Contrasts and Similarities of Acute Hemodynamic Responses to Specific Antagonism of Angiotensin II ([Sar<sup>1</sup>, Thr<sup>8</sup>] A II) and to Inhibition of Converting Enzyme (Captopril)


SUMMARY The early blood pressure and hemodynamic effects of the converting enzyme inhibitor (CEI), captopril, were compared in 23 hypertensive patients with those of a specific angiotensin II antagonist (AA), [Sar<sup>1</sup>, Thr<sup>8</sup>] A II. AA reduced mean arterial pressure (MAP) > 10 mm Hg only in seven of 23 patients vs 15 of 23 who responded to CEI (p < 0.02). With both drugs, changes in MAP were not associated with significant changes in cardiac output (p > 0.10 for both drugs), but correlated with changes in systemic resistance (TPR); r = 0.84, p < 0.001 for AA and r = 0.71, p < 0.001 for CEI. Changes in TPR and MAP correlated significantly and inversely with log plasma renin activity in both instances; for AA, r = −0.829 and for CEI, r = −0.737; p < 0.001 for both. The slopes of the two regression lines were not significantly different but the intercepts were + 8.47 mm Hg for AA vs −10.17 mm Hg for CEI (p < 0.001). This quantitative difference in response could be attributed either to an agonistic effect of [Sar<sup>1</sup>, Thr<sup>8</sup>] A II or to an additional vasodilator effect of captopril.

THE RENIN-ANGIOTENSIN system may be affected by many factors. Two of these are of particular interest because of their therapeutic or diagnostic potential inhibition of converting enzyme and specific antagonism of angiotensin II. Both have been used in hypertensive patients and normotensive subjects but no direct comparison of their effects in the same patients have been reported. Such a comparison may be important because of the question surrounding the mechanisms of the antihypertensive effect of converting enzyme inhibition. Converting enzyme inhibitors have other effects beside interference with generation of angiotensin II. Therefore, the agonistic properties of angiotensin II antagonist must also be considered. We have, therefore, used an angiotensin antagonist [Sar<sup>1</sup>, Thr<sup>8</sup>] A II, which has minimal agonist properties compared with Saralasin and [Sar<sup>1</sup>, Ala<sup>8</sup>] A II. Comparison of the effects of the angiotensin antagonist with those of the converting enzyme inhibitor may help identify similarities in the blood pressure (BP) response to both classes of drugs.

Our initial experience with the converting enzyme inhibitor captopril showed that its antihypertensive effect could be seen as soon as 20-30 minutes after oral administration. Therefore, we could compare the early effects of captopril with those of an angiotensin antagonist, [Sar<sup>1</sup>, Thr<sup>8</sup>] A II, by giving both drugs successively in the same sitting to the same patients, under the same circumstances. The hemodynamic and humoral effects of both were compared, as well as the correlates of the BP response to each.

Material and Methods

Patient Population

Twenty-three hypertensive patients participated in this study. In 14, diagnosed as essential hypertensives, no cause for the rise in BP was detected by extensive clinical and laboratory investigations, including renal arteriography and special studies for primary aldosteronism or pheochromocytoma, when warranted. Seven had documented renal arterial disease by selective arteriography; one had renal parenchymal disease (glomerulonephritis), and one persistent hypertension despite unilateral nephrectomy for atherosclerotic renal arterial disease and a patent vessel to the remaining kidney. Two patients (one with essential and the other with renovascular hypertension) were in the malignant phase of the disease at the time of the study. The group included seven females and 16 males with an age range of 43-77 years. Sixteen patients were on no therapy for at least 2 weeks before the study; the other seven were taking only furosemide (80-160 mg/day). Explanations of the investigational nature of the drugs and of the details of the hemodynamic procedure were given and all patients gave their written informed consent to participate in the study. All patients were given an isocaloric diet (containing 100 mEq sodium and 80 mEq potassium per day) that was started at least 4 days before the study. Metabolic equilibration was evaluated by daily measurement of body weight and determination of the 24-hour urinary excretion of sodium and potassium.
Experimental Design

All studies were performed in the morning after an overnight fast after 30 minutes of supine rest.

