SCIENTIFIC LETTER

Prediction of beneficial effect of β blocker treatment in severe ischaemic cardiomyopathy: assessment of global left ventricular ejection fraction using dobutamine stress cardiovascular magnetic resonance

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Patients with severe ischaemic cardiomyopathy have a combination of viable and non-viable myocardium. In the presence of substantial ischaemic, but viable myocardium, β blocker treatment may improve left ventricular ejection fraction (LVEF) because of a reduction in oxygen consumption and a restoration of β adrenergic signalling pathways. However, not all patients show a positive response to this treatment[1] and some can suffer from side effects.[2] Therefore, it is desirable to identify patients with a high likelihood of beneficial response to β blockers.

Models currently used to detect viable myocardium are based upon segmental analysis. Dobutamine induced segmental improvement before treatment is suggested to have a relation between regional contractile reserve and improvement in global LVEF after β blocker treatment. However, improvement of remote tissue is not evaluated and this may also contribute to the improvement of LVEF after treatment. Thus, direct measurement of LVEF during low dose dobutamine stimulation may represent contractile reserve of the entire left ventricle.

Cardiovascular magnetic resonance imaging (MRI) is a highly reproducible, validated, and observer independent imaging method for the measurement of global LVEF, and can be used to evaluate LVEF at rest as well as during dobutamine stress. Furthermore, Bellenger and co-workers described that calculated sample sizes for assessment of LVEF for MRI were substantially smaller than recently published values for ultrasound. The measurement of a 3% change in LVEF required only 15 patients.[3]

Accordingly, the purpose of the present study was to evaluate the feasibility for prediction of β blocker treatment effect on LVEF by MRI measurement of LVEF during low dose dobutamine, in patients with severe ischaemic cardiomyopathy.

PATIENTS AND METHODS

Patients with chronic stable coronary artery disease (CAD) ($n = 26$, average age 64 years, all men) and LVEF $< 40\%$ on resting technetium-99m single photon emission computed tomography (Tc-99m SPECT), were enrolled consecutively. Three patients refused to continue treatment because of side effects, two patients appeared claustrophobic at follow up, and one patient was unwilling to undergo repeated MRI. Previous myocardial infarction was present in all of the patients (> 4 months before entrance into the study). All patients had significant CAD on angiography (> 70% reduction in luminal diameter) and had an average of 2.1 (1) stenosed vessels. The patients did not undergo revascularisation treatment for the following reasons: the patient had poor target vessels; the patient did not qualify for revascularisation because of prior existing co-morbidity; the patient refused to undergo revascularisation. Carvedilol was started at an initial dose of 3.125 mg twice daily and was subsequently titrated, at one week intervals as tolerated, up to a target dose of 25 mg twice daily.[4] Other medications included diuretics 90%, anticoagulants 100%, angiotensin converting enzyme inhibitors 56%, nitrates 29%, digoxin 35%, calcium inhibitors 18%, and lipid lowering agents 65%. The congestive heart failure classification by the New York Heart Association (NYHA) was determined at baseline and follow up by the patient's cardiologist, who was unaware of the MRI data.

Patients were studied by MRI before starting treatment and at follow up. LVEF was determined at rest and during low dose dobutamine stress (10 μg/kg/min) before starting treatment. Each patient gave informed consent to the study protocol that was approved by the local ethics committee.

A 1.5 Tesla MRI system (Philips Medical Systems, The Netherlands) with five element synergy coil and vector ECG gating was used. The entire heart was imaged in short axis view during multiple 15 second breath holds, using a steady state free precession (field of view 400×400 mm^2, matrix size 256×256, slice thickness 10.00 mm). MRI images were analysed on a remote workstation. LVEF was calculated using MASS software (Medis, The Netherlands).

Reported data are expressed as mean (SD). Responders to β blocker treatment were defined as having an improvement in resting LVEF $\geqslant 5\%$ between baseline and follow up.[5] Differences in LVEF during dobutamine stress versus resting LVEF, both before treatment, and LVEF at follow up versus resting LVEF before treatment, were calculated. To assess intra- and inter-observer agreements, 12 patients were re-analysed and intraclass correlation coefficients (ICC) were calculated. Linear regression analysis was performed to determine the relation between these differences. When applicable, paired two tailed Student *t* tests were used, otherwise, two sample two tailed Student *t* tests were used. A probability value of $p < 0.05$ was considered significant.

RESULTS

Of the 20 remaining patients, β blocker treatment was tolerated and their target dose was reached; other medication remained unchanged. The intra- and inter-observer reliability of the LVEF measurement was excellent (ICC = 0.97 and 0.99, respectively).

