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Angiotensin Converting Enzyme Inhibition in Patients with Congestive Heart Failure

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SUMMARY **The etiology of afterload elevation in congestive cardiac failure is unclear, but experimental evidence suggests a role for the renin-angiotensin system in maintaining elevated peripheral vascular resistance. The angiotensin converting enzyme inhibitor SQ20,881 was administered to eight patients with congestive cardiac failure (four hypertensives, four normotensives) during or one day after diagnostic cardiac catheterization. Various hemodynamic measurements performed before and during blockade indicate that this agent caused improvement in cardiac function in all patients by decreasing afterload. This improvement correlated with the decrease in total vascular resistance but was independent of the baseline blood pressure and plasma renin activity. These results suggest that inhibition of angiotensin converting enzyme is a worthwhile approach to the treatment of congestive heart failure, although its exact mechanism of action remains unclear.**

THE ROLE OF THE renin-angiotensin system in congestive cardiac failure is not fully understood. This condition is usually characterized by decreased cardiac output and increased left ventricular end-diastolic pressure accompanied by raised peripheral resistance. Measurements of plasma renin activity and angiotensin in experimental or clinical heart failure have yielded conflicting results, with reports of either high, normal or low levels.[1-4] A recent experimental study[5] seemed to reconcile these contradictory findings by using angiotensin blockade in different stages of congestive cardiac failure. The data have suggested that the renin-angiotensin system remained activated only when circulatory impairment was severe or compensation was inadequate. Thus, uncompensated cardiac failure, like other low cardiac output states, may exhibit elevated plasma renin activity leading to raised peripheral vascular resistance in order to maintain effective arterial pressure. However, the resulting increased impedance to left ventricular outflow could, conceivably, further depress cardiac performance.[6] Elimination of angiotensin in this case might induce a fall in peripheral vascular resistance resulting in left ventricular unloading and thus constitute a rational form of therapy.

In this study, we studied the effects of angiotensin blockade by the converting enzyme inhibitor SQ20,881 (teprotide) on cardiovascular hemodynamics in eight patients — four hypertensive and four normotensive — undergoing conventional medical therapy for congestive cardiac failure and varying degrees of coronary insufficiency.

Methods

Patients with recent severe congestive heart failure were studied either at the time of diagnostic cardiac catheterization (six patients) or the day after catheterization in the coronary care unit (two patients). All patients received conventional doses of digitalis and diuretics. Vasodilating agents were withheld for 48 hours. They were maintained on a 2,000 mg NaCl diet. At the time of the study their functional class ranged from II–IV. Indications for catheterization included evaluation of valvular heart disease, left ven-

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tricular function, determination of the presence and extent of coronary occlusive disease and/or the presence of a discrete ventricular aneurysm. Their clinical profiles are shown in table 1. The experimental nature of this study was duly explained to the patients and informed consent was obtained. Medications were omitted on the morning of the study.

Cardiac catheterization was performed in the fasting state after premedication with 10 mg diazepam orally. A Cournand needle was inserted percutaneously into the left brachial artery and catheters were positioned in the pulmonary artery, coronary sinus, and left ventricle. Control measurements, obtained in the steady state after manipulation had ceased for 10 minutes, included heart rate, right atrial, pulmonary artery, left ventricular, and brachial artery pressures. Cardiac output determinations were made simultaneously by the thermodilution and direct Fick techniques. Coronary flow was measured by the thermodilution technique[7] utilizing thermistor (Wilton Webster Lab) catheters placed in the coronary sinus 2 cm from its orifice in the right atrium, as verified by angiography. Flow measurements were made in duplicate and showed a variability of less than 15%. Blood oxygen and lactate content were measured in samples obtained from the left ventricle, pulmonary artery and coronary sinus. Plasma renin activity in peripheral venous blood was measured by radioimmunoassay of generated angiotensin I[8] (normal range 2–10 ng/ml/hr). From these measurements the following calculations were derived: left ventricular stroke work index, systemic vascular resistance, coronary resistance and myocardial oxygen consumption. Subsequently, 1 mg/kg teprotide was injected rapidly into an antecubital vein, and the above measurements were repeated 30–35 minutes after injection. Following this study, the patients had diagnostic left ventricular and coronary angiography, after which they were restarted on conventional medical treatment.

