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Effects of renin inhibition compared to angiotensin converting enzyme inhibition in conscious dogs with pacing-induced heart failure

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Abstract

Objective: To compare the effects of angiotensin converting enzyme inhibition (ACEI) (captopril 1 mg/kg i.v.) to direct renin inhibition (CP80794 3 mg/kg i.v.) on left ventricular and systemic hemodynamics and peripheral blood flows in advanced congestive heart failure (CHF). **Methods:** Conscious chronically instrumented dogs ($n = 14$) were treated with captopril, 1 mg/kg, i.v., or CP80794, 3 mg/kg, i.v., before and after development of advanced CHF induced by 4–7 weeks of rapid ventricular pacing. After advanced CHF, comparisons between the inhibitors were made at equihypotensive doses. **Results:** In advanced CHF, both agents caused comparable reductions in mean arterial pressure (MAP) (-22% from 79 ± 4 mmHg) and comparable increases ($P < 0.01$) in cardiac output (CP80794, 1.4 ± 0.3 to 1.8 ± 0.1 l/min; captopril, 1.4 ± 0.1 to 1.9 ± 0.1 l/min). Neither agent had a significant effect on LV contractility. In contrast, CP80794 caused a greater ($P < 0.05$) increase in renal blood flow ($66 \pm 6\%$ from 64 ± 5 ml/min) compared to captopril ($33 \pm 4\%$ from 66 ± 7 ml/min). **Conclusions:** Renin inhibition with CP80794 and ACEI with captopril caused comparable hemodynamic effects in advanced CHF. However, CP80794 caused significantly greater increases in renal blood flow and suppressed renin activity to a greater degree than captopril.

Keywords: Renin inhibition; ACE inhibitors; Heart failure; Blood flow, peripheral; Hemodynamics; Dog, anesthetized

1. Introduction

The widespread use of angiotensin converting enzyme inhibitors (ACEI) in the treatment of early and advanced heart failure has resulted in consistent improvements in both systemic hemodynamics [1,2] and survival [3–5]. However, despite the incontrovertible evidence of significant clinical benefit, the precise mechanism whereby ACEI exert their salutary effects remains controversial. ACEI not only block the conversion of angiotensin I to angiotensin II, but also prevent the degradation of bradykinin and stimulate the production of prostaglandins [6,7] that contribute significantly to the vasodilation and hemodynamic benefits associated with ACEI [8–10]. Moreover, the initial reduction in plasma AII levels with ACEI in congestive heart failure (CHF) patients returns to the elevated pre-treatment levels, even though ACE activity remains inhibited. Whether this 'escape' of plasma AII levels is due to induction of alternative enzymes which catalyze the formation of AII [11,12] or an excess of substrates, renin and AI [13,14], is unclear. Renin inhibitors have been introduced which act specifically to block the conversion of the substrate proximal to that of ACEI. Unlike ACEI, these agents do not affect the degradation of bradykinin or prostaglandins and direct renin inhibition is unassociated with the significant increases in plasma renin activity [15,16]. While renin inhibitors have been shown to have potent hypotensive effects in sodium-deficient animals and man [17–20], in general, the agents have poor oral bioavailability which hinders chronic evaluation of their efficacy. Therefore, less is known about their effects in

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heart failure, where the renin–angiotensin system has been shown to be activated.

Accordingly, the purpose of the present study was to compare the acute hemodynamic effects of the specific renin inhibitor, CP80794, with the ACEI, captopril, in conscious dogs with pacing-induced heart failure in its advanced decompensated stages. Both agents were administered intravenously to circumvent differences in oral bioavailability. Dose–response curves were created to select a maximum equihypotensive dose. CP80794 is a tripeptide renin inhibitor with a cyclohexylnorstine ester moiety on the C-terminus that results in a highly selective inhibition of plasma renin activity with an IC_{50} of 0.7 nM in both dogs and man [19,20]. In contrast to what has been reported in anesthetized, sedated, or acutely instrumented preparations [21–30], the model of pacing-induced heart failure in the conscious dog is associated with progressive contractile dysfunction and ventricular dilatation, but maintenance of cardiac output until the advanced stages (4–7 weeks of pacing) [31,32], when, if left untreated, activation of the renin–angiotensin system is manifest. Thus, the animals used in the present investigation were studied at the point where significant declines in cardiac output and concomitant increases in plasma renin activity were evident.

