Hemodynamic, Hormonal, and Renal Actions of Adrenomedullin 2 in Experimental Heart Failure

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Background—Adrenomedullin 2 (AM2) is a novel member of the calcitonin gene-related peptide family that is thought to play a regulatory role in circulatory homeostasis under normal physiological conditions. The effects of AM2 in heart failure have not been investigated previously.

Methods and Results—Two incremental doses of human AM2 (10 and 100 ng[kg-min] for 90 minutes each) were given by intravenous infusion to 8 sheep with pacing-induced heart failure. Compared with time-matched control infusions, AM2 produced dose-dependent increases in left ventricular dP/dt(max) (control 1168±138 mm Hg/s versus AM2 high-dose 1402±130 mm Hg/s; P<0.01) and cardiac output (2.09±0.66 L/min versus 3.81±0.30 L/min; P<0.001) and reductions in calculated total peripheral resistance (40±6 mm Hg(L-min) versus 21±4 mm Hg(L-min); P<0.001), mean arterial pressure (74.4±2.4 mm Hg versus 66.2±2.5 mm Hg; P<0.001), and left atrial pressure (23.3±1.0 mm Hg versus 18.8±1.3 mm Hg; P<0.001). AM2 administration also induced significant elevations in plasma cAMP (P<0.01) in association with rises in atrial (P<0.05) and brain (P<0.01) natriuretic peptides and plasma renin activity (P<0.01). Despite the increase in renin activity, plasma aldosterone levels were not significantly altered, whereas the aldosterone/plasma renin activity ratio was reduced (P=0.08). Plasma vasopressin, endothelin-1, and catecholamines levels were also unchanged by AM2. Renal effects of AM2 included increased excretion of sodium (P<0.05), cAMP (P<0.01), and creatinine (P<0.05), with augmented creatinine clearance (P<0.05), and a trend for urine output to rise (P=0.068).

Conclusion—These results indicate that AM2 administration has favorable effects on cardiovascular, endocrine, and renal indexes in heart failure and identify the peptide as a potential therapeutic target in this disease. (Circ Heart Fail. 2008;1:134-142.)

Key Words: adenomedullin 2 • heart failure • hemodynamics • hormones • renal function
peptide is also reported to enhance regional blood flow to the heart, liver, spleen, adrenal glands, and kidneys. 

Intravenal infusion of AM2 in the rat induces a rise in renal blood flow in association with a decrease in renal vascular resistance and augmentation of urine flow and sodium excretion. However, these studies suggest a regulatory role for AM2 in blood pressure-volume homeostasis in normal physiological settings, other work indicates that the peptide may also be involved in the pathophysiology of cardiovascular disease. Gong et al. showed that AM2 levels are augmented in both the blood and the right ventricular tissues of rats with chronic hypoxia-induced hypertension, and the expression of AM2, CLR, and the 3 RAMPs are upregulated in the rat ventricular myocardium following ischemic injury. In addition, treatment with AM2 following hypoxic injury ameliorates the subsequent decline in cardiac function (at least in part through the augmentation of coronary perfusion and LV [dP/dt] and attenuates oxidative stress levels.

The combination of hemodynamic, renal, and cardioprotective actions reported for AM2 to date are likely to prove beneficial in the setting of heart failure (HF). Indeed, administration of the related peptide, AM, has previously been shown to have salutary effects in this disease. However, the actions of AM2 in HF cannot be predicted from the data available on AM given the differences in receptor binding affinities and, possibly, receptor types demonstrated between the 2 peptides. We, therefore, investigated, for the first time, the integrated effects of AM2 in HF using an experimental ovine model.

**Methods**

**Surgical Preparation**

Eight Coopworth ewes (48 to 60 kg) were instrumented via a left lateral thoracotomy under general anesthesia (induced by 17 mg/kg thiopentone; maintained with halothane–nitrous oxide). Two polyvinyl chloride catheters were inserted in the left atrium for blood sampling and measurement of left atrial pressure (LAP); a Konigsberg pressure-tip transducer was inserted in the aorta to record mean arterial pressure (MAP) and into the apex of the left ventricle to obtain maximum derivatives of pressure over time [LV dP/dt(max)] as an index of contractility; an electromagnetic flow probe was placed around the ascending aorta to measure CO; a 7F thermodilution catheter was inserted in the pulmonary artery for administration of treatments; and a 7F His-bundle electrode was stitched subepicardially to the wall of the left ventricle for subsequent rapid pacing. A bladder catheter was inserted per urethra for urine collections. Animals recovered for 14 days before commencing the study protocol. During the experiments, the animals were held in metabolic cages, fed a standard laboratory diet (500 g of sheep pellets and 250 g chaff/fd containing 80 mmol sodium and 200 mmol potassium), and had free access to water.

