Effects of hydralazine versus propranolol on blood velocity patterns in patients with carotid stenosis

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Summary

1. Since endothelial damage due to flow disturbances is of postulated significance in the pathogenesis of atherosclerosis, this study examined the effects of antihypertensive drugs on carotid flow patterns in patients with known carotid stenosis. A Doppler Echoflow unit was used to display arterial velocities in red (normal range), yellow (increased velocity) and blue (abnormally increased velocity thought to represent turbulence and other departures from laminar flow).

2. Twenty patients were studied before drug, then during intravenous administration of hydralazine, 6-12 mg, and propranolol, 2-5 mg, over 10-15 min each, with return to baseline between drugs.

3. After hydralazine, the occurrence of abnormal high velocity flow patterns increased in 17 of 20 patients; there was no change in three patients. Propranolol reduced the occurrence of abnormal high velocity flow patterns in 19 of 20 patients ($P < 0.00001$; chi-square).

4. These effects of antihypertensive drugs on arterial velocity patterns may be important in the selection of antihypertensive drugs to prevent or minimize the progression of atherosclerosis.

Key words: atherosclerosis, carotid stenosis, haemodynamics, hydralazine, hypertension, propranolol.

Introduction

It is clear that mortality and such complications of hypertensive arteriolar disease as intracerebral haemorrhage and lacunar strokes are reduced by the treatment of hypertension [1,2]; however, the results of various studies of long-term treatment of hypertension have differed with respect to prevention of atherosclerotic complications such as myocardial infarction. Russell [3] has reviewed the evidence that hypertensive strokes represent arteriolar disease rather than atherosclerotic disease. Despite significant reduction of stroke and congestive heart failure, myocardial infarction was not reduced in the Veterans Administration Cooperative Trial [1] (in which a fixed combination of thiazide, hydralazine and reserpine was used), or in the study of Beever et al. [2] (in which thiazide and methyldopa were used). β-Adrenoceptor blockers, on the other hand, have been associated with a significant reduction of myocardial infarction in the Goteborg primary prevention trial of hypertension treatment [4], and in the Norwegian study of secondary prevention of myocardial infarction with timolol [5]. It appears likely that the degree of blood pressure reduction by antihypertensive drugs is not the only feature determining the long-term outcome for patients, with respect to atherosclerotic complications of hypertension. It has been suggested that some differences in outcome may result from certain adverse effects of these drugs on plasma lipids [6]; another property that may determine different outcomes is the effect of antihypertensive drugs on arterial flow disturbances such as turbulence [7-9].
According to one widely held hypothesis of the pathogenesis of atherosclerosis, the lesion in the arterial wall occurs as a reaction to injury by haemodynamic forces, and by other injurious agents such as platelets and hyperlipidaemia [10, 11]. The localization of the disease to sites of disturbed flow such as bifurcations, points to haemodynamic factors as being important in the endothelial damage that may initiate the process [12].

We have previously shown that antihypertensive drugs have different effects on blood velocity in rhesus monkeys [7] and in hypertensive patients [13]. We have shown, in hypertensive hyperlipidaemic rabbits [9], that propranolol was significantly more effective than hydralazine in preventing the occurrence of aortic atherosclerosis, even though hydralazine was more effective than propranolol in reducing blood pressure. We have postulated that the mechanism by which propranolol reduced the development of atherosclerosis may have been through its haemodynamic effects, perhaps by reducing the occurrence of flow disturbances at arterial bifurcations [13]. The present study was undertaken to determine the effects of propranolol versus hydralazine on the occurrence of abnormal flow velocity patterns, in patients with angiographically proven carotid stenosis.

Methods

Twenty patients (17 men, three women, age 50-74 years) (mean age 63.2 ± 8.56 SD years) with known carotid stenosis were studied within a week after angiography. None had angina or asthma, or was taking antihypertensive drugs. Informed consent was given to a protocol approved by the University Committee on Ethics. A Doppler Echoflow unit (Diagnostic Electronics, Lexington, MA, U.S.A.) was used to produce flow maps of the stenosed carotid artery. The device constructs a two-dimensional image of flow velocities in the artery, using a three-level colour code: red represents Doppler shifts from 800 to 3600 Hz, yellow from 3600 to 5000 Hz and blue over 5000 Hz. With an emitted frequency of 4.0 MHz, and assuming an angle of incidence of 45°, these Doppler shifts correspond to blood velocities of 21-95 cm/s for red, 95-132 cm/s for yellow and >132 cm/s for blue [14]. The occurrence of turbulence is manifested by vascular bruits, and has been verified by spectral analysis of the audio Doppler signal. With standard assumptions of normal blood density and viscosity, and a carotid diameter of 4 mm, a blood velocity of 132 cm/s gives a Reynolds number of 1995, well into the turbulent range for the carotid bifurcation during pulsatile flow [15, 16]. This device has been correlated with angiographic findings in over 400 cases, and gives a 96% likelihood of detecting a 70% stenosis [17]. The occurrence of high blood velocities in the range displayed in blue is abnormal, and is regarded as representing departures from laminar flow, including turbulence and vortex formation [14].

