Hemodynamics of a New Angiotensin Antagonist, [Sar\(^{1}\), Thr\(^{8}\)]A II, in Hypertensive Man

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SUMMARY  Hemodynamic responses to a new angiotensin II antagonist, [Sar\(^{1}\), Thr\(^{8}\)]A II, were studied in 17 hypertensive patients whose plasma renin activity (PRA) ranged from 0.2-42.0 ng/ml/hr. With infusion of 1.0 \(\mu\)g/kg/min, mean arterial pressure (MAP) rose \(\geq 10\) mm Hg in six patients, was unchanged in six patients, and decreased \(\geq 10\) mm Hg in five patients. There was no significant change in either cardiac index or heart rate in any of these groups, so variations in MAP were related only to corresponding change in total peripheral resistance (\(\Delta\)TPR) \((r = 0.913, p < 0.001)\). The response of both MAP and TPR to the antagonist correlated closely with control PRA \((r = -0.812\) and \(-0.889\) respectively, \(p < 0.001\) for both). Stability of both cardiac index and pulmonary wedge pressure suggested that [Sar\(^{1}\), Thr\(^{8}\)]A II did not alter cardiac performance. These results contrast with the depression in cardiac output reported to occur with saralasin in compensated hypertensive patients regardless of blood pressure response to that drug. Such differences in hemodynamic response between two angiotensin antagonists imply that conclusions regarding cardiovascular role of A II cannot be inferred from results with one antagonist alone. Further, because of the absence of cardiac output depression, [Sar\(^{1}\), Thr\(^{8}\)]A II might be safe for patients with cardiac disease.

ANGIOTENSIN II antagonists are frequently used to define the role of the renin-angiotensin system in cardiovascular homeostasis. Response of arterial pressure to saralasin is usually taken as an indication that the hypertension investigated was "vasoconstrictive and angiotensinogenic." When hemodynamic studies showed that [Sar\(^{1}\), Ala\(^{8}\)]A II reduced cardiac output regardless of blood pressure response,\(^6\) it led to speculations regarding the effects of angiotensin on capacitance vessels, myocardial contractility or parasympathetic tone.

However, increasing experience with angiotensin analogs has revealed important differences among various antagonists in their agonist potential,\(^4\) influence on catecholamine release,\(^6\) and cardiac effects.\(^7\) Of the different antagonists, only [Sar\(^{1}\), Ala\(^{8}\)]A II and [Sar\(^{2}\), Ile\(^{8}\)]A II have been administered to man.\(^5, 8-10\) The fall in cardiac output with saralasin reported by deCarvalho et al.\(^2\) and the demonstration of cardiac hypertrophy with its chronic use in rats\(^7\) led us to try a new angiotensin antagonist, [Sar\(^{1}\), Thr\(^{8}\)]A II.\(^14\) Results in hypertensive patients with a wide spectrum of plasma renin activity (PRA) showed not only that the antagonist was effective in reducing arterial pressure in patients with elevated PRA, but especially that its hemodynamic responses were related principally to changes in peripheral resistance with no significant alteration in cardiac output.

Methods

Patients

Seventeen patients with mild to severe hypertension of varying etiology, including two in the malignant phase of the disease, were studied hemodynamically during intravenous infusion of [Sar\(^{1}\), Thr\(^{8}\)]A II. None had cardiac decompensation or renal failure; all had discontinued their antihypertensive drug regimens for at least 2 weeks before study, except for diuretics. The subjects were given adequate and clear explanations regarding both the drug and the procedure and all freely gave their written informed consent to the study. The 17 patients displayed a wide range of PRA at the time of hemodynamic study; five were untreated, partly because of the type of hypertension (table 1) and because of diuretic therapy. Five patients were untreated, having received no antihypertensive medication for at least 3 weeks before the test; three of them were among those who showed either a rise of pressure or no blood pressure response to the drug. The other two were among those whose arterial pressure was lowered by the antagonist. The remaining 12 patients were on diuretic therapy with either furosemide (eight patients) or hydrochlorothiazide (four patients). The effect of diuretics on blood response to A II antagonists has been related to their PRA stimulation rather than to the drug used;\(^8, 10, 15\) hence, the diversity of diuretics used according to the patient's condition helped in evaluating response to [Sar\(^{1}\), Thr\(^{8}\)]A II over a wide range of PRA.