2. Methods

2.1. Surgical instrumentation [31,32]

Seventeen mongrel dogs of either sex weighing between 23–31 kg were fasted overnight and sedated with xylazine (2 mg/kg i.m.), intubated, and anesthetized with halothane anesthesia (1–1.5 vol%). Through an incision in the left fifth intercostal space, Tygon catheters (Norton Plastics and Synthetics Division, Akron, OH) were placed in the descending thoracic aorta, left atrium (LA) and right atrium (RA, $n = 5$). A Transonics flow probe ('S' series, 24 mm, $n = 12$) (Transonics Co., Utica, NY) was placed around the ascending aorta and a solid-state miniature pressure transducer (P22, Konigsberg Instruments, Pasadena, CA) was implanted in the left ventricle through an apical stab wound. A sutureless pacing lead (model 831, Pacesetter System, Sylmar CA) was placed on the epicardium of the right ventricular (RV) free wall. All catheters and leads were externalized infrascapularly, the thoracotomy was closed in layers, and the chest evacuated of air. Three of these original animals succumbed from heart failure prior to study in heart failure and were excluded from analysis, leaving 11 male and 3 female dogs for chronic study. In addition to the above cardiac instrumentation, Doppler flow probes were placed on the left circumflex coronary artery (3–4 mm) in 6 dogs. In 5 separate dogs, a laparotomy was performed following thoracic surgery and Doppler flow probes were placed on the celiac (6–8 mm), mesenteric (6–8 mm), renal (4–6 mm) and iliac arteries (6–8 mm) to determine regional blood flows. These animals did not receive Transonics aortic flow probes and were, therefore, only included in the protocol to identify the effects of renin inhibition versus ACE inhibition on peripheral flows.

All dogs were allowed to recover for 2 weeks during which time they were trained to lie quietly on the experimental table. Catheters were flushed daily and filled with a solution of 50% heparin such that each catheter was filled with 1000–1500 units. Cephalothin (50 mg/kg i.v.) was administered twice daily for the first 7 days postoperatively. The animals used in the study were maintained in accordance with the *Guide for the Care and Use of Laboratory Animals* (DHEW Publication No. (NIH) 85-23, revised 1985) and the Standing Committee on Animal Care of Harvard Medical School.

2.2. Experimental protocol

All animals were studied in both the control state and in advanced heart failure which was induced by rapid right ventricular pacing as described previously [31,32]. Briefly, right ventricular pacing was initiated at 240 beats per minute using a programmable miniature cardiac pacemaker (model 4543, PACE Medical, Waltham, MA) which was worn externally and secured to the animal's vest. At the time of study, the pacing was terminated for at least 30 min and all experimental recordings were made during the intrinsic sinus rhythm. Rapid right ventricular pacing was maintained for an average of 36 days during which severe congestive heart failure developed as manifested by elevated LA pressures and depressed cardiac outputs. Clinical signs of heart failure included lethargy, anorexia, exercise intolerance and abdominal ascites. In addition, plasma renal activity was monitored and the animals were studied when they manifest at least a threefold increase (above baseline) in plasma renin activity.

All hemodynamic measurements were made in the intrinsic sinus rate with the animal fully conscious while lying quietly on the experimental table. All dogs were fed a standard, non sodium restricted diet and received no medications other than the aforementioned study drugs. Nine dogs received both CP80794 and captopril in the control state and during the advanced stages of heart failure. Dose–response relationships were established to CP80794 by bolus injection of 0.1, 1.0 and 3.0 mg/kg. The vehicle for CP80794 (hydroxypropyl β-cyclodextran) was used as control. The dose–response relationship to captopril was established by bolus injection of 0.01, 0.1 and 1.0 mg/kg. In the control state, dogs received CP80794 prior to captopril after it was determined that CP80794 had no hemodynamic effects in the control state in the sodium-replete, conscious dog. In heart failure, the order in which the drugs were administered was randomized with at least 1 day separating the administration of the two

agents. After the dose–response data were established, further analyses in heart failure were conducted at maximum equihypotensive doses which caused comparable decreases in mean arterial pressure.

