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Effect of Low Dose Aspirin on Cardiorenal Function and Acute Hemodynamic Response to Enalaprilat in a Canine Model of Severe Heart Failure

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Objectives. **This study examined the effect of low dose aspirin on cardiorenal and neurohumoral function and on the acute hemodynamic response to enalaprilat in a canine model of heart failure.**

Background. **Low dose aspirin is frequently prescribed for patients with systolic dysfunction who also benefit from angiotensin-converting enzyme inhibition. Although high doses of potent cyclo-oxygenase inhibitors cause fluid retention and vasoconstriction and antagonize the effects of angiotensin-converting enzyme inhibitors, the effects of low dose aspirin in heart failure are unknown.**

Methods. **A model of heart failure was produced in 11 mongrel dogs by rapid ventricular pacing (250 beats/min for 12 to 14 days). Five dogs received 325 mg aspirin/day for the final 4 days of pacing before the acute experiment; six control dogs received no aspirin. Cardiorenal and neurohumoral function was measured during chloralose anesthesia. Hemodynamic and renal responses to enalaprilat were assessed.**

Results. **Both groups demonstrated severe heart failure with decreased cardiac output; increased atrial pressures and systemic resistance; activation of plasma renin activity, aldosterone and atrial natriuretic factor; and sodium retention. Low dose aspirin had no detrimental effect on cardiorenal or neurohumoral function. Mean arterial pressure, pulmonary capillary wedge pressure and systemic vascular resistance decreased to a similar degree with enalaprilat in both groups. There was no difference between the groups with respect to renal response to enalaprilat.**

Conclusions. **The present study demonstrates that low dose aspirin has no adverse effect on hemodynamic, neurohumoral or renal function in heart failure. Furthermore, aspirin has no adverse effect on the acute response to enalaprilat. These findings suggest that there is no contraindication to concomitant treatment with low dose aspirin and angiotensin-converting enzyme inhibitors in humans with heart failure.**

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Multiple studies (1–5) have documented the beneficial effects of angiotensin-converting enzyme inhibition therapy on morbidity and mortality in patients with ventricular systolic dysfunction in the presence and absence of symptoms of congestive heart failure. Patients with or at risk for concomitant coronary artery disease may also benefit from therapy with low dose aspirin because it has been demonstrated to be effective for the primary and secondary prevention of cardiac events (6–11). Thus, therapy with both angiotensin-converting enzyme inhibitors and low dose aspirin may frequently be recommended for patients with ventricular dysfunction and coronary artery disease. Although the mechanisms of actions of angiotensin-converting enzyme inhibitors are multiple, recent investigations (12,13) have emphasized the non-angiotensin II mechanisms that mediate the action of angiotensin-converting enzyme inhibitors, including the inhibition of bradykinin metabolism and subsequent enhancement of vasodilatory prostaglandin generation.

The potential interaction of aspirin and angiotensin-converting enzyme inhibitor therapies is of clinical interest because previous studies (14–16) have reported the detrimental effects of large doses of potent prostaglandin inhibitors on hemodynamic and renal function in patients with heart failure. Previous studies (16–18) have also reported antagonism of the beneficial effects of angiotensin-converting enzyme inhibitors in hypertension or heart failure by large doses of potent prostaglandin inhibitors. Although not specifically investigated, the effect of small doses of prostaglandin inhibitors on hemodynamic and renal function in heart failure was thought to be insignificant. However, Hall et al. (19) recently reported that a single dose of aspirin (325 mg) blunted the acute hemodynamic effect of enalaprilat in patients with heart failure.

In recognition of the lack of data regarding the effect of low dose aspirin in severe heart failure and the provocative findings of Hall et al., the current study was designed to examine the effect of low dose (325 mg/day for 4 days) aspirin on cardiorenal and neurohumoral function and on the acute hemody-

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namic response to enalaprilat in a canine model of severe heart failure produced by rapid ventricular pacing. We hypothesized that low dose aspirin would not have a detrimental effect on hemodynamic, neurohumoral or renal function in severe heart failure and would not attenuate the acute hemodynamic response to enalaprilat.

