Disparate effects of methyldopa and clonidine on cardiac mass and haemodynamics in rats

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Summary
1. Wistar-Kyoto and spontaneously hypertensive rats were given either methyldopa (400 mg day\(^{-1}\) kg\(^{-1}\)) or clonidine (0.1 or 0.3 mg day\(^{-1}\) kg\(^{-1}\)) for 3 weeks commencing at 20 weeks of age.
2. Both drugs significantly decreased mean arterial pressure in spontaneously hypertensive but not Wistar-Kyoto rats. Heart rate was significantly increased in spontaneously hypertensive rats by methyldopa, whereas clonidine significantly decreased heart rate. The higher dose of clonidine also decreased heart rate in Wistar-Kyoto rats. Both cardiac output and total peripheral resistance decreased slightly, but not significantly, with both agents.
3. Methyldopa, but not the lower equipotent depressor dose of clonidine, reduced left ventricular hypertrophy in spontaneously hypertensive rats. However, the higher dose of clonidine also significantly decreased the heart to body weight ratio despite an increased total peripheral resistance presumably due to the \(\alpha\)-adrenergic agonist effect.
4. Minimal changes in organ blood flows were noted with both drugs.
5. These results suggest that neither systemic haemodynamics nor central inhibition of adrenergic drive are primary factors responsible for the regression of hypertrophy.

Key words: antihypertensive treatment, haemodynamics, hypertension, reversal of hypertrophy, spontaneously hypertensive rats.

Introduction
Left ventricular hypertrophy is a common consequence of long-standing essential and experimental hypertension. This hypertrophy had been ascribed to the increased overload although recent studies suggest that other factors may also contribute to its development. Regression of left ventricular hypertrophy can result from treatment with certain antihypertensive agents (e.g. methyldopa) but not others (e.g. hydralazine) (Sen, Tarazi, Kharrallah \& Bumpus, 1974). Indeed, some antihypertensive agents such as minoxidil may even aggravate the left ventricular hypertrophy (Sen, Tarazi \& Bumpus, 1977).

One factor that may contribute to the development of left ventricular hypertrophy is enhanced sympathetic nervous activity. In the present study we have determined the effect of two centrally active antihypertensive agents, methyldopa and clonidine, on systemic and regional haemodynamics and cardiac mass. Both compounds inhibit cardiovascular adrenergic nervous input and decrease arterial pressure. Thus, if adrenergic inhibition is important in regression of left ventricular hypertrophy, both agents should similarly change cardiac mass.

Methods
Twenty-week-old Wistar-Kyoto (WK) rats and spontaneously hypertensive (SH) rats were treated for 3 weeks with either methyldopa or clonidine. Methyldopa (400 mg day\(^{-1}\) kg\(^{-1}\)) was given by gastric tube in divided doses (twice daily). In contrast, clonidine was given in two dose schedules divided three times daily (i.e. 0.1 mg day\(^{-1}\) kg\(^{-1}\) and 0.3 mg day\(^{-1}\) kg\(^{-1}\)). After 3 weeks therapy and under ether anaesthesia, catheters (PE 50) were placed in the right and left ventricles and abdominal aorta through the jugular vein, carotid and femoral arteries respectively.

The catheters were filled with heparinized 0.9\% (w/v) NaCl and exteriorized at the back of
placed in a small plastic chamber. All catheters were connected to Statham pressure transducers and arterial, left ventricular and right ventricular pressures were recorded on a Hewlett-Packard direct-writing polygraph. After 45 min recordings of systemic haemodynamics were obtained. The direct Fick method (Walsh, Tsuchiya & Frohlich, 1976) was used to determine cardiac output, and regional haemodynamics were determined with radioactive microspheres (15 ± 5 μm; 3M Company), labelled with either 85Sr, 51Cr or 141Ce, injected into the left ventricle. The microspheres were suspended in NaCl solution (154 mmol/l = saline) containing one drop of Tween 80 and placed into precalibrated silastic tubing so that 0.45 ml of the sonicated suspension contained approximately 40 000 microspheres. The microspheres in the tubing were then injected into the left ventricle with 0.4 ml of saline over a 20 s period, then followed by a flush injection of 0.4 ml of saline. The validation and reproducibility of this technique have been reported previously (Tsuchiya, Walsh & Frohlich, 1977).

All rats were killed by exsanguination and the heart, brain, lungs, kidneys, splanchnic organs, testis, skin and skeletal muscle were removed and weighed. Larger organs were cut into several pieces and placed in several scintillation vials in order to increase the geometric efficiency of counting. Radioactivity was counted in a gammawell scintillation counter (3 inch crystal, 1½ inch well diameter) with a multichannel analyser.

Cardiac output was calculated by dividing oxygen consumption by the arteriovenous blood oxygen difference. Total peripheral resistance was calculated by dividing mean arterial pressure by cardiac output. Fractional distribution of cardiac output was calculated from the ratio of organ radioactivity to total injected radioactivity. Organ blood flow was calculated by multiplying the percentage distribution of cardiac output to that organ by the cardiac output, and the specific organ vascular resistance was determined by dividing mean arterial pressure by that organ blood flow. All results are expressed as mean ± SE. Student's *t*-test was used to ascertain statistically significant differences.

