Adrenomedullin-epinephrine cotreatment enhances cardiac output and left ventricular function by energetically neutral mechanisms

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1Surgical Research Laboratory, Department of Clinical Medicine, Faculty of Health Sciences, University of Tromsø, and 2Department of Cardiothoracic and Vascular Surgery, University Hospital of North Norway, Tromsø, Norway

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Stenberg TA, Kildal AB, How OJ, Myrmel T. Adrenomedullin-epinephrine cotreatment enhances cardiac output and left ventricular function by energetically neutral mechanisms. Am J Physiol Heart Circ Physiol 302: H1584–H1590, 2012. First published February 3, 2012; doi:10.1152/ajpheart.00887.2011.—Adrenomedullin (AM) used therapeutically reduces mortality in the acute phase of experimental myocardial infarction. However, AM is potentially deleterious in acute heart failure as it is vasodilative and inotropically neutral. AM and epinephrine (EPI) are cosecreted from chromaffin cells, indicating a physiological interaction. We assessed the hemodynamic and energetic profile of AM-EPI cotreatment, exploring whether drug interaction improves cardiac function. Left ventricular (LV) mechanodynamics were evaluated in 14 open-chest pigs using pressure-volume analysis and the pressure-volume area-myoxygen consumption (PVA-MVO2) framework. AM (15 ng·kg−1·min−1, n = 8) or saline (controls, n = 6) was infused for 120 min. Subsequently, a concurrent infusion of EPI (50 ng·kg−1·min−1) was added in both groups (AM-EPI vs. EPI). AM increased cardiac output (CO) and coronary blood flow by 20 ± 10% and 39 ± 14% (means ± SD, P < 0.05 vs. baseline), whereas controls were unaffected. AM-EPI increased CO and coronary blood flow by 55 ± 17% and 75 ± 16% (P < 0.05, AM-EPI interaction) compared with 13 ± 12% (P < 0.05 vs. baseline) and 18 ± 31% (P = not significant) with EPI. LV systolic capacitance decreased by −37 ± 22% and peak positive derivative of LV pressure (dP/dtmax) increased by 32 ± 7% with AM-EPI (P < 0.05, AM-EPI interaction), whereas no significant effects were observed with EPI. Mean arterial pressure was maintained by AM-EPI and tended to decrease with EPI (+2 ± 13% vs. −11 ± 10%, P = not significant). PVA-MVO2 relationships were unaffected by all treatments. In conclusion, AM-EPI cotreatment has an inodilator profile with CO and LV function augmented beyond individual drug effects and is not associated with relative increases in energetic cost. This can possibly take the inodilator treatment strategy beyond hemodynamic goals and exploit the cardioprotective effects of AM in acute heart failure.

left ventricular energetics; conductance catheter

ADRENOMEDIULLIN (AM) is a 52-amino acid peptide originally isolated by its ability to elevate cAMP in rat platelet assays (20). This peptide participates in cardiovascular homeostasis as an autocrine or paracrine factor with vasodilative and chronotropic properties (15). AM administration consistently augments cardiac output (CO) and facilitates forward flow in vivo (5, 29, 34), but experimental findings with respect to the direct cardiac effects of AM are diverging (14, 41). Evidence has suggested, however, that AM is inotropically neutral within what is potentially the therapeutic dose range (24). AM reduces ischemia-induced arrhythmias, limits infarct size, attenuates ischemia-reperfusion injury, and lowers mortality in rodent models (25, 30, 31, 33). The cardioprotective effects are therapeutically attractive, and the hemodynamic profile of AM is advantageous in experimental heart failure models (35). The hypotensive effect, however, is possibly detrimental in ischemic heart failure, and profound hypotension after AM administration to patients with acute myocardial infarction has been reported (16).

Interestingly, AM and catecholamines are both secreted from chromaffin cells through Ca2+-dependent regulated exocytosis after cholinergic stimulation (17). Adrenal medullary basal catecholamine release and catecholamine levels in plasma are both increased by AM (1, 43), whereas AM release from chromaffin cells is augmented by dibutyryl cAMP, a membrane-permeable analog of cAMP (21). AM release from cultured rat vascular smooth muscle cells is also augmented by epinephrine (EPI) (40). Thus, there is evidence indicating a physiological interaction between AM and catecholamines such as EPI. Furthermore, cAMP is a well-recognized second messenger in AM signal transduction, and both negative and positive modulation of β-adrenergic signaling by AM has been reported in vitro (10, 13). It is presently unknown whether AM can modulate hemodynamic and inotropic responses to β-adrenergic stimulation in vivo.

