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Effect of Methyldopa Treatment on Cardiac Function and Myocardial Blood Flow in Mongrel Dogs (39236)

MUSTAFA F. LOKHANDWALA, JOSEPH P. BUCKLEY, AND BHAGAVAN S. JANDHYALA

Cardiovascular Research Division, Department of Pharmacology, College of Pharmacy, University of Houston, Houston, Texas 77004

While the therapeutic usefulness of methyldopa as an antihypertensive agent has been well documented (1-5), controversy still exists concerning the mechanism of antihypertensive action of methyldopa (6-14) and only a paucity of information is available regarding the effects of this agent on hemodynamics and myocardial function in experimental animals. We recently reported that administration of methyldopa to mongrel dogs for a period of 3 days produces impairment of sympathetic neuronal function to various organs responsible for the maintenance of cardiovascular homeostasis (13, 14), and suggested that inhibition of sympathetic nerve function to the heart cannot be explained by the false neurotransmitter theory (14). In view of the altered peripheral sympathetic nerve function to the cardiovascular organs following methyldopa treatment, the present study was undertaken to investigate the changes in coronary and systemic hemodynamics as well as myocardial function in mongrel dogs following treatment with methyldopa.

Methods. Mongrel dogs of either sex weighing between 15-20 kg were treated orally with methyldopa, 100 mg/kg, twice daily for 3 days, and an equal number of dogs received a placebo (lactose) and served as the control group.

At the end of the treatment period, the animals were anesthetized with sodium pentobarbital (35 mg/kg, iv) and prepared for recording of blood pressure from the femoral artery using a Statham P-23 AC pressure transducer. One of the femoral veins was cannulated for the administration of drugs. Heart rate was obtained from the pressure pulse by utilizing a biotachometer (BT-1200, Narco-Bio Systems, Inc.). The trachea was intubated and the animals were placed on positive pressure ventilation using a Harvard respirator (Model 607). Following bilateral cervical vagotmy, a thoracotomy was performed on the left side of the chest wall at the fourth intercostal space. The ascending aorta was freed from the surrounding tissue and a Statham electromagnetic flow probe (12-mm i.d.) was placed around it to monitor cardiac output utilizing a Statham electromagnetic flowmeter (model SP 2202). The left anterior descending coronary artery was isolated, and coronary blood flow was similarly monitored employing a 2-mm flow probe. A polyvinyl catheter was introduced into the apex to monitor left atrial pressure by using a Statham P23V pressure transducer.

In order to evaluate the ability of the myocardium to handle external volume load in the treated and control groups, left ventricular function curves were obtained by placing a large polyethylene catheter into the right atrium via the right jugular vein and infusing Tyrode's solution warmed at 37° at a constant rate of 12-14 ml/sec utilizing a Harvard pulsatile pump (Model 1421) until the cardiac output reached peak level (usually within 40-60 sec). Changes produced in the left atrial pressure, blood pressure, heart rate, and cardiac output throughout the period of infusion were monitored on the physiograph.

In the experiment described above, certain parameters were directly recorded on a Narco-Bio Systems physiograph while certain other parameters were mathematically calculated.[1] All the data are reported as

[1] Total peripheral resistance (mm Hg/liter/min) = [mean blood pressure (mm Hg)]/[cardiac output (liter/min). Left ventricular stroke volume (ml/beat) = [cardiac output (ml/min)]/[heart rate (beats/min)]. Left ventricular stroke work (gm·meters/beat) = {stroke volume × [mean blood pressure − left atrial pressure] × 13.6}/1000. Left ventricular minute work (kg·meters/beat) = {cardiac output × [mean blood pressure − left atrial pressure] × 13.6}/1000.

mean ($\bar{X}$) ± standard error of the mean (SEM). Differences between the means of two groups were evaluated using Student's *t* test and two tailed hypothesis. The difference between the two means was considered statistically significant when $P < 0.05$.

Results. Three-day oral treatment with methyldopa produced a significant decrease in mean blood pressure and heart rate of pentobarbital anesthetized dogs when compared to the control group (Table I). The drug treatment also produced a decrease in total peripheral resistance and a slight but significant increase in stroke volume, while cardiac output was not significantly affected. The resting values of left ventricular stroke work or left ventricular minute work for the two groups were not significantly different from each other (Table I). The studies on coronary hemodynamics revealed that methyldopa treatment produced a significant decrease in coronary vascular resistance while there was a slight but insignificant increase in the coronary blood flow (Fig. 1).

