REFERENCE

1. Malouf JF, Enriquez-Savano M, Pellikka PA, et al. Severe pulmonary hypertension in patients with severe aortic valve stenosis: clinical profile and prognostic implications. J Am Coll Cardiol 2002;40:789–95.

REPLY

We appreciate the interest of Dr. Rahimtoola in our study of pulmonary hypertension in patients with aortic stenosis (1), and we appreciate his comments underscoring the importance of the data. Unfortunately, it was not possible to present all the data we collected as space is limited by the *Journal*. Below are the responses to the specific queries made:

1. Left ventricular ejection fraction was derived by two-dimensional echocardiography using visual estimate in all patients and combining it to M-mode measurements in 23 patients (49%). This approach has been proven in previous studies to be highly predictive of outcome, at least as well as angiography (2).
2. The mean ± SD (range) Doppler-derived calculations of the pulmonary artery systolic pressure (PASP) assuming a mean right atrial pressure of 10 mm Hg were:

   79.5 ± 8.0 mm Hg (74–106) for the entire group

   82.0 ± 11.6 mm Hg (74–106) for the No-AVR (aortic value replacement) group

   78.8 ± 6.8 mm Hg (74–102) for the AVR group

These data confirm, irrespective of the estimated right atrial pressure, that the pulmonary hypertension in our study population was indeed severe.

3. With regard to coronary disease, 34 patients (72%) underwent selective coronary angiography—AVR group, 32 patients (86%); No-AVR group, 2 patients (20%). These rates are well expected, as the small but definite risk of coronary angiography is not warranted in patients who either refuse surgery or are not considered candidates for surgery.

A total of 19 patients had initially unprotected obstructive coronary artery disease—17 among the AVR-group patients, all of whom underwent coronary artery bypass graft surgery (CABG). The remaining 15 patients (all in the AVR group) had either normal or minimally diseased coronary arteries (12 patients) or patent grafts from prior CABG (3 patients). The five-year survival rate of AVR patients who underwent CABG (58%, SE 0.16) was not significantly different (p = 0.87) from that of AVR patients without obstructive coronary disease on angiography, including those with previous bypass and patent grafts (48%, SE 0.18). Moreover, there was no significant difference in the severity of pulmonary hypertension between these two AVR subgroups (PASP 78.4 ± 4.8 mm Hg [74–87] for isolated AVR patients vs. 79.6 ± 8.7 mm Hg (74–102) for AVR patients who needed CABG; p = 0.9). This suggests that the poor outcome in this subset of patients is indeed the result of pulmonary hypertension rather than that of coronary disease.

4. The five-year survival (mean ± SE) for AVR patients, including operative mortality, was 48 ± 12%; the p value in comparison to expected survival was <0.0001. Indeed, despite treatment, this group is at high risk, although less than historical controls with similar levels of pulmonary hypertension but no aortic stenosis (AS) (3). Hence, an important conclusion of our study is that it is essential that patients be operated on before they reach such a considerable level of pulmonary hypertension. Nevertheless, as operative results continuously improve, the postoperative survival excluding operative mortality, in our mind, is also important and supports hope of a better outcome for patients with AS and severe pulmonary hypertension who otherwise are at very high risk.

We appreciate the interest of Dr. Rahimtoola, which allows underscoring further the importance of detecting pulmonary hypertension in patients with aortic stenosis.

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Coronary Atherosclerosis and Body Iron Stores

We read with great interest the study by Gaenzer et al. (1) in a recent issue of the *Journal*. The investigators studied associations between iron status and early functional and structural vascular abnormalities in patients with hereditary hemochromatosis and found that impaired endothelial function and increased intima-media thickness (IMT) may be associated with iron overload, with subsequent induction of oxidative stress. Gaenzer and colleagues suggested that iron-depletion therapy, which normalizes endothelial function, may reduce the increased risk of cardiovascular events.