Control values including cardiac output, BP, heart rate (HR), and plasma renin activity (PRA) were first obtained after stabilization during infusion of normal saline (placebo) at a constant rate of 1 ml/min. An infusion of [Sar¹, Thr⁸]A II in normal saline vehicle was then started at the same constant rate of 1 ml/min; the antagonist was given in graded doses of 0.3, 1, 3, 5 and 10 μg/kg/min, and each level was maintained for 10 minutes; the total amount of fluid infused in any one study did not exceed 60–70 ml. BP and HR were monitored constantly; the indices measured with the control period were again determined in all patients at the 1 μg/kg/min level regardless of BP response. In four patients, the antagonist was then discontinued because a clear response had been obtained; in the others, the infusion was continued to higher levels and hemodynamic measurements were obtained at the maximum level of infusion (usually 10 μg/kg/min).

Sufficient time (usually 30–60 minutes) was allowed after discontinuance of [Sar¹, Thr⁸]A II for complete recovery of BP and HR to control values. A second battery of control studies was then obtained and captopril (25–150 mg) was given orally. The dose of captopril given was determined in one of two ways: 1) In 11 patients captopril was given the day before the experiment, beginning with 25 mg and doubling the dose every 30 minutes until either a maximum of 150 mg was given or a depressor response (reduction of mean arterial pressure > 10 mm Hg) was obtained. The total amount of drug attained that day was given as a single dose on the day of the study after recovery from the effect of [Sar¹, Thr⁸]A II; 2) in 12 patients captopril was given only after [Sar¹, Thr⁸]A II, in gradually increasing dosage as described above, either to a maximum of 150 mg or until a depressor response was obtained. With this approach we could determine if the order of therapy (captopril first or [Sar¹, Thr⁸]A II first) affected the outcome of the study. No statistically significant difference was found between the effects of captopril given on 2 successive days, once before the angiotensin antagonist and the next day after [Sar¹, Thr⁸]A II infusion. Therefore, the results reported are those comparing the effects of [Sar¹, Thr⁸]A II with those obtained with captopril given on the same day (table 1).

Hemodynamic Measurements

After taking blood samples to determine PRA and plasma volume, cardiac output was determined by thermodilution in 10 patients; the thermistor was positioned into the pulmonary artery and 10 ml ice-cold 5% dextrose and water were used for each determination. Cardiac output was calculated as the average of three determinations that did not differ by more than 5%, as described previously. In the three other patients cardiac output was measured by the dye-dilution technique using indocyanine green. In all 13 patients, cardiac output was determined before and during [Sar¹, Thr⁸]A II infusion, and then again just before and 30 minutes after oral administration of the maximum captopril dose. The 30-minute interval was selected because it was observed that the BP lowering effect of captopril became evident in 20–30 minutes after oral administration of the drug.

BP was obtained by sphygmomanometer at 5-minute intervals throughout the study in all patients who did not have an intra-arterial catheter; in the three patients who had a dye-dilution study, BP was continuously recorded via the intra-arterial catheter. MAP was calculated as diastolic pressure and one-third pulse pressure; total peripheral resistance (TPR) was calculated as the ratio of MAP to cardiac index and expressed in arbitrary units, as described previously. ECG (lead II) was recorded continuously during the study; in addition, a 12-lead ECG was obtained before and at the end of the study (1½ and 3 hours after captopril).

Analytical Procedures

PRA was determined by radioimmunoassay of generated A I and results were expressed in ng/ml/hr. Normal values for the laboratory are 0.4–2.6 for a daily intake of 100 mEq sodium. Plasma volume was determined by radioiodinated serum albumin (RISA) using a 10-minute equilibration period, and total blood volume was calculated from plasma volume and simultaneously measured hematocrit as previously described. Values were expressed in percent of normal to allow inclusion of both sexes in calculation of averages. Normal values for the laboratory average 30.9 ± 3 (sb) ml/cm for men and 24.1 ± 2.4 ml/cm for women.

Analysis of results

Results were analyzed in two ways. First, using PRA, plasma volume and cardiac output as three independent variables, the BP response to each drug was correlated with the control values of these three in-
Results

Blood Pressure Response

Responses to the two drugs were not the same in all patients (fig. 1). Seven (group 1) had equivalent depressor response to both compounds (−31.6 ± 4.3 and −24.5 ± 3.3 mm Hg, respectively; p < NS); eight had a depressor response to captopril (−17 ± 1.2 mm Hg) but no significant BP response to [Sar\(^1\), Thr\(^4\)]AII (group 2), while none of the other eight (group 3) had a depressor response to either drug. An agonist (pressor) response occurred only in five patients, all of group 3, and only in response to [Sar\(^1\), Thr\(^4\)]AII. In summary, all patients who had a depressor response to the angiotensin antagonist had a similar response to captopril, but not all patients whose pressure was reduced significantly by captopril had a depressor response to the antagonist.

