Hemodynamic Correlates of Saralasin-induced Arterial Pressure Changes

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SUMMARY Angiotensin antagonists have proved useful in elucidating the clinical role of the renin-angiotensin system; and their diagnostic and therapeutic efficacy in hypertension has been the subject of many reports but the hemodynamic effects remain unknown. Therefore, saralasin was infused intravenously (1.3 mg/min for 30 min) in 26 sodium-depleted patients with hypertension. Systemic hemodynamic alterations were determined before, during, and after infusion. On the basis of mean arterial pressure (MAP) changes, patients were classified as responders, nonresponders, or pressor-responders (MAP changes ≥ 10 mm Hg). MAP fall in responders was achieved through reduced cardiac output and/or total peripheral resistance, with minimal or absent reflexive heart rate increase. In nonresponders, despite no change in MAP, output fell in parallel with stroke index and left ventricular ejection rate. In pressor-responders, saralasin increased vascular resistance. Thus, in addition to variable effects on vascular receptors, saralasin produced inhibitory cardiac effects either through altered venous return or inhibition of contractility.

RECEPTOR BLOCKING AGENTS for angiotensin II have provided a useful approach for elucidating the physiological and pathophysiological effects of the renin-angiotensin system in man. This includes the potential for new diagnostic and therapeutic approaches to hypertensive diseases. Among a series of angiotensin II analogs that have been synthesized, saralasin acetate (1-Sar-8-Ala-angiotensin II) has emerged as a competitive inhibitor of angiotensin II in a variety of tissues, in vitro and in vivo. However, its specific target organ effects are variable depending on its structural similarity to the natural hormone and to the state of sodium balance. In clinical studies, it has been reported to be a safe and effective means for detecting angiotensin-mediated hypertension in man when given by continuous infusion or by intravenous bolus injections, provided adequate sodium depletion is induced. Its side effects have been limited to an initial transient pressor response in most patients; a sustained pressor response, usually in low renin essential hypertensive patients; a marked hypertensive effect, mainly in patients receiving vasodilator therapy; and to pheochromocytoma crisis probably through direct tumor stimulation of catecholamine release by the analog. In spite of these data characterizing this synthetic analog, no information is available concerning its hemodynamic effects in patients.

Material and Methods

Nineteen men and seven women, aged 23 to 64 years (mean ± SEM: 50 ± 2) with sustained hypertension (defined as 150/90 mm Hg or above on at least three separate and controlled occasions) gave their informed consent to be subjects of this study. Twenty-three either had never received any antihypertensive therapy at all or had discontinued their medications at least four weeks previously; however, two patients continued to receive a diuretic and one methyldopa because of the severity of their hypertension. Patients with cerebrovascular accident, myocardial infarction, malignant hypertension, and cardiac failure and pregnant patients were specifically excluded from this study. All were admitted to the clinical research ward and underwent complete history, physical examination, and laboratory evaluation; no special diet was prescribed.

The following schedule of tests was established: arterial pressure recording, every 5 minutes for a period of 15 minutes, four times daily, on two consecutive days. Routine serum biochemistry (electrolytes, creatinine, triglycerides, and SMA-12), complete blood count, peripheral plasma venous renin activity, urinalysis, and a 24-hour urinary collection for electrolytes and endogenous creatinine clearance were obtained. An electrocardiogram, chest X-ray, intravenous pyelogram, aortogram, and selective renal arteriography, bilateral renal venous renin plasma activity, and blood volume (red cell mass and plasma volume) determinations were obtained prior to study. Plasma renin activity was determined by radio-immunoassay of angiotensin I in peripheral blood withdrawn with the patient supine. Blood volumes (i.e., plasma volume and red cell mass) were determined with radiiodinated human serum albumin (125I) and red cells labeled with radioactive chromium (51Cr), administered to the patient in the morning in a fasting, supine state.