Hemodynamic Investigation

Study Protocol

Hemodynamic studies were performed after overnight fast, in quiet surroundings and without premedication. After a 30-45-minute rest period, blood samples were obtained for biochemical analyses.
and measurements of PRA; this was followed by determination of plasma volume and cardiac output. The [Sar¹, Thr⁴]A II was then administered in normal saline as a constant infusion of 1 ml/min; to keep the infusion rate constant while increasing the dose, separate concentrations were used to give the drug in graded doses of 0.1, 0.3, 3.0, 5.0 and 10.0 µg/kg/min. Each level was maintained for 10 minutes; the total amount of normal saline administered did not exceed 60–70 ml in any patient. Hemodynamic determinations were repeated at the end of these periods. Response to the angiotensin antagonist was defined by the blood pressure change after the 10-minute infusion of 1.0 µg/kg/min. An increase in mean arterial pressure ≥ 10 mm Hg defined pressor-responders (agonist effect), a decrease by 10 mm Hg or more indicated a predominant antagonistic effect (responders); nonresponders maintained stable mean arterial pressure (± 9 mm Hg) throughout the infusion.3

Methods
In the first five studies, cardiac output was determined by dye-dilution (indocyanine green); catheters were passed percutaneously into an antecubital vein and the brachial artery and advanced under fluoroscopic guidance into the right atrium and the ascending aorta, respectively. Determinations were made as previously described.16 Intra-arterial recordings were resorted to initially because the magnitude and rapidity of blood pressure response to [Sar¹, Thr⁴]A II could not be anticipated. Once the safety of infusion was established, the remaining 12 studies were performed by the thermodilution technique, while brachial arterial pressures were obtained by sphygmomanometer at 2-minute intervals throughout the infusion. Details of the method and its close correlation with the indocyanine green technique have been described for our laboratory.17 A lead II ECG was continuously recorded. Simultaneous determinations of blood pressure (mm Hg), cardiac output (l/min), heart rate (beats/min) and pulmonary wedge pressure (mm Hg) were made in triplicate. Calculated indices, including mean arterial pressure (mm Hg), total peripheral resistance index (arbitrary units) and cardiac index were determined by standard formulas.16

Plasma volume was determined by radioiodinated serum albumin using a 10-minute equilibration period, and total blood volume was calculated from that volume and simultaneous hematocrit measured in quadruplicate.16 Normal values of our laboratory, expressed as ml/cm to minimize effects of age, sex and obesity, average 18.4 ± 2.0 (males) and 15.3 ± 1.7 (females). PRA was determined by samples obtained after the patient was resting supine for at least 30 minutes and just before RISA injection, using a 3-hour incubation followed by radioimmunoassay for A-1.16 Normal values for subjects on a regular hospital diet range in our laboratory from 0.2–2.7 ng • ml⁻¹ hr⁻¹.

Analysis
The hemodynamic effects of the angiotensin antagonist were analyzed in relation to three independent variables determined immediately before its administration: level of PRA, magnitude of intravascular volume and level of cardiac output. Statistical analysis was performed by standard methods19 using paired t test and least-square linear regression methods, where applicable.

Results
None of the patients manifested either subjective or objective adverse effects from the drug or the test. There were no significant changes in CBC, serum electrolytes and urine acid, BUN, serum creatinine, serum enzymes (SGOT, alkaline phosphatase, LDH, CPK) or ECG that could be attributed to the infusion.