Two patients (7 and 8) were studied in the cardiac care unit 24 hours after left ventriculography, at which time the resting hemodynamic measurements had returned to levels identical to those obtained at catheterization before angiography. They received 0.3 and 0.2 mg/kg/I.V. teprotide, respectively, and had serial hemodynamic measurements at 15, 30, 60 minutes and hourly thereafter for the next 5 hours. Measurements were carried out via a Swan-Ganz thermodilution catheter and a radial arterial line. In these two patients, coronary blood flow was not measured and cardiac output determinations were made in triplicate by the thermodilution technique only. This method has been found to correlate closely with the Fick method in our laboratory ($r = 0.95$). Except for these two patients, reported values for cardiac output are those obtained by the Fick method.

The paired t test was used to determine statistical significance of the data. Results are expressed as mean ± SEM and were considered significant at the $P < 0.05$ level.

Results

The hemodynamic data and plasma renin levels before and after injection of teprotide are shown in table 2. It is apparent that the control levels of plasma renin activity were unrelated to the patients' blood pressure. One hypertensive patient had high plasma renin activity, one patient had normal plasma renin activity and two patients had low plasma renin activity. Of the four normotensive patients, one had low-normal plasma renin activity and three with severe decompensated heart failure had elevated levels. All patients exhibited abnormal cardiac function as shown by markedly elevated left ventricular end-diastolic pressures and decreased or low normal cardiac out-

TABLE 1. *Clinical Data*

Patient	Age/Sex	Functional Class	Other diagnoses	Medication
1. Hypertensive	52/F	II-III	s/p MI, angina pectoris, peripheral vascular occlusive disease s/p bypass	Digoxin, thiazides, methyldopa
2. Hypertensive	59/F	II	Attacks of atrial fibrillation, questionable angina pectoris	Digoxin, thiazides, reserpine
3. Hypertensive	63/F	II	s/p MI, diabetes mellitus, mitral regurgitation	Lanoxin, spironolactone methyldopa
4. Hypertensive	57/M	III-IV	Multiple admissions with pulmonary edema	Digoxin, furosemide, prazosin
5. Normotensive	70/M	III	s/p MI × 3, angina pectoris, left ventricular aneurysm	Digoxin, furosemide, nitrol paste
6. Normotensive	63/F	IV	s/p MI, angina pectoris, diabetes mellitus, valvular heart disease	Digoxin, furosemide, nitrol paste, insulin
7. Normotensive	66/M	IV	Coronary artery disease, s/p mitral valve replacement and left anterior descending bypass	Digoxin, furosemide, nitrol paste
8. Normotensive	75/M	IV	Coronary artery disease	Digoxin, furosemide, nitrol paste

Abbreviations: MI = myocardial infarction.

TABLE 2. *Hemodynamic Parameters Before and After Injection of SQ20881*

Patient	Heart rate	PRA (ng/ml/hr)	Systemic BP (mm Hg) Systolic	Diastolic	Mean	LVEDP	Mean PAP	Coronary flow (ml/min)
1. Baseline	84	19.7	224	100	141	26	30	168
30″ after injection	83	89.0	184	81	109	12	17	95
2. Baseline	73	1.03	207	96	130	25	30	85
30″ after injection	75	1.35	196	91	123	24	27	113
3. Baseline	92	1.33	177	91	120	32	38	170
30″ after injection	89	1.32	178	88	118	29	30	141
4. Baseline	75	7.4	154	105	121	39	46	113
30″ after injection	71	13.0	145	96	112	29	43	112
5. Baseline	93	3.55	129	67	88	28	36	255
30″ after injection	89	6.30	122	63	83	23	33	194
6. Baseline	113	12.8	90	69	76	31	41	142
30″ after injection	107	38.0	87	48	64	25	37	87
7. Baseline	88	18.9	80	50	60	25§	40	
30″ after injection	88	60.0	75	40	52	20§	35	
8. Baseline	75	13.0	132	50	77	26§	43	
30″ after injection	74	58.0	115	38	74	16§	36	
Mean ± SEM Baseline	87 ± 5	9.7 ± 2.6	149 ± 18	78 ± 8	102 ± 11	30 ± 2	38 ± 2	149 ± 24
Mean ± SEM 30″ after	85 ± 4	33.4 ± 11.7*	138 ± 16	68 ± 8*	92 ± 9*	24 ± 3*	32 ± 3*	144 ± 30

