was observed. As mentioned above, because the patient groups and clinical conditions are different, it would be inappropriate to directly apply the previous data to our patients.

In conclusion, our work dealt primarily with the hemodynamic effects of supplemental oxygen in conscious humans with severe heart failure. We agree with Broca et al. that other "clinical" measures during oxygen administration in patients with heart failure are warranted.

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Selection Bias in Thrombolytic Trials

Jha et al. (1) compared the characteristics and mortality outcomes of Canadian patients who participated in two thrombolytic trials (GUSTO and LATE) with those in patients with acute myocardial infarction who did not participate. Administrative discharge data were used for nonparticipants to obtain demographic and "comorbidity scores." No physiologic data were available for nonparticipants. The authors found that trial participants were younger, more likely to be male and had a lower comorbidity score. Participants also had lower in-hospital mortality "after adjustment for age, gender, revascularization and comorbidity scores." The authors conclude that there is selection bias in the recruitment of trial participants, with favoring of lower risk patients.

In essence, what the authors have described are differences in demographics, comorbidity scores and mortality between a population of patients who are eligible for thrombolysis (participants) compared with an unselected group of all patients with acute myocardial infarction (nonparticipants). Nonparticipants thus include both thrombolysis eligible and ineligible patients. It is well known that many patients with acute myocardial infarction are ineligible for thrombolysis on the basis of late presentation, absence of chest pain, nondiagnostic electrocardiographic findings, uncontrolled hypertension or other contraindications (2). Data reveal that these patients are older, more likely to be male and more likely to have a higher degree of comorbidity (3).

Outcomes among those who are ineligible for thrombolysis is worse than for those who are eligible and receive thrombolytic agents (2,3). Thus, one would *expect* a mixed group of thrombolysis eligible and ineligible patients to be older, more likely to be male and to have a higher degree of comorbidity than a group of only thrombolysis eligible patients. To conclude that there was true selection bias in the recruitment of study participants, one needs to compare the characteristics of participants with those who were nonparticipants but met study criteria for randomization. Because Jha et al. do not have access to data that would allow this comparison, they cannot show true selection bias. Additionally, observational studies, such as this one, which attempt to show outcome differences, must adjust for case mix of the different patient groups. The authors duly note that outcome in acute myocardial infarction is highly dependent on a number of physiologic variables, such as admission heart rate, blood pressure and Killip class. None of these data were available for nonparticipants. In the absence of these data, it is difficult to determine whether outcome differences occurred due to differences in treatment received or because of differences in unmeasured baseline characteristics.

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Reply

In part, Sada simply echoes a caveat that we presented along with our findings, namely, that better characterization of patients would be important to explain observed outcome differences (1). We also agree that examination of eligibility for thrombolysis in all participants would be the most rigorous way to pin down selection bias. That is where the agreement ends.

Sada would have us believe that thrombolysis eligibility alone accounts for the observed differences between trial participants and nonparticipants. Ironically, one of the references (2) he cites to support his argument was actually a meticulous dissection of the extent of underutilization of thrombolysis, wherein the authors championed the importance of treating elderly patients and those presenting 6 to 12 h from symptom onset. The second study cited by Sada was by Cragg et al. (3). It examined patients presenting to one center between

1986 and 1988, stated that only 16% of the patients were treated with thrombolytics and cited a whole series of now-obsolete criteria as reasons for deeming patients ineligible for treatment. Among those criteria were age >76 years, presentation >4 h from symptom onset, any previous coronary artery bypass surgery, angioplasty in the preceding 2 weeks and left bundle branch block. We are puzzled as to why Sada cited this study; but having cited it, he might at least have got the authors' message right. Cragg et al. (3) directly challenged the age limits on enrollment in thrombolysis trials as likely to cost many lives and also wrote: "Apart from the significant age difference, why protocol-treated patients had such low-risk characteristics was unclear; the inclusion and exclusion criteria did not specifically preclude enrollment for patients with many of these high-risk characteristics."

The evidence for underuse of thrombolytic therapy among elderly patients continues to roll in. The most recent study (4) in 11 European countries showed that up to 55% of patients with acute myocardial infarction were eligible for thrombolysis. However, compared with those >65 years old, the odds ratios for use of thrombolysis among eligible patients by age bracket were as follows: 65 to 74 years, 0.55 (95% confidence interval [CI] 0.34 to 0.89); 75 to 84 years, 0.24 (95% CI 0.14 to 0.40); and >85 years, 0.04 (95% CI 0.02 to 0.10).

As our article suggested (4), it seems plausible that arbitrary enrollment restrictions in early trials shaped the early perceptions of eligibility for thrombolysis, and these biases have continued to influence patient selection in both newer trials and ordinary practice. The causes, effects and epiphenomena are hard to tease apart; and more studies are needed. However, what matters now is optimizing the use of thrombolysis around the world and ensuring that any new therapies for acute myocardial infarction are tested in a proper spectrum of low and high risk patients of all ages.

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