Hemodynamic studies were performed in the morning after an overnight fast as described previously but modified to be performed in the sodium-depleted state by administration of furosemide (80 mg p.o.) the previous evening. In brief, small polyethylene catheters were introduced percutaneously into an antecubital vein and brachial artery, and were advanced centrally. Baseline cardiac output determinations were performed in triplicate from indocyanine green dye dilution curves, with the patient lying supine. Pressures and electrocardiograms were recorded continuously on a multichannel polygraph. From these records hemodynamic indices were measured or derived. After recording baseline values, saralasin was infused intravenously at a rate of 1.3 mg/min for 30 minutes with an infusion pump; and cardiac
output determinations were repeated during the third and tenth minutes of infusion, immediately upon cessation of infusion, and 30 minutes thereafter. Mean arterial pressure was calculated as the sum of one third of pulse pressure and the diastolic pressure. For evaluation of individual responsiveness to saralasin, patients whose mean arterial pressure demonstrated a fall equal to or greater than 10 mm Hg during infusion (after transient initial pressor response) were considered responders; patients whose mean arterial pressure failed to change by more than 9 mm Hg were considered nonresponders; and patients whose pressures rose by 10 mm Hg or more were termed pressor-responders.

The results were evaluated statistically by the two-tailed Student's t-test for paired and unpaired data analysis, and are expressed as the mean ± one standard error of the mean.

Results

Study Population

Since at present there is no absolute way of determining whether a patient with a renal arterial lesion has renovascular hypertension other than remission of hypertension following adequate surgery, patients whose predominant clinical finding was renal arterial lesion were classified as having renal arterial disease (RAD); those with a renal parenchymal abnormality were considered to have renal parenchymal disease (RPD); and those patients without any identifiable anatomical abnormality were classified as having essential hypertension (EH), after exclusion of other causes of hypertension. Thus, renal arterial disease was found in five of the eight responders, three of 11 nonresponders, and in three of the seven pressor-responders (table 1). In none of the three nonresponders with RAD was there a renal venous renin ratio (of affected to nonaffected kidney) greater than 1.6; and only one of the pressor-responders demonstrated this increased ratio (a patient with bilateral RAD). Renal parenchymal disease was diagnosed in one responder (a patient with dysplastic kidney and chronic glomerulonephritis) and two nonresponders (one patient each with a huge parapelvic renal cyst and hypernephroma). Mean arterial pressures prior to furosemide were 132 ± 4.9 mm Hg for responders, 128 ± 6.3 mm Hg for nonresponders, and 119 ± 5.6 mm Hg for pressor-responders. There were no significant differences between groups with respect to mean arterial pressure and plasma volume; however, resting supine peripheral venous renin activity was highest in the responder group (P < 0.001; table 1).

Further, after furosemide and prior to saralasin infusion, heart rates and mean arterial pressures were similar (table 2). Each of the three groups demonstrated similar hemodynamic indices, but total peripheral resistance was significantly different in nonresponders and pressor-responders from the responders (P < 0.001).

Systemic Hemodynamic Effects

Mean arterial pressure. Mean arterial pressure (MAP) fell in the responder group by 14% 10 min after the infusion was started (from 133 ± 6.6 to 114 ± 6.5 mm Hg) and by 16% at the time the infusion was terminated (to 112 ± 6.8 mm Hg) (fig. 1). In only one patient in this group did the pressor response (at 3 min of infusion) exceed 10 mm Hg. Mean arterial pressure remained reduced 30 min after infusion was discontinued (121 ± 5.2 mm Hg), although the pressure fall (with respect to control values) exceeded 10 mm Hg in only three patients. In contrast, pressure remained unchanged in the nonresponder group, except for the transient pressor response during the third minute of infusion. This pressor response, from 133 ± 8 to 142 ± 7 mm Hg, exceeded 10 mm Hg in six patients. The patients of the pressor-responders group consistently demonstrated persistent pressure increases during and after infusion; and significant pressure increase (> 10 mm Hg) was present at the end of infusion and 30 min thereafter in all patients. (The individual hemodynamic responses for each patient are detailed in table 3.)

Table 1. Study Population—Clinical Details

<table>
<thead>
<tr>
<th>No. patients</th>
<th>Responders</th>
<th>Nonresponders</th>
<th>Pressor-Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>48 ± 4.5</td>
<td>48.5 ± 3.3</td>
<td>53 ± 2.5</td>
</tr>
<tr>
<td>Hypertension:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renovascular</td>
<td>5</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Renal parenchymal</td>
<td>2</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>132 ± 4.9</td>
<td>128 ± 6.3</td>
<td>119 ± 5.6</td>
</tr>
<tr>
<td>Plasma volume (ml/cm body ht)</td>
<td>15.8 ± 0.78</td>
<td>15.9 ± 0.97</td>
<td>17.2 ± 1.06</td>
</tr>
</tbody>
</table>

*P <0.001 when compared to both other groups.