Patients were studied in the recumbent position before drug, and again after intravenous injections of hydralazine, and then propranolol. This sequence was determined by pilot studies that showed the heart rate response to intravenous propranolol was too long-lasting (up to 2 h) to randomize the sequence. Because of changes in the Echoflow picture from day to day, it was necessary to complete each study at one sitting.

Hydralazine was given as repeated boluses of 1-2 mg at intervals of 1-2 min, the heart rate and blood pressure being checked before each new bolus. The Echoflow recording was made after 15 min, after a total of 6-16 mg of hydralazine had been given, and after a heart rate increase of 10 beats/min or more.

After a rest period of 30 min, during which the heart rate and blood pressure returned to within 10% of baseline values, intravenous propranolol was given in boluses of 0.25-0.5 mg every 2-3 min, to achieve a heart rate reduction of 10 beats/min or more, with blood pressure and heart rate being determined between injections. (All subjects had a continuous ECG monitor displayed on a Hewlett-Packard 7803 B monitor throughout the study. The maximum dose of propranolol used was 5 mg over 15 min.)

The 60 flow maps were then reviewed in a batch, by three independent observers without knowledge of the drug used; the two drug recordings were compared in each case with the baseline recording, and a determination was made as to whether the drug in each case had increased the occurrence of abnormal flow patterns, produced no change, or the drug had reduced the occurrence of abnormal velocities. These determinations were based on changes in extent and distribution of the occurrence of yellow (accelerated flow) and blue (abnormal high velocity) patterns. In most cases it was quite clear that changes had occurred, with hydralazine 'bringing out' blue flow patterns that had not been present at baseline, and propranolol causing them to disappear. In some cases no change had occurred, and those were reported as 'no change'.

Results

Intravenous hydralazine increased the occurrence of abnormal flow patterns in 17 of 20 patients,
with no change in three. Intravenous propranolol decreased the occurrence of abnormal flow patterns in 19 of 20 patients (chi-square analysis on a 3 x 2 contingency table gave \( P < 0.00001 \)).

Discussion

The results observed in this study appear to support the hypothesis that antihypertensive drugs may have different effects on the occurrence of arterial flow disturbances. Although the occurrence of abnormally high velocities on the Echo-flow cannot be equated directly with turbulence, the designers of the instrument believe that the occurrence of high velocity patterns in the range displayed as blue do represent departures from laminar flow, with such high frequency shifts expected only when blood is moving toward the probe, as in turbulence, or with the formation of vortices [14]. The differences observed here suggest that propranolol probably does reduce the occurrence of arterial flow disturbances at sites of carotid stenosis, whereas hydralazine probably increases the occurrence of arterial flow disturbances. These differences are of particular interest in view of our previous finding that propranolol was significantly more effective than hydralazine in preventing the occurrence of aortic atherosclerosis in hypertensive hyperlipidaemic rabbits, even though the hydralazine-treated rabbits had significantly lower blood pressures and had lower cholesterol levels than the propranolol-treated rabbits [9].

Taken with the evidence that some antihypertensive drugs have adverse effects on plasma lipids [6], these studies suggest that more attention should be given to the other pharmacological effects of antihypertensive drugs, such as their haemodynamic effects, and that simple reduction of blood pressure may not be the complete answer to the reduction of atherosclerotic risk in hypertensive patients. The results of long-term trials of hypertension therapy may in fact be determined by such drug effects; for example, in a large Australian trial [18] the incidence of myocardial infarction and death were both significantly higher in the group assigned to hydrochlorothiazide, than in an untreated control group, or in a group assigned to propranolol. To answer the question raised by our observations, the haemodynamic effects of antihypertensive drugs would have to be taken into account in the design of long-term treatment trials.

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References