In addition to hemodynamic and potentially cytoprotective effects, AM appears to be involved in insulin regulation, fatty acid mobilization, and glucose metabolism (13, 26). These metabolic effects of AM, either alone or in combination with EPI, can potentially influence left ventricular (LV) energetics due to alterations in the concentration of free fatty acids in plasma (23). There is evidence indicating that AM has favorable energetic properties (29), but the relation between total mechanical work and myocardial O2 consumption (MVO2) has not been quantified.

In the present study, we assessed the hemodynamic and contractile effects of potentially therapeutic levels of AM in a pig model. In addition, we analyzed whether low-dose AM infusion modulates the hemodynamic and contractile effects of β-adrenergic stimulation by a low-dose EPI infusion in physiologically intact animals. The effects of both individual and combined treatments on LV energetics were quantified through the assessment of total mechanical work and MVO2 within the pressure-volume area (PVA)-MVO2 framework.

METHODS

The experimental protocol was approved by the local steering committee of the Norwegian Animal Research Authority and was conducted in compliance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (1996). Fourteen castrated male pigs (Norwegian Landrace, Sus scrofa domesticus) weighing 27 ± 2 kg were habituated to the animal facilities for 4–7 days and fasted overnight before the experiment with free access to water. The premedication, anesthetic protocol, surgical preparation of the...
open-chest model, conductance volumetric technique, and LV energetic assessment method have been previously detailed (28).

**Instrumentation.** Animals were anesthetized, tracheostomized, and ventilated via a volume-controlled ventilator (Servo 900 D, Elema-Schönander). A 7-Fr balloon catheter for preload reductions and transient caval occlusions was placed in the inferior caval vein. The hemiazygos vein was ligated to avoid mixture of systemic blood into the coronary sinus. Transit-time flow probes (Medi-Stim PB series, Medi-Stim) were placed on the pulmonary trunk, coronary, left femoral, and left carotid arteries for measurements of CO, coronary blood flow (CBF), muscular blood flow, and cerebral blood flow. The great cardiac vein was catheterized through the superior caval vein and coronary sinus for blood sampling. A 7-Fr dual-field combined pressure-conductance catheter (CD Leycom) was inserted into the LV via the right carotid artery to measure LV volume and pressure. A 7-Fr balloon catheter for preload reductions and transient caval occlusions was placed in the inferior caval vein. The hemiazygos vein was ligated to avoid mixture of systemic blood into the coronary sinus for blood sampling. A 7-Fr dual-field combined pressure-conductance catheter (CD Leycom) was inserted into the LV via the right carotid artery to measure LV volume and pressure. Intravascular volume was maintained with a glucose-enriched (1.25% via the right carotid artery to measure LV volume and pressure-conductance catheter (CD Leycom) was inserted into the LV and coronary sinus for blood sampling. A 7-Fr dual-field combined pressure-conductance catheter (CD Leycom) was inserted into the LV via the right carotid artery to measure LV volume and pressure. Intravascular volume was maintained with a glucose-enriched (1.25% via the right carotid artery to measure LV volume and pressure-conductance catheter (CD Leycom) was inserted into the LV via the right carotid artery to measure LV volume and pressure.

**Experimental protocol.** In preliminary experiments, the porcine dose-response relationship to intravenous infusions of human AM (1 and 10–150 ng·kg⁻¹·min⁻¹, Bachem) was established (Fig. 1). Low-dose AM (15 ng·kg⁻¹·min⁻¹) was chosen to achieve a moderate increase in CO while minimizing heart rate (HR) and mean arterial pressure (MAP) alterations, thus aiming at a potentially tolerable level in settings with acute ischemia and hemodynamic instability.