A possible association between body iron status and the risk of coronary heart disease was first supported by findings from a Finnish study relating increased levels of both serum ferritin and dietary iron to an increased risk of myocardial infarction in men (2). It is believed that inflammation and oxidation are important mechanisms involved in the complex pathological process of atherogenesis (3). Free radical production is catalyzed and accel-

erated in the presence of iron (4) and this has been used as a possible explanation for the higher incidence of ischemic heart disease in young and middle-aged men compared to premenopausal women, as ferritin concentrations are three times higher in men than in premenopausal women (5). In contrast, more recently published data, like the studies by Aronow (6), Moore et al. (7), and Ascherio and colleagues (8), do not support the hypothesis of a relationship between serum ferritin and atherosclerosis risk.

It is noteworthy that the putative role of iron in the development of atherosclerosis is based primarily on clinical and epidemiological studies. However, only few reports investigating correlations between serum concentration of ferritin and anatomic diagnosis of coronary atherosclerosis assessed by coronary arteriography are available in the published data. We (9) could recently demonstrate that, in patients referred for coronary angiography, higher ferritin concentrations and transferrin-saturation levels (as measures of the amount of circulating iron available to tissues) are not associated with an increased extent of coronary atherosclerosis (as assessed angiographically). In that study (9), estimates of the relative risk of coronary heart disease for the quintile with the highest concentration of serum ferritin as compared with the lowest quintile were 0.83 (95% confidence interval, 0.63 to 1.24).

Another important point seems to be that all the iron indicators used to relate iron status to coronary artery disease (CAD) are affected by inflammation. As a result, an association between CAD and higher serum ferritin levels could be confounded by inflammation (10). A shortcoming of the study by Gaenzer et el. (1) is the lack of information on inflammatory markers such as C-reactive protein.

In summary, early functional and structural vascular abnormalities in patients with hereditary hemochromatosis may predict both extent of coronary atherosclerosis and the risk of cardiovascular events in this particular patient group, but in subjects without hereditary hemochromatosis our results and data from others do not support the hypothesis that body iron stores, as measured by serum ferritin and transferrin saturation, are related to the risk of CAD. In patients with hereditary hemochromatosis, enhancement of atherogenesis may involve additional mechanisms beyond iron.

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REPLY

We agree with Dr. Auer and colleagues that ferritin levels in our study (1) may be both a reflection of increased iron stores linked to primary iron overload and an indication of a chronic inflammation, as ferritin expression is also regulated by inflammatory cytokines (2,3).

To rule out the possibility that increased ferritin levels in hemochromatotic patients are a reflection of an ongoing inflammatory response we performed conventional serum tests for C-reactive protein (CRP), which were all normal in the hemochromatotic subjects included in our study. However, we cannot rule out that by using a high-sensitive CRP assay we could have found low-grade inflammation not detected by the conventional test (4), which would have been of interest because, at least in diabetics, elevated levels of CRP have been associated with early structural changes of arteries (5) and because iron is known to increase formation of hydroxyl radicals during an inflammatory process (6), which will then exert harmful effects toward the endothelium.

However, in our study, changes in endothelial-dependent dilation (EDD) very well correlated with transferrin saturation in a way that higher transferin saturation (TfS) was associated with increased oxidative stress, increased intima-media thickness, and decreased EDD. This observation argues against an important role of inflammation in our setting. This notion is based on the fact that, during inflammation, drastic changes in iron homeostasis and distribution occur, which frequently lead to the development of anemia of chronic disease (7). This condition is characterized by high ferritin levels and low transferrin saturation, the later just being the opposite of what is observed in hemochromatotic patients, even in our study.

Finally, our data demonstrate a close relationship among iron overload, impaired EDD, and increased intima-media thickness, which may not be primarily referred to an underlying inflammatory condition. Nonetheless, determination of high-sensitive CRP will be attractive to see whether iron overload may induce low-grade inflammation in hemochromatotic patients.