Control supine PRA differed significantly among the three groups (fig. 1); it averaged 34.2 ± 8.6 ng/ml/hr in group 1, 2.84 ± 0.67 in group 2 and 1.72 ± 0.59 in group 3. The difference between groups 2 and 3 was not statistically significant (p > 0.05), but the differences between groups 1 and 3 as well as between groups 1 and 2 were both significant (p < 0.05) (fig. 1).

Correlation of BP Response to Control PRA

As suggested from group averages, BP response to both drugs seemed to depend on control PRA levels. This was better demonstrated by correlation analysis, which avoided arbitrary separation of patients into groups. The response of MAP to both [Sar\(^1\), Thr\(^4\)]AII and to captopril was significantly correlated with control supine log PRA; r = −0.829 for the former and r = −0.737 for the latter (p < 0.001 for both). The regression line was defined by the following equations: 1) ΔMAP = −19.42 log PRA + 8.47 for the angiotensin antagonist and 2) ΔMAP = −11.72 log PRA −10.17 for captopril. The slopes of the two lines were similar but their intercepts were significantly different (p < 0.001) (fig. 2).

Relationship of BP Response to Blood Volume

Total blood volume was measured in all 23 patients before the study; there was no statistically significant difference between responders and nonresponders either in the case of [Sar\(^1\), Thr\(^4\)]AII (78.7 ± 2.97 %N vs 92.7 ± 4.55, p > 0.05) or of captopril (86.6 ± 5.21 vs 92.8 ± 4.07, NS). MAP response was not significantly related to intravascular volume, either for the angiotensin antagonist (r = 0.081, NS) or for captopril (r = 0.265, NS).

Hemodynamic Correlates of BP Response

Response of MAP to either drug correlated significantly with changes in TPR (fig. 3) with a correlation coefficient of 0.84 (p < 0.001) for [Sar\(^1\), Thr\(^4\)]AII and 0.71 (p < 0.001) for captopril (ΔMAP = 1.87 ΔTPR −5.908 and ΔMAP = 1.25 ΔTPR −7.937, respectively). There was no correlation with either drug between response of MAP and changes in cardiac output. Further, the BP response to [Sar\(^1\), Thr\(^4\)]AII or to captopril was not related to pretreatment hemodynamic values (r values of ΔMAP with control cardiac output were −0.190 and −0.262, respectively, both NS).

Changes in HR or cardiac index with either drug were small. Variations of HR during an invasive
hemodynamic study in our laboratory were ± 6.6 beats/min (2 SD). Of the patients receiving captopril only five of 23 had an increase in HR by more than 6 beats/min (one of them an increase of 28 beats/min); the other 18 had relatively stable rates (−2 to +5 beats/min). After the angiotensin antagonist, HR increased in one patient by 8 beats/min and decreased in three patients by more than 6 beats/min, while in 19 it varied by −4 to +5 beats/min. Despite this great degree of overlap, the effect of both drugs tended to be in opposite directions, captopril toward some increase in rate and [Sar¹, Thr⁸]A II toward a slight decrease, so that the difference between averages reached statistical significance (+3.9 ± 1.4 with captopril vs −0.6 ± 0.8 for the antagonist, $p < 0.006$). Although there were obvious differences in BP responses to the two drugs, these could not fully explain the small but significant difference in HR because no correlation was found between ΔMAP and ΔHR with either drug ($r = −0.10$ and −0.31, respectively; $p = NS$ for both).

**Discussion**

Both captopril and this angiotensin antagonist showed similar hemodynamic effects; in both cases BP response was related primarily to changes in TPR (fig. 3), while cardiac output was not altered significantly. These results confirm our previous observations in two groups of patients. The predominant effect of [Sar¹, Thr⁸]A II on peripheral resistance contrasts with the hemodynamic action of Saralasin, which was found to reduce cardiac output in most patients regardless of BP response. Further, [Sar¹, Thr⁸]A II was reported to have less agonistic effect in dogs when compared
with [Sar⁴, Ala⁶]IA II and [Sar⁴, Ile⁶]IA II. Angiotensin antagonists are thus not necessarily synonymous in terms of their cardiovascular effect; the use of [Sar⁴, Thr⁶]IA II was particularly useful in this case because the similarity of its hemodynamic effect with captopril allowed closer analysis of the correlates of their effect on TPR and BP.

