Exercise first-pass radionuclide ventriculography in detection of coronary artery disease

Sir,

We read with interest the paper by Stone and his colleagues¹ on the detection of coronary artery disease by the method of exercise first-pass radionuclide angiography. We were, however, puzzled by the criteria used for an abnormal exercise response.

These are quoted as the development of a new regional wall motion abnormality, a post-exercise ejection fraction of <50%, or a fall in ejection fraction of at least 10%. It is not stated if this is an absolute fall of 10% (for example 50% to 40%) or a relative fall from the initial level (for example 50% to 45%). Most importantly, the data from which these criteria were derived are not presented, though eight normal patients were studied. The results for these eight subjects were summarised as a mean rise of ejection fraction from 72.1% to 73.5% after exercise, but details of the individual responses are not given.

Others using similar first-pass techniques have demonstrated that the ejection fraction in patients with proven ischaemic heart disease may remain unchanged or even rise after exercise, while normal controls invariably have a significant increase (that is $\geq 5\%$ absolute), leading to the conclusion that an abnormal response may be not only a fall of exercise ejection fraction, but a failure of it to increase adequately.²⁻³ Patients with ischaemic heart disease who did not experience chest pain at the end-point of exercise are more likely to maintain or increase their ejection fraction.

These investigators performed their studies in the erect posture (surely more physiological than supine); further workers, however, using the gated acquisition method of radionuclide angiography have performed supine exercise studies.⁴⁻⁵ These have also shown that exercise in patients with ischaemic heart disease may be associated with a rise in ejection fraction. High resting levels may be associated with no augmentation after exercise even in normal subjects, and one study⁶ has suggested that the degree of augmentation may decrease with age, though this may be an artefact of covert heart disease, as many of the older subjects had wall motion abnormalities. The criterion for an

abnormal exercise response in our laboratory⁷⁻⁸ is failure to augment the ejection fraction by at least 5% (absolute units), except where the resting level is $\geq 75\%$, when any fall is deemed abnormal. The normal subjects of Stone and his colleagues had a very high mean resting level (72.1%) and it would be interesting to see whether the individual data conformed to these criteria. Thirty-two of their 34 patients would be abnormal judged by ejection fraction alone.

The development of angina during exercise in all of them suggests that they were a highly selected group. The statement that this technique is "valuable in the screening . . . of patients with heart disease" may be correct, but seems unwarranted based solely on this limited study in a highly selected population.

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References

- 1 Stone D, Dymond D, Elliott AT, Britton KE, Banim SO, Spurrell RAJ. Exercise first-pass radionuclide ventriculography in detection of coronary artery disease. *Br Heart J* 1980; **44**: 208-14.
- 2 Berger HJ, Reduto LA, Johnstone DE, *et al*. Global and regional left ventricular response to bicycle exercise in coronary artery disease. *Am J Med* 1979; **66**: 13-21.
- 3 Rerych SK, Scholz PM, Newman GE, Sabiston DC Jr, Jones RH. Cardiac function at rest and during exercise in normals and in patients with coronary heart disease. *Ann Surg* 1978; **187**: 449-64.
- 4 Borer JS, Bacharach SL, Green MV, *et al*. Real-time radionuclide cineangiography in the noninvasive evaluation of global and regional left ventricular function at rest and during exercise in patients with coronary-artery disease. *N Engl J Med* 1977; **296**: 839-44.
- 5 Caldwell JH, Hamilton GW, Sorensen SG, Ritchie JL, Williams DL, Kennedy JW. The detection of coronary artery disease with radionuclide techniques: a comparison of rest-exercise thallium imaging and ejection fraction response. *Circulation* 1980; **61**: 610-9.

- 6 Port S, Cobb FR, Coleman RE, Jones RH. Effect of age on the response of the left ventricular ejection fraction to exercise. *N Engl J Med* 1980; **303**: 1133-7.
- 7 Berger HJ, Johnstone DE, Sands JM, Gottschalk A, Zaret BL. Response of right ventricular ejection fraction to upright bicycle exercise in coronary artery disease. *Circulation* 1979; **60**: 1292-300.
- 8 Berger HJ, Matthay RA, Pytlik LM, Gottschalk A, Zaret BL. First-pass radionuclide assessment of right and left ventricular performance in patients with cardiac and pulmonary disease. *Simin Nucl Med* 1979; **9**: 275-95.

This letter was shown to Dr Stone and his colleagues who reply as follows.

Sir

Drs Marx, Berger, and Zaret have raised some interesting points about the role of exercise radionuclide ventriculography in the detection of coronary artery disease and in the discrimination between normality and abnormality. The development of new regional wall abnormalities on exercise has been shown to be a sensitive marker for the detection of coronary artery disease.^{1,2} Criteria based on changes in ejection fraction have to consider: (1) reference values for normal individuals and (2) the intrinsic variability in the technique used for imaging. The eight normal individuals in our paper³ did show a small mean rise of ejection fraction on exercise though five of the patients demonstrated small decreases in ejection fraction of no greater than 5% absolute. Marx and his colleagues state that any decrease in ejection fraction is deemed abnormal when the resting level of ejection fraction is greater than 75%. We suggest that this does not take into account the intrinsic error or variability of the technique, and the change in ejection fraction from, for example, 75% to 71%, could certainly be within the error of the technique and not necessarily a true decrease. Using their criteria, six of our eight normal patients would be classified as abnormal.