Preblockade Hemodynamic Setting
Patients investigated showed a wide range of hemodynamic, volume and PRA values (table 1). Cardiac index before infusion of the antagonist varied from 1.8 l/m/m² to 4.25 l/m/m²; correlatively, the calculated total peripheral resistance varied from 26–63 units (normal values for the laboratory average 3.1 ± 0.5 l/m/m² and 29 ± 7 units, respectively). Similarly, intravascular volume and PRA levels varied from −28% to +32% of normal and from 0.2–42 ng/ml, respectively. There was a significant inverse correlation between total blood volume and PRA (r = 0.470, p < 0.05); plasma renin levels correlated significantly with mean arterial pressure (r = 0.479, p < 0.05) but not with total peripheral resistance (r = 0.089) or cardiac index (r = 0.095).

Hemodynamic Response
Arterial Blood Pressure
Responses to various levels of [Sar¹, Thr⁴]A II infusion are detailed in table 1. In all cases except patient 3, the trend of arterial pressure response to the angiotensin antagonist was already evident at the 0.3-µg/kg/min level. In patient 3, mean arterial pressure increased by 12 mm Hg at the 0.3-µg/kg/min infusion level and then returned to control during the administration of 1.0 µg/kg/min. It rose again with continued infusion at 3.0 µg/kg/min. In no case did a patient who showed a rise in arterial pressure at the 0.3 level develop a depressor response at any of the higher levels of infusion up to 5.0 µg/kg/min. Infusion levels were increased to 10.0 µg/kg/min in 14 patients, two with hemodynamic determinations who are included in this series and 12 without hemodynamic determinations who are not. In all 14, the pressor response seen at lower doses was maintained at higher levels of infusion.

The slope of arterial pressure response to [Sar¹, Thr⁴]A II was variable. Only four patients demonstrated increased response to increasing doses;
<table>
<thead>
<tr>
<th>Pt no.</th>
<th>Diagnosis</th>
<th>Control</th>
<th>0.3 µg/kg/min</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>PRA (ng/ml/hr)</td>
<td>TBV (%)</td>
</tr>
<tr>
<td>1</td>
<td>Essential</td>
<td>0.2</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>Essential</td>
<td>0.3</td>
<td>104</td>
</tr>
<tr>
<td>3</td>
<td>Essential</td>
<td>1.0</td>
<td>144</td>
</tr>
<tr>
<td>4</td>
<td>Essential</td>
<td>1.5</td>
<td>102</td>
</tr>
<tr>
<td>5</td>
<td>Essential</td>
<td>0.7</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td>Essential</td>
<td>1.3</td>
<td>84</td>
</tr>
</tbody>
</table>

Abbreviations: PRA = plasma renin activity; TBV = total blood volume; MAP = mean arterial pressure; HR = heart rate; CI = cardiac index; TPR = total peripheral resistance.

one of six showed an increasing pressor response and three of five had an accentuated depressor response. In the 13 other patients, the hemodynamic response achieved at low dose levels was not accentuated with increased dosage (table 1, fig. 1). Since depressor responses (reduction of mean arterial pressure by ≥10 mm Hg) were evident in all patients at the 1.0-µg/kg/min level of infusion, and since no fall in blood pressure occurred at a higher dose without already being evident at the 1.0 µg dose, this level was chosen as the basis for classification of blood pressure response.

By this definition, there were five responders and six nonresponders and six in whom mean arterial pressure rose by 10 mm Hg or more (pressor-responders). Included among the latter six was patient 3, who showed an agonist response at the 0.3- and 3.0-µg/kg/min levels, but little change at the 1.0 level. His inclusion or exclusion from calculations did not alter significance of the results.

