Letters to the Editor

Ischemia-Modified Albumin and Myocardial Ischemia

Sbarouni et al. (1) reported on "Ischemia-Modified Albumin [IMA] in Relation to Exercise Stress Testing [EST]" in a previous issue of the *Journal*. Although the investigators found significant differences in the IMA values at baseline, peak exercise, and after EST, there was no relation between the IMA changes and the result of the EST. The researchers stated that changes in IMA levels do not reflect myocardial ischemia and that IMA does not seem to improve the accuracy of EST. Although these are highly interesting results, some important points must be considered in this study.

Previous studies have shown that IMA is a marker of myocardial ischemia, and it was accepted that IMA is an early marker to help in ruling out patients with acute coronary syndrome (2,3). Interestingly, Sbarouni et al. (1) concluded that IMA levels do not indicate myocardial ischemia different from these other studies. False negative and false positive results of exercise testing are important clinical problems in diagnosis of coronary artery disease (CAD). The sensitivity and specificity of EST range between 60% and 70% (4,5). Approximately 30% to 40% more false negative results may be obtained in clinical practice. Therefore, each positive EST is not accepted as a sign of myocardial ischemia. However, in the study by Sbarouni et al. (1), a positive stress test is accepted as indicative of myocardial ischemia. It is not mentioned how many patients with positive EST have myocardial ischemia. In our opinion, lack of this important information may change the study results.

Other conflicts and controversial subjects are related to results from postexercise IMA levels. Because plasma IMA levels increase within minutes after myocardial ischemia, peak exercise IMA levels may not indicate myocardial ischemia. However, postexercise IMA levels may be helpful to determine myocardial ischemia during exercise. Previously, it was demonstrated that IMA levels decrease after physical exercise, and it was hypothesized that this immediate decrease may have been attributable to interference in the IMA measurement by lactate produced during skeletal muscle ischemia (6,7) However, release of lactate after EST in patients with peripheral vascular disease has been reported (8) Although Sbarouni et al. (1) concluded that a decrease in IMA levels is associated with hemoconcentration, it was unknown whether peripheral vascular disease was present in the study population. Therefore, possible peripheral vascular disease in patients may affect IMA levels via increased lactate concentration.

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Ischemia-Modified Albumin: The Importance of Oxidative Stress

We read with interest the recent study by Sbarouni et al. (1) which adds to the growing body of evidence regarding ischemia-modified albumin (IMA). Interestingly, in their study, the IMA levels dropped significantly at peak exercise in both patients with positive and negative exercise stress-test responses, suggesting that the observed changes in IMA levels may not reflect myocardial ischemia. In addition to Sbarouni et al. (1), other investigators have previously shown reduced IMA levels immediately after exercise in different clinical conditions: for example, exercise-induced skeletal muscle ischemia in patients with peripheral vascular disease (2) and induced forearm ischemia in normal volunteers (3). The possible explanations for the observed IMA changes after exertion include an increase in albumin levels due to hemoconcentration and the resultant decrease in the nonbound portion of cobalt. It has also been suggested that this immediate decrease in IMA concentration may be attributable to interference with the IMA measurement by lactate produced during skeletal muscle work or ischemia. These findings are important for 2 main reasons: 1) they may cast doubt as to whether IMA changes are truly representative of cardiac ischemia in patients with chest pain,

and 2) they raise issues as to the nature of the true stimulus for an increase in IMA concentrations in patients with chest pain.

There is little doubt, if any, that IMA levels increase during myocardial ischemia triggered by a primary reduction of blood flow, as seen in patients during percutaneous coronary intervention (PCI). Several studies have shown a good correlation among objective markers of myocardial ischemia, such as lactate levels (4) isoprostane concentrations (5) and IMA levels, in this setting. We have therefore suggested that increased IMA levels may result from increased oxidative stress whether caused by ischemia reperfusion injury or other mechanisms linked to primary reductions of coronary blood flow (5) or muscle damage (6). Indeed, results from in vitro work from our group support this hypothesis and suggest that the generation of reactive oxygen species can at least transiently modify the N-terminal region of albumin to yield increased levels of IMA (7). It is conceivable that the greater the magnitude of reactive oxygen species formation the higher the elevation of IMA levels. The production of reactive oxygen species during balloon occlusion and reperfusion in patients undergoing PCI (8) and in the acute coronary syndrome setting (9)—where intracoronary thrombosis causes serious reductions in coronary blood flow—may result in the chemical modification of albumin that leads to IMA production. Increased oxidative stress production in these circumstances, together with the lack of antagonistic influences to IMA measurements that appear to occur during skeletal muscle exercise (1–3), can explain the consistent finding of increased IMA levels. Increased oxygen free-radical production, however, is commonly found in a wide variety of medical conditions other than myocardial ischemia, and this may at least partly explain both IMA's baseline variability and relatively low specificity (9).

Further studies are required to understand the mechanisms leading to increased IMA levels in different clinical conditions of myocardial ischemia and nonischemic conditions. Moreover, future research should be specifically targeted toward identifying the exact nature of albumin modification and the reasons for the intriguing findings in relation to exercise, as reported by Sbarouni et al. (1). Only when these vital mechanisms are elucidated, should clinical studies be carried out to explore the true potential role of this marker in clinical practice.

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Reply

We appreciate the interest of Dr. Kalay and colleagues in our study assessing ischemia-modified albumin (IMA) levels in exercise stress testing (1). We address their comments:

1. All our patients had angiographically documented coronary artery disease, the exercise stress test (EST) being part of their regular follow-up, and the criteria we used for positivity were rather strict—2-mm horizontal or downsloping ST depression. In addition, our findings do not differ from Van der Zee et al. (2), who also observed a significant decrease of IMA plasma levels at peak exercise and subsequent return to baseline, without any difference between positive and negative exercise tests. In that study, single-photon emission computed tomography (SPECT) imaging, a more sensitive and specific method compared to treadmill testing, was used. Therefore, in that respect, we believe inaccuracies in the EST results (false positive or negative) cannot be substantiated.
2. Regarding the timing of IMA sampling, percutaneous coronary intervention (PCI) studies have shown a significant increase in IMA plasma levels immediately following balloon deflation and a return to baseline within 6 to 12 h (3,4), so we would think that peak exercise is the appropriate time point to assess whether IMA increases in exercise-induced ischemia.
3. Although we cannot exclude occult peripheral atherosclerosis in our patients, none of the study participants had clinically significant peripheral vascular disease, by history, physical examination or clinical presentation. Additionally, in no patient was the EST limited by skeletal muscle ischemia, rendering the mechanism of peripheral lactic acidosis as a cause of decreased exercise IMA levels extremely unlikely. Furthermore, a very recent report observed that the rise in IMA plasma levels after PCI parallels that of transmyocardial lactate, immediately after obstructive balloon inflation (5).

In the letter by Drs. Roy and Kaski regarding our study (1) they state that IMA decrease at exercise may relate to either albumin or lactate increase. Albumin plasma levels have been