As the Yale group correctly points out, some patients with proven coronary artery disease may show a rise in ejection fraction on exercise. The claim, however, that normal controls invariably have a significant increase in ejection fraction is not borne out by careful evaluation of the published reports. The study by Rerych *et al.*,⁴ referred to by Marx and his colleagues, reported the response in 30 normal individuals undergoing upright bicycle exercise. Three of these patients (10%) did not show the 5% increase in absolute ejection fraction demanded by the Yale laboratory, and one of their patients in fact showed a small decrease in ejection fraction on exercise. Similarly, in another study, nine of 39

healthy male volunteers showed a decrease in ejection fraction at maximal exercise.⁵ The point is well made, however, that the resting level of ejection fraction in normal subjects may dictate the magnitude of response to maximal exercise. The mean resting ejection fraction in our group of normal subjects was similar to the group reported by Osbakken *et al.*⁶ in which normal subjects with high resting ejection fraction failed to increase their ejection fraction on exercise.

The criteria which we used to define abnormality in our group of patients were thus selected to provide the maximum discriminatory value between normal and abnormal. We are glad to have the opportunity to make it clear that an absolute decrease of 10% in ejection fraction was required for abnormality, not a relative decrease from the initial level. Using these criteria, we found a 73% sensitivity for patients with single and double vessel disease and a 95% sensitivity for detecting triple vessel disease. These criteria provide maximum specificity in addition to high sensitivity.

Another important factor in determining the response to exercise is the imaging and exercise procedure performed in each individual laboratory. Berger and colleagues² imaged their patients in the upright position at the moment exercise was terminated. We have used a similar procedure in the supine position to minimise motion artefact during imaging. We concede that upright exercise is more physiological than supine exercise, but in our laboratory the best reproducibility has been obtained with supine imaging which minimises variations in patient-detector relation.

From a purely physiological viewpoint, imaging should be carried out during peak exercise, which is when patients develop their symptoms, rather than at the moment exercise is stopped. Temporal variations in the performance of the exercise study also have a profound influence on the response of ejection fraction. Foster *et al.*⁷ have recently shown that in normal subjects mean ejection fraction may not increase during peak exercise but universally increases at the moment exercise stops. These differences in imaging procedures may also partially explain the different responses of normal subjects obtained from various laboratories.

Finally, the development of angina in all of our patients may suggest that they were a selected group. In the experience of Berger *et al.*,² angina did affect the sensitivity of the technique. On the other hand, Borer *et al.* found abnormalities in patients with and without angina. Our study was designed to test the sensitivity of the technique in patients with proven ischaemic heart disease. We agree that its use as a screening test does depend upon its application to the appropriate population⁸ which is clearly the next stage in its

assessment now that its value in patients with known coronary disease has been demonstrated.

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References

- 1 Borer JS, Bacharach SL, Green MV, Kent KM, Epstein SE, Johnston GS. Real-time radionuclide cineangiography in the noninvasive evaluation of global and regional left ventricular function at rest and during exercise in patients with coronary-artery disease. *N Engl J Med* 1977; **296**: 839–44.
- 2 Berger HJ, Reduto LA, Johnstone DE, *et al.* Global and regional left ventricular response to bicycle exercise in coronary artery disease. *Am J Med* 1979; **66**: 13–21.
- 3 Stone D, Dymond D, Elliott AT, Britton KE, Banim SO, Spurrell RAJ. Exercise first-pass radionuclide ventriculography in detection of coronary artery disease. *Br Heart J* 1980; **44**: 208–14.
- 4 Rerych SK, Scholz PMM, Newman GE, Sabiston DC Jr, Jones RH. Cardiac function at rest and during exercise in normals and in patients with coronary heart disease. *Ann Surg* 1978; **187**: 449–64.
- 5 Foster C, Anholm JD, Pollack ML, *et al.* Responses to graded exercise testing with radionuclide angiography in apparently healthy individuals (abstract). *Med Sci Sports Ex* 1980; **12**: 117.
- 6 Osbakken MD, Merrill D, Boucher CA, Okada RD, Strauss HW, Pohost GM. Low end systolic volume at rest – an explanation for failure of increase in ejection fraction during exercise in normal patients (abstract). *J Nucl Med* 1980; **21**: p7.
- 7 Foster C, Anholm J, Hellman C, Carpenter J, Pollock M, Schmidt DH. Left ventricular function at rest, peak exercise and immediately post-exercise (abstract). *Circulation* 1980; **62**, suppl 111: 129.
- 8 Epstein SE. Implications of probability analysis on the strategy used for noninvasive detection of coronary artery disease. *Am J Cardiol* 1980; **46**: 491–9.