The ability of the myocardium of the treated and control groups to handle external volume load is represented in forms of various ventricular function curves in Figs. 2 and 3. Increases in left ventricular stroke work, left ventricular minute work, and left ventricular stroke volume produced during the infusion of Tyrode's solution are plotted against changes in left atrial pressure. None of these curves of the treated dogs differed significantly from the control group (Fig. 2). Although the resting levels of blood pressure and heart rate were significantly less in the treated dog, the relative changes in these parameters observed following infusion of Tyrode's solution were identical in both groups of dogs (Fig. 3).

Discussion. The present study has demonstrated that methyldopa treatment to mongrel dogs for a period of 3 days produces significant alterations in blood pressure and heart rate. These results are in agreement with our earlier reports (13, 14), as well as the reports of other investigators (15, 16). Furthermore, the results obtained from the study on systemic hemodynamics revealed that the antihypertensive effect of methyldopa is predominantly mediated by a decrease in peripheral resistance since no changes in cardiac output occurred following the drug treatment. This finding is consistent with the clinical evidence describing a similar action of the drug (17, 18).

Studies on the effect of methyldopa treatment on coronary hemodynamics revealed that the drug possessed a beneficial effect on the coronary circulation since it produced a significant decrease in coronary vascular resistance, which was accompanied by a secondary increase in myocardial blood flow. Since under normal physiological conditions, the sympathetic nervous system plays little role in regulating coronary blood flow (19, 20), the mechanism(s) of the observed changes produced by the drug treatment cannot be accounted for by the effect of the

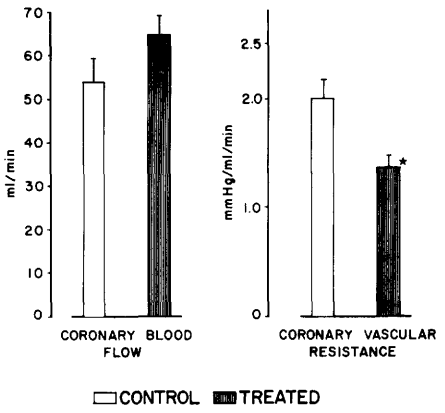

FIG. 1. Effect of methyldopa treatment (100 mg/kg, orally twice daily for 3 days) on coronary blood flow and coronary vascular resistance of pentobarbital anesthetized dogs ($N = 7$, $^*P < 0.05$).

TABLE I. EFFECT OF METHYLDOPA TREATMENT (100 mg/kg, ORALLY TWICE DAILY FOR 3 DAYS) ON SYSTEMIC HEMODYNAMICS OF PENTOBARBITAL ANESTHETIZED DOGS ($N = 7$, $^*P < 0.05$).

Pretreatment	M.B.P.[a] (mm Hg)	H.R. (beats/min)	C.O. (liters/min)	L.V.S.V. (ml/beat)	T.P.R. (mm Hg/liter/min)	L.V.S.W. (gm. meters/beat)	L.V.M.W. (kg. meters/beat)
Control	110 ± 4.0	130 ± 3.0	1.40 ± 0.20	10.8 ± 0.60	78.6 ± 4.6	15.5 ± 1.7	2.02 ± 0.18
Treated	95* ± 5.0	112* ± 6.0	1.39 ± 0.25	12.4* ± 0.50	68.2* ± 5.1	14.8 ± 1.2	1.78 ± 0.20

[a] M.B.P., Mean Blood Pressure; H.R., Heart Rate; C.O., Cardiac Output; L.V.S.V., Left Ventricular Stroke Volume; T.P.R., Total Peripheral Resistance; L.V.S.W., Left Ventricular Stroke Work; L.V.M.W., Left Ventricular Minute Work.

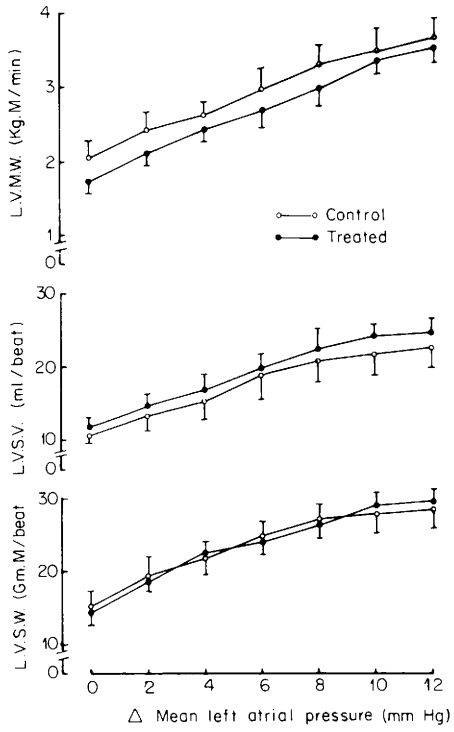

FIG 2. Effect of methyldopa treatment (100 mg/kg, orally twice daily for 3 days) on increases in left ventricular stroke work (L.V.S.W.), left ventricular stroke volume (L.V.S.V.), and left ventricular minute work (L.V.M.W.) produced with corresponding changes in the left atrial pressure during the infusion of Tyrode's solution ($N = 7$).