The isolated effect of AM and the interaction between AM and a concurrent infusion of EPI (AM-EPI) were compared with the individual effect of EPI in a time-matched control group receiving saline as vehicle. After baseline measurements, the AM group (n = 8) received a continuous infusion of AM, whereas the control group (n = 6) received a continuous infusion of saline. A second set of measurements was obtained 120 min after baseline recordings. Subsequently, both groups received a concurrent infusion of EPI (50 ng·kg⁻¹·min⁻¹) with the third set of measurements obtained at steady state (~15 min).

**LV energetics.** LV MVO₂ was plotted as a function of PVA as described by Suga (39). The PVA-MVO₂ relation at each measurement set was assessed by preload alteration and differing levels of steady-state LV mechanical work. MAP and CBF were allowed to reach uninfluenced levels between the successive preload reductions to ensure unimpaired LV function. At each preload, steady-state pressure-volume data were recorded for 10 s with simultaneous blood sampling from the great cardiac vein to calculate cardiac O₂ extraction. PVA and MVO₂ were calculated as previously described (28).

**RESULTS**

The hemodynamic variables were matched between groups at baseline with the exception of a higher HR in the control group (62 ± 7 vs. 88 ± 6 beats/min, P < 0.05). LV systolic and diastolic function, LV energetics, and VA matching were similar in both groups at baseline. Hemodynamic and LV functional data are shown as percent changes from baseline values in Fig. 2. Corresponding absolute data and PVA-MVO₂ parameters are shown in Tables 1–3.

**LV function and VA matching.** The effects of AM, EPI, and AM-EPI on LV function are shown in Figs. 2 and 3. LV function, as assessed by dp/dt max, showed that AM alone had no observable effect on contractility. AM-EPI increased dp/dt max by 32 ± 14% compared with baseline (P < 0.05), whereas the control group had an initial −14 ± 12% decrease with saline (P < 0.05) and with EPI dp/dt max was still −2 ± 14% [P = not significant (NS)] compared with baseline. Interaction analysis showed a significant interaction with AM-EPI (P < 0.05). Global LV function, as measured by PRSW,
Fig. 2. Hemodynamics and left ventricular (LV) function shown as percent changes from BL values. A: CO and HR were augmented to a greater extent with AM-epinephrine (EPI) cotreatment (AM-EPI) than with the individual drugs. MAP was also preserved with AM-EPI, B: CBF was greatly improved by AM-EPI cotreatment, whereas carotid (Car) and femoral (Fem) blood flows were less affected. C: LV systolic capacitance (ESV120), peak positive derivative of LV pressure (dP/dtmax), and preload recruitable stroke work (PRSW) results showing that AM-EPI cotreatment improved LV function to a greater degree than the individual drugs. Open circles, control group; filled circles, AM group. Within-group differences: *P < 0.05 vs. BL values and †P < 0.05 vs. AM or control; between-group differences: ‡P < 0.05; interaction: §§P < 0.05 (by two-way repeated-measures ANOVA).

showed that AM had no effect on LV function when administered alone. With AM-EPI, PRSW increased by 40 ± 14% compared with baseline values (P < 0.05), whereas EPI alone produced a nonsignificant 23 ± 27% increase. Through interaction analysis using absolute data, an interaction between AM-EPI was observed (P < 0.05; Table 2). ESV120 decreased by −37 ± 22% with AM-EPI compared with baseline (P < 0.05), whereas it was unaltered with the individual drugs (19 ± 18% vs. 16 ± 42%, AM vs. EPI, P = NS). The effect of AM-EPI cotreatment was a greater reduction in ESV120 compared with EPI infusion in the control group, and a significant interaction was detected (P < 0.05; Fig. 2 and Table 2).

VA matching was assessed using the ratios of E/E′ es and PRSW/SVR. Afterload, as assessed by E′ es, predominantly reflecting arterial compliance, showed no systematic changes. The ratio of E/E′ es was unaltered across all conditions. SVR primarily reflects peripheral vasconstriction, and, in contrast to E′ es, SVR was reduced with AM, EPI, and AM-EPI (−14 ± 13%, −23 ± 10%, and −34 ± 14%, P < 0.05 vs. baseline by one-way ANOVA). The ratio of PRSW/SVR increased with AM, EPI, and AM-EPI (22 ± 18%, 58 ± 44%, and 120 ± 41%, P < 0.05). A significant interaction was detected with PRSW/SVR, and thus forward flow facilitation was augmented to a greater extent by AM-EPI than by the individual drugs (P < 0.05).