Methods

Canine model of chronic severe heart failure. An experimental model of chronic severe heart failure was produced in 11 male mongrel dogs (17 to 25 kg) by rapid ventricular pacing at 250 beats/min for 12 to 14 days, as previously described (20–23). The experimental protocol was approved by the Mayo Clinic Institutional Animal Care and Use Committee and was conducted according to the guiding principles of the American Physiological Society. Permanent programmable pacemakers (modified model 8426, Medtronic) were implanted during sodium pentobarbital (30 mg/kg body weight) anesthesia. A left thoracotomy and 1- to 2-cm pericardotomy were performed. A screw-in epicardial pacemaker lead was implanted in the right ventricular epicardium and tunneled subcutaneously to the pulse generator, which was implanted in the dorsal neck. The incisions were closed in layers, and the dogs received antibiotic drugs for 3 days after the procedure. The animals were allowed to recover for 2 weeks. Throughout the study the dogs were fed standard laboratory dog chow (Laboratory Canine Diet 5506, Purina Mills). A baseline two-dimensional guided M-mode echocardiogram was acquired for assessment of ventricular size and systolic function. Ejection fraction was calculated using the method of Quinones et al. (24). Venous blood was obtained for measurement of atrial natriuretic peptide, aldosterone and plasma renin activity. The pacemaker was then programmed to 250 beats/min, and pacing was continued for 12 to 14 days. Four days before the acute experiment, five dogs were selected at random to receive long-term therapy with 325 mg of aspirin administered at ~4 PM daily (aspirin group) for a total of four doses; six dogs received no aspirin (control group). The last aspirin dose was administered on the evening before the acute study, and the animals were kept on a fast but allowed free access to water.

Acute experiment. The pacemaker was briefly deprogrammed, and a repeat echocardiogram was acquired in sinus rhythm. On the day of the acute experiment, venous blood was collected for measurement of salicylate levels. The pacemaker was again deprogrammed briefly while dogs were temporarily anesthetized with sodium thiopental (10 to 15 mg/kg) and then anesthetized with chloralose anesthesia (40 mg/kg, with supplemental doses as needed). Sodium thiopental was chosen because of its rapid onset, short half-life and minimal or no effect on peripheral vascular resistance or arterial blood pressure (25). Similarly, in our experience choralose has the least effect on canine hemodynamic function of the common anesthetic agents. A flow-directed balloon-tipped pulmonary artery catheter was inserted through the external jugular vein for measurement of intracardiac pressures and cardiac output by thermodilution techniques (American Edwards Laboratories). The femoral artery was cannulated for measurement of systemic arterial pressure and the vein for blood sampling. A bolus of inulin was administered followed by a constant infusion at 1 ml/min. A left flank incision was made and a ureter cannulated for urine collection. An electromagnetic flow probe (Carolina Instruments) was placed around the renal artery for measurement of renal blood flow. The pacemaker was reprogrammed at 220 beats/min for the acute experiment. The animals were suspended in the prone position and allowed to equilibrate for 60 min.

A baseline 30-min urinary clearance was obtained, and hemodynamic measurements were made. Blood was collected for measurements of atrial natriuretic peptide, aldosterone, plasma renin activity, electrolytes and inulin levels. Enalaprilat (0.625 mg) was then administered intravenously. The enalaprilat dose was chosen by utilizing the recommended initial dose for humans and the subsequent confirmation of a significant hemodynamic effect of 0.625 mg in a pilot study. Hemodynamic measurements were repeated at 15, 30 and 90 min, and two 30-min urinary clearances were performed with calculation of blood for electrolytes and inulin midway through each clearance.