These results were obtained in the early period (about 30 minutes) after administration of captopril. Our previous report described longer-term effects of therapy (3-5 days); however, both studies revealed the same hemodynamic pattern of response, namely, a predominant effect on peripheral resistance with no significant alteration in HR or cardiac output. This pattern contrasts with the hemodynamic changes observed with β-adrenergic blockers, which were postulated to act primarily through interference with renin release. Unlike propranolol, which can induce several hemodynamic patterns that can vary with time, captopril resulted in a primary effect on peripheral resistance both in the very early phase of treatment and during its maintenance.

With both approaches — inhibition of converting enzyme and competitive antagonism of angiotensin II — immediate BP response was correlated in the same way to the three independent variables investigated. In both cases, BP response did not correlate with either total blood volume or pretreatment hemodynamic profile. The correlation coefficients between MAP response and either total blood volume or control cardiac output were very low and statistically insignificant. In contrast, BP response to both captopril and [Sar⁴, Thr⁶]IA II was significantly related to control supine PRA (fig. 2). This applied to the whole group of patients as well as to each etiological subgroup (16 essential hypertensive patients and seven with renal arterial disease).

Despite these important similarities in the acute hemodynamic effects of [Sar⁴, Thr⁶]IA II and of captopril, there were some contrasts suggesting that their antihypertensive actions involve somewhat different mechanisms. Thus, although BP response to both correlated significantly with control supine PRA, there were two significant differences. The first was in the frequency and degree of BP reduction; the intercept of the regression line defining the action of captopril was negative, in contrast to the positive intercept with [Sar⁴, Thr⁶]IA II (fig. 1). The second difference was that pressor responses (> 10 mm Hg MAP) were arterial pressure more than the angiotensin antagonist. This was reflected in the higher frequency of responders to converting enzyme inhibition than to [Sar⁴, Thr⁶]IA II (fig. 1). The second difference was that pressor responses (> 10 mm Hg MAP) were encountered only with [Sar⁴, Thr⁶]IA II.

Although both drugs apparently lowered BP acutely by interfering with the renin angiotensin system, additional effects peculiar to either of them can influence this response. This could be an additional vasodilator effect of captopril or a masking agonistic effect of the angiotensin antagonist. Supporting this first possibility is the report by Thurston and Swales, who showed that converting enzyme inhibition (CEI) by SQ 20,881 given with a Saralasin infusion significantly reduced BP in anesthetized, salt-depleted normal and Goldblatt two-kidney, one-clp hypertensive rats. They concluded that this additional vasodepressor action of CEI that could not be blocked by Saralasin was related to its bradykinin-potentiating action. Other investigators had also suggested that part of the hypotensive action of CEI could be due to its enhancement of bradykinin-kallikrein system. Some circumstantial evidence also incriminated a vasodilator effect of CEI regardless of its interference with the renin-angiotensin system. However, the hemodynamic responses to CEI and to bradykinin are not identical; in contrast to the minimal acute effects of captopril on cardiac output and HR, bradykinin is expected to induce a hyperkinetic circulation. Moreover, the extent of inhibition of converting enzyme — at least by SQ 20,881 — has been recently questioned by Oparil et al. On the other hand, some evidence could be found in our results in favor of the alternative possibility of an agonistic effect of [Sar⁴, Thr⁶]IA II in some patients. An actual pressor response was noted in seven patients, exceeding 10 mm Hg in five. Although less prominent than some of the pressor responses reported with Saralasin, their obvious presence in some cases might suggest that they could play a hidden role in reducing the extent of the depressor response in others. The importance of that agonistic effect might lessen as the depressor response becomes more accentuated; this would explain the significant difference between responses to [Sar⁴, Thr⁶]IA II and to captopril in group 3 and group 2, but not in group 1 (fig. 1). This observation in man would then be consistent with the findings of Bravo et al. in dogs; [Sar⁴, Thr⁶]IA II was found to produce a pressor response in salt-depleted dogs but not when salt depletion led to a marked depressor effect.

This study confirmed once again that angiotensin antagonists as well as CEIs have surprisingly little effect on HR despite significant reduction in BP. The explanations for this finding are still speculative; captopril was reported to blunt baroreceptor reflex sensitivity in conscious normotensive rabbits. However, Cody et al. have demonstrated adequate cardiovascular responses to head-up tilt in patients receiving captopril, even when combined with diuretic therapy or a low-sodium diet. Experience with angiotensin antagonists both in man with Saralasin and in dogs with [Sar⁴, Thr⁶]IA II, suggested that these antagonists might enhance parasympathetic activity. To suggest that CEIs have the same effect would be pure speculation. There was a weak but significant correlation between ΔMAP and ΔHR with [Sar⁴, Thr⁶]IA II (r = -0.52, p < 0.01); no such correlation was obtained for captopril (r = -0.20, NS). When all data were taken together, the correlation coefficient was -0.44 (p < 0.01). Therefore, one could deduce that baroreceptor effects
might explain the difference in HR response between the antagonist and captopril. However, the changes in HR with both drugs showed a wide scatter; furthermore, the difference in HR effects between captopril and [Sar^1, Thr^4] Ang II, although statistically significant, appeared too small to be biologically significant or to allow complex interpretations.

