

SCIENTIFIC LETTER

Intensive statin treatment improves baroreflex sensitivity: another cardioprotective mechanism for statins?

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Heart 2002;88:415-416

The beneficial effect of statins is likely to result from their ability to reduce cholesterol induced atherogenesis, but novel mechanisms have also been found, such as their anti-inflammatory properties. Another possible mechanism for the benefit of statins follows from the fact that statin treatment increases the bioactivity of vascular nitric oxide (NO).¹ The importance of this relates not only to the antiatherosclerotic effect of NO but also to the recently described effect of NO on the baroreflex. Indeed, NO synthase inhibition has been shown to produce baroreceptor dysfunction in humans.² One could therefore hypothesise that statin mediated increases in vascular nitric oxide activity might also improve baroreflex sensitivity (BRS). If so, this could be a novel mechanism contributing to cardiac mortality reduction, since baroreflex dysfunction is well known to be a strong independent predictor of cardiac mortality.³

METHODS

Ten otherwise healthy men (mean (SD) age 49.5 (8.7) years) with hypercholesterolaemia (at least > 7.5 mmol/l before starting cholesterol treatment) were recruited. Each subject provided informed consent in writing and the Tayside ethics committee on medical research approved the study. Subjects were studied on four occasions separated by three, six week periods during which they rotated through usual treatment, diet only, diet plus cholestyramine, and diet plus atorvastatin 10 mg, respectively. On each study day subjects' responses to infused noradrenaline (norepinephrine) in the fasting state were determined between 0900 and 1300. Subjects adhered to their diet except before each assessment when each subject was fasted for 10 hours and abstained from alcohol, caffeine, and nicotine for 24, 24, and 2 hours, respectively. At 0900 on each study day, two 18 gauge intravenous cannulae were inserted under local anaesthetic into forearm veins, one in the right antecubital fossa, for infusions of noradrenaline, and one in the left antecubital fossa, for blood sampling. An infusion of noradrenaline was administered in stepwise 10 minute infusions (0.05, 0.10, and 0.20 µg/kg/min for 10 minutes at each dose level) by the use of an infusion pump (IMED, San Diego, California, USA). Noradrenaline was used instead of phenylephrine to test the baroreflex as it was felt to be more physiological than phenylephrine and because it had been used in a landmark study by Nickenig.⁴

Supine blood pressure and heart rate were measured in triplicate at the start for baseline value and every five minutes thereafter during the study (Dinamap critical signs monitor 1846, Critikon, Tampa, Florida, USA). The infusion was stopped if the systolic blood pressure rose by 50 mm Hg. The delta R-R interval/delta systolic blood pressure (= BRS) was plotted from points where at least a 15 mm Hg increase in systolic blood pressure had occurred. Data points associated with < 15 mm Hg systolic increase were ignored in keeping with the methodology in the landmark paper by La Rovere and colleagues.³ The resultant R-R intervals were plotted against the delta systolic blood pressure, and the computerised best fit

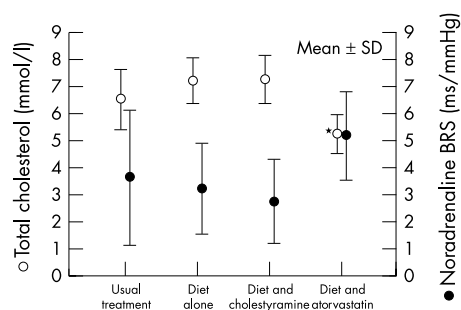


Figure 1 Effect of various cholesterol lowering treatments on total cholesterol and baroreflex sensitivity (BRS) in hypercholesterolaemic men. * $p < 0.05$ for total cholesterol and BRS.

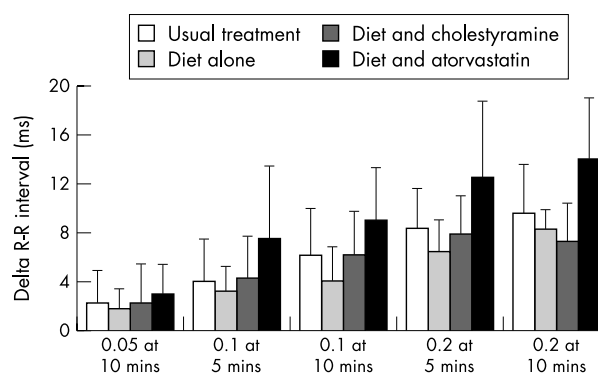


Figure 2 The effect of various cholesterol lowering treatments on the heart rate response to infused noradrenaline (µg/kg/min). Blood pressure responses to noradrenaline were identical on each of the four treatments. The gradient of delta R-R responses from dose 0.1 µg/kg/min at 10 minutes and at 0.2 µg/kg/min at 10 minutes was significantly different on atorvastatin and diet compared to the other three treatments ($p < 0.05$).

slope was used in analysis.⁵ All data were analysed using the SAS software package. A repeated measure analysis of variance was performed on the BRS data. The haemodynamic responses (blood pressure and R-R interval) were analysed by multiple comparisons Scheffe using SPSS.

