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External Counterpulsation Increases Capillary Density During Experimental Myocardial Infarction

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Summary

An acute infarction model was used to evaluate the microcirculatory effects of enhanecd external counterpulsation (EECP). Capillary density (CD) and diameter were measured in 6 controls and 8 EECP treated dogs. Significant increases in CD were observed after EECP in the infarct zone versus controls ($p < 0.01$). However, there were no significant differences in diameter after EECP treatment in either infarct or non- infarct zones. This finding suggests that collateral recruitment is a mechanism whereby EECP may improve perfusion to regions of mycardial ischemia.

Introduction

Enhanced external counterpulsation (EECP) is an effective noninvasive treatment for coronary artery disease. EECP uses ECG signals to modulate the timing of inflation and deflation of three sets of compressive air cuffs wrapped around the calves, lower thighs and upper thighs, including the lower buttocks. During diastole, the cuffs inflate sequentially to create a retrograde arterial pressure wave and, at the same time, push venous blood toward the heart. The result is augmented diastolic central aortic and coronary perfusion pressure and increased venous return. Rapid, simultaneous deflation of the cuffs at the onset of systole produces systolic unloading and decreased cardiac workload (1, 2). External counterpulsation has improved survival in patients with acute myocardial infarction complicated by shock (2, 5). In stable angina it has been demonstrated to

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produce sustained improvement in: myocardial perfusion with exercise, exercise tolerance, and angina functional class (3, 4, 6). While the immediate hemodynamic effects of increased coronary diastolic perfusion pressure, increased venous return, decreased afterload, and increased cardiac output may clearly produce immediate benefit and ameliorate symptoms, the basis for the lasting effects of EECP are less clear. It has been postulated that the recruitment or development of collaterals might provide a possible mechanism whereby the transient hemodynamic effects of EECP could effect a more lasting improvement in myocardial perfusion and provide relief of coronary ischemia and angina. To test this hypothesis an experimental dog model was developed to evaluate, during acute myocardial infarction, the effect of EECP on the microvascular circulation in control and infarcted regions of the myocardium.

Methods

The study was performed using 14 anesthetized, intubated, open chest mongrel dogs; 6 dogs served as the Control group and 8 dogs comprised a group treated with EECP. An acute myocardial infarction was induced by ligating the apical branch (distal to the origin of all major diagonals) of the left anterior descending coronary artery under direct visualization.

In the EECP group of dogs, pneumatic cuffs were applied to the upper legs and buttocks. The EECP group was treated immediately after occlusion with EECP for 80 minutes, and again for 60 minutes at 5 hours post occlusion. The Control group did not receive EECP. Central aortic pressures were continuously monitored and recorded at baseline and during EECP for comparison. All animals were sacrificed after 6 hours.

Transverse sections of myocardium of 2-3 mm thickness were obtained from both the Infarct and Non-Infarct zones in each dog in both the EECP treated and the Control groups. Regions of infarcted myocardium was identified by staining using the Nitro-BT dye. A non-infarcted zone was taken over the high lateral wall and stained blue. The myocardial sections were frozen, sectioned at 75 micron thickness (10 slices from each region), and stained using Bell's enzyme microvascular histochemistry alkaline phosphatase method (7).

Each sample was examined under a microscope at 10 X magnification. Capillary density (capillaries/cm^2) was calculated as the average number of capillary branch points per cm^2. Six sample areas (2 from each of the subendocardial, intramyocardial, and epicardial layers) were examined. The diameter (micrometers) of 30 capillaries from each slice were also measured in both EECP and Control groups in Infarct and Non-infarct zones at three layers: subendocardial, intramyocardial, subepicardial.

Statistical analysis was performed, comparing the capillary density and

the capillary diameter in both the EECP and Control groups, using the unpaired Students t test, with significance assumed at a level of $p < 0.05$. The paired t test was used to compare the effect of EECP on central hemodynamics in the EECP group, with significance assumed at a level of $p < 0.05$. All calculated values are given as the mean ± standard deviation.

Results

There was no significant difference in the size of the dogs in the Control (13.08 ± 6.20 kg) and EECP (13.88 ± 2.64 kg) groups. There was a significant decrease in the central aortic systolic pressure during EECP from 131.35 ± 3.43 mm Hg to 127.45 ± 3.70 mm Hg ($p < 0.05$). The effect of EECP on central augmented diastolic pressure was even greater, with diastolic pressure significantly increased from 96.85 ± 4.62 mm Hg at baseline to 141.25 ± 5.51 mm Hg during EECP ($p < 0.01$).

