Haemodynamic comparison of amlodipine and atenolol in essential hypertension using the quantascope

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- 1 We have utilised a non-imaging echo-Doppler cardiac output device, using the principle of attenuated compensation volume flow (ACVF), to assess the cardiovascular effects of amlodipine and atenolol over 3 months in 24 patients with essential hypertension.
- 2 Both amlodipine and atenolol, at 4 and 12 weeks, similarly reduced mean arterial pressure (12 weeks amlodipine -12.6 mmHg, atenolol -14.9 mmHg; $P < 0.01$ for each *vs* baseline).
- 3 The heart rate fell on atenolol, both at 4 weeks (amlodipine -3 *vs* atenolol -12 beats min^{-1} ; $P < 0.05$) and 12 weeks (-1 *vs* -11 beats min^{-1} ; $P < 0.05$), without change on amlodipine.
- 4 Stroke volume initially rose on atenolol without change on amlodipine (4 weeks amlodipine -1.3 ml *vs* atenolol $+10.1$ ml; $P = 0.05$) but between drug effects were not different at 12 weeks.
- 5 The systemic vascular resistance was reduced on amlodipine (12 weeks: amlodipine -176 dyn s cm^{-5} ; $P < 0.05$) without change on atenolol (atenolol -48 dyn s cm^{-5} ; NS).
- 6 The cardiac stroke work was lowered on amlodipine both at 4 weeks ($P < 0.01$) and 12 weeks ($P < 0.05$) and statistically different from the unaltered atenolol values at both time points.
- 7 Skin nutrient flow or fingertip temperature was not altered by either treatment.
- 8 These results are consistent with contrasting mechanisms of action – vasodilator for amlodipine and decreased cardiac pumping for atenolol. The greater reduction in cardiac stroke work on amlodipine compared with atenolol warrants further investigation during longer-term studies.

Keywords amlodipine atenolol hypertension quantascope

Introduction

Amlodipine is a calcium entry blocker of the dihydropyridine class. It inhibits the 'slow' channel influx of calcium into cardiac and vascular tissue. Its main site of action is the peripheral vasculature, although it also produces vasodilation in the coronary vascular bed [1]. It produces marked peripheral arteriolar vasodilatation with little or no cardiodepressant action [2–4]. In contrast, β -adrenoceptor blockade usually results in a dose-dependent reduction in cardiac performance; the initial reflex increase in peripheral vascular resistance is attenuated during long-term therapy [5]. However,

the mode of action in reducing blood pressure is still uncertain.

Doppler ultrasound has previously been used to measure volume blood flow in clinical situations [6,7] and during pharmacodynamic intervention [8,9]. Cardiac output is estimated from the product of mean blood velocity and aortic cross-sectional area (requiring direct visualisation of the vessel using an imaging system). A non-imaging method of estimating blood volume flow rate which does not require measurement of the angle of insonation or lumen area has been

described [10]; it has been demonstrated to be useful in monitoring the effects of acute drug intervention in man [11].

We have now undertaken the following study to outline the haemodynamic profile of amlodipine in essential hypertension. For control, the profile of atenolol, a cardioselective β -adrenoceptor blocking drug was investigated in a parallel group.

Methods

Study design and patients

Twenty-four consecutive patients (mean aged ($\pm$ s.d.) for atenolol 60 ± 8 and amlodipine 53 ± 10 years respectively) with essential hypertension (diastolic phase V blood pressure 95–110 mmHg) were studied. Patients were similar for major demographic variables (height atenolol 162 ± 7 , amlodipine 166 ± 11 cm; weight 73 ± 20 , 81 ± 18 kg respectively). Following 2 weeks placebo washout, supine systolic (158 ± 21 , 156 ± 15 mmHg for atenolol and amlodipine respectively), diastolic (94 ± 9 , 93 ± 7 mmHg) and mean blood pressure (115 ± 12 and 114 ± 8 mmHg) was not different between the groups. Patients were randomised in a double-blind manner to amlodipine 5 mg or atenolol 50 mg with dose-titration to amlodipine 10 mg or atenolol 100 mg after 4 weeks sustained therapy (if diastolic phase V pressure persisted > 90 mmHg). Two patients received amlodipine 5 mg and twelve amlodipine 10 mg; atenolol 50 mg and 100 mg were given to four and six patients respectively. All measurements were taken 24 h after dosing; blood pressure and central cardiovascular flow and peripheral temperature variables were recorded recumbent following 15 min quiet rest. Measurements were repeated at 5 min intervals until four consecutive and reproducible ($<10\%$) sets of values had been obtained. The study was approved by the Queen's University Ethics Committee.