Table 1. Hemodynamics

<table>
<thead>
<tr>
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<th>AM Group</th>
<th>Control Group</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>AM-EPI</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>93 ± 8</td>
<td>95 ± 13</td>
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<tr>
<td>Mean pulmonary artery pressure, mmHg</td>
<td>17 ± 2</td>
<td>19 ± 13</td>
</tr>
<tr>
<td>Central venous pressure, mmHg</td>
<td>9 ± 1</td>
<td>6 ± 1</td>
</tr>
<tr>
<td>Cardiac output, ml/min</td>
<td>2,028 ± 443</td>
<td>2,441 ± 625*</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>62 ± 7</td>
<td>80 ± 15*</td>
</tr>
<tr>
<td>End-systolic volume, ml</td>
<td>25 ± 6</td>
<td>29 ± 9</td>
</tr>
<tr>
<td>End-diastolic volume, ml</td>
<td>57 ± 7</td>
<td>59 ± 10</td>
</tr>
<tr>
<td>End-systolic pressure, mmHg</td>
<td>106 ± 8</td>
<td>107 ± 12</td>
</tr>
<tr>
<td>End-diastolic pressure, mmHg</td>
<td>15 ± 2</td>
<td>13 ± 2</td>
</tr>
<tr>
<td>Coronary blood flow, ml/min</td>
<td>87 ± 12</td>
<td>122 ± 24*</td>
</tr>
<tr>
<td>Carotid blood flow, ml/min</td>
<td>214 ± 62</td>
<td>227 ± 55</td>
</tr>
<tr>
<td>Femoral blood flow, ml/min</td>
<td>94 ± 27</td>
<td>111 ± 39</td>
</tr>
<tr>
<td>E′ es, mmHg/ml</td>
<td>3.3 ± 0.4</td>
<td>3.6 ± 0.6</td>
</tr>
<tr>
<td>SVR, dyn·s·cm⁻⁵</td>
<td>3,516 ± 484</td>
<td>3,047 ± 705</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 8 animals in the adrenomedulin (AM) group and 6 animals in the control group. EPI, epinephrine; AM-EPI, AM and EPI cotreatment; E′ es, arterial elastance; SVR, systemic vascular resistance. Within-group differences: *P < 0.05 vs. baseline and †P < 0.05 vs. AM or control; between-group differences: ‡P < 0.05; interaction: §§P < 0.05 (by two-way repeated-measures ANOVA).
crease in LV systolic function during AM-EPI cotreatment.
indicating that other mechanisms are responsible for the in-
as response, and altered HR could potentially explain the increased
tions has not been previously described. Our data show
intravenous administration of AM (36). However, whether
addition, increased sympathetic activity has been seen with
ion of the sympathetic nervous system. As stated, an interrelationship
PVA-MV˙O2 relationships within each group
Our study supports evidence suggesting physiologically rel-
LV energetics. PVA-MV˙O2 relationships within each group
slope, contractile efficiency; β, myocardial O2 consumption;
Values are means ± SD; n = 8 animals in the AM group and 6 animals in the control group. LV, left ventricular; MV˙O2, myocardial O2 consumption; β, myocardial O2 consumption; α, end-systolic elastance [slope of the
intercept, unloaded MV˙O2; y-intercept, unloaded MV˙O2. MV˙O2 is
by 10.220.33.5 on July 1, 2017 http://ajpheart.physiology.org/ Downloaded from
HEMODYNAMIC INTERACTIONS WITH AM-EPI COTREATMENT