2.3. Data analysis [31,32]

The hemodynamics were recorded simultaneously on a multichannel magnetic tape recorder (Honeywell 101) and played back on a strip chart recorder (Gould 3800). Continuous recordings of LV dP/dt were derived from the LV pressure signals with operational amplifiers connected as differentiators with a frequency response of 700 Hz. The differentiators were calibrated directly by substituting a triangular wave signal of known slope for the pressure signal. A cardiotachometer triggered by the LV pressure waveform provided a continuous record of heart rate. Mean arterial pressure (MAP) was derived through the use of an electronic filter applied to the phasic arterial pressure signal. Mean cardiac output was derived using a similar electronic filter applied to the phasic flow signal obtained from a Transonic flow probe (24 mm, Transonics, Utica, NY) placed on the ascending aorta. Mean peripheral flows were similarly derived from phasic signals obtained from pulsed Doppler flow probes placed on the left circumflex coronary artery, celiac artery, mesenteric artery, renal artery, and iliac artery. The flow in milliliters per minute in these peripheral arteries was calculated as the product of the measured mean velocity in centimeters per second and the internal cross-sectional area of the respective arteries at the site of implantation of the Doppler flow probes, obtained when the animals were euthanized. The mean systemic vascular resistance was calculated as the quotient of the mean arterial pressure (mmHg) and systemic cardiac output (l/min) and expressed in metric resistance units ($\text{dyne} \cdot \text{s} \cdot \text{cm}^{-5}$) by multiplying by 80.

Plasma renin activity was determined at baseline and at 5 min following the bolus administration of each agent. Three milliliters of arterial blood were withdrawn, placed in a cold tube containing EDTA, centrifuged and plasma was stored at -70°C for determination of plasma renin activity using the radioimmunoassay of Haber et al. [33].

3. Results

3.1. The dose–response relationship for CP80794 and captopril in control dogs

Table 1 reveals the resting hemodynamics in the conscious dogs studied in the control state and then in the advanced heart failure state. There was a 18% decrease ($P < 0.01$) in LV systolic pressure and a 13% decrease ($P < 0.01$) in mean arterial pressure during the progression to advanced heart failure. The LV end-diastolic pressure increased from 5 ± 1 to 24 ± 1 mmHg ($P < 0.01$). There was evidence of significant contractile dysfunction as evidenced by a greater than 50% reduction in LV dP/dt from 2858 ± 249 mmHg/s ($P < 0.01$). Heart rate increased by 35 ± 4 beats/min from 90 ± 5 beats/min ($P < 0.01$). Resting cardiac output declined significantly from 2.49 ± 0.11 l/min in the control state to 1.36 ± 0.42 l/min in advanced heart failure ($P < 0.01$). There was a marked increase in calculated systemic vascular resistance ($P < 0.01$) in advanced heart failure. These hemodynamic perturbations were accompanied by clinical signs (edema, ascites, and muscle wasting) and symptoms (dyspnea, anorexia, and lethargy) in all dogs as observed by the investigators. Plasma renin activity increased greater than four-fold ($P < 0.01$) from 0.6 ± 0.1 ng/ml/h in control to 2.8 ± 0.5 ng/ml/h in advanced heart failure. Three of the initial cohort of animals studied in the control state suc-

Table 1
Baseline hemodynamics and regional blood flow prior to pacing and during advanced heart failure in conscious dogs

	Pre-pacing	CHF
LV systolic pressure (mmHg) ($n = 9$)	120 ± 3	102 ± 2 [b]
LV end-diastolic pressure (mmHg) ($n = 9$)	5 ± 1	24 ± 1 [b]
LV dP/dt (mmHg/s) ($n = 9$)	2858 ± 249	1359 ± 137 [b]
Mean arterial pressure (mmHg) ($n = 9$)	90 ± 2	79 ± 4 [a]
Right atrial pressure (mmHg) ($n = 5$)	2 ± 1	11 ± 1 [b]
Cardiac output (l/min) ($n = 9$)	2.49 ± 0.11	1.36 ± 0.42 [b]
Heart rate (min^{-1}) ($n = 9$)	90 ± 5	125 ± 4 [b]
Systemic vascular resistance ($\text{dyne} \cdot \text{cm} \cdot \text{s}^{-5}$) ($n = 9$)	2930 ± 119	5031 ± 508 [b]
Plasma renin activity (ng/ml/h) ($n = 9$)	0.6 ± 0.1	2.8 ± 0.5 [b]
Left circumflex coronary blood flow (ml/min) ($n = 6$)	45 ± 3	39 ± 2 [a]
Celiac blood flow (ml/min) ($n = 5$)	131 ± 12	90 ± 9 [a]
Mesenteric blood flow (ml/min) ($n = 5$)	183 ± 13	96 ± 8 [a]
Renal blood flow (ml/min) ($n = 5$)	120 ± 14	64 ± 5 [a]
Iliac blood flow (ml/min) ($n = 5$)	54 ± 7	44 ± 4 [a]

[a] $P < 0.05$ compared to Pre-pacing.
[b] $P < 0.01$ compared to Pre-pacing.

