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Effects of Angiotensin and Angiotensin Blockade on Coronary Circulation and Coronary Reserve

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Angiotensin is a potent coronary vasoconstrictor, but little is known of the effects of long-term activation of the renin-angiotensin system on coronary reserve in humans. The effects of exercise on coronary hemodynamics were determined in eight patients with mild essential uncomplicated hypertension, before and after treatment with furosemide (50 mg, to ensure activation of the renin-angiotensin system). Coronary sinus blood flow was measured by thermodilution technique, intra-arterial blood pressure was measured from the ascending aorta, and plasma renin activity was determined by radioimmunoassay. Oxygen supply and demand were derived (using coronary sinus blood flow multiplied by the arteriovenous oxygen difference to equal oxygen supply and heart rate multiplied by the mean systolic blood pressure to equal oxygen demand) both at rest and during isometric exercise (handgrip to 50 percent of maximal effort for three minutes). The study was a single-blind crossover (furosemide versus placebo) design. Furosemide produced a significant reduction in coronary sinus blood flow, associated with an increase in coronary vascular resistance. Changes in mean arterial pressure and heart rate were insignificant. Slight reductions in plasma volume and mean right atrial pressure were observed. During isometric exercise, the increase in oxygen supply for a given increment in oxygen demand was attenuated by furosemide. The contribution of the renin-angiotensin system to this effect was determined by the short-term administration of 25 mg of the angiotensin converting enzyme inhibitor captopril. Forty-five minutes after oral captopril, coronary reserve was restored to pretreatment values. In conclusion, furosemide modulates coronary reserve, and it is likely that this is because furosemide mediates activation of renin-angiotensin system, thus reducing the vasodilatory capacity of the coronary arteries.

Patients with mild to moderate uncomplicated arterial hypertension are frequently treated with diuretics [1]. Despite the widespread use of diuretics, little has been reported regarding their effect on the coronary circulation. We have previously observed a reduction in coronary sinus blood flow and an increase in coronary vascular resistance in furosemide-treated hypertensive patients compared with that in untreated matched hypertensive subjects [2]. We have therefore extended these observations to assess the effect of treatment with furosemide on coronary reserve, and to determine whether any such changes are the result of stimulation of the renin-angiotensin system using the angiotensin converting enzyme inhibitor captopril.

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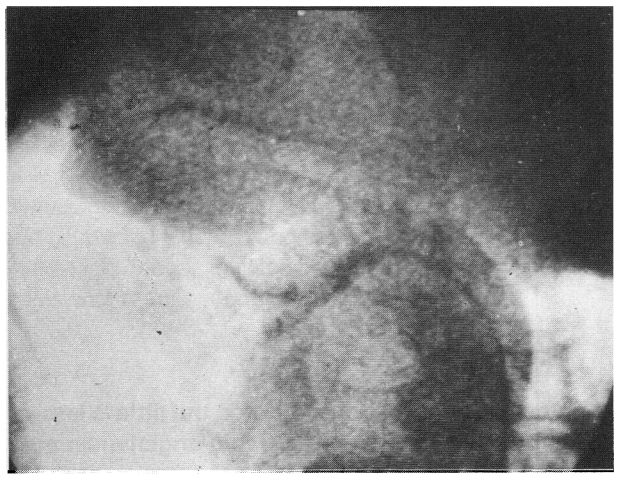

Figure 1. *The image of the coronary sinus was recorded on tape and was utilized as a guide for repositioning of the tip of the thermodilution catheter in the same position during the second hemodynamic study.*

PATIENTS AND METHODS

Patient Selection. Eight patients with uncomplicated mild essential hypertension were studied: all were men ranging in age from 36 to 51 years (average, 44). Criteria for enrollment in the study included: (1) supine diastolic blood pressure values between 95 and 105 mm Hg throughout the first week in the hospital (control period); (2) exclusion of secondary forms of hypertension on routine screening tests; (3) absence of current or previous heart failure, myocardial infarction, or angina pectoris; normal electrocardiographic results at rest and during bicycle exercise; and normal chest radiographic and echocardiographic results; (4) no antihypertensive treatment during the four weeks before hospitalization; (5) informed consent after complete information on the purpose and the protocol of the study.