An example of the subendocardial layers showing capillary density is shown in Figure 1 for the control and infarcted regions in a Control and EECP treated dog. Significant increases in capillary density were observed

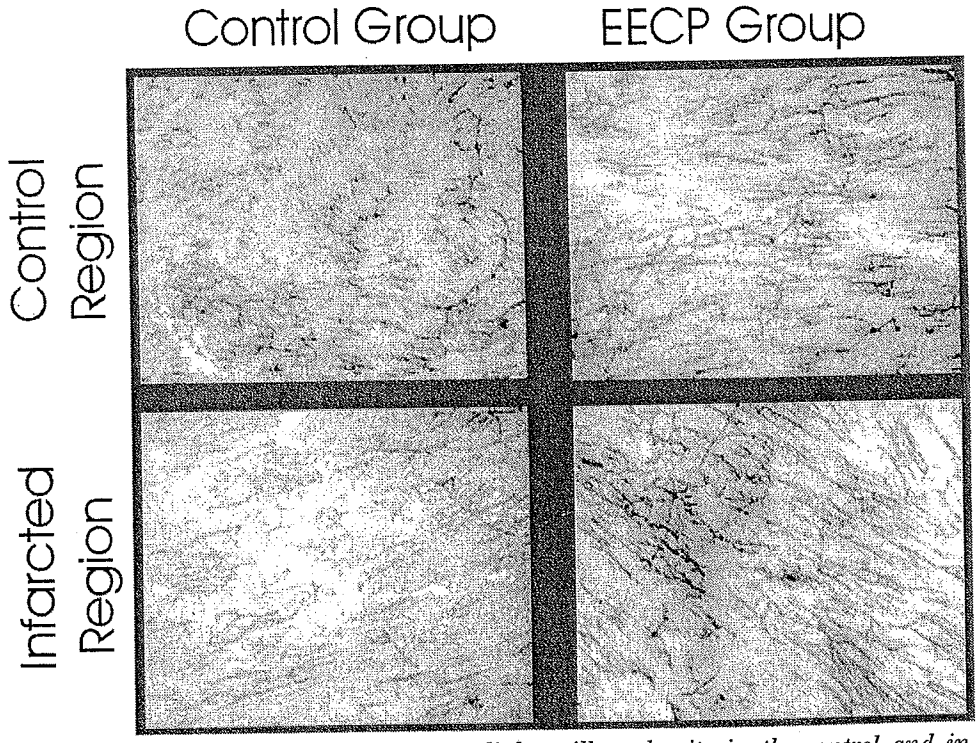

Figure1: Photomicrographs of subendocardial capillary density in the control and infarcted regions of a control and an EECP treated dog.