*P <0.05.
†P <0.02.
‡P <0.01.
§Pulmonary wedge pressure.
Abbreviations: PRA = plasma renin activity; LVEDP = left ventricular end-diastolic pressure; PAP = pulmonary artery pressure; LVSWI = left ventricular stroke work index.

puts at the time of study. Left ventricular stroke work index was depressed in five of the eight patients. In the control state, total pulmonary vascular resistance was significantly elevated in each patient and in six of the eight, systemic vascular resistance was elevated irrespective of the resting blood pressure.

All patients exhibited a fall in blood pressure within minutes after injection of teprotide, and the decrease in mean arterial pressure (from 102 ± 11 to 92 ± 9 mm Hg) was significantly correlated with the pretreatment levels of plasma renin activity (r = 0.844). The left ventricular end-diastolic pressure also declined significantly, but became normal in only one (patient 1). The change in left ventricular end-diastolic pressure or pulmonary capillary wedge pressure also correlated with the level of baseline plasma renin activity (r = 0.862), as well as the change in systemic blood pressure (r = 0.754).

The cardiac index and stroke volume index showed a substantial increment in all patients and correlated significantly with the fall in total peripheral vascular resistance (r = 0.726) (fig. 1). These changes were unrelated to the pretreatment plasma renin activity. The increase in cardiac index ranged from 6.5%–36% with a mean of 21.5 ± 4.2%. The systemic and pulmonary vascular resistance decreased consistently in all patients, the reduction varying between 8%–33% for the former and 12%–47% for the latter. There was no correlation between the fall in systemic vascular resistance or pulmonary vascular resistance and the pretreatment level of plasma renin activity.

Changes in coronary blood flow and coronary resistance varied during blockade, but were not signifi-

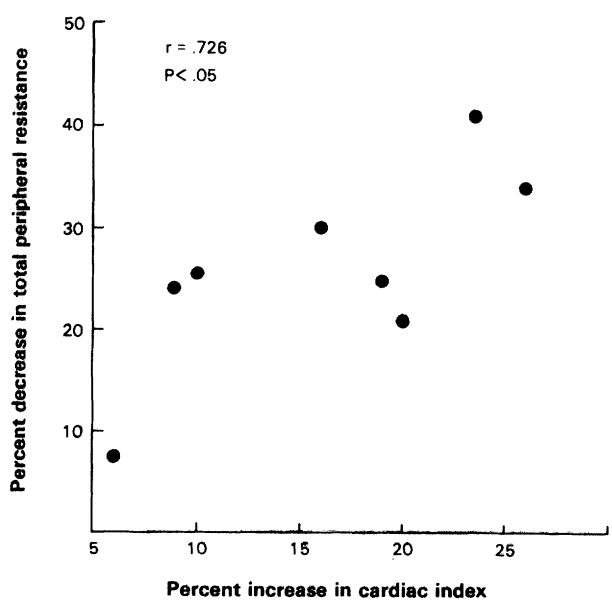

FIGURE 1. *Correlation between percent fall in total peripheral vascular resistance and percent change in cardiac index.*

TABLE 2. *(Continued)*

Cardiac output (l/min)	Cardiac index (l/min/m²)	Stroke volume index (cc/bt/m²)	LVSWI	Vascular resistance (dyne/sec/cm⁻⁵) Systemic	Pulmonary	Coronary	MVO_2
5.21	3.24	39	106	2286	457	66667	17
5.72	3.55	43	99	1720	244	96000	9
4.85	2.83	37	101	2504	435	128000	10.3
5.96	3.49	44	112	1881	379	89911	14.0
3.47	2.49	27	51	2915	886	54117	19
3.69	2.65	31	57	2688	656	65248	15
2.28	1.09	14	20	4243	1600	70088	19
3.11	1.48	21	29	2851	1025	66428	16
4.80	2.67	29	37	1498	593	26039	21
6.01	3.34	36	47	1181	525	34315	19
2.55	1.82	16	15	2500	1281	34930	12
2.86	2.04	19	17	1861	1028	42289	7
3.88	2.47	28	21	1340	824		
5.08	3.23	37	28	787	551		
4.96	2.59	34	49	1242	1000		
5.92	3.09	42	57	865	797		
4.00 ± 0.40	2.40 ± 0.23	28 ± 3.2	50 ± 12.6	2316 ± 351	884 ± 144	63306 ± 14743	16.4 ± 1.7
4.79 ± 0.48‡	2.85 ± 0.26‡	34 ± 3.4‡	56 ± 12	1729 ± 272†	650 ± 101	65698 ± 11242	13 ± 1.8