Protocol. The study was of a single-blind crossover design. The patients were randomly assigned to receive either furosemide (50 mg orally for one week) or placebo. Four patients were treated with furosemide first, and four received placebo first. No differences due to the temporary sequence in the administration of placebo and furosemide were observed. Throughout the study period, all patients maintained a constant sodium intake (130 meq/liter per day). Body weight, systolic and diastolic blood pressure, heart rate, and 24-hour urinary volume were measured daily. Plasma sodium and potassium levels and plasma volume (using iodine 125-labeled human albumin, Sorin) were measured before and after each treatment period. Hemodynamic studies were performed in duplicate at the end of each treatment period (one week) before and 45 minutes after the oral administration of captopril (25 mg). Baseline values for coronary sinus blood flow, heart rate, mean arterial pressure, and mean right atrial pressure were determined at rest. Blood samples were taken from the coronary sinus and from the arterial line for oxygen content determination. Subjects were then requested to perform handgrip exercise to 50 percent of maximal effort for three minutes, and the effect of this isometric exercise on the foregoing parameters was determined.

Hemodynamic Studies. All hemodynamic studies were performed in the morning without premedication. A number 5 French polyethylene catheter was introduced percutaneously (using local anesthesia with 1 percent lidocaine) into the brachial artery and advanced under fluoroscopic control to the ascending aorta for direct measurement of blood pressure. Phasic and mean arterial pressures were recorded continuously during the study by means of a Statham strain-gauge transducer (P23db) connected to a Battaglia Rangoni recorder (model KO-380). Heart rate was derived from the electrocardiographic tracing, which was recorded continuously during the hemodynamic studies. Coronary sinus blood flow was determined by the continuous thermodilution technique of Ganz et al [3] using a preshaped coronary sinus catheter (number 7 French, Wilton Webster) introduced through an antecubital vein (right arm) and positioned using fluoroscopy in the coronary sinus. The anatomy of the coronary sinus was visualized in each patient by injecting small volumes (2 to 3 ml) of radiopaque contrast medium (71 percent Urografin) and recorded on electromagnetic tape (Sony VO-5800PS) (**Figure 1**). The image of the coronary sinus recorded on tape was utilized as a guide for repositioning of the tip of the thermodilution catheter relative to collateral veins during the second hemodynamic study. The room temperature indicator solution (5 percent glucose) was injected at 70 ml/minute through the thermodilution catheter for 15 seconds. The deflections caused by changes in thermistor resistance as a result of blood temperature changes were measured by means of a Wheatstone bridge (Wilton Webster) and recorded on a Battaglia Rangoni recorder (model KO-380). Coronary sinus blood flow was obtained using the formula:

$$\text{Flow} = \text{Vi} \times 1.08 \times (\text{TG} - \text{Ti}/\text{TG} - \text{Tm} - 1)$$

where Vi = volume of injectate (ml/minute); TG, Ti, Tm are temperatures of blood, injectate, and mixture of blood and injectate; 1.08 is a constant derived from the density and specific heat of glucose solution and blood. Coronary sinus blood flow measurements were repeated until three successive determinations demonstrated homeostasis. Coronary vascular resistance was calculated as the ratio of mean aortic pressure to coronary sinus blood flow. Coronary sinus venous blood was taken simultaneously with arterial blood for determination of oxygen immediately after each measurement of coronary sinus blood flow. Oxygen content was measured directly using a 282 CO-OXIMETER SYSTEM INSTRUMENTATION LABORATORY (Lexington, Massachusetts). Myocardial oxygen supply was calculated as the product of coronary sinus blood flow and percent arteriovenous oxygen difference. Myocardial oxygen demand was determined as the product of heart rate and mean systolic blood pressure (rate-pressure product). Mean right atrial pressure was measured with a floating venous catheter (number 4 French polyethylene) introduced percutaneously through a peripheral vein (generally, antecubital vein of the left arm). In each patient, three measurements of coronary sinus blood flow were made at rest and during isometric exercise. In order to exclude any Valsalva effect during exercise, mean right atrial pressure was monitored continuously [4], and the position of the coronary sinus catheter was checked by injection of small volumes (1 to 2 ml) of contrast medium. The increase in oxygen

TABLE I Effects of Captopril in Eight Patients with Essential Hypertension during Placebo and Furosemide Periods