Cardiac hemodynamic variables assessed included mean arterial pressure, right atrial pressure, pulmonary capillary wedge pressure, cardiac output and systemic vascular resistance. Systemic vascular resistance was calculated using the following formula: Systemic vascular resistance = [(Mean arterial pressure − Right atrial pressure)/Cardiac output] × 80 dynes·s·cm^{-5}. Blood samples for atrial natriuretic peptide, aldosterone and plasma renin activity were placed in tubes containing ethylenediaminetetraacetic acid, immediately placed on ice and centrifuged at 2,500 rpm at 4°C. After extraction, plasma levels of atrial natriuretic peptide were measured by radioimmunoassay, as previously described (26). Plasma renin activity was determined by radioimmunoassay using the method of Haber et al. (27). Plasma levels of aldosterone were determined utilizing the method described by Sancho and Haber (28). Venous blood for sodium and inulin determinations was collected in heparinized tubes, placed on ice and centrifuged at 2,500 rpm at 4°C. Plasma and urinary sodium concentrations were measured using ion-selective electrodes (Beckman Instruments). Glomerular filtration rate was estimated by inulin clearance.

Statistical methods. Statistical analysis was performed using an IBM Primer statistics package. Intragroup comparisons were performed using one-way analysis of variance for repeated measures followed by the Student-Newman-Keuls test for individual comparisons. A simple paired Student t test was used to compare the ejection fraction before and after pacing in each group. Intergroup comparisons were performed using an unpaired t test. In all analysis, statistical significance was defined as $p < 0.05$.

Results

Effect of aspirin on cardiorenal and neurohumoral function in severe heart failure. Rapid ventricular pacing for 12 to 14 days produced a similar degree of ventricular dysfunction in both the control and aspirin groups. Ejection fraction decreased from 55 ± 2% to 26 ± 4% ($p < 0.05$) in the control group and from 53 ± 2% to 30 ± 4% ($p < 0.05$) in the aspirin group. Long-term administration of aspirin resulted in an average trough salicylate level of 3.2 ± 0.9 mg/dl (therapeutic level 2 to 20 mg/dl). Salicylate levels were undetectable in the two control dogs where they were measured. The baseline hemodynamic, neurohumoral and renal profiles in the control and aspirin groups are depicted in Figure 1. Both groups demonstrated findings consistent with severe heart failure, with low cardiac output, increased pulmonary capillary wedge pressure and systemic vascular resistance and activation of atrial natriuretic peptide, aldosterone and plasma renin activity and identical renal profiles with sodium retention. There was no difference between the aspirin and control groups and no trends toward any difference in any variables. There was no difference in baseline serum sodium levels between the groups.

Effect of aspirin on the acute hemodynamic and renal response to enalaprilat. The hemodynamic profile at baseline and at 15, 30 and 90 min after enalaprilat for the control and aspirin groups is shown in Table 1. Mean arterial pressure, pulmonary capillary wedge pressure and systemic vascular resistance decreased to a similar degree with enalaprilat in both the groups. Cardiac output, renal blood flow and right atrial pressures did not change with enalaprilat in either group. There was no significant difference between the hemodynamic values at baseline or at 15, 30 and 90 min after enalaprilat between the groups. Although blood pressure tended to return closer to baseline in the aspirin group at 90 min, it was not significantly different between the two groups. The renal response to enalaprilat is depicted in Table 2. There was no statistically significant change in urine flow, urinary sodium excretion, glomerular filtration rate or fractional excretion of sodium with enalaprilat in either group. The change in renal function with enalaprilat was also analyzed and revealed no significant differences between groups. Although the number of dogs studied may be too small to reflect small differences in the renal response to enalaprilat, the reported renal variables reflect the severe sodium retention in this anesthetized model of severe heart failure and do not demonstrate any trends that would suggest an apparent difference.

Discussion

The present study demonstrates that low dose aspirin therapy had no adverse effect on hemodynamic, neurohumoral or renal function in this well established canine model of severe heart failure characterized by systolic dysfunction and profound hemodynamic compromise analogous to that found in patients with severe heart failure (20–23). Furthermore, low dose aspirin therapy had no attenuating effect on the acute hemodynamic or renal response to enalaprilat. In the current study, enalaprilat produced the expected reductions in mean arterial pressure, systemic vascular resistance and filling pressures, but these effects were equivalent whether or not the animals had received therapy with low dose aspirin.