Table 2. LV function and ventriculoarterial matching

<table>
<thead>
<tr>
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<th>AM Group</th>
<th>AM-EPI</th>
<th>Control Group</th>
<th>EPI</th>
</tr>
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<tbody>
<tr>
<td>Ees, mmHg/ml</td>
<td>2.5 ± 1.3</td>
<td>2.5 ± 1.4</td>
<td>3.3 ± 1.2</td>
<td>2.0 ± 0.6</td>
</tr>
<tr>
<td>Vo, ml</td>
<td>−26 ± 21</td>
<td>−24 ± 27</td>
<td>−19 ± 22</td>
<td>−33 ± 8</td>
</tr>
<tr>
<td>ESV1, ml</td>
<td>29 ± 9</td>
<td>35 ± 10</td>
<td>23 ± 12†</td>
<td>29 ± 10</td>
</tr>
<tr>
<td>PRSW, mmHg</td>
<td>37 ± 7</td>
<td>60 ± 12</td>
<td>80 ± 13**§§</td>
<td>54 ± 15</td>
</tr>
<tr>
<td>dP/dtmax, mmHg/s</td>
<td>1.410 ± 208</td>
<td>1.459 ± 265</td>
<td>1.868 ± 317**§§</td>
<td>1.546 ± 224</td>
</tr>
<tr>
<td>dP/dtmin, mmHg/s</td>
<td>−1.762 ± 217</td>
<td>−1.891 ± 249</td>
<td>−2.042 ± 322*</td>
<td>−1.906 ± 254</td>
</tr>
<tr>
<td>β, mmHg/ml</td>
<td>0.068 ± 0.026</td>
<td>0.072 ± 0.036</td>
<td>0.092 ± 0.048</td>
<td>0.083 ± 0.028</td>
</tr>
<tr>
<td>α</td>
<td>0.66 ± 0.79</td>
<td>0.86 ± 1.29</td>
<td>0.45 ± 0.51</td>
<td>0.47 ± 0.34</td>
</tr>
<tr>
<td>EVD20s, ml</td>
<td>62 ± 9</td>
<td>67 ± 10</td>
<td>55 ± 10‡</td>
<td>50 ± 8</td>
</tr>
<tr>
<td>τ, ms</td>
<td>49 ± 6</td>
<td>44 ± 4</td>
<td>38 ± 3</td>
<td>40 ± 5</td>
</tr>
<tr>
<td>Ees/Ees</td>
<td>1.5 ± 0.4</td>
<td>1.7 ± 0.6</td>
<td>1.1 ± 0.4</td>
<td>1.9 ± 0.4</td>
</tr>
<tr>
<td>PRSW/SVR, l/min</td>
<td>1.32 ± 0.17</td>
<td>1.61 ± 0.38</td>
<td>2.93 ± 0.81**§§</td>
<td>1.50 ± 0.37</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 8 animals in the AM group and 6 animals in the control group. LV, left ventricular; Ees, end-systolic elastance [slope of the end-systolic pressure-volume relationship (ESPVR)]; Vo, initial volume (volume axis intercept of the ESPVR); PRSW, preload recruitable stroke work; Ees/Ees, and PRSW/SVR, measures of ventriculoarterial matching (see text for details). Within-group differences: *P < 0.05 vs. baseline and †P < 0.05 vs. AM or control; between-group differences: §P < 0.05; interaction: $P < 0.05 (by two-way repeated-measures ANOVA).

DISCUSSION

Our study supports evidence suggesting physiologically relevant interactions between AM, β-adrenergic signaling, and the sympathetic nervous system. As stated, an interrelationship between the signaling and release of AM and catecholamines has been observed in several models (1, 40, 43), and modulation of β-adrenergic signaling has been reported (10, 13). In addition, increased sympathetic activity has been seen with intravenous administration of AM (36). However, whether cotreatment could produce hemodynamically relevant interaction effects has not been previously described. Our data show that the increase in CO is paralleled by a chronotropic response, and altered HR could potentially explain the increased contractility observed with AM-EPI. However, a higher absolute HR was seen in the control group at baseline, and with AM-EPI and EPI, the HR was similar between groups, thereby indicating that other mechanisms are responsible for the increase in LV systolic function during AM-EPI cotreatment.