Doppler ultrasound: Principle of operation

The Doppler principle states that the frequency shift of a reflected wave is proportional to the velocity of the object which reflects it. The conventional method of applying this principle to measure aortic blood flow firstly determines the area under the systolic velocity signal (systolic velocity integral) and secondly measures the aortic diameter using an imaging method; the latter allows the aortic area to be determined. Then multiplying the systolic velocity integral by the aortic flow area gives the cardiac stroke output. The attenuation compensation volume flowmeter (ACVF) provides a method for determining absolute volume flow which does not require direct imaging of the aorta [12]. Two concentric parallel ultrasound beams (narrow and wide beams) are generated. By pre-calibration, the area within the narrow beam at any focused depth is known; this provides a measure of the attenuation of the ultrasound signal by the tissues allowing the relative flow to be translated into absolute volume flow [11].

A commercial pulsed wave Doppler flowmeter system, based on the ACVF principle, was used in this study to measure cardiac output (Quantascope-Vital Science). Using a 2 MHz two element annular array transducer, the attenuation compensation volume method (ACVF) has the potential to measure flow rate without direct visualisation of the aorta. It requires the implementation of a uniform wide beam to encompass the whole vessel and a narrow reference beam placed totally within the lumen. By using a specially designed annular array probe, a 3 cm uniform beam and a narrow reference beam are produced, at a depth usually between 4 and 6.5 cm. Cardiac output is then calculated by the product of the mean Doppler frequency from the wide beam and the ratio of the backscattered Doppler powers from both beams. The measurement of flow rate is then independent of lumen area, beam-vessel angle, and the velocity profile across the vessel. The flowmeter is used clinically by placing the probe in the suprasternal notch of patients lying in the supine position; cardiac waveforms are averaged on a beat to beat basis. Cardiac output, stroke volume, stroke length, flow acceleration and time averaged mean velocity can then be computed from the averaged waveforms. The following variables were derived:

Systemic vascular resistance = Mean pressure/Cardiac output (dyn s cm^{-5}).

Stroke work = Stroke volume $\times$ Mean arterial pressure $\times 0.0136$ (g m).

Skin thermal clearance

The use of thermal clearance to measure skin blood flow has been advocated by Holti & Mitchell [13] as a simple non-invasive method of measuring the 'nutrient' component of skin blood flow. It consists of a centrally heated annulus and a series of thermocouples which senses the temperature difference between the inner and outer rings. The essential relationship between the resulting thermal temperature difference and nutrient skin blood flow is inverse, i.e. increasing skin blood flow reduces the difference between the inner and outer ring whereas vasoconstriction increases the difference [14].

Statistical analysis

This was undertaken using 2 way analysis of variance (MANOVA:SPSS-PC) partitioning the variance between patients, treatment and time; a multiple range test (Dunnett's) was used to compare the individual differences at each time point with $P < 0.05$ being considered significant [15].

Results

The studies were completed without incident in any patient.

Haemodynamic effects of amlodipine (Table 1; Figures 1–2)

Amlodipine reduced systemic mean arterial blood pressure (-13 mmHg; $P < 0.01$) without change in heart rate, cardiac output or time averaged mean velocity. There were no significant changes in stroke volume or stroke length. Aortic acceleration was significantly increased at 4 weeks ($+132$ cm s $^{-2}$; $P < 0.05$) but by 12 weeks it was not significantly different from control. There was a trend towards a fall in systemic vascular resistance by 4 weeks (-114 dyn s cm $^{-5}$; $P = 0.07$) which was significant at 12 weeks (-176 dyn s cm $^{-5}$; $P < 0.05$). Stroke work was reduced by amlodipine at 4 weeks ($P < 0.01$); the impact was less after 12 weeks although still significant ($P < 0.05$). Skin thermal clearance and finger tip temperature were unaltered.