Cardiac Output, Heart Rate and Pulmonary Wedge Pressure

The variations in arterial pressure with infusion of [Sar¹, Thr⁸]A II were related in all but one patient to changes in total peripheral resistance. Those patients who showed an agonist response did so by increasing total peripheral resistance, whereas the fall in blood pressure in all five responders was associated with a reduction in resistance. Cardiac output was altered by more than 8% in only seven of the 17 patients. In only one could the change in output be considered the cause of the rise in blood pressure (patient 3); in the other six, cardiac output changed in the opposite direction of the blood pressure response. In summary, no significant correlation was found between change in cardiac output and response of arterial pressure to [Sar¹, Thr⁸]A II, either at the 1.0-µg/kg/min infusion level (r = 0.478, p > 0.05) (fig. 2), or at the maximum level of blood pressure response for each patient (r = 0.389, p > 0.10). In contrast, the blood pressure response was closely related to changes in total peripheral resistance. A highly significant correlation was found between responses of mean arterial pressure and total peripheral resistance to [Sar¹, Thr⁸]A II, both at the defined level of infusion (1.0 µg/kg/min) (r = 0.917, p < 0.001) and at the level producing the maximal blood pressure response in each patient (r = 0.884, p < 0.001).

Heart rate was not significantly changed by the antagonist regardless of the blood pressure response (−1.2 beats/min ± 3.45 s.d. of the difference). In the five patients with depressor response (−22.8 mm Hg, range −14 to −42) heart rate remained essentially un-
There was no response depressor (broken line) and for those showing a depressor response (broken line). Omitted for the sake of clarity were the data from patients whose mean arterial pressure did not change significantly (± 10 mm Hg).

FIGURE 1. The blood pressure response to increasing doses of [Sar1, Thr8]A II are shown only for patients showing an agonistic effect (solid line) and for those showing a depressor response (broken line). Omitted for the sake of clarity were the data from patients whose mean arterial pressure did not change significantly (± 10 mm Hg).

pressure response to [Sar1, Thr8]A II and changes in heart rate ($r = -0.438$, $p > 0.05$).

Cardiac performance was assessed in 14 patients by determining response of pulmonary wedge pressure to the alterations in cardiac output and arterial pressure produced by [Sar1, Thr8]A II. The pulmonary wedge pressure was normal initially, and showed no significant changes during the infusion (table 2). Only among the five pressor-responders was there a tendency for the wedge pressure to rise, but even in those cases, the change was statistically insignificant.

Correlates of Arterial Pressure Response

**Blood Volume and PRA**

Both the arterial pressure and peripheral resistance response to [Sar1, Thr8]A II were significantly correlated with level of PRA determined immediately before the infusion (fig. 3). This was true for responses both to low (0.3 μg/kg/min) and higher (1.0 μg/kg/min) levels of infusion. Correlation coefficients were obtained and their significance was: 1) for Δmean arterial pressure at 0.3 level, $r = -0.863$, $p < 0.001$; at 1.0 level, $r = -0.889$, $p < 0.001$; 2) for Δtotal peripheral resistance at 0.3 level, $r = 0.678$, $p < 0.01$; at 1.0 level, $r = -0.812$, $p < 0.001$. In contrast, there was no significant difference in blood pressure response to [Sar1, Thr8]A II between patients

<table>
<thead>
<tr>
<th>Table 1. (Continued)</th>
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<tbody>
<tr>
<td>1.0 μg/kg/min</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
</tr>
<tr>
<td>117</td>
</tr>
<tr>
<td>136</td>
</tr>
<tr>
<td>120</td>
</tr>
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<td>131</td>
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<td>116</td>
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<td>94</td>
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<td>137</td>
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with expanded and those with contracted plasma volume. Although patients with a depressor response to the antagonist had a lower average plasma volume than nonresponders or those with a pressor response, the difference was not significant (87.2%N ± 6.3 SE vs 95.7 ± 5.5, p > 0.05). Correlations between intravascular volume and either mean arterial pressure or total peripheral resistance response to the antagonist were of questionable statistical significance and much weaker than the correlation of these responses with control PRA levels (r for ∆TPR + TBV was 0.353, p > 0.05; for ∆MAP + TBV, r = 0.419, p > 0.05).

Preblockade Hemodynamic Indices

The wide range of control values was used to determine the blood pressure response to the antagonist. No correlation, however, was found between mean arterial pressure response to [Sar¹, Thr³]A II and either control cardiac output (r = −0.054, NS) or control total peripheral resistance (r = 0.206, NS).