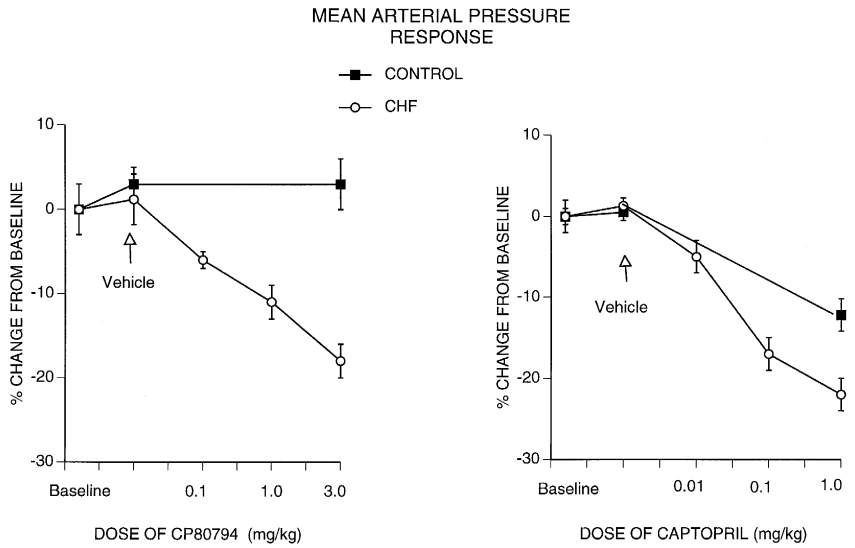

Fig. 1. The dose–mean arterial pressure response relationship to increasing doses of CP80794 and captopril in the control state and in advanced heart failure (CHF) in conscious dogs.

cumbed prior to study in advanced heart failure and were excluded from the overall analysis.

Fig. 1 represents the mean arterial pressure responses to increasing doses of the renin inhibitor, CP80794, and the ACE inhibitor, captopril, in conscious dogs studied in the control state prior to pacing and after the development of advanced CHF. The vehicles in which the respective drugs were administered had no effects on MAP. The renin inhibitor had no effects on MAP even at the highest doses administered in the conscious dogs studied in the sodium-replete state. This was associated with a decrease in plasma renin activity from 0.7 ± 0.1 ng/ml/h to less than 0.1 ± 0.1 ng/ml/h ($P < 0.01$). In contrast, captopril caused a progressive dose-related decrease in MAP in the control state with the largest dose (1 mg/kg) resulting in a $12 \pm 3\%$ decrease in resting MAP. In contrast to CP80794, captopril caused a significant increase in plasma renin activity from 0.6 ± 0.2 to 1.3 ± 0.4 ng/ml/h ($P < 0.05$) in the control state. In advanced heart failure, there was again no effect of the respective vehicles used to administer the drugs on MAP responses. However, in contrast to what was observed in the dogs studied in control, the renin inhibitor, CP80794, caused dose-related decreases in MAP while suppressing plasma renin activity from 2.8 ± 0.7 to less than 0.1 ng/ml/h ($P < 0.01$). At the maximum dose tested for each agent, CP80794 (3 mg/kg) caused comparable peak reductions in MAP ($22 \pm 2\%$) to that of captopril (1 mg/kg). However, in contrast to CP80794, capto-

Table 2
The peak effects of CP80794 and captopril at equihypotensive dose on LV and systemic hemodynamics and regional blood flow in conscious dogs with advanced heart failure

	CP80794 (3 mg/kg)		Captopril (1 mg/kg)	
	Baseline	Peak response	Baseline	Peak response
LV systolic pressure (mmHg) ($n = 9$)	102 ± 4	89 ± 4 [b]	101 ± 3	88 ± 4 [b]
LV end-diastolic pressure (mmHg) ($n = 9$)	24 ± 1	19 ± 4 [b]	24 ± 1	20 ± 1 [a]
LV dP/dt (mmHg/s) ($n = 9$)	1429 ± 135	1543 ± 268	1382 ± 242	1389 ± 252
Mean arterial pressure (mmHg) ($n = 9$)	80 ± 2	63 ± 2 [b]	79 ± 3	60 ± 4 [b]
Right atrial pressure (mmHg) ($n = 5$)	11 ± 1	8 ± 2 [a]	10 ± 1	8 ± 1 [a]
Cardiac output (l/min) ($n = 9$)	1.38 ± 0.28	1.81 ± 0.11 [b]	1.39 ± 0.12	1.87 ± 0.14 [b]
Heart rate (min^{-1}) ($n = 9$)	124 ± 4	113 ± 5 [a]	119 ± 4	109 ± 6 [a]
Systemic vascular resistance (dyne·cm·s^{-5}) ($n = 9$)	4818 ± 334	2969 ± 251 [b]	4877 ± 482	2665 ± 191 [b]
Coronary blood flow (ml/min) ($n = 6$)	37 ± 3	34 ± 2 [a]	39 ± 3	36 ± 2 [b]
Celiac blood flow (ml/min) ($n = 5$)	92 ± 9	108 ± 9 [a]	89 ± 9	107 ± 8 [a]
Mesenteric blood flow (ml/min) ($n = 5$)	92 ± 8	79 ± 4	96 ± 5	105 ± 7 [a]
Renal blood flow (ml/min) ($n = 5$)	71 ± 7	106 ± 8 [b]	69 ± 6	87 ± 7 [a]
Iliac blood flow (ml/min) ($n = 5$)	46 ± 5	54 ± 3 [a]	41 ± 6	57 ± 3 [a]