Table 2. Baseline Hemodynamic Indices

<table>
<thead>
<tr>
<th>Indices</th>
<th>Responders</th>
<th>Nonresponders</th>
<th>Pressor-Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>133 ± 7</td>
<td>133 ± 8</td>
<td>114 ± 10</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>89 ± 8</td>
<td>86 ± 5</td>
<td>73 ± 2</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>2.4 ± 0.1</td>
<td>2.9 ± 0.2</td>
<td>2.5 ± 0.4</td>
</tr>
<tr>
<td>Total peripheral resistance (T.P.R. units)</td>
<td>36 ± 2.3*</td>
<td>26 ± 2.5</td>
<td>23 ± 2.2</td>
</tr>
<tr>
<td>Stroke index (ml/beat/m²)</td>
<td>29 ± 3.2</td>
<td>34 ± 2.2</td>
<td>35 ± 2.8</td>
</tr>
<tr>
<td>Mean rate of left ventricular ejection/m² (ml/sec/m²)</td>
<td>109 ± 8</td>
<td>130 ± 10</td>
<td>129 ± 10</td>
</tr>
</tbody>
</table>

*P <0.001 when compared to each of the other groups.
**Heart rate.** Despite the remarkable pressure fall in the responders, heart rate was not consistently increased; and at the end of infusion, three of the eight patients demonstrated a slower heart rate (table 3). Only two patients (nos. 3 and 6) showed a real increased heart rate coinciding with the peak hypotensive response. However, in the other groups, heart rate fell appropriately when arterial pressure transiently increased at the onset of infusion (from 86 ± 5 to 83 ± 5 beats/min for nonresponders and from 72 ± 2 to 69 ± 3 for pressor-responders). During and after saralasin infusion, no consistent change in heart rate was observed in the nonresponder group.

**Cardiac index.** In the responder group, during most of the infusion and thereafter, cardiac index was reduced in seven and six of the eight responders at 10 and 30 min of infusion, respectively; and in the latter six patients this reduced output was maintained 30 min after the infusion was discontinued. Therefore, in six of the eight responders, the cardiac output responses were consistently reduced during most of the infusion. In eight of the nonresponders, cardiac index remained unchanged or was reduced by the third minute; and it was reduced in eight and ten patients after 10 and 30 min of infusion, respectively. After discontinuation of infusion, it remained decreased in eight patients. If the transient pressor responses observed during the third minute are excluded, cardiac index during infusion was consistently reduced in eight of the eleven patients. In the pressor-responding group, cardiac index remained unchanged or was reduced at the third minute in all patients; at 10 and 30 min it was reduced in four and five patients, respectively; and it was reduced in three patients 30 min after the infusion was discontinued. In general, stroke index changes paralleled those of cardiac index; but in view of the variability of heart rate, stroke volume was reduced at the end of infusion in six responders, nine nonresponders, and three pressor-responders.

**Total peripheral resistance.** The angiotensin II receptor inhibitor reduced total peripheral resistance in only four patients of the responder group at 10 and 30 min of infusion and 30 min after discontinuation of infusion (table 3). However, during saralasin infusion, changes were consistently unidirectional in only three patients. By way of comparison, total peripheral resistance was reduced or unchanged in four patients of the nonresponder group at the third and tenth minute of infusion, in two patients at the end of infusion, and in three patients 30 min after infusion. However, total peripheral resistance increased in six of the 11 nonresponder patients and in all but two of the pressor-responders.

