SCIENTIFIC LETTER

Usefulness of myocardial contrast echocardiography with nicorandil stress for the detection of coronary artery stenosis

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Heart 2006;92:1331–1332. doi: 10.1136/hrt.2005.080242

Intravenous myocardial contrast echocardiography (MCE) during pharmacological stress has emerged as a promising tool to detect myocardial perfusion abnormalities in patients with coronary artery disease (CAD). In the testing, dipyridamole or adenosine is commonly used as a stressor agent. Most patients, however, develop certain minor side effects during administration of these agents.¹ Nicorandil, a hybrid ATP-sensitive potassium channel opener and nitrate compound, has been suggested to exert a coronary vasodilatation effect with few adverse reactions.² This study tested the hypothesis that MCE with nicorandil may provide comparable diagnostic accuracy for the detection of coronary stenosis with fewer adverse reactions than with the conventional stress MCE with dipyridamole.

METHODS

This study enrolled 88 consecutive patients with suspected CAD but with no history of infarction who were scheduled for coronary angiography. The mean (SD) age of the patients was 66.3 (9.7) years. The study was approved by the hospital ethics committee and informed consent was obtained from all patients.

The patients were randomly assigned to two groups undergoing MCE: with dipyridamole infusion (dipyridamole group, $n = 44$) and with nicorandil infusion (nicorandil group, $n = 44$).

MCE was performed with ultraharmonic imaging equipped with a broadband phased-array transducer (S3) transmitting and receiving at frequencies of 1.3 MHz and 3.6 MHz. A high-power setting with various pulsing intervals (1–4 beats) was used. Images were acquired in four-, two- and three-chamber views, permitting myocardial perfusion assessment in three major vascular territories: anterior/left anterior descending coronary artery, inferior/right coronary artery and posterior/left circumflex coronary artery, respectively. As a contrast medium, Levovist (200–300 mg/ml; Schering, Berlin, Germany) was administered at a continuous infusion rate of 90 ml/h. Stress MCE images were acquired after either dipyridamole administration¹ or a bolus injection of nicorandil (Chugai Pharmaceutical Co, Tokyo, Japan). Nicorandil was diluted to 1 mg/ml with physiological saline and injected rapidly as a bolus injection (0.1 mg/kg) for 5 s, then stress images were recorded within 3 min. A regional perfusion defect was considered present when a defect that did not occur at rest developed after stress at short triggering intervals (1:1 to 1:2) and recovered after the intervals were increased.

Coronary angiography and MCE studies were performed within 24 h. Coronary angiograms were quantitatively analysed and significant coronary artery stenosis was defined as $> 70\%$ lumen diameter stenosis.

Continuous variables were expressed as mean (SD). Sensitivity and specificity for detection of coronary stenosis in the nicorandil and dipyridamole groups were calculated and compared by χ^2 tests. A value of $p < 0.05$ was considered significant.

RESULTS

Clinical characteristics did not differ significantly between the dipyridamole and nicorandil groups. Quantitative coronary angiography detected significant stenosis in 55 patients (29 in the dipyridamole group, 26 in the nicorandil group). Forty-seven patients had single-vessel disease, eight had multivessel disease and 33 were free of any significant coronary stenosis. On a coronary circulation basis (three arteries for each patient), significant stenoses were detected in 37 of the 132 arteries in the dipyridamole group and in 28 of the 132 arteries in the nicorandil group. The number or territory of stenoses did not differ significantly between the groups.

No patients had anginal symptoms or arrhythmia during dipyridamole or nicorandil infusion. Haemodynamic responses were appropriate in both stress methods. In the dipyridamole group, however, 29 (66%) of the 44 patients had minor adverse reactions (flushing, sensations of warmth, headaches), whereas no patients in the nicorandil group had adverse reactions.

The quality of the rest and stress MCE images was adequate for diagnosis in all patients. Both stress agents provided similar images, predominantly characterised by a regional defect in the endocardium rather than the epicardium (fig 1). The sensitivity of nicorandil stress to diagnose significant coronary stenosis was higher than that of dipyridamole (86% *v* 62%, $p = 0.04$) whereas specificity did not differ significantly (94% *v* 94%, NS).

DISCUSSION

Dipyridamole or adenosine stress is an established technique for the detection of coronary stenosis by inducing coronary hyperaemia. Minor side effects, however, intrinsically limit these modes of stress imaging. In contrast, nicorandil has been reported to be safe and free from adverse reactions.

Nicorandil is an antianginal drug with not only a conventional nitrate effect but also an independent potassium channel-opening effect, leading to an increase in coronary blood flow mainly through dilatation of resistant coronary vessels.² Indeed, Hongo *et al*³ and Inoue *et al*⁴ reported that intracoronary administration of nicorandil was useful for the estimation of coronary flow reserve.^{3,4} A high level of diagnostic accuracy of nicorandil stress comparable with that of dipyridamole stress in our results therefore suggests that nicorandil has similar pharmacological effects on coronary flow distribution to those of dipyridamole, which decreases coronary flow reserve in a post-stenotic area ultimately resulting in MCE defects.

We did, however, find very few adverse reactions in the nicorandil group, which may contribute to high sensitivity for the detection of coronary stenosis in nicorandil stress MCE. Intermittent high-power MCE with short pulsing intervals, the setting for CAD detection, is based on an analysis of the microbubble refill rate for each destructive ultrasound pulse.⁵ In poststenotic myocardium, blood flow velocity is

Figure 1 Perfusion defects (black arrowheads) during dipyridamole and nicorandil stress myocardial contrast echocardiography.

lower and replenishment of microbubbles into the ultrasound cross section is less than that in normal myocardium, especially during hyperaemia. Thus, post-stenotic myocardium should be identified as a hypoperfused area in MCE. If the same myocardial cross section cannot be captured because of incomplete breath holding due to adverse reactions, another cross section of the myocardium contains extraneous undestroyed microbubbles. This may lead to the overestimation of myocardial perfusion. Thus, we believe that a lower frequency of adverse reactions during nicorandil stress is one of the reasons why sensitivity was higher with nicorandil stress MCE than with dipyridamole stress MCE.

Our study showed that nicorandil stress MCE achieved a high level of diagnostic accuracy comparable with that of dipyridamole stress for the detection of coronary stenosis while minimising adverse reactions.

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Competing interests: None declared.

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Accepted 24 February 2006

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