REPLY

My fellow authors and I appreciate the comments expressed in Dr. Horvath's letter, which largely claim that the sole reason for the negative results demonstrated in our study (1) relates to procedural differences between surgical versus percutaneous transmyocardial laser revascularization (TMR). Although we acknowledged in our study that full-thickness transmyocardial laser channels at surgery are indeed different from smaller non–full-thickness catheter-based transcendocardial channels (1), we believe strongly that our blinded study accurately highlights the potent placebo effects in this patient population. As such, this causes us to doubt the clinical benefits referenced in the surgical TMR literature. Our reasons are as follows: 1) of the 17 surgical TMR studies cited in our study (11 observational studies and 6 randomized trials vs. “best” medical therapy), the main benefit is subjective improvement in angina class, and in most studies performing quantitative ischemia assessments (such as nuclear perfusion imaging) there were no improvements after surgical TMR. 2) Without controlling for the placebo effects, the nonblinded percutaneous TMR literature also showed the same magnitude of subjective angina improvement as seen with surgical TMR, which in our study was neutralized in the presence of a sham control group. 3) There is no plausible and scientifically creditable explanation for the anti-ischemic actions of percutaneous or surgical TMR, as the prevailing theories of patent channels, epicardial denervation, and local angiogenesis have not been validated in experimental models or in patients.

To compound matters, in a retrospective analysis from the Society of Thoracic Surgeons (STS), the National Cardiac Database identified 3,717 patients at 173 U.S. hospitals who had received surgical TMR procedures over a 4-year period, and of these procedures, only 17% were TMR alone, whereas 67% were surgical TMR procedures. The National Cardiac Database validated in experimental models or in patients.

Finally, based on our disquieting experiences with percutaneous TMR in our study, we would strongly urge additional validating, blinded, randomized clinical trials to examine the safety and efficacy of combined TMR + CABG before widespread clinical use is advocated in the “real world.”

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REFERENCES


How Does Caffeine Increase Exercise Capacity But Decrease Myocardial Flow Reserve?

I read with interest a recent report by Namdar et al. (1) entitled, “Caffeine Decreases Exercise-Induced Myocardial Flow Reserve.” The investigators highlighted some study limitations but failed to mention the potential order effect with the dosing of caffeine. All subjects in both groups completed the exercise testing without caffeine ingestion first and then repeated the testing 1 h later following a 200-mg dose of caffeine. Previous research by our group has shown that prior exercise alters the sensitivity of users of caffeine and makes them respond like caffeine-naive subjects during subsequent exercise tests (2). This effect of previous exercise was evident 5 h following the earlier exercise challenge, as we had also previously demonstrated that the ergogenic effect of a 5-mg/kg dose of caffeine lasted for 6 h for caffeine-naive subjects in contrast to the shorter 3-h benefit noted for caffeine users (3). The adenosine receptor sensitivity, therefore, may have been altered before the caffeine exercise test. A better design perhaps would have been to increase subject numbers and assign subjects to a placebo or caffeine group where subjects were matched according to fitness and caffeine habituation.

Namdar et al. (1) also make no reference to the exercise science literature that has reported a fairly consistent ergogenic effect of caffeine on exercise performance with no evidence of altered oxygen consumption or cardiac output (4), and that caffeine has been shown to demonstrate its ergogenic effect even more so during acute hypobaric exposure (5,6). Exactly how the findings from this current study can be viewed in terms of this other literature is puzzling.

Finally, care must also be taken in the generalization of findings with the ingestion of caffeine to the consumption of coffee. We know that other ingredients in coffee may interfere with the ergogenic effect of caffeine (7) and these other ingredients can also counter the negative effects of caffeine on glucose tolerance (8–10).

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doi:10.1016/j.jacc.2006.09.012

REFERENCES


**REPLY**

Dr. McLellan points out that exercise has been shown to make subjects respond to subsequent exercise like caffeine-naïve subjects. We welcome this information, which seems to further strengthen our results (1), as it confirms that the sensitivity to caffeine is more pronounced during exercise.

However, based on our power calculation we cannot support the statement that increasing the study population and splitting it up into placebo and caffeine groups would have improved the quality of the study; as with the crossover design, each subject served as its own control, an advantage that would have been lost following the advice of Dr. McLellan.

Although some positive effects of caffeine on exercise performance might have been reported in studies more than 2 decades ago (as cited by Dr. McLellan), this seems to be challenged by more recent experiences, which have led to removing caffeine from the doping list (2). We remain reluctant to comment on this, however, based on our power calculation we cannot support the statement that increasing the study population and splitting it up into placebo and caffeine groups would have improved the quality of the study; as with the crossover design, each subject served as its own control, an advantage that would have been lost following the advice of Dr. McLellan.

Furthermore, it has been brought to our attention that the values for mean arterial pressure (MAP) in Table 1 of our report were regrettably incorrect. The correct values are given in the revised table (Table 1).

References


Management of Women With Acute Coronary Syndromes

In a recent study published in the *Journal*, Anand et al. (1) show that women with acute coronary syndromes underwent less coronary angiography and revascularization and had a higher rate of refractory ischemia and rehospitalization than their male counterparts. It is important to understand that these statements are true—true, but not necessarily related. The difference in total revascularization rates in high-risk female and male populations was only 2.5%; this rate difference could not negate the 8.6% difference in refractory ischemia/revascularization rates between genders. Indeed, there is no direct evidence that increasing the revascularization rate would change outcomes in these women. As Anand et al. (1) point out, there is a relative paucity of information regarding the appropriate treatment of coronary artery disease in women. Moreover, their data demonstrate the conundrum physicians face—namely, that women have a lower prevalence of disease but are harder to treat successfully.

Treatment mores demand that a treatment be of proven efficacy and acceptable harm. If a physician hesitates in applying treatment recommendations that are proven for men but not for women, to a female patient, is that gender bias or good evidence-based

### Table 1. Hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Normoxia (Baseline)</th>
<th>Caffeine</th>
<th>p</th>
<th>Normoxia (Baseline)</th>
<th>Caffeine</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SBP (mm Hg)</td>
<td>124 ± 12</td>
<td></td>
<td>120 ± 11</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DBP (mm Hg)</td>
<td>73 ± 10</td>
<td></td>
<td>71 ± 11</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MAP (mm Hg)</td>
<td>90 ± 9</td>
<td></td>
<td>87 ± 8</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR (beats/min)</td>
<td>66 ± 13</td>
<td></td>
<td>65 ± 11</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RPP (mm Hg × beats/min)</td>
<td>8,179 ± 1,933</td>
<td>7,771 ± 1,037</td>
<td>NS</td>
<td>9,996 ± 2,265</td>
<td>9,860 ± 3,362</td>
</tr>
</tbody>
</table>

**Corrections**

4N S8 9
11 NS 8
6 NS 9
8 NS 8
8 NS 9
4N S8 8
12 NS 12
8 NS 12
6 NS 12
2,360 NS 25,591

**References**


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