Non-invasive baroreflex testing should be used to assess prognosis

See page 1522 for the article to which this Editorial refers

This issue includes an important methodological paper[1] comparing 'non-invasive' measurement of baroreflex sensitivity (i.e. Finapres beat-to-beat arterial pressure) to the original 'invasive' method, (i.e. using intra-arterial pressure measurement) developed in Oxford more than 30 years ago[3]. Both methods are invasive in the sense that they use intravenous injections of a vasoconstrictor agent phenylephrine.

The importance of the paper[1] is twofold. First it represents by far the largest comparative study of the two methods, and second, baroreflex sensitivity measurement has recently been shown to give prognostic information for a range of cardiovascular problems notably post myocardial infarction[4], and heart failure/left ventricular dysfunction[5], which is additional to, and of equal power to, established markers such as ejection fraction.

The phenylephrine test measures the beat-to-beat lengthening in RR interval during the resulting ramp increase in arterial pressure. It is a measure of vagal tone, and of the increase in vagal tone resulting from the baroreflex response to a rise in arterial pressure. The methodology has been validated in numerous studies, but its use has hitherto been limited to research projects rather than clinical practice. This demonstration that baroreflex sensitivity determined by finger cuff pressure measurement in patients can give very similar information to the original method using direct intra-arterial pressure will therefore increase its routine applicability considerably. One limitation to the test is that there is considerable intra-individual variability in the measurement, so most workers use an average of two to three measures in the same steady state. Baroreflex sensitivity is rapidly decreased by arousal[6], or by exercise[7].

We do not fully understand why this measurement of autonomic function is so predictive. Vagal tone has been shown to raise the threshold for ventricular fibrillation in a dog model of ischaemic heart disease[9]. Baroreflex sensitivity may also be a marker for neurohumoral abnormalities, since baroreflex sensitivity is reduced by angiotensin (at the reflex centres in the medulla oblongata)[8], and by sympathetic arousal.

Another limitation is that the discriminatory ability of the test is reduced in groups where baroreflex sensitivity is low (e.g. in elderly subjects). Other measures of autonomic control (e.g. heart rate variability, or power spectrum analysis)[10] may be more useful. Again the mechanisms by which these latter tests can discriminate are at present poorly understood[11]. Low heart rate variability reflects many things—poor modulation of autonomic tone, but also it may be due to lack of ability to exercise, and so be related to severe cardiac damage, rather than autonomic factors[12].

In time these methods may be widely used clinically, but first we need to understand much more of the physiology and pathophysiology underlying the different tests.

I must declare an interest in that I have worked on and off with the group at Montesano for 8 years or more. They combine a large service load associated with the big cardiac transplantation service in Pavia, with a large bioengineering group who have developed sophisticated programmes to compare many of the tests of autonomic function used in patients before or after transplantation, or post-myocardial infarction. They are to be complimented on this useful validation of this easier methodology.

P. SLEIGHT
John Radcliffe Hospital,
Oxford, U.K.

References

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Patency, perfusion, performance — the desirable triplets of combination thrombolytic therapy

See page 1530 for the article to which this Editorial refers

The desirable goals of thrombolytic therapy in acute myocardial infarction are the urgent re-establishment and maintenance of coronary artery patency leading to restoration of perfusion of the myocardium and microvasculature, thereby optimizing residual left ventricular performance[1–3]. Patency, perfusion and performance therefore comprise a sequence upon which future effort tolerance and prognosis depend[4]. Whilst we now appreciate that perfusion may not always follow the re-establishment of patency, and performance may lag behind the restoration of perfusion, without patency there is neither perfusion nor performance[5–7].

Patency is therefore paramount and intense effort continues in the search for the most optimum and safest thrombolytic combination, for our current options are far from ideal. Even with ‘the gold standard’ thrombolytic cocktail of accelerated alteplase, aspirin and intravenous unfractionated heparin, which achieves early TIMI 3 patency in about 50% of patients, perfusion may occur in only two thirds of these, and reocclusion in up to a third by 3 months[6,8,9]. As thrombolytic schedules have become easier to administer by virtue of double-bolus (reteplase) or even single bolus fibrinolytics (tenecteplase, lanoteplase), there is growing concern about the apparent increase in the risk of intracerebral haemorrhage. Fortunately, as knowledge of the mechanics of occlusive clot formation and the dynamics of its many constituents unfold, so new opportunities for targeted intervention can be explored.

Fibrinolytics enhance the enzymatic conversion of plasminogen to plasmin, the serine protease responsible for the digestion of fibrinogen and fibrin, key requirements for both the white (platelet rich) and red (red-cell rich) components of clot. Although there may be further refinements of the properties of fibrinolytic drugs, such as more complete clot specificity and more potent protection from plasminogen activator inhibitors, it is the development and testing of the coadministration of new thrombolytic and anticoagulant drugs which dominate current phase II and III trials in acute ischaemic coronary syndromes. There are numerous potential combinations of new antiplatelet drugs (ADP receptor blockers, PT2 receptor blockers, glycoprotein IIb/IIIa receptor blockers), antithrombins (low molecular weight heparins, hirudin derivatives) and coagulation cascade inhibitors, such as antitissue factors. It is difficult at present to predict which of these combinations will emerge in pole position, but the possibility that, as with other cocktails, the ingredients may not combine advantageously must be considered.

In this issue Ronner and colleagues[10] present the results of a phase II randomized double-blind study assessing the safety and efficacy of one such combination, the addition of escalating doses of the