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LETTERS TO THE EDITOR

Hypertension and the Prothrombotic State

We read with interest the report by Pini et al. (1) that stated patients with isolated systolic hypertension had a higher prevalence of cardiac hypertrophy and carotid atherosclerosis than did those with diastolic hypertension. Indeed, hypertensive left ventricular hypertrophy is the most evident manifestation of hypertensive target organ damage, and such patients are at particularly high risk for strokes and heart attacks. We would like to propose an additional interpretation of their important observations.

Despite the vessels being exposed to high pressures, the main complications of hypertension (strokes, myocardial infarction) are, paradoxically, thrombotic rather than hemorrhagic — the so-called thrombotic paradox of hypertension or the Birmingham paradox (2). The findings by Pini et al. (1) would actually strengthen our view that hypertension confers a prothrombotic or hypercoagulable state by fulfilling the three different components of Virchow's triad for thrombogenesis. With regard to the latter, there ought to be changes in the blood flow, changes in the vessel wall, and changes in the blood constituents, for increased thrombogenesis. "Abnormal flow" is evident in hypertension, with blood vessels exposed to blood flow under high pressures, as well as abnormal coronary flow reserve and microcirculatory changes (3). We had previously reported abnormalities in prothrombotic factors, endothelial function, and platelet activation in patients with isolated systolic hypertension, comparable to that observed with systolic–diastolic hypertension (3–5).

The study by Pini et al. (1) certainly confirms the presence of "vessel wall abnormalities" with the high prevalence of cardiac hypertrophy and carotid atherosclerosis. Furthermore, hypertensive patients with target organ damage (5) show evidence suggestive of an even greater prothrombotic state, which would contribute to the high risk of vascular complications in such patients.

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REPLY

I have read the interesting letter by Profs. Nadar and Lip. Their speculation on the results of our study adds an additional interpretation of our data. However, our study focused on cardiac and vascular remodeling rather than on prothrombotic factors; thus, because we did not analyze whether isolated systolic hypertension was associated with direct evidence of a prothrombotic state we cannot provide substantive comments on the interesting speculations of Profs. Nadar and Lip.

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Questions Remain Regarding Patients With Aortic Stenosis and Severe Pulmonary Hypertension

Malouf et al. (1) have presented data in an uncommon but clinically important subgroup of patients with severe aortic stenosis and severe pulmonary hypertension. In their study, one subgroup of patients had aortic valve replacement and another was treated medically. The data are very interesting and important.

However, to understand fully the study groups and their outcomes, the investigators need to present additional information about the two subgroups:

1. How was left ventricular ejection fraction measured?
2. What was the actual calculated pulmonary artery systolic pressure (PASP) (mean ± SD, and range)?
3. What were the number and percentage of patients who underwent selective coronary arteriography? Of those who underwent coronary arteriography, what were the number and percentage who had significantly obstructive coronary artery disease? Also, did all patients with significantly obstructive coronary artery disease have coronary bypass graft surgery? It should be noted that the mean patient age was 78 ± 8 years.
4. What was the five-year survival, including operative mortality (mean ± SE) and the p value for the difference in survival?

These investigators are to be congratulated on this valuable study in a group of patients in whom additional data were needed.

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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-