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

D Patterson, J B C Dick, A D Struthers

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). 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. 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.

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 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.

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 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 gradient of delta R-R responses from dose (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.

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The resultant R-R intervals were plotted against the delta systolic blood pressure, and the computerised best fit slope was used in analysis. 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. 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).

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).

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noradrenaline between hypercholesterolaemics and normo-
cholesterolaemics. Despite the same blood pressure changes,
the reflex bradycardiac response to noradrenaline was signifi-
cantly 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. 8
Secondly, clinical studies have shown that baroreflex insensi-
tivity is independently associated with increased mortality
even when corrected for different levels of left ventricular
dysfunction. 9 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. 9 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.

**REFERENCES**

1 O’Driscoll G, Green D, Taylor RR. Simvastatin, improves endothelial
2 Spieker LE, Corti R, Binggeli C, et al. Baroreceptor dysfunction induced
by nitric oxide synthase inhibition in humans. J Am Coll Cardiol
3 La Rovere MT, Bigger JTJ, Marcus FI. Baroreflex sensitivity and heart-rate
variability in prediction of total cardiac mortality after myocardial
AT1 receptor function and density in hypercholesterolaemic men.
5 Smyth HS, Sleigh P, Pickering GW. Reflex regulation of arterial pressure
during sleep in man: A quantitative method of assessing baroreflex
stimulation and bradycardia during experimental acute myocardial
7 Townsend JN, Littler WA. Cardiac vagal activity: a target for intervention

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**At what point should ST elevation be measured?**

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ior 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, gleanig 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 throm-
bolysis trials.

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