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Effects of Enhanced External Counterpulsation on Renin-Angiotensin System in Experimental AMI

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Summary

The effects of enhanced external counterpulsation (EECP) on Renin-Angiotensin System (RAS) activity in acute MI (AMI) were studied in 18 dogs divided into three groups: Control (N=6), AMI (N=6) and AMI+EECP (N=6). The LAD in AMI groups was occluded, with EECP performed 60-180 minutes post occlusion in the AMI+EECP group. Plasma renin activity, angiotensin II, angiotensin converting enzyme were measured at baseline, 60, 120, and 180 minutes. Baseline values were similar. AMI significantly increased RAS activity and this activity increased with occlusion time. However, EECP reversed RAS changes towards control values. EECP decreases in RAS activity may be mediated by hemodynamic effects and shear stress induced increase in nitric oxide, and may potentially alter cardiovascular remodeling post AMI.

Introduction

Enhanced external counterpulsation (EECP) is a non-invasive treatment of coronary artery disease with demonstrated clinical benefit in acute MI and stable angina[1,2]. The hemodynamic effects produced by EECP include: diastolic augmentation, presystolic unloading, increased venous return, cardiac output and coronary blood flow[3]. These potent hemodynamic effects have been shown to have neurohormonal consequences, causing increases in nitric oxide, natriuretec peptides, and de-

creases in endothelin, malondialdehyde (a marker for lipid peroxidation)[4-7]. The hemodynamic effects would also be expected to blunt the activation of the adrenergic and renin-angiotensin systems (RAS) that occurs during myocardial infarction and with left ventricular dysfunction.

During AMI, RAS activation provides short term hemodynamic support, but has long term deleterious consequences for the cardiovascular system. Elevation of Angiotensin II, in particular, is associated with: hypertension, atherosclerosis/ thrombosis, myocardial fibrosis, adverse ventricular remodeling, adrenergic activation, cytokine activation, increased salt and water retention, increased aldosterone, endothelial dysfunction. These multiple adverse effects of angiotensin II have made it a prime target that has been shown to clinically benefit from angiotensin converting enzyme inhibitor (ACEI) treatment.

While counterpulsation during AMI has been demonstrated to increase capillary density, preserve myocardium[8,9] and to improve survival with shock, its effects on the RAS have not been studied. Since RAS activation may contribute to infarct size, reperfusion arrhythmias, ventricular remodeling and dilatation following myocardial ischemia or infarction (AMI), this study examines the potential myocardial protective effects of EECP due to its ability to down-regulate RAS activation in an experimental acute myocardial infarction (AMI) model.

Methods

Eighteen (18) adult, healthy mongrel dogs, weighing 10-15 kg, were divided randomly into three groups: Control (N=6), AMI (N=6) and AMI+EECP (N=6). All animals were anesthetized with intravenous sodium pentobarbital (30mg/kg), intubated, and ventilated with room air using a respirator. A left thoracotomy was performed through the fifth intercostal space, and the heart was suspended in a pericardial cradle. After a 20 minute equilibrium period (considered to be time 0 min or baseline), the distal portion of the left anterior descending (LAD) was occluded in the AMI and AMI+EECP groups. Sixty minutes later, EECP was administered to the AMI+EECP group for 120 minutes. All animals were sacrificed by a lethal injection of sodium pentobarbital at the end of the experiment.

Five ml of blood was collected from each animal at 0, 60, 120, and 180 minutes. Plasma renin activity (PRA) was determined using the radioimmunoassay ^{125}I-ANG I method and expressed as ng ANG I/ml/hr. [10] The angiotensin-converting enzyme (ACE) was analyzed using the liberated hippuric acid determined spectrophotometrically at 228 nm wavelength [11], using water as reference, and expressed as nmol/ml/min. Plasma angiotensin II (ANG II) was determined by radioimmunoassay

rabbit antibody with ^{125}I-labelled ANG II [12], expressed as pg/ml. Results were expressed as the mean ∀ SD and compared using the students unpaired t test; significance at $p < 0.05$.

Results

Baseline plasma values of renin, ACE and ANG II were the same in all three groups of animals, as shown in Tables 1-3. The RAS activity remained relatively unchanged in the control (sham-operated) group throughout the 3 hours of experiment, whereas the RAS activity increased significantly ($p<0.05$) in both the AMI and AMI+EECP when compared with control. In addition, the RAS concentrations increased as a function of the occlusion time, suggesting that circulating RAS was activated by the AMI. However, EECP therapy reversed the activation, even though the RAS activity was still significantly higher than control after 2 hours of treatment. In the AMI+EECP group, PRA and ACE activity were lower after two hours of EECP than after one hour of treatment.

Table 1	**Plasma Renin Activity** (ng ANG I/ml/h)			
Group	Baseline	60 minutes	120 minutes	180 minutes
Control	1.91 ± 0.31	1.84 ± 0.28	1.95 ± 0.27	1.99 ± 0.29
AMI	1.81 ± 0.36	2.63 ± 0.31*	3.10 ± 0.43*$^{\varphi}$	3.34 ± 0.43*$^{\varphi\kappa}$
AMI+EECP	1.93 ± 0.25	2.61 ± 0.35*	3.38 ± 0.49*$^{\varphi}$	2.73 ± 0.39*$^{\varphi\kappa}$

*p<0.05 vs baseline; $^{\varphi}$p<0.05 vs AMI at 60 min; $^{\kappa}$p<0.05 vs AMI

Table 2	**Plasma ACE** (nmol/ml/min)			
Group	**Baseline**	**60 minutes**	**120 minutes**	**180 minutes**
Control	22.42 ± 4.33	23.52 ± 5.16	24.11 ± 5.00	23.54 ± 4.48
AMI	23.21 ± 4.82	32.85 ± 6.45*	44.43 ± 5.28*$^{\varphi}$	49.77 ± 5.95*$^{\varphi\kappa}$
AMI+EECP	22.38 ± 4.40	37.74 ± 6.61*	43.27 ± 8.66*$^{\varphi}$	31.92 ± 6.60*$^{\varphi\kappa}$

*p<0.05 vs baseline; $^{\varphi}$p<0.05 vs AMI at 60 min; $^{\kappa}$p<0.05 vs AMI

Table 3	**Plasma ANG II** (pg/ml)			
Group	**Baseline**	**60 minutes**	**120 minutes**	**180 minutes**
Control	132 ± 27	134 ± 28	137 ± 30	129 ± 31
AMI	124 ± 29	204 ± 43*	281 ± 58*$^{\varphi}$	330 ± 51*$^{\varphi\kappa}$
AMI+EECP	123 ± 35	209 ± 41*	259 ± 56*$^{\varphi}$	272 ± 50*$^{\varphi\kappa}$

*p<0.05 vs baseline; $^{\varphi}$p<0.05 vs AMI at 60 min; $^{\kappa}$p<0.05 vs AMI

Conclusions

Acute myocardial infarction is associated with activation of the Renin-

Angiotensin System manifested as an increase in plasma renin activity, angiotensin converting enzyme activity, and angiotensin II levels. RAS activation increases as a function of occlusion time. However, treatment with EECP reverses the progressive increase.

EECP increases blood flow and shear stress, thereby increasing nitric oxide and decreasing RAS activity. This may have implications for the use of EECP in post MI remodeling. Further studies with longer EECP treatment time will be necessary to demonstrate the limits of EECP in suppressing RAS activation and to evaluate the clinical benefits on ventricular structure, function, and remodeling.

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