Haemodynamic effects of atenolol: (Table 1, Figures 1–2)

Atenolol reduced systemic mean arterial blood pressure (-15 mmHg; $P < 0.01$) and heart rate (-11 beats min $^{-1}$; $P < 0.01$). The small increase in stroke volume ($+10$ ml; NS) and stroke length ($+1.3$ cm; $P = 0.07$; 4 weeks) were not different from control. Atenolol did not alter time averaged mean velocity, cardiac output or stroke work; systemic vascular resistance was unaltered. Skin thermal clearance and fingertip temperature were unaltered.

Comparison of the haemodynamic effects of amlodipine and atenolol

The blood pressure-lowering actions of amlodipine and atenolol were similar at both 4 and 12 weeks. Heart rate was lowered to a significantly greater degree by atenolol at both 4 (-12 beats min $^{-1}$ vs -3 beats min $^{-1}$; $P < 0.05$) and 12 (-11 beats min $^{-1}$ vs -1 beat min $^{-1}$; $P < 0.01$) weeks. The stroke volume was different between the drugs at 4 weeks (amlodipine: -1 ml vs atenolol: $+10$ ml; $P = 0.05$) but not at 12 weeks. Stroke length demonstrated similar trends (4 weeks: amlodipine:

-0.1 cm vs atenolol: $+1.2$ cm; $P = 0.07$) but there was no statistical difference between the drugs at either of the two comparison times. The systemic vascular resistance fell on amlodipine (12 weeks) but was unaltered following atenolol. There was a reduction in stroke work by amlodipine significantly different from the unaltered value on atenolol both at 4 ($P < 0.01$) and 12 ($P < 0.05$) weeks.

Discussion

We used a modified non-imaging echo-Doppler method to evaluate the central haemodynamic effects of amlodipine and atenolol in essential hypertension. The application of Doppler ultrasound methods in the non-invasive measurement of cardiac output has been well described [6,8,9,16,17]. The need to measure the vessel diameter, the beam-vessel angle and the lack of optimal beam placement, in relation to the major axis of flow, have all contributed to errors in the resultant estimate of cardiac output. Our clinical validation studies suggested that cardiac output obtained by this technique was not systematically different from the thermodilution method [11]. For pharmacodynamic applications the reproducibility of a method is arguably just as important as absolute accuracy. Previous Doppler studies, not using the ACVF principle, suggest variability of $<10\%$ [18]; Voyles *et al.* [19], with 200 serial measurements in 10 normal subjects and two observers found pooled coefficients of variation of 9% and 10% without between-observer difference. Gisvold & Brubakk [20], with 10 repeated measurements in five subjects, found variability of between 6–11% while Huntsman [18] had a 9.4% coefficient of variability. Ng *et al.* [21] found the coefficient of variation for cardiac output and stroke volume to be 7.9% and 7.4% respectively in six healthy subjects. In 10 volunteers and 25 coronary patients with 8–10 consecutive estimates of flow, the stroke volume reproducibility was 3.8% and 4.4% respectively. The greatest variability was seen for flow acceleration (5.8% and 7.4% respectively). Thus the ACVF method