	Placebo		Furosemide	
	Control	Captopril	Control	Captopril
Heart rate (beat/minute)	71 ± 5	68 ± 6	76 ± 4	69 ± 5
Systolic blood pressure (mm Hg)	153 ± 9	149 ± 10	148 ± 8	129 ± 6
Diastolic blood pressure (mm Hg)	98 ± 7	96 ± 8	98 ± 5	86 ± 5
Mean arterial pressure (mm Hg)	116 ± 8	114 ± 5	115 ± 7	100 ± 6
Mean right atrial pressure (mm Hg)	4 ± 1	4 ± 1	2 ± 1	3 ± 1
Coronary sinus blood flow (ml/minute)	217 ± 21	224 ± 19	182 ± 15	211 ± 20
Coronary vascular resistance (mm Hg/ml/minute)	52 ± 3	51 ± 2	63 ± 3	47 ± 3
Arteriovenous oxygen difference (ml/dl)	10.6 ± 0.9	10.4 ± 1	10.5 ± 0.9	10.4 ± 0.8
Oxygen supply (ml/minute)	22.2 ± 2	23.0 ± 1	19.1 ± 1.5	22 ± 2
Rate-pressure product (mm Hg/beat/minute)	108 ± 13	102 ± 11	112 ± 12	89 ± 10

Values are mean ± SEM.

supply observed during exercise for a given increase in oxygen demand was taken as an index of coronary reserve.

Statistical Analysis. Hemodynamic data for both treatment periods and before and after captopril were compared and evaluated by the paired Student t test and expressed as mean ± SEM (Olivetti M24SP Computer). Statistical significance was accepted at the 95 percent confidence level ($p < 0.05$).

RESULTS

In all patients, furosemide increased supine plasma renin activity (from 0.8 ± 0.3 to 4.4 ± 0.8 mg/ml/hour; $p < 0.01$) and decreased plasma volume (from 19.8 ± 0.7 to 18.2 ± 0.4 ml/cm^2; $p < 0.05$). Body weight fell with diuretic administration by about 1 kg (75.6 ± 5.6 with placebo versus 74.7 ± 5.3 kg with furosemide; $p < 0.05$). No significant changes were observed in serum electrolyte values throughout the study.

Table I shows coronary hemodynamics during furosemide and placebo treatment, together with the response to the short-term administration of 25 mg of captopril.

Diastolic arterial pressure and heart rate were similar during furosemide and placebo periods, whereas systolic blood pressure and mean right atrial pressure were slightly reduced after one week of diuretic treatment. Coronary sinus blood flow was reduced (182 ± 15 versus 217 ± 21 ml/minute; $p < 0.01$) and coronary vascular resistance was increased (63 ± 3 versus 52 ± 3 mm Hg/ml/minute; $p < 0.05$) following activation of the renin-angiotensin system by furosemide. Rate-pressure product (taken as index of oxygen demand of the myocardium) was practically unchanged (112 ± 12 versus 108 ± 13 mm Hg/beat/minute; NS), whereas oxygen supply was slightly reduced by furosemide.

The administration of captopril (25 mg orally) did not significantly alter arterial pressure, mean right atrial pressure, and coronary hemodynamics during the placebo period. Coronary sinus blood flow was restored to pretreatment values by captopril when the renin-angiotensin system had been stimulated by the diuretic. The increase in coronary sinus blood flow was not related to an increase in rate-pressure product, since the latter was in fact reduced by captopril (89 ± 10 versus 112 ± 12; $p < 0.05$). Coronary vascular resistance decreased significantly following short-term converting enzyme inhibition (47 ± 3 versus 63 ± 3 mm Hg/ml/minute; $p < 0.01$) only after pretreatment with furosemide.

Table II summarizes the effects on coronary hemodynamics of isometric exercise (supine hand grip, 50 percent of maximal for three minutes) during the placebo period and after one week of treatment with furosemide. Blood pressure, heart rate, and mean right atrial pressure after three minutes of exercise were similar during placebo and furosemide periods. Coronary sinus blood flow was significantly lower when handgrip was performed after diuretic treatment (294 ± 28 versus 379 ± 31 ml/minute; $p < 0.01$), and coronary vascular resistance was higher (43 ± 5 versus 35 ± 6 mm Hg/ml/minute; $p < 0.05$). Following angiotensin converting enzyme inhibition, the effects of exercise on coronary sinus blood flow and coronary vascular resistance during treatment with

TABLE II Effects of Isometric Exercise in Eight Patients with Essential Hypertension before and after Captopril during Placebo and Furosemide Periods