cant overall. Myocardial oxygen consumption declined in all but one patient. Patients who had the highest resting renin levels showed the greatest decrease in mean arterial pressure, left ventricular end-diastolic pressure, coronary flow and MVO_2.

Myocardial performance was significantly improved in all patients as shown by either a decrease in left ventricular end-diastolic pressure or a significant increase in left ventricular stroke work index, implying that their left ventricular function curve had shifted to the left (fig. 2). In addition, all but one patient demonstrated an increase in cardiac index despite a fall in MVO_2.

Variable and mostly insignificant changes were observed in the arterial lactates, from 12 ± 4 to 14 ± 3 mg/100 ml and the coronary sinus lactates from 15 ± 5 to 11 ± 4 mg/100 ml. Likewise, arterial-coronary sinus lactate differences showed no consistent change. Arterial oxygen content remained unchanged, from 15.7 ± 1.2 to 15.6 ± 1.2 ml/100 ml.

In the two patients (7 and 8) who had hemodynamic indices measured for up to 5 hours after the administration of teprotide, there was persistence of the lowered mean arterial pressure and increased cardiac output with decreased systemic vascular resistance. There was a gradual return to pretreatment

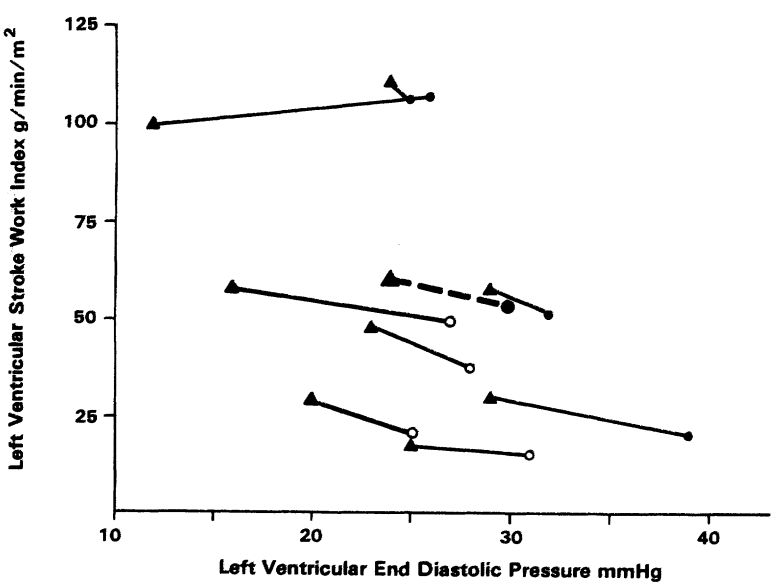

FIGURE 2. *Left ventricular end-diastolic pressure decreased in all but one patient, with no significant increase in left ventricular stroke work index, indicating a shift of the left ventricular function to the left. Dotted line indicates mean change for the group. Circles indicate baseline values and triangles indicate values during blockade. ● = hypertensive; ○ = normotensive subjects.*

levels of all measurements, but baseline values were not attained at 5 hours postmedication (fig. 3).

Discussion

Therapy for heart failure consisting of reducing the afterload with vasodilator drugs has recently been advocated either as an alternative or adjunct to the traditional approach of using diuretics and inotropic agents.[9] It has been shown that diuretics which reduce ventricular filling pressure may in fact decrease the cardiac output.[10] Inotropic drugs which increase the velocity of fiber shortening and the systolic arterial pressure will augment the oxygen demands of the myocardium,[11] whereas drugs which reduce the impedance to left ventricular outflow may increase the cardiac output and relieve the left ventricular wall tension. A variety of parenteral and oral vasodilator agents have been studied, including sodium nitroprusside,[12] phentolamine,[13] nitroglycerin,[14] hydralazine,[15] and prazosin.[16] Their effects vary[17] in terms of duration of action, degree of dilatation of the venous or arterial vessels, sympathetic stimulation, and influence on regional blood flows, particularly coronary flow.