Table 1 Echo-Doppler effects of amlodipine and atenolol

	Control	Atenolol 4 week	12 week	Control	Amlodipine 4 week	12 week
Systolic pressure (mmHg)	158 $\pm$ 21	140 $\pm$ 15 [†]	138 $\pm$ 18 [†]	156 $\pm$ 15	134 $\pm$ 11 [†]	137 $\pm$ 10 [†]
Diastolic pressure (mmHg)	94 $\pm$ 9	82 $\pm$ 9 [†]	82 $\pm$ 9 [†]	93 $\pm$ 7	82 $\pm$ 5 [†]	82 $\pm$ 7 [†]
Heart rate (beats min $^{-1}$)	76 $\pm$ 9	64 $\pm$ 6 [†]	65 $\pm$ 6 [†]	77 $\pm$ 10	74 $\pm$ 12	77 $\pm$ 12
Cardiac output (l min $^{-1}$)	6.2 $\pm$ 1	5.8 $\pm$ 1	5.8 $\pm$ 1	6.7 $\pm$ 1	6.2 $\pm$ 1	6.8 $\pm$ 1
Stroke volume (ml)	82 $\pm$ 13	92 $\pm$ 14	89 $\pm$ 18	88 $\pm$ 19	87 $\pm$ 19	89 $\pm$ 17
Stroke length (cm)	10.5 $\pm$ 2	11.7 $\pm$ 2	11.5 $\pm$ 3	11.5 $\pm$ 2	11.4 $\pm$ 2	12 $\pm$ 2
Flow acceleration (cm s $^{-2}$)	1006 $\pm$ 212	1025 $\pm$ 248	1074 $\pm$ 331	1046 $\pm$ 198	1178 $\pm$ 149*	1089 $\pm$ 180
Time averaged mean velocity (cm s $^{-1}$)	13.2 $\pm$ 2	12.3 $\pm$ 2	12.6 $\pm$ 3	14.6 $\pm$ 2	13.7 $\pm$ 2	14.9 $\pm$ 2
Systemic vascular resistance (dyn s cm $^{-5}$)	1521 $\pm$ 271	1425 $\pm$ 311	1473 $\pm$ 557	1395 $\pm$ 226	1281 $\pm$ 137	1220 $\pm$ 244*
Probe temperature (°C)	2.78 $\pm$ 0.2	2.51 $\pm$ 0.4	2.69 $\pm$ 0.3	2.68 $\pm$ 0.2	2.60 $\pm$ 0.2	2.58 $\pm$ 0.3
Finger temperature (°C)	28.5 $\pm$ 4.3	30.7 $\pm$ 4.1	30.7 $\pm$ 3.2	30.8 $\pm$ 3.4	31.7 $\pm$ 2.2	31.1 $\pm$ 2.9
Stroke work (g.m)	128 $\pm$ 7	126 $\pm$ 6	121 $\pm$ 7	137 $\pm$ 9	118 $\pm$ 8 [†]	122 $\pm$ 7*

Data are mean $\pm$ s.d. Statistics represent difference from control. * $P < 0.05$, [†] $P < 0.01$.

Figure 1 Comparative actions of atenolol and amlodipine on heart rate, stroke volume and systemic vascular resistance. Data are mean $\pm$ s.e. mean; statistics relate to comparison with baseline: * $P < 0.05$; ** $P < 0.01$. Open circles relate to amlodipine; closed to atenolol.

Figure 2 Comparative actions of atenolol and amlodipine on cardiac stroke work. Data are mean $\pm$ s.e. mean; statistics relate to comparison with baseline: * $P < 0.05$; ** $P < 0.01$. Open circles relate to amlodipine; closed to atenolol.

offers at least as good reproducibility as other echo-Doppler methods with the advantage that volume flow estimates may be obtained.

The ability of echo-Doppler methods to detect the action of drugs on cardiac performance is of interest. The first derivative of the velocity signal (acceleration)

is a sensitive indicator of inotropic state and relatively independent of loading conditions [22,23]; there is good agreement between myocardial contractile activity and maximal aortic acceleration [24]. Peak aortic velocity may also be altered by treatment; a sharp rise in the peak aortic flow velocity during inotropic stimulation with dobutamine has been demonstrated which was relatively unaffected by atrial pacing and nitrate infusion [25]. Clifton *et al.* [26] demonstrated that separation of the negative inotropic and chronotropic properties of propranolol was possible using echo-Doppler techniques (Exerdop); propranolol decreases in acceleration and velocity but atrial pacing to heart rates comparable with control exercise did not restore acceleration and velocity to the values recorded prior to drug administration. We have shown that peak acceleration and velocity increased following celiprolol 800 mg in normal volunteers in contrast to decreases following propranolol and atenolol; these positive inotropic actions of celiprolol were probably a consequence of partial agonist activity [27].