RESULTS

The patients had a mean (SD) blood pressure of 125 (10)/77 (8) mm Hg, a weight of 81 (7) kg, and were aged 49 (8) years. Only after atorvastatin 10 mg was given as the final therapeutic intervention did the serum cholesterol significantly ($p < 0.05$) fall from the three previous visits (fig 1). However, the baseline blood pressure just before noradrenaline was not significantly different between all four treatments.

We found that the blood pressure response to noradrenaline was unchanged, which agrees with Nickenig and colleagues⁴ who found no significant difference in the response to infused

noradrenaline between hypercholesterolaemics and normocholesterolaemics. Despite the same blood pressure changes, the reflex bradycardiac response to noradrenaline was significantly enhanced during intensive cholesterol reduction by atorvastatin (figs 1 and 2).

DISCUSSION

Our main finding is that intensive reduction of cholesterol with atorvastatin produces a significant improvement in BRS, which is likely to be attributable to statins improving endothelial function and vascular NO. Dissecting out this effect on baroreflex sensitivity, we found that noradrenaline effects on blood pressure were completely unaffected by different cholesterol concentrations, whereas the reflex bradycardia produced was much greater in the presence of atorvastatin.

The question arises whether the atorvastatin induced improvements in BRS could contribute to the reduced mortality seen with statin treatment. The suggestion that impaired BRS is an adverse prognostic feature comes from many sources. Firstly, animal studies have shown that during coronary artery ligation, vagal stimulation dramatically reduces arrhythmias and dramatically improves survival.⁶ Secondly, clinical studies have shown that baroreflex insensitivity is independently associated with increased mortality even when corrected for different levels of left ventricular dysfunction.³ The simplistic notion which arises is that baroreflex activity reflects parasympathomimetic activity which in turn exerts an antiarrhythmic effect opposing the proarrhythmic effect of the sympathetic nervous system. Indeed, it has been suggested that increasing vagal tone should be a new therapeutic strategy.⁷ With that in mind, atorvastatin induced improvements in BRS could well contribute to the improved cardiac mortality seen with statins.

In conclusion, intensive cholesterol reduction improves baroreflex sensitivity in hypercholesterolaemic man. Such a mechanism may well contribute to the reduced mortality seen with statin treatment.

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Accepted 26 April 2002

REFERENCES

- 1 **O'Driscoll G**, Green D, Taylor RR. Simvastatin, improves endothelial function within 1 month. *Circulation* 1997;**95**:1126–31.
- 2 **Spieker LE**, Corti R, Binggeli C, *et al*. Baroreceptor dysfunction induced by nitric oxide synthase inhibition in humans. *J Am Coll Cardiol* 2000;**36**:213–18.
- 3 **La Rovere MT**, Bigger JTJ, Marcus FI. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. *Lancet* 1998;**351**:478–84.
- 4 **Nickenig G**, Baumer AT, Temur Y, *et al*. Statin-sensitive dysregulated AT1 receptor function and density in hypercholesterolemic men. *Circulation* 1999;**100**:2131–4.
- 5 **Smyth HS**, Sleight P, Pickering GW. Reflex regulation of arterial pressure during sleep in man. A quantitative method of assessing baroreflex sensitivity. *Circ Res* 1969;**24**:109–21.
- 6 **Myers RW**, Pearlman AS, Hyman RM, *et al*. Beneficial effects of vagal stimulation and bradycardia during experimental acute myocardial ischemia. *Circulation* 1974;**49**:943–7.
- 7 **Townend JN**, Litter WA. Cardiac vagal activity: a target for intervention in heart disease. *Lancet* 1995;**345**:937–8.

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At what point should ST elevation be measured?



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Junior doctors are failing to recognise ST elevation, and there are wide variations in practice, suggests UK research. Given that junior doctors usually decide who should be given thrombolytic therapy, the finding is of some concern, and perhaps the time has come for a consensus to be reached, conclude the authors.

A sample of 63 junior doctors in emergency and general medicine from three large teaching hospitals in Manchester, England, took part in the study. Each doctor was shown three ECG complexes and asked to identify and quantify the degree of ST elevation, and to mark the points at which they had measured it.

ST elevation was missed completely in 12% of cases, and a wide variety of points along the ST segment were used to assess elevation, resulting in wide discrepancies. More than four out of 10 doctors measured more than 3 mm of ST elevation in ECG 1. Six doctors used the T wave. In ECG 3, almost half the doctors measured more than 2 mm of ST elevation; only eight measured it at the J point (1.6 mm or more).

Experienced clinicians are likely to rely on pattern recognition rather than absolute measurement of the ST segment, gleaned additional clues from other information on the ECG, such as reciprocal changes in other leads or Q waves, and the altered shape of the ST segment. But junior doctors are unlikely to have the benefit of this experience, and won't find any clues in many clinical textbooks and published thrombolysis trials.

▲ *Emergency Medicine Journal* 2002;**19**:126–128