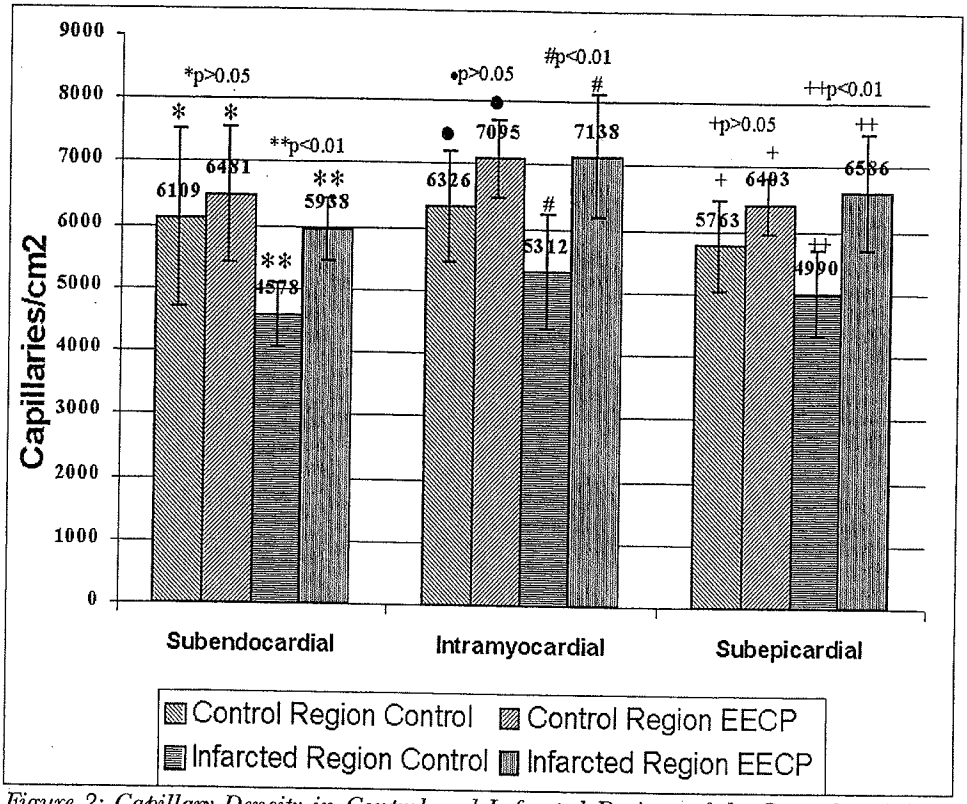

Figure 2: Capillary Density in Control and Infarcted Regions of the Control and EECP treated groups. Sample number in the control group N=120, EECP treated group N=160.

after EECP in the infarct zone compared to the Control group infarct zone. Lesser, but still significant differences in capillary density after EECP treatment were demonstrable in the non-infarct zone as compared to the Control group non-infarct zone (Figure 2). Capillary diameters showed no significant differences between the Control group (average diameter 6.58 μm ± 0.20 μm) and the EECP group (average diameter 6.65 μm ± 0.24 μm) in either the infarct or the non-infarct zones.

Conclusions

Enhanced external counterpulsation significantly augments central aortic diastolic pressure and decreases aortic systolic pressure, thereby increasing coronary perfusion pressure and decreasing left ventricular afterload. In the acute dog model, EECP significantly increases the capillary density in the infarcted regions by about 30%. A lesser, but still significant 10% increase in capillary density is also demonstrable in the non-infarcted regions of the myocardium. There were no significant changes in capillary

diameter in all regions of both groups.

These results demonstrate that capillary density in areas of acute myocardial infarction can be significantly and acutely increased in the experimental dog model. The observed microcirculatory effects may provide a bridge between the acute hemodynamic effects of EECP and the persistent clinical benefits of improved myocardial perfusion, exercise tolerance, decreased angina. Microcirculatory changes, including capillary recruitment and development, provide a potential mechanism of action of EECP during acute and chronic ischemia.

References

1. Zheng Z, Li T, Kambic H, Chen G, Yu Lm Cai S, Zhan C, Chen Y, Wo S, Chen G, Ma H, Chen P, Huang B, Nose Y. Sequential external counterpulsation (SECP) in China. Trans Am Soc Artif Intern Organs 1982;29:599-603.
2. Soroff, HS Hui JCK, Giron F. Historical review of the development of enhanced external counterpulsation technology and its physiological rationale. Cardiovasc Rev & Reports 1997;20:34-40.
3. Lawson WE, Hui JCK, Soroff HS, Zheng ZS, Kayden DS, Sasvary D Atkins H, Cohn PF. Efficacy of enhanced external counterpulsation in the treatment of angina pectoris. Am. J. Cardiol. 1992;70:859-862.
4. Lawson WE, Hui JCK, Zheng ZS, Oster Z, Katz JP, Dervan JP, Burger L, Jianag L, Soroff HS, Cohn PF. Three-year sustained benefit from enhanced external counterpulsation in chronic angina pectoris. Am. J. Cardiol. 1995;75:840-841.
5. Lawson WE, Cohn PF, Hui JCK, et al. Enhanced external counterpulsation: Review of U.S. clinical research to date. Cardiovasc Reviews and Reports 1997;18:25-29.
6. Arora RR, Chou TM, Jain D, Nesto RW, Fleischman B, Crawford L, McKiernan T. Results of the Multicenter Study of Enhanced External Counterpulsation (MUST- EECP): EECP reduces anginal episodes and exercise-induced myocardial ischemia. JACC 1999.
7. Bell MA, et al. Staining for microvascular alkaline phosphatase in thick celloidin sections of nervous tissue: morphometric and pathological applications. Microvas Res 1984;27:189-203.