**Study Protocol**

HF was induced by 7 days of rapid LV pacing at 225 beats per minute and maintained by continuous pacing for the duration of the study. On days 8 and 10 of pacing, each sheep received vehicle control (0.9% saline) and human AM2 (Bachem, Switzerland) according to a balanced, random-order design. AM2 was infused intravenously at 2 incremental doses of 10 ng/kg/min for 90 minutes (low dose [LD]), followed immediately by 100 ng/kg/min for a further 90 minutes (high dose [HD]). All infusions were administered in a total volume of 43 mL (0.9% saline) via the pulmonary artery catheter commencing at 1000 hours.

Using an online data acquisition system (PowerLab Systems, ADInstruments, Dunedin, NZ), hemodynamic recordings [MAP, LAP, CO, LV dP/dt(max) and calculated total peripheral resistance (CTPR = MAP/CO)] were performed at 15-minute intervals in the hour before treatment (baseline) and at 15, 30, 45, 60, and 90 minutes during both infusions and the postinfusion period. All measurements were made with the sheep standing quietly in the metabolic cage.

Blood samples were drawn from the left atrium 30 minutes and immediately pretreatment (baseline) and at 30, 60, and 90 minutes during both infusions and the postinfusion period. Samples were taken into EDTA tubes on ice, centrifuged at 4°C, and stored at either −20°C or −80°C before assay for cAMP, plasma renin activity (PRA), aldosterone, arginine vasopressin, cortisol, endothelin-1, atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and catecholamines. For each hormone, all samples from individual animals were measured in the same assay to avoid interassay variability. Hematocrit was measured with every blood sample taken. Samples for analysis of plasma sodium, potassium, and creatinine concentrations were drawn into heparin tubes at 90-minute intervals starting immediately pretreatment.

Urine collections were made at 90-minute intervals starting 90 minutes before treatment for the measurement of volume and sodium, potassium, creatinine, and cAMP excretion. Water intake was measured as per urine output.

The study protocol was approved by the Animal Ethics Committee of the University of Otago, Christchurch, New Zealand.

**Statistics**

Results are expressed as mean±SEM. Baseline hemodynamic and hormonal values represent the mean of the 4 and 2 measurements, respectively, made within the hour immediately pretreatment. Differences between the control and AM2 arms of the study were analyzed by two-way repeated measures analysis of variance (ANOVA). Overall treatment × time interactions are quoted in the text. Where significant differences were identified by ANOVA, the level of significance at individual time points in Figures 1 through 4 and Table was determined by Fisher’s protected least-significant difference tests. The repeated measures analysis also included a term for treatment sequence. The absence of any significant interactions of treatment with sequence in this study confirms the adequacy of the wash-out period.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Results**

Rapid LV pacing at 225 beats per minute for 7 days produced the hemodynamic, endocrine, and sodium-retaining hallmarks of congestive HF, with reduced CO, MAP, and renal function, elevated LAP and peripheral resistance, and widespread hormonal activation.

Compared with time-matched control data, infusion of AM2 induced gradual and dose-dependent increases in LV dP/dt(max) (LD +92 mm Hg/s, HD +234 mm Hg/s; P<0.01) and CO (LD +0.53 L/min, HD +1.72 L/min; P<0.001), in conjunction with decreases in MAP (LD −2 mm Hg, HD −8 mm Hg; P<0.001), LAP (LD −1.0 mm Hg, HD −4.5 mm Hg; P<0.001), and CTPR (LD −7 mm Hg/L/min, HD −19 mm Hg/L/min; P<0.001). As seen in Figure 1, statistically significant responses were noted with all hemodynamic indexes during both the LD and HD treatment periods. Although CO, LV dP/dt(max), LAP, and CTPR returned progressively to control levels during the 90 minutes following cessation of AM2 treatment, MAP rebounded above control measurements during this time (Figure 1). Hematocrit was significantly reduced during HD AM2 and remained...
suppressed for the duration of the postinfusion term (P<0.001) (Table).