In conclusion, despite the similarity in hemodynamic pattern and correlates of BP response to both drugs, they showed significant differences. A practical implication is the difficulty in predicting a therapeutic response to captopril from an intravenous infusion of [Sar^1, Thr^4] Ang II. Although MAP response to the former correlated significantly with response to the antagonist ($r = 0.873, p < 0.001$), the index of determination was only 76%, and the slope of the regression equation (0.66) was significantly different from identity. Further, the significant negative intercept ($-15.5$) meant that a patient who showed no hemodynamic response to [Sar^1, Thr^4] Ang II could still have a significant lowering of BP by captopril. This was the case in eight patients (group 2, fig. 1), although the test with both drugs was performed under the same circumstances with no significant difference in PRA levels measured immediately before administration of either agent. Given the rapidity of reduction of blood pressure by captopril, the practical value of an angiotensin-antagonist test is questionable.

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Thrombosed Björk-Shiley Mitral Prostheses

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SUMMARY During a 4.5-year period ending in January 1978, 224 patients were discharged from the hospital after Björk-Shiley mitral valve replacement. Follow-up records for all patients were available until the last date of inquiry on March 31, 1978.

Twelve patients presented to us 3–43 months (mean 17 months) after surgery with thrombosis of their mitral prostheses. A clinical syndrome consisting of acute onset of ischemic or pleuritic chest pain, dyspnea and rightsided cardiac failure is described. The prosthetic sounds, especially the opening click, are invariably absent or markedly muffled, but definitely abnormal mitral murmurs are infrequently detected. The echocardiogram is a useful adjunct in confirming the diagnosis. Total thrombotic encapsulation of the prosthesis may supervene within hours or days and is invariably fatal unless there is surgical intervention. Our first patient died because we failed to make an immediate correct diagnosis. Thereafter, the early recognition of the clinical features resulted in successful valve replacement.

In addition to the first patient, there were 18 deaths among the 224 patients. Although none of these 18 patients was examined by us, hospital records, telephone inquiries or necropsy reports revealed that six of them died because of thrombotic occlusion of their mitral prostheses.

We conclude that poor anticoagulant control was the principal factor predisposing to prothetic thrombosis in our experience. Eighteen patients (8%) sustained this complication during the study. Neither the original mitral valve lesion nor the size of the Björk-Shiley prosthesis was relevant. We have discontinued using the Björk-Shiley prosthesis for mitral valve replacement when we cannot be certain of ideal control of anticoagulant therapy.

THE FIRST SUCCESSFUL mitral valve replacement with a rigid component prosthesis was performed by Starr in 1960 using a caged-ball valve. Because of the problems with that prosthesis, which included hemodynamic limitations, thromboembolic complications, hemolysis and ball variance, numerous other valves have been designed. The Björk-Shiley tilting disc valve has frequently been used in both the aortic and mitral positions. Because of its low profile, it is particularly suitable for mitral valve replacement. The hemodynamics of the valve have been well studied and although normal flow characteristics are not attained, pressure differences across the prosthesis are acceptable with the larger sizes. In our clinical experience, the prosthesis is hemodynamically very satisfactory. The occurrence of thromboembolic complications is a serious event with any prosthetic valve, and the Björk-Shiley prosthesis is no exception.

This report documents the clinical features of 12 patients in whom thrombotic occlusion of the Björk-Shiley mitral prosthesis supervened. A characteristic clinical syndrome is described, the early recognition of which should markedly reduce the otherwise extremely high mortality. The causes of death of other patients not examined by us but who had also originally survived Björk-Shiley mitral valve replacement are briefly discussed.

Materials and Methods

From June 1973 to January 1978, it was our policy at the Johannesburg Hospital to use the Björk-Shiley prosthesis for mitral valve replacement. During this period a total of 224 white patients were discharged from hospital after Björk-Shiley mitral valve replacement. Follow-up data for 100% of these hospital survivors were obtained until the study was closed on March 31, 1978. At that time 19 patients had died, one

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