High dose cyclo-oxygenase inhibitors. High doses of potent cyclo-oxygenase inhibitors promote sodium retention, prevent generation of vasodilatory prostaglandins and increase filling pressures in patients with severe congestive heart failure (14–16). Previous studies (16,29–31) have clearly demonstrated that the acute and chronic hemodynamic response to angiotensin-converting enzyme inhibition is blunted by high doses of potent cyclo-oxygenase inhibitors, such as indomethacin, in normal subjects, hypertensive patients and patients with severely symptomatic heart failure (16,29–31). This suggests that potent cyclo-oxygenase inhibitors may block the enhanced production of prostaglandins mediated by the angiotensin-converting enzyme inhibition-induced increase in tissue levels of bradykinin.

Low dose cyclo-oxygenase inhibitors. A previous study (32) in patients with mild hypertension demonstrated no adverse effect of low dose aspirin (75 mg/day) on the blood pressure response to captopril. In addition, a preliminary report (33) in patients with heart failure treated with enalapril showed no attenuation of the blood pressure-lowering effect of enalapril when administered with low dose (300 mg/day) aspirin.

Aspirin dosage. We chose an aspirin dose equivalent to the higher end of the range reported to be effective for the primary and secondary prevention of ischemic events in patients with coronary artery disease but low when compared with equivalent doses of other nonsteroidal anti-inflammatory drugs already known to be detrimental in such patients. By administering the drug for 4 days, we allowed a steady state to occur and a reasonable time for any effect on prostaglandin production to develop.

In contrast, Hall et al. (19) reported a significant blunting of the response to enalapril in patients with severe heart failure who received a single dose of aspirin with or 1 to 3 days before the administration of enalapril. Furthermore, Hall and Rudolph (34) subsequently reported a decrease in serum sodium concentration associated with a single dose of aspirin in patients that was not observed with long-term low dose aspirin therapy in experimental heart failure in the current study. The reasons for the conflicting results reported by Hall et al. and those found in the current study may be multiple. The present study was performed during experimental heart failure with no other therapy, whereas the study of Hall et al. was performed in 18 patients who received different therapies in a complex schemata in different orders on different days during a prolonged hospital period. The 9 patients who received enalapril alone received it on the first day of the study and were compared with 18 patients who received enalapril along with, or 24 h after, aspirin on day 2 or 3 (and half of these patients had received enalapril previously). During the 3 days of the study, the patients were continuously monitored with Swan-Ganz catheters. Conceivably, previous therapy with