[a] $P < 0.05$ compared to baseline.
[b] $P < 0.01$ compared to baseline.

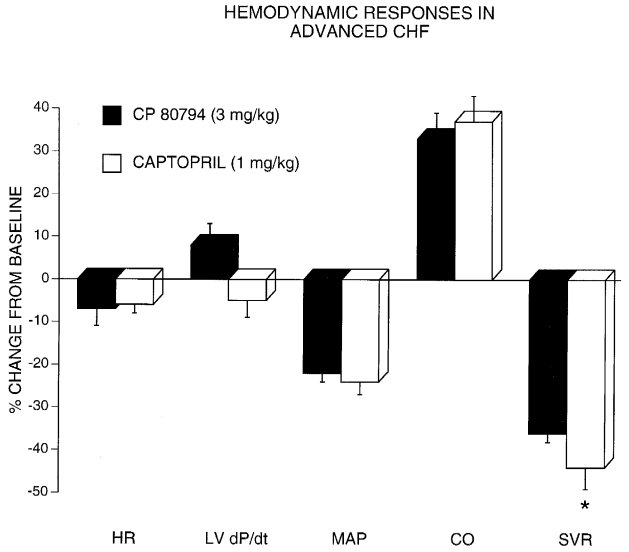

Fig. 2. A comparison between the hemodynamic effects of the renin inhibitor, CP80794 (3 mg/kg), and captopril (1 mg/kg) in conscious dogs with advanced heart failure (CHF) (* $P < 0.05$). CO = cardiac output; HR = heart rate; LV dP/dt = first derivative of LV pressure with respect to time; MAP = mean arterial pressure; SVR = systemic vascular resistance.

pril caused a further increase in plasma renin activity from 2.5 ± 0.3 to 4.4 ± 0.9 ng/ml/h ($P < 0.05$). These equihypotensive doses were used for subsequent analyses.

3.2. The peak effects of renin inhibition compared to ACE inhibition at equihypotensive doses in advanced heart failure

Table 2 depicts the peak effects of CP80794 (3 mg/kg) and captopril (1 mg/kg) at equihypotensive doses on resting hemodynamics in advanced heart failure. The peak effects of CP80794 in advanced heart failure were evident within the first 10 min and persisted for up to 45 min. CP80794 caused a 12% decrease in LV systolic pressure and a 22% decrease in MAP. LV end-diastolic pressure fell from 24 ± 1 to 19 ± 4 mmHg ($P < 0.05$). There was a small, but insignificant increase in LV dP/dt. Heart rate fell slightly while cardiac output increased from 1.38 ± 0.28 to 1.81 ± 0.11 l/min ($P < 0.02$). SVR was reduced from 4818 ± 334 to 2969 ± 251 dyn · s · cm^{-5} ($P < 0.05$).

The peak effects of captopril were evident within the first 5 min and persisted for greater than 60 min. Captopril caused a 12% decrease in LV systolic pressure and a 24% decrease in MAP ($P < 0.05$). LV end-diastolic pressure fell from 24 ± 1 to 20 ± 1 mmHg ($P < 0.05$). LV dP/dt was unchanged. Heart rate fell by 9% while cardiac output increased from 1.39 ± 0.12 to 1.87 ± 0.14 l/min ($P < 0.01$). SVR was reduced from 4877 ± 482 to 2665 ± 191 dyn · s · cm^{-5} ($P < 0.05$).

Fig. 2 compares the effects of renin inhibition with ACE inhibition on hemodynamic parameters in advanced heart failure. While the effects on heart rate and mean arterial pressure were comparable, captopril caused a slightly greater increase in cardiac output (CP80794 $+33 \pm 6\%$ vs. captopril $+37 \pm 6\%$, P = n.s.) and a resultant greater decline in SVR (CP80794 $-37 \pm 3\%$; captopril $-44 \pm 3\%$, $P < 0.05$).