Plasma cAMP concentrations were elevated during the HD AM2 infusion (HD +24 nmol/L; P<0.01) and promptly returned to control levels by 60 minutes postinfusion (Figure 2). PRA was also increased during HD AM2 (HD +1.35 nmol(L-h); P<0.01), and although plasma aldosterone levels were not significantly altered relative to control data (Figure 2), the aldosterone/PRA ratio was reduced (HD –54%; P=0.08) (Table). Plasma cortisol rose transiently during LD AM2 administration (LD +99 nmol/L; P<0.05), as shown in Figure 2. Both plasma ANP (HD +54 pmol/L; P<0.05) and BNP (HD +13 pmol/L; P<0.01) levels were augmented overall by AM2, with levels significantly raised compared with time-matched controls by the end of the HD treatment and continuing to rise during the 90-minute postinfusion period (Figure 3). Plasma epinephrine, arginine vasopressin (Figure 3), norepinephrine, and endothelin-1 (Table) concentrations were unaltered by AM2 administration.

The renal responses to AM2 included increases in urine sodium excretion (P<0.05), creatinine excretion (P<0.05; Figure 4), and creatinine clearance (P<0.05; Table)—all of which achieved significance during the HD infusion; however, urine cAMP excretion was elevated overall by AM2 relative to control data (P<0.01). The AM2 posttreatment collection period was characterized by further rises in these variables. Urine output also tended to be elevated by AM2 (P=0.068), particularly following cessation of AM2 infusion (Figure 4), whereas urine potassium excretion (Figure 4) and water intake (Table) did not differ significantly from controls. Similarly, plasma sodium, potassium, and creatinine concentrations were relatively unchanged by AM2 (Table).
Discussion

The present study reports for the first time the integrated hemodynamic, hormonal, and renal effects of AM2 administration in HF. We found that AM2 dose-dependently increased cardiac contractility and output in conjunction with reductions in CTPR, MAP, and LAP. AM2-induced rises in plasma cAMP were also associated with activation of the natriuretic peptides and PRA (but without stimulation of aldosterone), whereas renal responses to the peptide included augmented excretion of cAMP, sodium, and creatinine and an improvement in creatinine clearance.

One of the best known actions of AM2, as with AM, is its potent hypotensive activity. AM2’s blood pressure-lowering effects have been extensively demonstrated in both isolated arteries16,19,28 and normal animals2,11–14 and is reported to be due to direct vasodilatory actions of the peptide via activation of CLR/RAMP complexes located throughout the vasculature with subsequent production of intracellular cAMP.29 These findings are consistent with those in this study, in which decreases in MAP in sheep with HF occurred in conjunction with marked reductions in CTPR. Work in normal animals has also demonstrated a clear correlation between AM2-induced decreases in blood pressure and decreases in peripheral resistance.12,16,17 Although a number of studies have observed a more potent depressor effect of AM2 relative to AM,1,14 we found AM2’s MAP-reducing actions to be similar to those elicited by identical doses of AM used in a previous study in HF sheep.21 We did, however, note an appreciable difference in the persistence of the hypotensive effects of the 2 peptides, with the response to AM2 (dissipated by 30 minutes postinfusion) a third as protracted as that produced by AM.21 This concurs with data in the rat where the blood pressure-lowering effect of intravenous AM2 (absent after 20 to 30 minutes) was shown to be significantly less sustained than that evoked by AM.11 This disparity is unlikely to simply reflect differences in the half-lives of the peptides (as the duration of the other hemodynamic responses are similar for both AM and AM2) but may be a consequence of differing receptor affinities of the 2 peptides in light of a report by Kobayashi et al28 demonstrating that the vasodilator effect of AM2 in isolated pig...
arteries, although equipotent with AM, were blocked by CGRP (selective for CLR/RAMP1) but not by AM (preferentially activates CLR/RAMP2 and CLR/RAMP3), indicating that the vasodilatory response to AM2 is mediated by the CLR/RAMP1 complex.