	Placebo		Furosemide	
	Exercise	Exercise after Captopril	Exercise	Exercise after Captopril
Heart rate (beat/minute)	94 ± 8	99 ± 7	98 ± 10	95 ± 9
Systolic blood pressure (mm Hg)	188 ± 10	174 ± 9	179 ± 9	181 ± 10
Diastolic blood pressure (mm Hg)	109 ± 9	101 ± 9	106 ± 8	107 ± 8
Mean arterial pressure (mm Hg)	134 ± 9	125 ± 7	129 ± 7	132 ± 8
Mean right atrial pressure (mm Hg)	5 ± 2	3.5 ± 1	3 ± 1	4 ± 2
Coronary sinus blood flow (ml/minute)	379 ± 31	376 ± 32	294 ± 28	372 ± 28
Coronary vascular resistance (mm Hg/ml/minute)	35 ± 6	33 ± 4	43 ± 5	35 ± 3
Arteriovenous oxygen difference (ml/dl)	10.6 ± 1.0	10.5 ± 1.0	10.5 ± 1.2	10.7 ± 1.2
Oxygen supply (ml/minute)	40 ± 3	39 ± 4	30 ± 3	39 ± 3
Rate-pressure product (mm Hg/beat/minute)	176 ± 62	177 ± 20	175 ± 20	175 ± 19

Values are mean ± SEM.

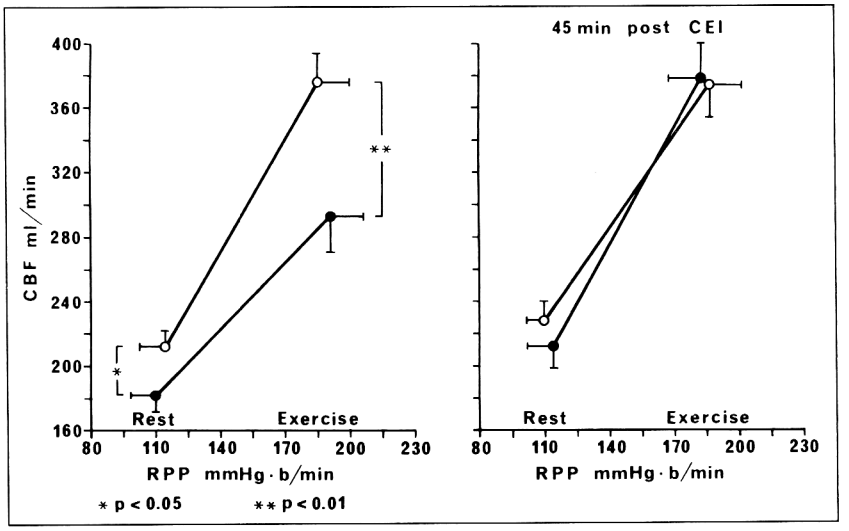

Figure 2. *Relationship between increase in rate-pressure product (RPP) associated with isometric exercise and the increase in coronary sinus blood flow (CBF) before and after captopril (CEI), during the placebo (○) period and during the furosemide (●) period.*

furosemide were similar to those observed during the placebo period (Table II).

Figure 2 shows the relationship between the increase in myocardial oxygen demand (rate-pressure product) associated with exercise and the increase in coronary sinus blood flow before and after activation and inhibition of the renin-angiotensin system. The increase in coronary sinus blood flow for a given increase in rate-pressure product was attenuated by furosemide (294 ± 28 versus 379 ± 31 ml/minute; $p < 0.01$). Forty-five minutes after oral captopril, coronary flow reserve was restored to pretreatment values.

COMMENTS

Angiotensin II has been shown to increase coronary vascular resistance [5,6]. Whether or not furosemide treat-

ment affects coronary hemodynamics in patients with mild arterial hypertension by mechanisms other than activation of the renin-angiotensin system remains to be elucidated. In this study, coronary vascular resistance was higher and coronary sinus blood flow was lower during the period of diuretic treatment than during the placebo period.