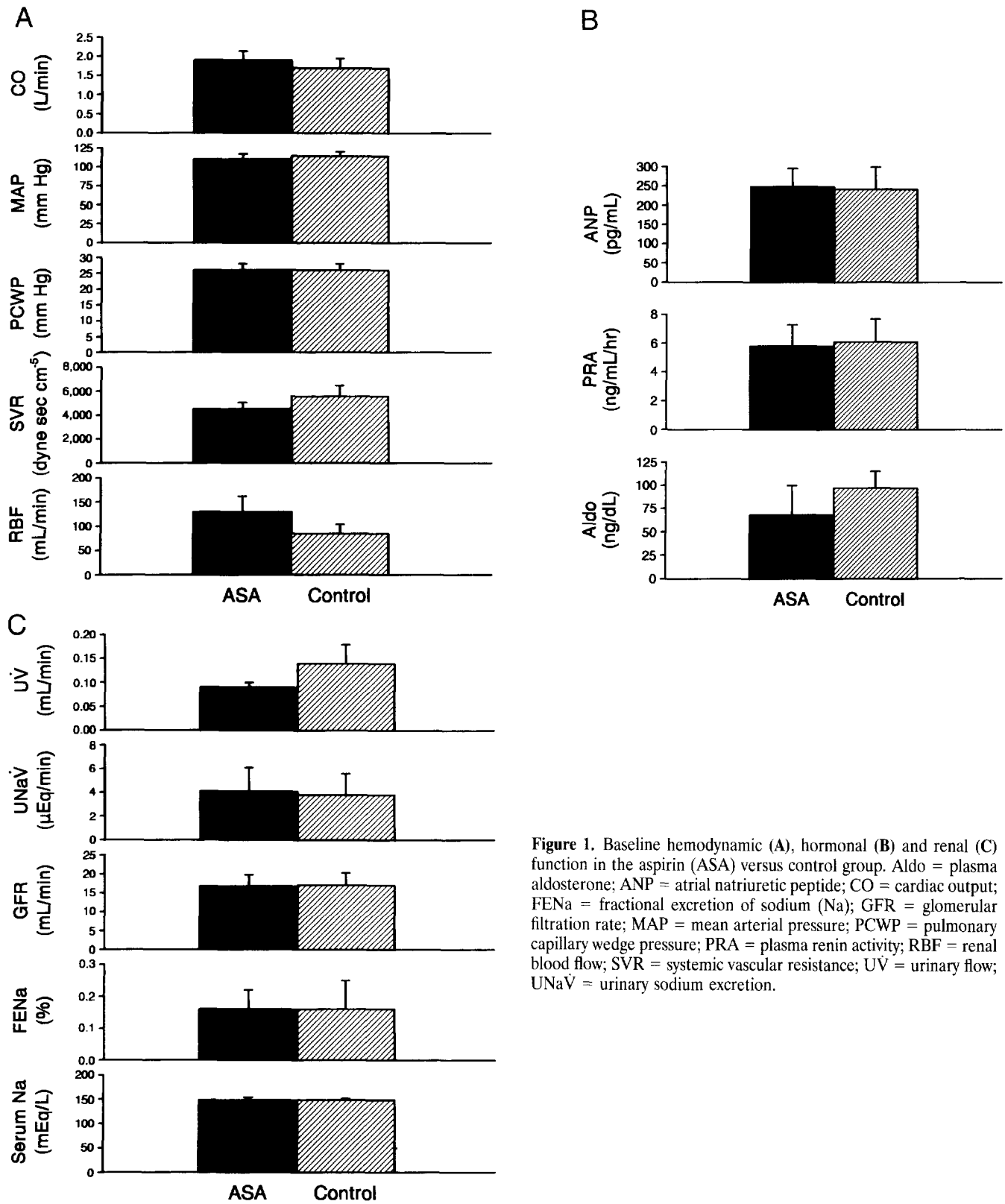

Figure 1. Baseline hemodynamic (**A**), hormonal (**B**) and renal (**C**) function in the aspirin (ASA) versus control group. Aldo = plasma aldosterone; ANP = atrial natriuretic peptide; CO = cardiac output; FENa = fractional excretion of sodium (Na); GFR = glomerular filtration rate; MAP = mean arterial pressure; PCWP = pulmonary capillary wedge pressure; PRA = plasma renin activity; RBF = renal blood flow; SVR = systemic vascular resistance; UV̇ = urinary flow; UNaV̇ = urinary sodium excretion.

enalapril, dietary and activity modification or group differences in the 9 patients with enalapril alone versus the 18 patients with enalapril and aspirin could affect the response to angiotensin-converting enzyme inhibition. The patients in the study by Hall et al. had been previously treated with diuretic drugs and may have been more decompensated, more dependent on activation of vasodilatory prostaglandins and, thus, more sensitive to aspirin.

Table 1. Acute Hemodynamic Response to Enalaprilat in a Canine Model of Severe Heart Failure

		Time After Enalaprilat Administration		
	Baseline	15 min	30 min	90 min
MAP (mm Hg)				
Control group	114 ± 6	95 ± 6*	102 ± 7*	102 ± 9
ASA group	110 ± 7	96 ± 8*	99 ± 9*	108 ± 8
CO (liters/min)				
Control group	1.66 ± 0.25	1.83 ± 0.28	1.55 ± 0.22	1.27 ± 0.17
ASA group	1.87 ± 0.24	1.97 ± 0.22	1.96 ± 0.29	1.89 ± 0.31
SVR (dynes·s·cm^{-5})				
Control group	5,562 ± 908	4,205 ± 707*	5,127 ± 548	5,958 ± 621
ASA group	4,501 ± 538	3,664 ± 515*	3,928 ± 616	4,652 ± 881
RAP (mm Hg)				
Control group	10.2 ± 1.7	9.42 ± 1.5	9.25 ± 1.6	11.6 ± 2.0
ASA group	10.2 ± 2.0	9.50 ± 1.9	9.50 ± 1.8	10.0 ± 1.9
PCWP (mm Hg)				
Control group	26.0 ± 1.4	22.3 ± 1.6*	23.1 ± 1.4*	24.6 ± 2.7
ASA group	26.0 ± 2.0	22.2 ± 1.7*	23.0 ± 1.7*	22.7 ± 1.7
RBF (ml/min)				
Control group	85 ± 19	96 ± 25	94 ± 24	89 ± 31
ASA group	130 ± 32	145 ± 36	149 ± 34	168 ± 37

