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.1

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.1

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 started if the systolic blood pressure rose by 50 mm Hg. The time required for a fall of > 15 mm Hg systolic increase were ignored in keeping with the methodology in the landmark paper by La Rovere and colleagues.1 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).

www.heartjnl.com
noradrenaline between hypercholesterolaemics and normo-cholesterolaemics. 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. Secondly, clinical studies have shown that baroreflex insensitivity is independently associated with increased mortality even when corrected for different levels of left ventricular dysfunction. The simplistic notion which arises is that baroreflex activity reflects parasympathomimetic activity which in turn exerts an antiarrhythmogenic 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. 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**

Intensive statin treatment improves baroreflex sensitivity: another cardioprotective mechanism for statins?
D Patterson, J B C Dick and A D Struthers

Heart 2002 88: 415-416
doi: 10.1136/heart.88.4.415

Updated information and services can be found at:
http://heart.bmj.com/content/88/4/415

These include:

References
This article cites 7 articles, 4 of which you can access for free at:
http://heart.bmj.com/content/88/4/415#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections
Hypertension (3006)
Epidemiology (3752)
Metabolic disorders (1030)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/