3.3. The peak effects on peripheral blood flow at equihypotensive doses (Tables 1 and 2)

With the development of advanced heart failure (Table 1), there were significant reductions in baseline left circumflex coronary blood flow from 45 ± 3 to 39 ± 2

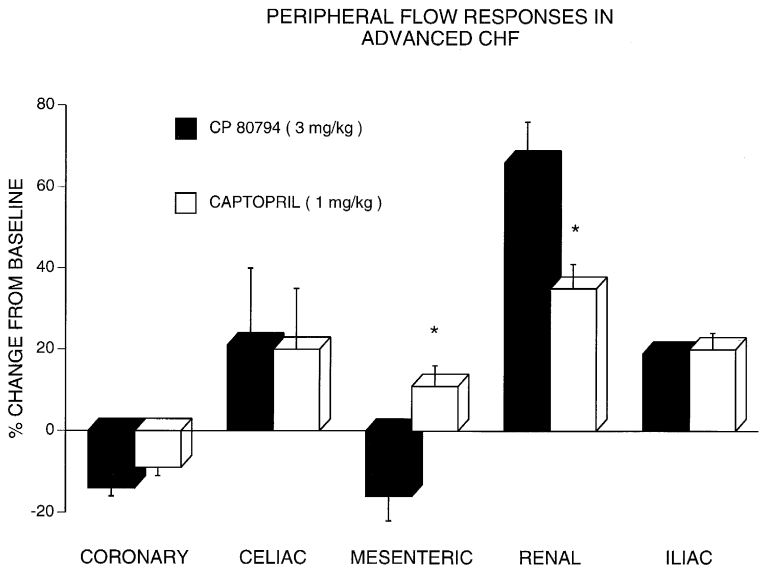

Fig. 3. A comparison between the effects of the renin inhibitor, CP80794 (3 mg/kg), and captopril (1 mg/kg) on peripheral blood flows in conscious dogs with advanced heart failure (* $P < 0.05$).

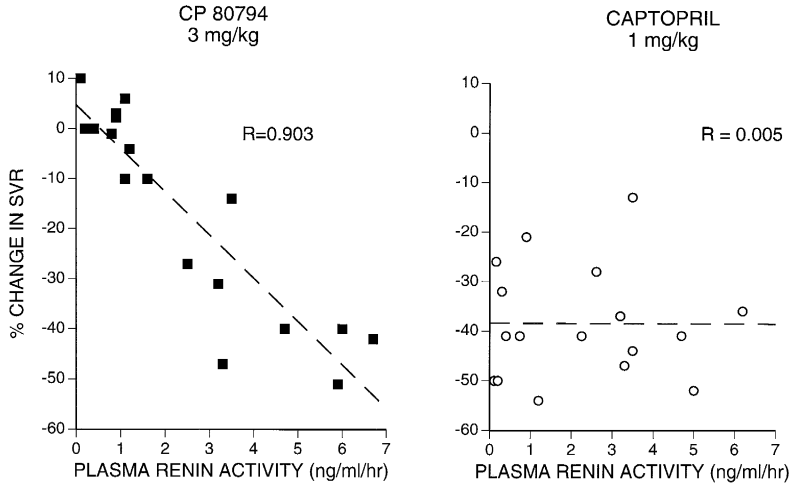

Fig. 4. Correlation between plasma renin activity and the vasodepressor response to CP80794 (3 mg/kg) and captopril (1 mg/kg). There was a significant negative correlation between plasma renin activity (PRA) and the vasodepressor response with CP80794, but not captopril. SVR = systemic vascular resistance.

ml/min ($P < 0.05$). Similarly, there were significant reductions in celiac blood flow ($-31 \pm 3\%$ from 131 ± 12 ml/min), mesenteric blood flow ($-48 \pm 3\%$ from 183 ± 13 ml/min), renal blood flow ($-44 \pm 6\%$ from 120 ± 14 ml/min) and iliac blood flow ($-16 \pm 3\%$ from 54 ± 7 ml/min), consistent with the global reductions in cardiac output ($-45 \pm 6\%$ from 2.49 ± 0.11 l/min).