**Results**

**Systemic haemodynamics**

Prolonged (3 weeks) treatment with methyldopa (400 mg day⁻¹ kg⁻¹) resulted in a significant fall (*P* < 0.05) in mean arterial pressure that was associated with a somewhat faster heart rate (*P* < 0.001) and insignificant reductions in cardiac output and total peripheral resistance in the SH rat (Table 1). There were no significant changes in systemic haemodynamics in the WK rat (Table 1). In contrast, although clonidine (0.1 mg day⁻¹ kg⁻¹) also decreased mean arterial pressure in the SH rat to the same pressure as that observed with methyldopa (*P* < 0.02), heart rate decreased (*P* < 0.02) (Table 1). However, the higher dose of clonidine (0.3 mg day⁻¹ kg⁻¹) did not reduce mean arterial pressure; in fact, it even tended to increase total peripheral resistance (Table 1). The higher dose significantly decreased heart rate (*P* < 0.05) and both doses tended to decrease cardiac output. Even in the WK rat the higher dose of clonidine reduced heart rate (*P* < 0.01) without producing other changes in systemic haemodynamics.

**Cardiac mass**

Methyldopa treatment reduced cardiac mass and the heart/body weight ratio in SH rats (3.9 ± 0.1 vs 3.7 ± 0.1; *P* < 0.05); however, this was not demonstrated in the WK rat (3.3 ± 0.1 vs 3.2 ± 0.1). In contrast, the lower dose of clonidine produced no change in cardiac mass or the heart/body weight ratio in either SH or WK rats despite a significant pressure fall in the SH rat. The higher clonidine dose that significantly reduced the heart/body weight ratio in SH rats (4.4 ± 0.1 vs 4.1 ± 0.1; *P* < 0.05) did so despite an increased total peripheral resistance.

**Organ flows**

The reduction in arterial pressure with methyldopa was associated with minimal regional haemodynamic changes. Only in the SH rat brain was the distribution of blood flow increased (1.00 ± 0.06 vs 1.24 ± 0.06% cardiac output/g of tissue; *P* < 0.05) and vascular resistance decreased (0.25 ± 0.02 vs 0.18 ± 0.02 unit/kg; *P* < 0.05). The higher dose of clonidine increased fractional distribution to skeletal muscle (0.07 ± 0.01 vs 0.11 ± 0.01% cardiac output/g of tissue; *P* < 0.02) and splanchnic organs (0.66 ± 0.04 vs 0.85 ± 0.06% cardiac output/g of tissue; *P* < 0.05) only in the WK rat. Significant reciprocal changes in vascular resistance also occurred in these organs (at least *P* < 0.05). With the higher dose of clonidine blood flow to the brain in WK rats increased (0.82 ± 0.04 vs 1.07 ± 0.05; *P* < 0.01) as vascular resistance fell (*P* < 0.02).
**Table 1. Effect of prolonged administration (3 weeks) of centrally acting antihypertensive agents on systemic and local haemodynamics in conscious rats**

Mean results ± se are shown. Significance (compared with control): *P < 0.05; **P < 0.02; ***P < 0.001.

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<thead>
<tr>
<th>No.</th>
<th>Body wt. (g)</th>
<th>Mean arterial pressure (mmHg)</th>
<th>Heart rate (beats/min)</th>
<th>Cardiac output (ml/min)</th>
<th>Cardiac index (ml min⁻¹ kg⁻¹)</th>
<th>Total peripheral resistance (units)</th>
<th>Heart wt. (g)</th>
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<th>SHR rats</th>
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**Discussion**

Left ventricular hypertrophy that accompanied experimental and essential hypertension had been generally held to result from increased afterload or increased impedence to the ventricle (Linzbach, 1960). Recent studies, however, have indicated that reduction of arterial pressure may not always have an effect on the hypertrophy to cause regression of ventricular mass. Indeed, methyldopa (and perhaps inhibitors of the renin–angiotensin system) seem to be the only agents that control arterial pressure and reverse left ventricular hypertrophy (Sen et al., 1974). Other antihypertensive agents, such as the vasodilators hydralazine and minoxidil, either have no effect or may actually aggravate ventricular hypertrophy (Sen et al., 1977).

The present study confirms earlier work (Sen et al., 1974) indicating that methyldopa does, in fact, lessen hypertrophy. Interestingly, a higher dose of clonidine actually decreased the heart/body weight ratio in SHR rats, but this dose most likely exerted an agonistic α-adrenoreceptor action, as evidenced by the increased total peripheral resistance and arterial pressure. Other investigators have shown that methyldopa treatment, in a dose that did not significantly reduce arterial pressure, decreased the size of the cardiac muscle cell (Tomanek, Davis & Anderson, 1979). Thus it appears that neither systemic haemodynamics nor central inhibition of adrenergic drive are the sole or primary factors responsible for the regression of myocardial hypertrophy. It seems unlikely that plasma renin activity is a primary factor since both methyldopa and clonidine decrease release of renin from the kidney and plasma renin activity (Sen et al., 1974). Thus, at the present time, the mechanisms by which those pharmacological agents cause regression of ventricular hypertrophy remain unclear. Nevertheless, it is most important that observations on the regression of ventricular hypertrophy (or inability to do so) are confirmed in the absence of haemodynamic changes.

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References