The use of a thermal clearance probe to measure fingertip skin blood flow has been found to be reproducible with a coefficient of variation of 2% between subjects [14]. These authors demonstrated reasonable agreement for thermal clearance with both venous occlusion plethysmography and photoelectric plethysmography ($r = 0.60-0.92$ for venous occlusion plethysmography and $0.64-0.93$ for photoelectric plethysmography). In our study, there was no consistent change in fingertip temperature or skin thermal clearance following either treatment. A previous randomised double-blind placebo controlled crossover study of 18 essential hypertensives compared the actions of nicardipine, propranolol, their combination and celiprolol on these same variables [28]. The thermal clearance values fell on all therapies suggesting an improvement in nutrient or A-V anastomotic skin blood flow; fingertip temperature increased only on the nicardipine/propranolol combination. Holti [29] undertook a double-blind comparison of labetalol and propranolol in 12 patients with Raynaud's phenomenon. Whereas labetalol did not alter finger-tip temperature, propranolol reduced the latter (21.6 to 16.8 °C: $P < 0.001$). The thermal clearance was unaltered by labetalol but increased (2.36 to 2.52 °C: $P < 0.01$) after propranolol. These data contrast with normal volunteers where acute therapy with propranolol, atenolol or celiprolol had little overall effect on nutrient flow in comparison with placebo (Silke, 1993). The relationship between the nutrient or A-V anastomotic skin flow and total skin blood flow or systemic vascular resistance in essential hypertension is the subject of further investigation.

Our results are consistent with previous observations of the haemodynamic effects of amlodipine and atenolol in man. Reflex tachycardia has also been shown by others not to occur after single oral doses or long term oral therapy with amlodipine [30-32] unlike other vasodilators with more marked acute actions [33]. This apparent absence of tachycardia has been attributed to amlodipine's gradual onset of action [32]. There is some conflicting evidence as to the effects of amlodipine on cardiac performance. In both *in vivo* and *in vitro* animal

models and in human isolated cardiac tissue, high concentrations of amlodipine have slight negative inotropic effects but are weaker than those of nifedipine [34,35]. In contrast, short term intravenous administration of amlodipine in doses of up to 20 mg did not produce evidence of cardiac depression in patients with coronary artery disease but instead resting cardiac output increased slightly (+37%) [2–4]. We did not find any alteration in cardiac output in the longer term with amlodipine 5 to 10 mg perhaps either because of the attenuation of any initial cardiac output changes with longer term therapy or the lower dose used. In fact our finding of an increase in aortic acceleration after 4 weeks of amlodipine would suggest that the reduction in afterload, due to the fall in systemic vascular resistance, offset any negative inotropism; the lack of impact at 12 weeks on acceleration despite a maintained reduction in vascular resistance may indicate greater negative inotropic actions during sustained therapy or conversely less sympathetic activation. Like other investigators, we showed that cardiac stroke work and systemic vascular resistance were reduced.

The effects of another dihydropyridine nifedipine (60 mg twice daily) were studied using echo-Doppler techniques before and 28 days following chronic dosing in nine subjects with essential hypertension [36]. Aortic stroke distance (continuous wave aortovelocity) at 2 h post-dosing increased by 29% from 15.5 to 20.0 cm; cardiac minute distance was also augmented. Although our data did not show such actions, one should emphasise that our measurements were determined at trough – 24 h following dosing.

Long-term β -adrenoceptor blockade characteristically reduces cardiac output and heart rate without a

change in systemic vascular resistance [5]. In this study atenolol decreased cardiac output and heart rate without change in systemic vascular resistance. It is of considerable interest that a major difference in cardiac stroke work was seen, despite similar achieved reductions in the blood pressure. The implication of such differences between amlodipine and atenolol in cardiac work for therapeutic goals such as reversal of left ventricular hypertrophy cannot be answered based on these studies, it would be of interest to test such a relationship during longer-term studies.

In summary, this double-blind randomised study compared the chronic haemodynamic effects of amlodipine with atenolol in patients with essential hypertension. The results demonstrated that at similar achieved anti-hypertensive effects, amlodipine reduced systemic vascular resistance and cardiac stroke work in contrast to atenolol which reduced heart rate, increased stroke volume without effect on systemic vascular resistance or cardiac stroke work. These results are compatible with the known mechanism of action of amlodipine and atenolol; the former having direct vasodilator actions in contrast to the predominant impact of atenolol on cardiac output. Some but not all of the initial differences were minimized during longer term therapy. The significance of the greater reduction in cardiac stroke work by amlodipine awaits further evaluation.

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