AM can enhance the baroreceptor reflex response through cAMP- and PKA-dependent signaling in the nucleus tractus solitarius, the terminal site for primary baroreceptor afferents (11). Increased HR and cardiac sympathetic nerve activity have also been reported, with the effect being more pronounced with AM than with pressure-matched nitroprusside administration (4). Interestingly, the inotropic effect of CGRP has been attributed to indirect myocardial sympathetic activation through an increased interstitial concentration of norepinephrine (18). AM belongs to the CGRP peptide superfamily and partly shares receptor complexes with calcitonin receptor-like receptor (CL) and receptor activity-modifying protein (RAMP)2 and RAMP3, which constitute AM receptors, whereas CL and RAMP1 form the CGRP receptor (15). To which extent AM may stimulate myocardial sympathetic signaling remains to be clarified. Adrenal chromaffin cells used as models of catecholamine-releasing neurons have been shown to release AM through cAMP-mediated mechanisms (22), and catecholamine release after AM administration has also been reported (1). Thus, a hypothetical feedback system regulating myocardial sympathetic activity may be envisioned.

AM reduces Ees and SVR and affects potent vasodilation in resistance vessels (6, 24, 34), whereas preload is maintained (24). Thus, in addition to the chronotropic response, reduced afterload with concomitantly less effect on capacitance vessels and sustained venous return may also explain why AM potently augments CO. It is uncertain whether AM has inotropic properties in vivo as there are reports of both positive and unaltered inotropy (24, 29). Positive inotropic effects in vivo

Table 3. LV energetics

<table>
<thead>
<tr>
<th></th>
<th>AM Group</th>
<th>AM-EPI</th>
<th>Control Group</th>
<th>EPI</th>
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<tbody>
<tr>
<td>Pressure-volume area, J-beat⁻¹·100 g⁻¹</td>
<td>0.64 ± 0.13</td>
<td>0.68 ± 0.21</td>
<td>0.61 ± 0.17</td>
<td>0.59 ± 0.09</td>
</tr>
<tr>
<td>MV˙O2, J-beat⁻¹·100 g⁻¹</td>
<td>1.76 ± 0.26</td>
<td>1.87 ± 0.29</td>
<td>1.75 ± 0.31</td>
<td>1.58 ± 0.28</td>
</tr>
<tr>
<td>y-Intercept</td>
<td>0.51 ± 0.12</td>
<td>0.53 ± 0.10</td>
<td>0.44 ± 0.12</td>
<td>0.35 ± 0.12</td>
</tr>
<tr>
<td>Slope</td>
<td>1.93 ± 0.14</td>
<td>2.01 ± 0.29</td>
<td>2.19 ± 0.42</td>
<td>2.17 ± 0.68</td>
</tr>
<tr>
<td>R²</td>
<td>0.96 ± 0.02</td>
<td>0.98 ± 0.01</td>
<td>0.98 ± 0.02</td>
<td>0.97 ± 0.04</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 8 animals in the AM group and 6 animals in the control group. MV˙O2, myocardial O2 consumption; y-Intercept, unloaded MV˙O2; slope, contractile efficiency; R², coefficient of determination.
have predominantly been observed with relatively load-sensitive measures of LV function. AM in doses ranging from 20 to 200 ng·kg$^{-1}$·min$^{-1}$ confer no inotropic effect, as assessed by the ESPVR (24); thus, AM is probably inotropically neutral within the potentially therapeutic dose range. We found no evidence of any inotropic effect with low-dose AM, and preliminary dose-response experiments revealed no inotropic effect with doses ranging from 10 to 150 ng·kg$^{-1}$·min$^{-1}$ (data not shown). AM-EPI cotreatment caused moderate elevations of $dP/dt_{\text{max}}$ and PRSW, with both being larger than with EPI as the only active drug, and a significant AM-EPI interaction was thus observed. The ESPVR was unaltered, as assessed by $E_{\text{es}}$ and $V_0$, and there were no differences in $\alpha$ or $\beta$ describing the EDPVR. The calculation of systolic capacitance accounts for the potential covariance between $E_{\text{es}}$ and $V_0$, and the reduction in ESV$_{120}$ with AM-EPI exceeded the sum of the individual drug effects, thus implying that the end-systolic stiffness (i.e., contractility) was increased through AM-EPI interaction. As shown in Fig. 3, AM-EPI produced a leftward shift of the ESPVR together with increased $E_{\text{es}}$, thereby indicating an improved contractile performance within the measured pressure range. The functional parameters $dP/dt_{\text{max}}$, PRSW, and ESV$_{120}$ were unaltered by AM, thereby indicating that the interaction effect is synergistic in nature.