Discussion

The hemodynamic pattern of response to a new angiotensin antagonist, [Sar¹, Thr³]A II, was relatively simple and generally consistent; changes in arterial pressure were closely related to alterations of peripheral resistance (r = 0.917, p < 0.001) as cardiac output remained essentially unchanged. Both the arterial pressure and total peripheral responses were closely correlated with control PRA (r = 0.888, and 0.831, respectively, p < 0.001 for both). The preblockade hemodynamic setting, which plays a large role in pattern of response to neural blocking agents,²¹,²² did not appear to influence response to the angiotensin antagonist. Neither resting cardiac output nor peripheral resistance was correlated with arterial pressure response to [Sar¹, Thr³]A II (r = −0.054 and 0.206, respectively; both NS).

The predominant effect of [Sar¹, Thr³]A II on peripheral resistance in hypertensive patients confirms results obtained in dogs with experimental renovascular hypertension.²³ In normotensive dogs, the antagonist led to more consistent reductions in cardiac output, whereas effects on total peripheral resistance depended on salt balance.²³ This difference in hemodynamic pattern of response between normotensive and hypertensive animals is not surprising; a similar difference between normotensive and hypertensive subjects was frequently noted in the relative roles played by cardiac output and peripheral resistance in response to various forms of stress.²⁵,²⁶

The consistent hemodynamic responses to [Sar¹, Thr³]A II and the close correlation between effects on arterial pressure and peripheral resistance contrast with the more complex results reported with saralasin. The blood pressure response to this more widely used antagonist was usually associated with a significant reduction of cardiac output in most,²⁷,²⁸ but not all,¹¹ hypertensive subjects. The correlation to PRA with hemodynamic response to saralasin was therefore reported to be closer with peripheral resistance than with arterial pressure changes.¹¹ In normotensive patients, the correlation to PRA was weaker and of no statistical significance (r = 0.206).

Table 2. Pulmonary Wedge Pressure (PWP) and Cardiac Index (CI) During [Sar¹, Thr³]A II Infusion

<table>
<thead>
<tr>
<th>Response (n)</th>
<th>Control (mm Hg)</th>
<th>CI (l/m²/min)</th>
<th>PWP (mm Hg)</th>
<th>[Sar¹, Thr³] (1.0 µg/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BP</td>
<td></td>
<td></td>
<td>[BP]</td>
</tr>
<tr>
<td>Pressor responders</td>
<td>121 ± 7</td>
<td>2.67 ± 0.15</td>
<td>5 ± 1</td>
<td>134 ± 8</td>
</tr>
<tr>
<td>No BP change</td>
<td>109 ± 3</td>
<td>2.60 ± 0.28</td>
<td>3 ± 1</td>
<td>116 ± 5</td>
</tr>
<tr>
<td>Responders</td>
<td>140 ± 10</td>
<td>2.72 ± 0.23</td>
<td>4 ± 1</td>
<td>117 ± 9</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

None of the changes in CI or PWP were significant regardless of blood pressure response.

Abbreviations: BP = blood pressure; CI = cardiac index; PWP = pulmonary wedge pressure.
patients with heart failure, saralasin could lower peripheral resistance with either no significant change or even a slight increase in cardiac output. Their results to a possible role of renin in the increased resistance usually seen in cardiac decompensation. None of our patients, however, showed any evidence of heart failure; their results, therefore, are compared with those reported for patients in a similar situation, namely, compensated hypertensive disease. Because of the influence of saralasin in systemic and renal blood flow in hypertensive patients, it was concluded that its cardiovascular effects could not be correctly evaluated from changes in arterial pressure alone. In contrast, the response of hypertensive patients to [Sar¹, Thr⁸]A II showed a close correlation between its effects on arterial pressure and peripheral resistance ($r = 0.917, p < 0.001$) and, therefore, an equal correlation of both effects with control PRA.