The unloading effects of furosemide on the heart (slight reductions in plasma volume, right atrial pressure, and systolic arterial pressure) may be responsible for a reduction in the myocardial oxygen requirements and therefore for a metabolic regulation of coronary sinus flow [7]. It is well established, in fact, that the heart regulates its own blood supply by elaborating coronary vasodilators in proportion to its rate of energy expenditure [8]. However, the observation that 45 minutes after oral captopril, coronary sinus blood flow and coronary vascular resistance were restored to pretreatment values strongly suggests that the activation of the renin-angiotensin system due to furosemide is responsible for the increase in coronary vasomotor tone at rest. In addition, angiotensin converting enzyme inhibition produces coronary vasodilatation only if the renin-angiotensin system has been chronically activated by diuretic treatment. The effects of captopril on the coronary circulation are best described in terms of reduced angiotensin II levels [9,10], although a possible contribution by increased bradykinin or stimulated prostaglandins cannot be ruled out completely [9,11–13]. It is therefore plausible that the mechanism responsible for the increase in coronary sinus blood flow produced by captopril in high-renin conditions is a direct effect on coronary resistance of the reduction in angiotensin II.

In physiologic conditions, coronary sinus blood flow can increase two to four times to meet the increased myocardial oxygen demands associated with exercise [14]. Increased myocardial oxygen supply is normally obtained by an increase in coronary sinus blood flow, with little if any contribution from an increase in oxygen extraction. Therefore, the increase in coronary sinus blood flow during exercise can only be achieved by coronary vasodilatation.

In our study, the increase in coronary sinus blood flow for a given increment in pressure work was attenuated by furosemide treatment. The contribution of the renin-angiotensin system to this effect was assessed by the short-term administration of captopril. The fact that coronary flow reserve was restored to pretreatment values after captopril suggests that activation of the renin-angiotensin system reduces the coronary reserve in patients with mild

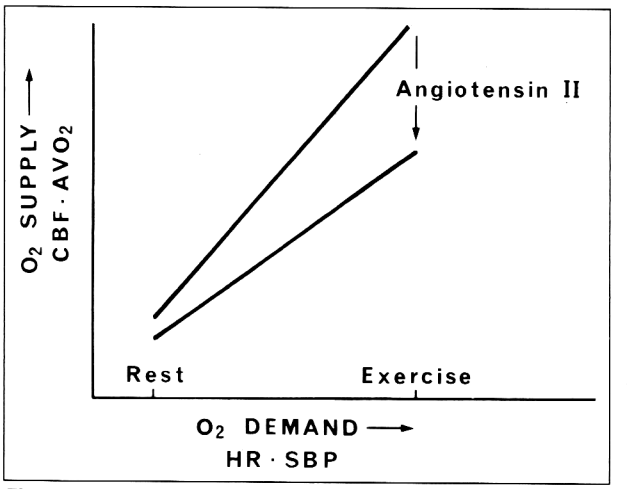

Figure 3. *Furosemide modulates coronary flow reserve and it is likely that this is because diuretic treatment mediates activation of the renin-angiotensin system, thus reducing the vasodilatory capacity of the coronary arteries.*

essential hypertension. We advance, therefore, the hypothesis that angiotensin II may alter the control mechanisms of coronary sinus blood flow by reducing the extent of coronary artery vasodilatation during exercise (**Figure 3**). Angiotensin II has, in fact, been shown to affect coronary resistance at very low blood concentrations, although systemic pressure and cardiac work were not affected [5]. Whether or not the sensitivity of the coronary artery to angiotensin II is increased in patients with mild arterial hypertension remains to be elucidated.

In conclusion, in patients with mild hypertension without left ventricular hypertrophy and negative results on exercise testing, renin-angiotensin system activation by furosemide reduces coronary sinus blood flow at rest by increasing coronary vascular resistance in the absence of significant changes in heart rate and mean arterial blood pressure. Coronary flow reserve is also reduced following activation of the renin-angiotensin system. Converting enzyme inhibition by captopril reverses the coronary hemodynamic changes induced by diuretic treatment and restores the coronary flow reserve. These observations suggest that the renin-angiotensin system, if stimulated, exerts a direct effect on coronary vasomotor activity and that converting enzyme inhibition induces coronary vasodilatation only in the presence of an activated renin-angiotensin system.

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Discussion

Dr. Robertson: Do you think it is possible that, by choosing furosemide, you may have minimized the effects of angiotensin II on the coronary arteries? The reason I ask this question is that sodium depletion, with or without diuretics, certainly minimizes the pressor effects of angiotensin.

Dr. Magrini: Well, we chose furosemide because it is the most standardized way to activate the renin-angiotensin system.

Dr. Robertson: The point I was trying to make is slightly different. If you activate the renin system without involving any sodium depletion, then you might get more marked effects than those you observed after furosemide.

Dr. Magrini: This is possible.