**Discussion**

This study provides the first clinical information concerning the hemodynamic alterations induced by saralasin infusion in man with a variety of forms of hypertension. These data show that the reduced arterial pressure in patients responding to saralasin resulted from decreased cardiac output and/or total peripheral resistance. Patients with a depressor response (i.e., responder group) demonstrated a reduced cardiac output alone (four patients), reduced total peripheral resistance (two patients), or a reduction in both indices (in the remaining two). Although the patients of the nonresponder group demonstrated no significant change in arterial pressure, the angiotensin II analog did produce significant hemodynamic alterations in most patients: reduced cardiac and stroke indices and left ventricular ejection rate associated with an increased total peripheral resistance. Patients who revealed a pressor response also demonstrated a fall in cardiac output, but this was consistent
Table 3. Individual Responses to Saralasin Infusion

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Baseline</th>
<th>3rd Minute</th>
<th>10th Minute</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>CI</td>
<td>SI</td>
</tr>
<tr>
<td>1</td>
<td>55</td>
<td>2.4</td>
<td>43.0</td>
</tr>
<tr>
<td>2</td>
<td>111</td>
<td>1.9</td>
<td>17.8</td>
</tr>
<tr>
<td>3</td>
<td>68</td>
<td>2.5</td>
<td>37.5</td>
</tr>
<tr>
<td>4</td>
<td>125</td>
<td>3.0</td>
<td>23.0</td>
</tr>
<tr>
<td>5</td>
<td>89</td>
<td>1.9</td>
<td>21.8</td>
</tr>
<tr>
<td>6</td>
<td>96</td>
<td>2.0</td>
<td>20.4</td>
</tr>
<tr>
<td>7</td>
<td>90</td>
<td>2.7</td>
<td>29.4</td>
</tr>
<tr>
<td>8</td>
<td>77</td>
<td>2.6</td>
<td>34.0</td>
</tr>
</tbody>
</table>

Mean ± 1 SEM 89 ± 8 2.4 ± 0.1 28.5 ± 3.2 35.5 ± 2.3 109 ± 8.0 88 ± 8 2.5 ± 0.2 30.1 ± 3.3 34.7 ± 2.2 95 ± 16.4 90 ± 7.8 2.2 ± 0.2

Abbreviations: HR = heart rate (beats/min); CI = cardiac index (L/min/m²); SI = stroke index (ml/beat/m²); TPRI = total peripheral resistance index (mmHg/m²); MRLVE = left ventricular ejection rate (ml/sec/m²).

Only during the initial pressure rise; a later and more prolonged elevated arterial pressure was explained mainly by an increased vascular resistance.

In recent years, angiotensin II has been shown to influence the cardiovascular system in a number of different ways, in addition to its known very potent vasoconstrictor properties. Fundamental interactions with many different organ systems have been documented, including the central and peripheral nervous system, the adrenal cortex and medulla, and the kidney.\(^\text{18-23}\) Considerably less interest has been directed to the hemodynamic responses of patients with hypertension who were submitted to angiotensin II blockade, despite the varied clinical and physiological characteristics in hypertension of different clinical forms and despite the heterogeneity of saralasin responses.

One of the more intriguing hemodynamic changes observed was shared by most of the responders and non-responders: a reduced cardiac output independent of changes in total peripheral resistance and arterial pressure. And, despite this fall in cardiac output, there was no significant reflexive change in heart rate or left ventricular ejection rate. However, in contrast, the hemodynamic findings in pressor-responders were similar to those induced by angiotensin II infusion: an unchanged or reduced cardiac index and increased TPR. These latter hemodynamic changes in the patient with hypertension who demonstrated a pressor response to saralasin are consistent with an agonistic angiotensin II vascular response.

The purpose of this study was not to relate renin classification of patients with hypertension to hemodynamics. In fact, the converse was the case; we were interested in determining the hemodynamic responses of patients with hypertension to saralasin infusion. Nevertheless, these studies showed that patients who responded with a fall in arterial pressure had the highest plasma renin activity; and these patients had roughly four times the level of PRA of either the nonresponders or pressor-responders. The latter two groups, however, had roughly the same PRA.