Table 2 depicts the peak effects of the renin inhibitor, CP80794 (3 mg/kg), and the ACE inhibitor, captopril (1 mg/kg), on coronary, celiac, mesenteric, renal and iliac blood flows in advanced heart failure. In advanced heart failure, the renin inhibitor, CP80794, caused a further $13 \pm 3\%$ decline ($P < 0.02$) in coronary blood flow and a $16 \pm 4\%$ reduction in mesenteric blood flow. In contrast, there was a $23 \pm 14\%$ increase (P = n.s.) in celiac blood flow, a $66 \pm 6\%$ increase ($P < 0.01$) in renal blood flow, and a $30 \pm 6\%$ increase ($P < 0.05$) in iliac blood flow.

Captopril caused a $9 \pm 2\%$ decrease in left circumflex coronary blood flow from 39 ± 3 ml/min, but a $20 \pm 5\%$ increase in celiac blood flow, a $11 \pm 4\%$ increase in mesenteric blood flow ($P < 0.05$), a $33 \pm 4\%$ increase in renal blood flow ($P < 0.02$) and a $29 \pm 4\%$ increase in iliac blood flow. Fig. 3 compares the effects of renin inhibition with ACE inhibition on peripheral blood flows in advanced heart failure. Both agents had comparable effects on left circumflex coronary blood flows, celiac blood flows and iliac blood flows. However, there were significant differences in the effects on mesenteric and renal blood flows. While the renin inhibitor, CP80794, caused a modest further decrease in mesenteric blood flow, captopril caused a modest increase in mesenteric blood flow ($P < 0.05$). With respect to the effects on renal blood flow, the renin inhibitor, CP80794, caused a nearly two-fold greater increase ($P < 0.05$) in renal blood flow compared to captopril.

3.4. The effects on plasma renin activity at equihypotensive doses

In both the control and advanced heart failure states, the renin inhibitor had a significant suppressive effect on plasma renin activity with inhibited levels falling below the lower limit detectable by this sensitive assay. In contrast, captopril stimulated plasma renin activity in both the control state and advanced heart failure. Fig. 4 reveals a significant ($P < 0.01$) inverse correlation ($r = 0.903$) between the plasma renin activity and the vasodepressor effects of the renin inhibitor, CP80794 (3 mg/kg). In contrast, there was no correlation ($r = 0.005$) between baseline plasma renin activity and the effect of captopril (1 mg/kg) on the systemic vasodepressor response, suggesting that the vasodilator response to captopril was independent of plasma renin activity.

4. Discussion

While the acute and chronic hemodynamic effects of ACE inhibitors have been studied in this model in anesthetized dogs [28–30] and swine [26], this is the first comparative study between ACE inhibitors and a selective renin inhibitor in conscious dogs with advanced heart failure in which LV, systemic and peripheral blood flow effects were examined. In contrast, while the effects of renin inhibitors have been studied in sodium-depleted dogs [17–20] and animals with renin-dependent hypertension [34], this is the first study to examine the effects in an experimental model of heart failure in conscious dogs. After dose–response curves for mean arterial pressure responses were generated, the dose used to compare the two agents was the maximum dose with comparable ef-

fects on mean arterial pressure (−20%) in advanced heart failure. This protocol was designed to examine the LV, systemic, and peripheral vascular effects following a single intravenous bolus administration that caused comparable decreases in perfusion pressures and, therefore, induced comparable activation of baroreflexes. While these effects may not represent the effects following chronic oral administration, the lack of oral bioavailability with CP80794 (< 10%) in humans dictated that this was the most logical experimental design.

The selectivity of the renin inhibitor is evidenced in the absence of a significant hemodynamic effect in the conscious dogs studied in the control state, where plasma renin activity averaged 0.6 ng/ml/h. Specifically, in the 5 dogs in which peripheral vascular responses were measured at baseline, there was no change in either systemic or renal vascular resistance following CP80794 in control. In contrast, despite similar resting plasma renin activity, captopril had a significant vasodepressor effect (−12%) in the control dogs. This is in keeping with the other effects of ACE inhibition to increase both bradykinin [35–37] and vasodilatory prostaglandins [38] which can cause hypotension independent of the inhibition of angiotensin II. It remains controversial as to the importance of these nonselective effects of ACE inhibitors in the hemodynamic benefits associated with their administration in both hypertension and heart failure. However, it is well recognized that these properties may predispose to side-effects seen commonly with these agents such as angio-edema [39] and cough [40–42]. It is conceivable that these additional vasodilatory properties of ACE inhibitors accounted for the greater decline in systemic vascular resistance in dogs with advanced heart failure. An additional piece of evidence in favor of the selectively of the renin inhibitor was the effects on plasma renin activity. In contrast to CP80794, ACE inhibition with captopril stimulated plasma renin activity both in the control state and in advanced heart failure. It has been suggested that the stimulation of plasma renin activity by ACE inhibitors may contribute to an escape from the effects of ACE inhibition and compromise the full effects of these agents [12–14]. In this regard, it is important to note that Hoit et al. [12] have recently identified a serum chymase capable of converting angiotensin I to angiotensin II, despite inhibition of ACE with captopril, in conscious baboons. Such ACE-independent activity reinforces the notion that captopril-induced increases in plasma renin activity may be counterproductive. Such a counterregulatory increase in plasma renin activity is not evident with the selective renin inhibitor.