AM2 administration produced significant dose-dependent increases in CO in our sheep with HF, a response demonstrated previously in normal animals. Although this effect is likely to be due at least in part to the concomitant fall in cardiac afterload (as judged by decreases in MAP and CTPR), it is probable that the peptide also possesses positive inotropic activity given that we likewise observed marked rises in LV dp/dt(max). More conclusive evidence that AM2 acts as an inotrope comes from work by Dong et al., showing that the peptide acutely enhances cultured cardiomyocyte contractile function (in association with enhanced intracellular Ca(2+) release and decay rate). Positive inotropism has also been reported for AM, and both AM2 and AM have been shown to augment LV systolic pressure and dp/dt, together with an increase in coronary artery perfusion flow (and ventricular myocardial cAMP content) in the isolated perfused rat heart. As with any inotropic agent (acting via cAMP), there is a potential concern of arrhythmogenesis and an increase in myocardial oxygen demand with AM2. Although there have been no reports concerning the relation between these detrimental effects and AM2, recent studies with AM demonstrate that this peptide not only has antiarrhythmic actions (reducing the incidence of both ventricular ectopics and fibrillation) in rats following myocardial infarction, but AM was also shown to enhance LV myocardial contraction and improve LV relaxation without increasing myocardial oxygen consumption in myocardial infarction patients. Whether these favorable properties also apply to AM2, and in the setting of HF, requires further investigation.

Additional hemodynamic actions of AM2 in this study included a decline in LAP (similar to the fall seen with AM in sheep with HF), most likely as a result of the vigorous rise in CO, although venodilator actions of the peptide may...
also have contributed. A decrease in blood volume is unlikely to be involved as there was no associated rise in hematocrit. In fact, hematocrit was observed to fall during the HD infusion, and drop even further still postinfusion, at which time filling pressures had risen back to control levels and urine output tended to increase. A decrease in hematocrit was also noted following AM2 administration in normal sheep, and it suggests a shift of fluid from extravascular to intravascular space. Taken together, our findings indicate that AM2 (like AM) plays a role in the regulation of cardiovascular function in the setting of HF.

A consistent finding in studies investigating the actions of AM2, both in vitro and in vivo, is an increase in the levels of AM2’s intracellular second messenger, cAMP. A significant rise in plasma cAMP was also seen in this study during the HD infusion of AM2 in association with prominent hemodynamic responses. Although circulating cAMP was not raised significantly during the LD infusion, it is likely that levels of the second messenger were elevated sufficiently at the tissue level in view of the bioactivity observed during this period. AM2 administration at the higher dose was also accompanied by a significant increase in PRA, a result previously observed in response to AM2 in normal sheep. The activation of PRA is likely to have occurred as a consequence of the falls in arterial pressure (and subsequent stimulation of afferent renal arteriolar baroreceptors), although it is also possible that AM2, similar to AM, acts directly on renal juxtaglomerular granular cells to enhance renin release. Despite the substantial rise in PRA (and presumably angiotensin II), however, plasma aldosterone levels were unchanged relative to control data. This suggests a relative suppression of angiotensin II-induced aldosterone secretion, with the aldosterone/PRA ratio showing a 54% reduction by the end of the HD AM2 infusion period. AM treatment in ovine HF also produced a marked decline in the aldosterone/PRA ratio (49% fall), a finding in keeping with reports that the AM peptide has direct inhibitory actions on aldosterone secretion at the adrenal glomerulosa. Whether a similar direct effect exists for AM2 remains to be seen. Of interest, in contrast to the lack of aldosterone activation observed in this study, AM2 administration in normal sheep resulted in a modest rise in circulating aldosterone levels (approximately 400 pmol/L). However, given the corresponding and pronounced 2.4 nmol(L-h) increase in PRA activity, one might have expected an even greater elevation in aldosterone, as the aldosterone/PRA ratio in these normal animals actually dropped to half that of the time-matched controls—a response similar to that seen in the HF sheep. This would argue that a relative inhibition of angiotensin II-induced aldosterone secretion is also evident in normal animals following AM2 infusion, despite the rise in actual plasma levels.

From a clinical perspective, activation of the renin-angiotensin system by AM2 plainly has potentially adverse effects. However, as new treatments are likely to be used in combination with angiotensin-converting enzyme inhibition therapy, any prospective deleterious consequences would be avoided. Indeed, we have previously found that coadministration of AM and an angiotensin-converting enzyme inhibitor in experimental HF produces significant decreases in circulating angiotensin II and aldosterone, in association with larger reductions in ventricular filling pressures, cardiac afterload, and improvements in CO compared with either treatment alone. Furthermore, despite the greater falls in blood pressure seen with combined treatment, renal function was maintained at a level similar to that observed with angiotensin-converting enzyme inhibition alone.