In keeping with the principle of unloading the left ventricle by reducing the peripheral vascular resistance, we have successfully treated the heart failure of a known high-renin hypertensive patient with the specific angiotensin antagonist saralasin.[18] The results were gratifying, but it was argued that such an approach would probably only be appropriate

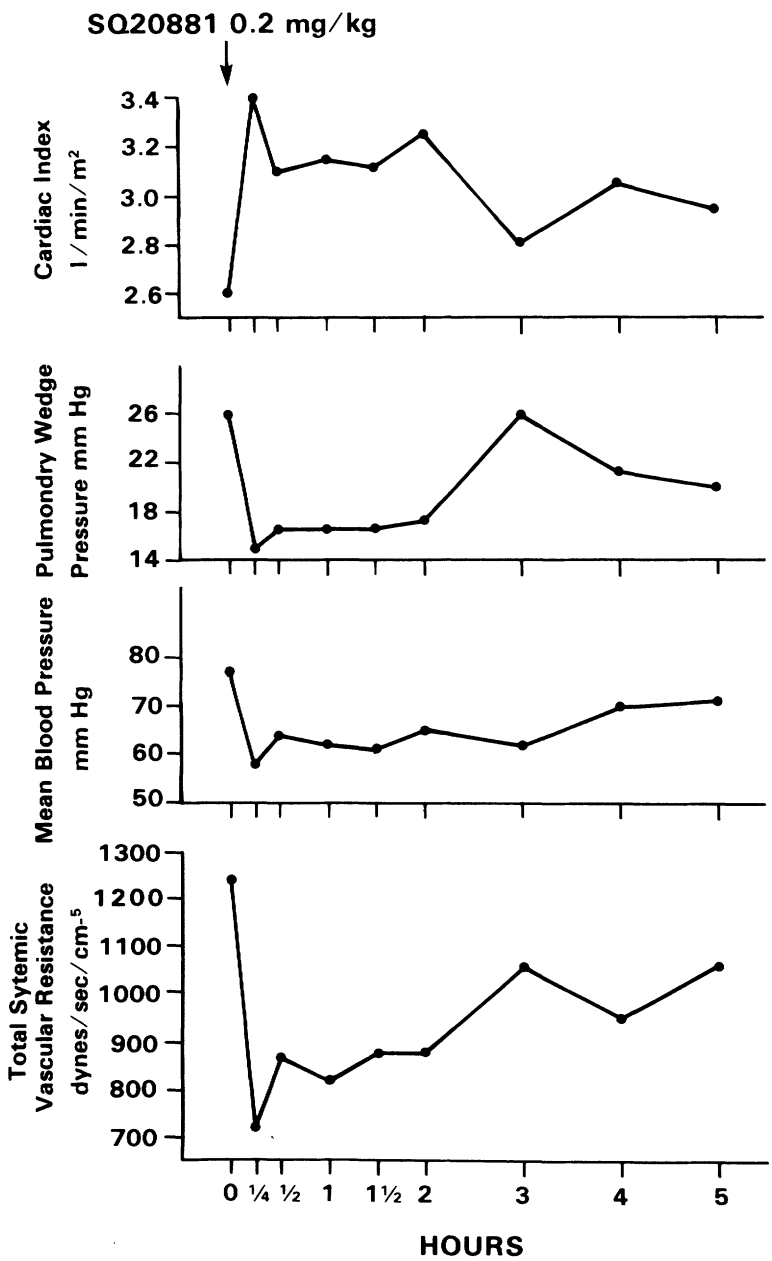

FIGURE 3. *Hemodynamic changes over a 5-hour period after a single injection of SQ20,881 in a normotensive patient (no. 28) with congestive cardiac failure.*

for highly selected cases of pump failure due to angiotensinogenic hypertension.