It is of interest to note that while both agents increased cardiac output in advanced heart failure (Fig. 2), this was accomplished by decreasing LV afterload, rather than by increasing the contractile state. Additional salutary effects associated with this mechanism of increased pump performance was the significant decline in resting heart rate following the administration of both agents, despite decreases in mean arterial pressure. These observations are in keeping with reduced sympathetic nervous system activity associated with unloading the failing heart, with either ACE inhibitors or the renin inhibitor, CP80794. Furthermore, the observed decline in heart rate in the face of an increase in cardiac output supports an increase in stroke volume as the mechanism of improvement of LV pump performance.

Perhaps of greatest interest were the observed effects of each agent on regional blood flows. There are few prior studies which have documented the effects of ACE inhibitors on regional [44–46] as opposed to total systemic flows [26,30,43,48] and these have generally been limited to the study of renal perfusion. To our knowledge, this is the first study to document regional blood flows in response to a renin inhibitor in an experimental model of heart failure. We observed a small but significant decline in coronary blood flow in the conscious dogs with advanced pacing-induced heart failure similar to that reported previously from this [47] laboratory employing this experimental model. However, others [23] have observed significant increases in coronary blood flow in advanced heart failure, principally in acutely instrumented anesthetized dogs. Importantly, in the present study, both agents caused significant declines in coronary blood flow. Given the improvement in LV performance and the decline in heart rate, we assume that the reductions in coronary blood flow were a result of reduced myocardial metabolic requirements due to more favorable ventricular vascular coupling. However, we did not measure MVO_2 and, therefore, cannot conclude with certainty that this was the mechanism. We have previously observed that acute reductions in LV end-diastolic pressure result in overall reductions in coronary blood flow [47], but preferential increases in subendocardial perfusion. In the present study, we used Doppler flow probes to make multiple measurements of LCX coronary blood flow over time and did not examine the effects of these agents on transmyocardial blood flow.

Renal blood flow was significantly reduced in advanced heart failure in the conscious dogs contributing to the sodium-avid state which has been observed in this model [28–30]. Notably, the renin inhibitor, CP80794, had a significantly greater increase in renal blood flow (Fig. 4) compared to the ACE inhibitor despite the fact that the ACE inhibitor increased overall cardiac output to a slightly greater extent than did the renin inhibitor, CP80794. This may be due to the disparate effects on plasma renin activity where CP80794 completely abolished plasma renin activity, while captopril significantly increased plasma renin activity. These differences were not attributable to differences in sodium content of the diet or other pharmacological interventions. Importantly, the renin inhibitor had no effect on renal blood flow in the conscious dogs studied in the control state while captopril caused a slight, but insignificant decrease in renal blood flow, perhaps related to the decrease in mean arterial pressure with ACE

but not renin inhibition. Thus, the effects on renal blood flow seemed most pronounced in the heart failure state.

In contrast, mesenteric blood flow was reduced further in dogs following administration of the renin inhibitor, CP80794, while mesenteric flow tended to increase in dogs with advanced heart failure when they received ACE inhibitor. This disparate response suggests the possibility that the effects of ACE inhibitors on mesenteric flow may be mediated by the non-selective effects of prostaglandin or bradykinin degradation, as this response was not observed with selective renin inhibition with CP80794. No such differences were observed in the celiac or iliac beds. Whether and to what extent these selective differences in regional perfusion are observed with chronic administration is unknown. Given that these dogs in advanced heart failure were fasted for 8 h prior to study, it seems unlikely that vasoactive gastrointestinal hormones can account for the differences.

In conclusion, the effects of acute intravenous administration of the renin inhibitor, CP80794, on LV and systemic hemodynamics are comparable to the effect of the ACE inhibitor, captopril, in conscious dogs with dilated cardiomyopathy induced by rapid ventricular pacing. However, there are significant and potentially clinically important differences in the effects on plasma renin activity and specifically renal blood flow between the renin inhibitor, CP80794, and the ACE inhibitor, captopril. Whether these differences extend to more chronic administration remains to be determined.

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