The rise in plasma ANP and BNP concentrations observed during the HD AM2 infusion (ANP +54 pmol/L, BNP +13 pmol/L) may be considered surprising given the concomitant falls in LAP and MAP, which alone would be expected to attenuate the secretion and release of these peptides, yet concur with results seen following AM2 administration in normal sheep. Both these studies demonstrated a further rise in plasma natriuretic peptide levels postinfusion (this study: ANP 110 pmol/L, BNP 19 pmol/L), presumably in response to the attendant rises in LAP and MAP. No other works have examined the effect of AM2 on ANP/BNP secretion, and information concerning the impact of AM on these peptides is conflicting. In this regard, Sato et al reported that AM attenuates ANP gene expression and secretion in cultured cardiomyocytes, whereas Horio et al found the peptide actually augmented endothelin-stimulated ANP secretion (but without effect in unstimulated conditions). In addition, in vivo studies have shown that AM enhances the ANP response to acute volume loading in normal sheep, and in both experimental and human HF, infusion of the peptide resulted in sustained plasma ANP/BNP concentrations in the face of significant falls in filling pressures and MAP. Presuming there is no effect of AM2 to inhibit the plasma clearance rate of ANP and BNP, the findings of this study indicate that AM2 augments natriuretic peptide secretion. It is conceivable that AM2, similar to AM, amplifies the ANP-secretory response to endothelin and volume loading given the greater elevations in plasma ANP/BNP levels seen in this setting of congestive HF (which exhibits cardiac overload and increased circulating endothelin) when compared with that observed in normal unstimulated sheep. Whatever the mechanism(s), the ability of AM2 to increase circulating levels of ANP and BNP, with their known vasodilatory and natriuretic actions, their effects to inhibit adverse hormone systems and cellular growth and proliferation, can be seen as beneficial in HF.

Despite the stimulus of blood pressure reductions, circulating arginine vasopressin, catecholamines, and endothelin-1 levels were not significantly elevated during AM2 administration. It is possible that the accompanying enhancement of CO (and, therefore, pressure to sino-aortic volume receptors), the improvement in HF status, or even a direct action of AM2, may have acted to counterbalance the hypertensive stimulus for activation of these systems. Again, although the exact mechanism(s) of action requires further study, the resulting profile is desirable should AM2 be considered as a potential HF therapy.

The rise in plasma cortisol levels seen following the administration of AM2 in this study may be related to the concurrent hemodynamic actions of the peptide, including a modest reduction in blood pressure, or perhaps be a consequence of the mild pyrogenic reaction that occurs in some of
these chronically instrumented animals following flushing of the fluid-filled lines. Although a similar observation was made in response to AM infusion in HF sheep, the cortisol increase did not achieve statistical significance. Recent work by Taylor and Samson, however, suggests that AM peptides may be involved in the neuroendocrine responses to stress, as central AM2 administration in the rat elevates circulating adrenocorticotropic (corticotropic) and corticosterone levels.

AM2 infusion in sheep with HF produced a significant natriuresis and a trend for urine output to increase. These results are similar to those observed following intrarenal administration of the peptide in normal rats and occurred despite a considerable reduction in arterial pressure. Likely mechanisms mediating this response include an AM2-induced increase in renal blood flow, an effect previously demonstrated in the rat, and, conceivably, the direct inhibition of tubular sodium reabsorption given the presence of the peptide in renal tubular cells (both cortex and medulla). We also noted a rise in creatinine clearance, evincing an increase in glomerular filtration, which is again in keeping with the location of AM2 in the endothelial cells of glomerular capillaries. The concurrent overall increase in urine cAMP excretion further supports direct actions of AM2 within the kidney. Additional effects of AM2 to augment plasma levels of ANP and BNP may also have played a part in the renal responses seen in this study. The renal effects of AM in HF are comparable to those produced using AM2, and presumably, so is the mode of action, with AM reported to directly reduce proximal and distal fractional sodium reabsorption and renal vascular resistance and to increase renal blood flow. Supplemental increases in most renal indexes measured following cessation of AM2 infusion most likely relate to the coincident rebound in MAP and the further substantial rise in circulating natriuretic peptide concentrations. Although there was no natriuresis seen following AM2 administration in normal sheep, there was also no significant decline in sodium excretion—a response that might have been expected given the accompanying fall in blood pressure in these animals, perhaps suggesting a shift in the pressure—natriuresis curve. The coincidental rise in plasma aldosterone and only minimal elevation in plasma natriuretic peptide levels may have contributed to the differences in the AM2-induced renal response observed between the 2 states (normal and HF). In addition, AM2-induced increases in CO are more likely to have played a part in enhancing renal function in the setting of HF.