Abbreviations: CAD, coronary artery disease; ICC, intraclass correlation coefficients; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; NYHA, New York Heart Association; Tc-99m SPECT, technetium-99m single photon emission computed tomography

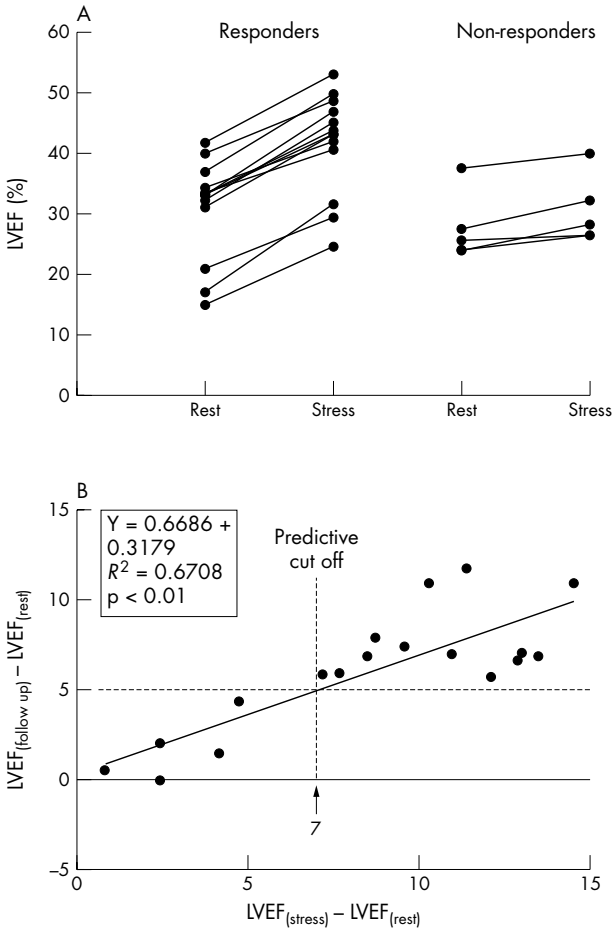

Figure 1 (A) Comparison of responders and non-responders to carvedilol treatment, showing the effect of low dose dobutamine stress before starting treatment. Note the increase in LVEF during dobutamine infusion at baseline in responders ($p < 0.01$), as compared to the modest improvement in non-responders ($p > 0.05$). (B) Linear regression analysis of the difference in LVEF during dobutamine stress versus resting LVEF, both before treatment, and the difference in LVEF at follow up versus resting LVEF before treatment.

In all patients, mean (SD) LVEF at baseline before carvedilol treatment was 31 (8)% at rest (mean LVEF according to Tc-99m SPECT was 29 (7)%), increasing to 40 (9)% ($p < 0.01$) during dobutamine infusion. After a mean of 7 (4) months of carvedilol treatment, mean LVEF at rest had improved to 37 (9)% ($p < 0.01$) compared to baseline resting LVEF. All patients had significant CAD on angiography with an average of 2.1 (1) stenosed vessels.

In responders ($n = 15$), mean LVEF had improved from mean 32 (8)% at baseline to 40 (8)% ($p < 0.01$) at follow up, whereas non-responders ($n = 5$) showed negligible improvement between baseline (28 (6)%) and follow up (29 (5)%, $p > 0.05$). During dobutamine, mean LVEF in responders increased to 42 (8)%; in non-responders to 31 (6)% (fig 1A). Figure 1B shows the relation between LVEF change caused by low dose dobutamine stress at baseline and treatment effect at follow up. Carvedilol therapeutic effect can be predicted at baseline by using the formula: β blocker induced LVEF improvement $= 0.66 \times (LVEF_{stress} - LVEF_{rest}) + 0.34$ ($R^2 = 0.67$, $p < 0.01$). An induced improvement in LVEF $\geq$ 7% predicts a positive response $\geq$ 5% at follow up.

In responders, the average NYHA improved from 2.3 (0.5) at baseline to 1.8 (0.6) at follow up ($p < 0.05$), whereas in non-responders the average NYHA did not change (2 (0) to 2 (0), not significant).

DISCUSSION

In this preliminary study, we demonstrate the feasibility of MRI to predict β blocker treatment effect in patients with severe ischaemic cardiomyopathy. The present study shows that LVEF as determined during low dose dobutamine MRI before treatment can predict the increase in LVEF after β blocker treatment in patients with severe ischaemic cardiomyopathy (fig 1B).

Currently, only contractile reserve in segments with wall motion abnormalities at rest is evaluated. With MRI measurement of LVEF during dobutamine infusion, contractile reserve of the entire left ventricle is evaluated. MRI is able to detect even small changes in the patients' LVEF because of high reproducibility.[3] To our knowledge, this is the first such study to predict response to β blocker treatment with MRI assessment of LVEF during dobutamine infusion.

The small number of patients is a limiting factor; a larger prospective study is needed to prove the validity of the prediction rule and to extend the current observations on improvement in NYHA class.

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