drug on the sympathetic nervous system (14, 21–23). A direct coronary dilator effect of methyldopa may play a role in producing a decrease in coronary vascular resistance, since such an effect of the drug on smooth muscle has been observed in other vasculatures (12, 24). While these mechanisms are speculative and cannot be fully explained from the present studies, this effect is of utmost clinical significance. The effect of methyldopa in patients with coronary artery disease has been a subject of major controversy (2, 25, 26). Robinson (27) has described increased risk factors for developing coronary artery disease in patients on antihypertensive therapy. Thus, the effects of methyldopa on coronary hemodynamics observed in the present study emphasize the beneficial aspects of the drug treatment.

The usefulness of left ventricular function curves in evaluating an agent for its effect on myocardial contractility has been demonstrated by various investigators (28–30). Sarnoff and Berglund (28) have shown that stroke work which is a function of stroke volume and aortic pressure, is an index of the ability of the ventricle to eject blood against a given afterload or peripheral resistance at a given end diastolic fiber length. It has been demonstrated by various investigators that factors that tend to increase myocardial contractility shift this curve to the left (28, 31, 32), and certain other factors that cause diminution in myocardial contractility or performance shift the curve to the right (33, 34). In addition, Smith and Nash (35) and Jandhyala *et al.* (36) have shown that ventricular function curves can be used successfully to study the effect that a pharmacological agent may have on myocardial performance. In the present study, methyldopa treatment did not produce any changes in left ventricular function curves in comparison with the control group, suggesting that the drug treatment does not affect the contractility of the myocardium and therefore, its ability to handle external vol-

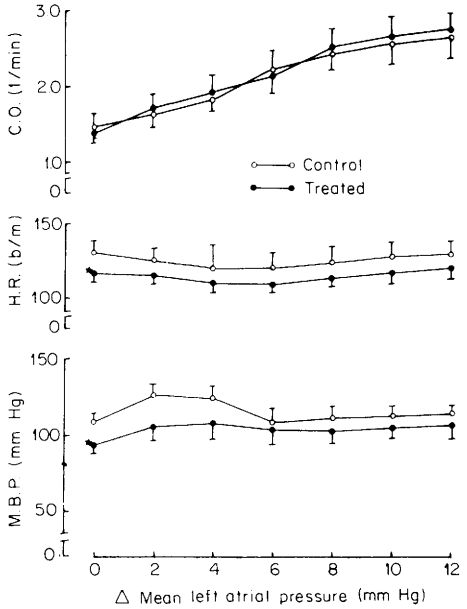

FIG. 3. Effect of methyldopa treatment (100 mg/kg, orally twice daily for 3 days) on increases in mean blood pressure (M.B.P.), heart rate (H.R.), and cardiac output (C.O.) produced with corresponding changes in the left atrial pressure during the infusion of Tyrode's solution ($N = 7$, $^*P < 0.05$).

ume load is not compromised following the drug treatment. These results indicate that despite the reduction in sympathetic transmission to the heart, which is responsible for the bradycardia observed following methyldopa treatment (13, 14), the ability of the sympathetic nervous system and that of the myocardium to respond to external volume load is not affected by the drug treatment. This could be explained partly due to the fact that sympathetic innervation to the S-A node which controls the heart rate and to the ventricles controlling the contractility may differ in their physiological responsiveness under a given situation (37), and therefore, it may be possible that 3-day treatment with methyldopa preferentially affects the sympathetic transmission controlling the heart rate (13, 14), without significantly altering the sympathetic transmission to the ventricles or its ability to respond to external stress. An alternate explanation for the ability of the myocardium to respond effectively to the volume load may reside in the fact that the reduction in the afterload or peripheral resistance produced by methyldopa was beneficial in improving or maintaining cardiac performance during external stress.

Conclusions. Administration of methyldopa (100 mg/kg, orally twice daily for a period of 3 days) to mongrel dogs produced significant reductions in blood pressure and heart rate. The hypotensive effect of the drug was due to a reduction in peripheral resistance. Methyldopa treatment also produced a significant decrease in coronary vascular resistance. Studies on the left ventricular function indicated that treatment with methyldopa does not compromise the ability of the myocardium to respond to an increased work load. Thus, the beneficial effect of this agent on the myocardial circulation, together with its lack of any detrimental effect on the cardiac function suggest that methyldopa may be an effective agent for the control of hypertension.

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