The reduction of cardiac output by saralasin despite the lowering of afterload was not easy to explain, especially in hypertensive patients with a depressor response. Some suggested a stimulation of parasympathetic activity and others either reduction in venous tone or inhibition of myocardial contractility. In comparison, the hemodynamic pattern produced by [Sar¹, Thr⁸]A II appeared more straightforward if the main action of angiotensin II was on peripheral vessels. Alterations in peripheral resistance would then be expected to predominate in the effect of angiotensin analogs whether agonist or antagonist. The lack of rise in cardiac output even when arterial pressure and peripheral resistance fell could be related to venodilation in association with reduction in arteriolar resistance. There is no evidence to suggest a reduction in cardiac contractility by this angiotensin antagonist, as has been postulated to explain the reduction in cardiac output after saralasin. Pulmonary wedge pressure was not significantly altered even when peripheral resistance and arterial pressure were increased by the antagonist (table 2).

Their hemodynamic pattern of action is not the only difference among angiotensin antagonists. Both saralasin and [Sar¹, Ile⁸]A II were found to release catecholamines from the adrenal medulla, whereas [Sar¹, Thr⁸]A II did not. In normotensive rats, saralasin led to cardiac hypertrophy in the absence of significant changes in arterial pressure, while administration of [Sar¹, Thr⁸]A II under the same conditions did not produce ventricular hypertrophy. These differences raise an important caveat to the proposition that hemodynamic response to angiotensin antagonist can be taken at face value as indices of the role of A II in control of cardiovascular function. This assumption was predicated on the basis that in contrast with other agents that inhibit the renin-angiotensin system, these antagonists reduce blood pressure only through competitive inhibition of A II at its receptor site. Our observations in man and in animals indicate that conclusions as to the cardiovascular role of angiotensin II cannot be deduced from studies limited to one angiotensin antagonist alone. There are enough differences in their spectrum of actions to caution against extrapolations and assumptions in that regard.

The reason for lack of significant changes in heart rate despite marked falls in arterial pressure is not clear. Frequently, this has occurred in investigations of other antagonists that interfere with the renin-angiotensin system. Cody et al. observed it during oral therapy with the converting enzyme inhibitor SQ 14,225, as did Sancho et al. using SQ 20,881. Bravo and Tarazi reported the same absence of tachycardia despite a reduction of blood pressure in dogs given [Sar¹, Thr⁸]A II, while Wallace et al. first described the same phenomenon in a large group of patients given saralasin. A possible cause could be a blunting by these agents of baroreceptor responses to blood pressure alterations. However, in preliminary studies of responses to head-up tilt during [Sar¹, Thr⁸]A II infusion, both the nonresponders and patients with a depressor response to the drug had a heart rate in-
crease of approximately 20 beats/min after 45° tilt for 5 minutes. Another explanation for this phenomenon was suggested by observations with two different angiotensin antagonists both in man and in experimental animals.24 Increase in parasympathetic activity could blunt heart rate response to a reduction in arterial pressure at rest and yet not interfere with blood pressure response to posture. Atropine reversed hemodynamic effects of [Sar¹, Thr⁴]A II in normotensive dogs.24 Studies with atropine in patients given [Sar¹, Thr⁴]A II could not be done because of ethical constraints during the first trials of a new compound.

In summary, it was shown that [Sar¹, Thr⁴]A II in doses of 1.0 μg/kg/min could effectively lower arterial pressure in hypertensive patients with increased PRA, and that the reduction of mean arterial pressure was significantly correlated with initial PRA. This reduction in arterial pressure was due to a lowering of peripheral resistance; cardiac output was practically unchanged. In this respect, [Sar¹, Thr⁴]A II differed significantly from the hemodynamic pattern produced by saralasin. Implications of these findings are both practical and theoretical; an agent that does not lower cardiac output or interfere with cardiac performance would be safer in patients. Conclusions regarding the role of angiotensin in cardiovascular homeostasis should not depend only on the response to any one antagonist, but should take into account differences among various antagonists as well as theoretically possible, intrinsic pharmacologic effects of any compound.

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References


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