Although the exact mechanisms underlying AM2’s actions within the kidney require clarification, the ability of this peptide to enhance renal function (increased creatinine clearance and sodium excretion) despite a reduction in arterial pressure, in this already underperfused and congested setting, is clearly beneficial and should be of considerable clinical interest, especially in light of difficulties in developing novel drugs for acute HF.

This study, designed to examine the effects of acute (hours) infusion of incremental doses of AM2, cannot provide information regarding the possible development of tolerance to more prolonged administration of the peptide. However, previous experience with longer term (4-day) infusions of AM in experimental ovine HF demonstrates that AM-induced hemodynamic, hormonal, and renal changes were sustained over the 4-day study period. Similarly, 14-day infusions of AM in both normal and hypertensive rats produced persistent reductions in systolic blood pressure, whereas transgenic mice overexpressing AM in their vasculature exhibit significantly lower blood pressures than their wild-type littermates. These results indicate that tolerance to AM did not occur (at least for the time span and doses used) and suggest that the peptide may participate in both short- and long-term regulation of the indexes measured, although this may not be the case for other variables. Whether the same is true for AM2 requires additional study.

In conclusion, the present study demonstrates that systemic administration of AM2 in experimental HF improves cardiac contractility and output in conjunction with reductions in CTPR, MAP, and LAP; increases in plasma cAMP, the natriuretic peptides, and PRA (without activation of aldosterone); and augmentation of renal function. Our data indicate that AM2 is involved in cardiovascular and volume regulation in this setting and raise the question of whether AM2 or an agonist acting on its receptors might find a place in the treatment of HF in man. Acute HF, in particular, which requires new therapeutic approaches, may benefit from treatment with an agent such as AM2, which reduces cardiac preload and afterload substantially, increases CO, improves glomerular filtration rate, and induces a natriuresis but does not activate adverse neurohormonal systems (with the exception of the renin system). Accordingly, we believe that studies of AM2 administration in patients with acute HF are warranted. Our study also demonstrates equivalent hemodynamic, hormonal, and renal effects for AM2 relative to those shown for AM in ovine HF, and there appears to be, at least for the data currently available, no overt superiority of 1 peptide over the other in terms of a prospective therapy in acute HF. However, given the reported differences in receptor affinities, and possibly type, dissimilarities in bioactivity between AM2 and AM may yet be uncovered. Future studies investigating circulating levels of AM2 in health and disease, and more particularly, the administration of specific antagonists of the peptide, would help unmask the role of endogenous AM2.

Acknowledgments
We are grateful to the Animal Laboratory staff of the University of Otago, Christchurch, for assistance with animal studies and the Christchurch Cardioendocrine Laboratory staff for hormone assays.

Sources of Funding
Support was provided through grants from the National Heart Foundation of New Zealand and the Health Research Council of New Zealand.

Disclosures
None.
References


**CLINICAL PERSPECTIVE**

The present study demonstrates that systemic administration of adrenomedullin 2 (AM2) in experimental heart failure improves cardiac contractility and output in conjunction with reductions in total peripheral resistance, mean arterial pressure and left atrial pressure; increases in plasma cyclic AMP, natriuretic peptides, and plasma rennin activity (without activation of aldosterone); and augmentation of renal function. Our data indicate that AM2 is involved in cardiovascular and volume regulation in this setting and raise the question of whether AM2 or an agonist acting on its receptors might find a place in the treatment of heart failure in humans. Acute heart failure, in particular, which requires new therapeutic approaches, may benefit from treatment with an agent such as AM2, which reduces cardiac preload and afterload substantially, increases cardiac output, improves glomerular filtration rate, and induces a natriuresis but does not activate adverse neurohormonal systems (with the exception of the renin system).
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Circ Heart Fail. 2008;1:134-142; originally published online January 1, 2008;
doi: 10.1161/CIRCHEARTFAILURE.107.755504
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3289. Online ISSN: 1941-3297

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