That cardiac output was reduced independent of pressure and heart rate changes indicated that diminished venous return or changes in central blood volume cannot provide the sole explanation; additional factors probably were involved. First among these considerations, angiotensin II has been shown to alter inotropic properties of cardiac muscle, depending upon its ability to increase transmembrane ion movements.\(^\text{24}\) This apparently was blocked by specific receptor antagonism. In addition, increased release or decreased reuptake of norepinephrine from the active adrenergic nerve endings\(^\text{19-23}\) or the unlikely sensitization of the myocardium to the effects of sympathetic vasomotor discharge could alter inotropic properties of myocardium. Furthermore, angiotensin II has been shown to stimulate certain central nervous system areas\(^\text{6, 20, 21}\) resulting in increased arterial pressure, probably through increased sympathetic outflow or reduced parasympathetic cardiovascular input. It is possible that a significant portion of the hypertensive effect of angiotensin II may be mediated through direct action on the central nervous system; if so, this might be blocked by saralasin. Supporting this thesis are the findings that saralasin crosses the blood-cerebrospinal fluid barrier to antagonize central effects of angiotensin II,\(^\text{22}\) and that anteroventral third ventricular lesions prevent the development of renal hypertension.\(^\text{23}\)

Thus, it would seem that in the responder group, saralasin acted primarily as an angiotensin II antagonist operating through competitive inhibition of the arteriolar angiotensin II receptors, although additional receptor actions in heart or
brain are possible. In the other two groups (in which PRA was substantially lower), saralasin could have acted as an arteriolar agonist, producing vasoconstriction, reflexive bradycardia, and reduced cardiac output. Alternatively, it could also have acted by competitively antagonizing angiotensin II receptors in brain centers or myocardium.

In conclusion, hemodynamic responses to saralasin infusion in sodium-depleted hypertensive patients were dependent on complex interactions between cardiac output and vascular resistance changes. In those patients who responded to saralasin infusion, the angiotensin II analog acted as a competitive antagonist at the arteriolar level. In those patients who failed to respond or who demonstrated a pressor response, the arteriolar effect was more akin to a receptor agonist. The responses of the heart could have resulted from a combination of effects on venous return, direct or indirect inhibition of myocardial contractility, and possibly effects mediated through altered autonomic cardiovascular control.

References

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Efficacy of Dopamine, Dobutamine, and Epinephrine During Emergence from Cardiopulmonary Bypass in Man

Petter A. Steen, M.D., John H. Tinker, M.D., James R. Pluth, M.D., Donald A. Barnhorst, M.D., and Sait Tarhan, M.D.

SUMMARY Hemodynamic effects of dobutamine and dopamine (both 5, 10, 15 μg/kg/min) and epinephrine (0.04 μg/kg/min) were studied immediately following cessation of cardiopulmonary bypass in 34 patients with preoperative evidence of left ventricular dysfunction. Significant increases in mean cardiac index were seen with dobutamine (15, 25, and 26% respectively), and epinephrine (30%). The largest increases occurred with dopamine (44, 53, and 64 percent respectively). Responses varied from patient to patient, however. Seven patients developed marked output increases without concomitant increases in arterial pressure, whereas seven others showed “satisfying” increases in arterial pressure without appreciable output increases. Heart rate increases were small and few arrhythmias were noted. We conclude that dopamine, epinephrine, and dobutamine all are effective inotropic agents during the immediate post-bypass period, with variations discussed in detail. None possess the disturbing chronotropic and arrhythmogenic effects of isoproterenol (previously studied). Efficacy of administration of inotropic drugs seems best assessed by serial output measurements during this period.

with moderate increases in cardiac index without significant heart rate increases, in sharp contrast to isoproterenol. Isoproterenol (0.02 μg/kg/min) caused a mean heart rate increase of 43.9%, with multiple premature ventricular contractions, and little change in output.

In this study, our objectives were twofold: first, to provide a comparison of the effects of three inotropic agents (dobutamine, dopamine, and epinephrine) during the period immediately following emergence from cardiopulmonary bypass; and second, to make recommendations regarding appropriate methods of monitoring the efficacy of inotropic drug administration in this specific situation.

Methods

Thirty-four patients were studied, usually with two of the three drugs in each patient. Dopamine and dobutamine were usually studied in two infusion rates, epinephrine in one infusion rate. This resulted in 56 patient-inotropic drug exposures, and a total of 81 inotropic drug dosages. Patients were studied who had documented evidence of left ventricular dysfunction preoperatively, based upon review of catheterization data and history/physical exam. Elevated left ventricular end diastolic pressure ( > 15 torr), ventricular hypokinesia, and/or ejection fraction < 50% were present. All patients were New York Heart Association functional class III or IV. Twenty-three underwent valve replacement, seven had coronary artery bypass grafting, and four had both. Table 1 summarizes patient data.
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