*$p < 0.05$ versus baseline. Data presented are mean value ± SEM. ASA = aspirin; CO = cardiac output; MAP = mean arterial pressure; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; RBF = renal blood flow; SVR = systemic vascular resistance.

Findings in anesthetized animals cannot always be considered representative of conditions in conscious humans. The present study was performed during anesthesia maintained with chloralose. This agent is recognized to produce less depression of baroreceptor and chemoreceptor reflexogenic responsiveness and does not appear to exert a marked or sustained depression of cardiac function (35). Because enalaprilat induced similar quantitative and qualitative effects in anesthetized dogs and conscious humans, it is unlikely that the presence of anesthesia profoundly influenced our findings.

Unlike the Hall et al. (19) study, the present study used intravenous administration of angiotensin-converting enzyme inhibition to ensure that the response was independent of factors that may influence absorption and strictly controlled competing influences and exogenous factors. It is possible that the systemic effects of oral enalapril differ from those of intravenous enalaprilat. However, although only ~60% of oral enalapril is absorbed by humans, it then requires deesterification by the intact liver and kidneys to the active form (enalaprilat), which supports our contention of a more reliable test condition with direct intravenous administration of enalaprilat. Although the full resolution of this issue requires more study in humans, the current study importantly supports the lack of detrimental action of low dose aspirin on the acute hemodynamic response to angiotensin-converting enzyme inhibition.

Table 2. Acute Renal Response to Enalaprilat in a Canine Model of Severe Heart Failure

		Enalaprilat Administration	
	Baseline	30 min	60 min
Urinary volume			
Control group	0.14 ± 0.04	0.17 ± 0.06	0.18 ± 0.08
ASA group	0.09 ± 0.01	0.11 ± 0.04	0.09 ± 0.03
$U\dot{N}aV$			
Control group	3.8 ± 1.8	6.6 ± 3.4	4.9 ± 2.5
ASA group	4.1 ± 2.0	9.7 ± 6.7	9.5 ± 2.5
FENa			
Control group	0.16 ± 0.09	0.31 ± 0.14	0.22 ± 0.11
ASA group	0.16 ± 0.06	0.23 ± 0.15	0.23 ± 0.10
GFR			
Control group	17.0 ± 3.3	13.3 ± 2.6	15.5 ± 2.9
ASA group	16.8 ± 2.9	16.6 ± 5.9	18.1 ± 5.5

*$p < 0.05$ versus baseline. Data presented are mean value ± SEM. ASA = aspirin; GFR = glomerular filtration rate; FENa = fractional excretion of sodium; $U\dot{N}aV$ = urinary sodium excretion.

The effect of low dose aspirin on the chronic hemodynamic response to angiotensin-converting enzyme inhibition in patients with heart failure is unknown. A preliminary report (36) of a subgroup analysis of patients in the Studies of Left Ventricular Dysfunction study did reveal a trend toward a decreased mortality benefit in patients treated with aspirin. However, the ability of such an analysis to separate the effects of aspirin alone from the general differences in mortality as a result of the higher prevalence of coronary artery or diffuse atherosclerotic disease, or both, in aspirin-treated patients is unclear. The full resolution of this question will require more study.

Conclusions. The current findings suggest that low dose aspirin therapy in heart failure is not detrimental and does not antagonize the short-term hemodynamic effects of angiotensin-converting enzyme inhibition. Further investigation into the chronic interaction between aspirin and angiotensin-

converting enzyme inhibition in patients with left ventricular dysfunction should be performed before abandoning coadministration of these two efficacious agents.

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