AM is metabolically active and confers lipolytic properties in vitro (13), and catecholamines and sympathomimetic drugs are known to increase free fatty acids in plasma (27). Combining lipolytic drugs that can increase free fatty acids in plasma could potentially induce a mechanoenergetic inefficiency that would be unwanted therapeutically in the ischimically challenged heart (23). This is the first study to characterize LV energetics using total mechanical work related to $MVO_2$ with systemic administration of AM. Favorable energetic properties of AM have been reported with an increase in contractility paralleling a reduction in $MVO_2$, thus implying an increased mechanoenergetic efficiency (29). However, afterload reduction and relatively less energetic cost with volume versus pressure work may explain the finding, and the relationship between total mechanical work and $MVO_2$ must be assessed to describe any influence on LV energetics (39). We found no evidence of altered mechanoenergetic efficiency or unloaded $MVO_2$ with AM, EPI, or AM-EPI.

The vascular response after AM administration is heterogeneous with increased blood flow in the heart, lungs, kidneys, adrenal glands, and spleen, whereas the splanchnic bed is relatively unaffected (19). In agreement with earlier studies (7, 44) showing that AM infusion augments CBF, we found that low-dose AM produced a relatively large increase in CBF. This effect was further enhanced by AM-EPI cotreatment, and the extent of CBF elevation suggests that the drugs interact. Importantly, PVA-$MVO_2$ data indicate that the observed increase is not metabolically induced, as unloaded $MVO_2$ contractile efficiency, and total mechanical work were similar between groups. In vitro studies (2, 42) have shown that AM...
mediates coronary vasodilation through nitric oxide (NO) synthesis (NOS) and EDHF pathways. In the isolated rat aorta, AM causes endothelium-dependent vasodilation by Ca^{2+}-mediated activation of the phosphatidylinositol 3-kinase (PI3K)/Akt pathway, which, in turn, activates endothelial NOS (eNOS) and NO production (32). In endothelial cells, cAMP accumulation and mobilization of intracellular Ca^{2+} stores via phospholipase C and inositol 1,4,5-trisphosphate formation have been observed after AM exposure (38). In addition to PI3K activation, increased levels of intracellular Ca^{2+} in endothelial cells can also produce vasodilation through the EDHF pathway with opening of endothelial small- and intermediate-conductance Ca^{2+}-activated K^+ channels inducing hyperpolarization of vascular smooth muscle (8). Interestingly, NO production in canine myocardial microvessels after exposure to AM or isoproterenol is substantially enhanced in subjects with heart failure despite eNOS downregulation, an effect abolished by NOS, PKA, and PI3K inhibition (45). Thus, cAMP and PI3K appear to serve as compensatory pathways that can sustain or augment NO production in situations with eNOS downregulation and endothelial dysfunction. Furthermore, as both pathways have been implicated in AM and β-adrenergically induced vasorelaxation (45), they could potentially serve to explain the substantial augmentation of CBF observed with AM-EPI cotreatment.

Conclusions. The main observations presented in this study is that low-dose AM is inotropically neutral and increases CO primarily through vasodilation and chronotropy, that low-dose AM-EPI cotreatment has the hemodynamic profile of an inotrope with CO and LV function augmented beyond individual drug effects, and that this functional enhancement is not associated with disproportionate increases in energetic expenditure.

Thus, low-dose AM-EPI cotreatment has a hemodynamic profile that is attractive in ischemic heart failure and circulatory compromise with cardiac unloading, increased CO and inotropy, maintained systemic perfusion pressure, and mechanoenergetic neutrality. In addition, AM is potentially attractive in settings of ischemia and heart failure due to its effect on infarct size, arrhythmias, and mortality. In combination with an inotrope, this can take the inotrope treatment strategy beyond purely hemodynamic goals by exploiting the pleiotropic effects while supporting the circulation with an inotrope. The chronotropic effect of AM-EPI, however, is a concern in acute heart failure and should be evaluated in future studies.

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Disclosures

No conflicts of interest, financial or otherwise, are declared by the author(s).

Author Contributions


References