The present study includes four hypertensive and four normotensive subjects with heart failure and with different degrees of coronary artery disease. Four (one hypertensive and three normotensives) had elevated plasma renin activity and three had plasma renin activity below the normal range. The converting enzyme inhibitor teprotide was chosen instead of saralasin for its more consistent vasodepressor action[19] and lack of angiotensin-like activity. The possible potentiation of bradykinin by this agent,[20] with its additional vasodilating effect, would probably be of further benefit for our purposes. Previous clinical experience has shown this agent to be safe and devoid of undesirable side effects.[21]

Inhibition of angiotensin-converting enzyme resulted in a significant decrease in systemic and pulmonary vascular resistance. The consequent fall in systemic blood pressure and left ventricular end-diastolic pressure truly represents "unloading" of the left ventricle. As a result, the cardiac output increased in all patients by an average of 21.5%. Two normotensive patients had undergone angiography 24 hours earlier. In our experience the possible myocardial depressant effect of the contrast medium lasts less than 30 minutes, and its osmotic diuretic effect lasts no more than 12 hours. At the beginning of the experiment their baseline data were identical to those measured during cardiac catheterization on the previous day. In these two patients, the hemodynamic measurements after teprotide were repeated hourly for up to 5 hours (fig. 3) and were found to remain substantially improved over the baseline levels. Moreover, all patients felt a subjective symptomatic improvement lasting for several hours after the study. This is consistent with the known long duration of action of SQ20881. In a study on hypertensive subjects, it was determined that its maximal blood pressure lowering effect could be achieved with a dose of 0.5 mg/kg and that higher doses up to 4 mg/kg only prolonged this effect for up to 16 hours, depending on the dosage used.[21]

The observed hemodynamic improvement after teprotide is achieved at no additional oxygen cost to the heart, as indicated by the lack of significant change in the myocardial oxygen consumption. Although it might be anticipated that myocardial oxygen consumption would decrease in patients whose heart rate-blood pressure product was lowered, we considered it important to make direct estimates of MVO_2. Recent experimental studies in our laboratory have shown an increase in cardiac output and coronary blood flow following the administration of teprotide to salt-depleted dogs. These changes were accompanied by a significant decrease in myocardial oxygen extraction and no change in myocardial oxygen consumption.[22] We were unable to show any consistent change in either coronary blood flow or myocardial oxygen consumption in this series of patients, all of whom showed a significant fall in diastolic blood pressure.

As expected from the use of this drug as an antihypertensive agent,[19, 23] the reduction in blood pressure correlated with the baseline plasma renin activity and this relationship held true for both the hypertensive and normotensive subjects. However, the resulting elevation in stroke volume index and cardiac index, which was observed to variable degrees in all patients, did not correlate with the pretreatment levels of plasma renin activity. The increase in cardiac index was unrelated to the baseline systemic vascular resistance, but correlated well with the fall in systemic vascular resistance, suggesting that it was partly the mechanical effect of vasodilatation which caused this increase. The possibility of influencing the direct effect of angiotensin on the myocardium by this agent is difficult to assess since some experimental studies have suggested that angiotensin increases myocardial contractility[24, 25] while others indicated the opposite.[26, 27] The fact that the fall in systemic vascular resistance did not correlate with the baseline plasma renin activity raises the question as to whether angiotensin elimination per se was the sole cause of these findings, or whether some additional effects of converting enzyme inhibition (i.e., accumulation of bradykinin) might contribute in a way that is still poorly understood.

Although the elevated systemic vascular resistance found in congestive heart failure is well-recognized, its mechanisms remain unclear. Zelis et al.[28] have shown that there appear to be at least two major mechanisms producing alterations in the peripheral vasculature. The first mechanism is augmented sympathetic activity which produces arteriolar constriction and redistribution of blood flow. The second mechanism is a component of arteriolar stiffness. It has been suggested that the stiffness of the capacitance vessels may be related to sodium and water retention in the vascular walls. The present study suggests that perhaps a third mechanism, the activity of the renin-angiotensin system, may play a role in maintaining an increased systemic vascular resistance in some patients with congestive heart failure.

In conclusion, our preliminary experience with the use of angiotensin-converting enzyme inhibition in the treatment of congestive heart failure indicates that this approach is worthwhile. Cardiac function improved in all patients by decreasing afterload, and lasted for several hours after a single injection. This improvement did not depend on the baseline blood pressure or plasma renin activity, but correlated with the fall of the peripheral vascular resistance. Regardless of its exact mechanism of action, inhibition of the converting enzyme has no adverse effects and appears to be a promising therapeutic modality for congestive heart failure.

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