fibroblasts. TGF-beta1 increased (p<0.05) the soluble and nonsoluble collagen production to 1346±129 and 639±54 dp/mg DNA, respectively. Lisinopril decreased the TGF-beta1-stimulated soluble and nonsoluble collagen production to 1001±118 (p<0.05) and 461±46 (p<0.01) dp/mg DNA, respectively. Bestatin (100 microM) reduced the soluble collagen production in basal and TGF-beta1-treated cardiac fibroblasts by 35±6% (p<0.05) and 15±1% (p<0.01) respectively, while it did not affect the nonsoluble collagen production in basal and TGF-beta1-treated fibroblasts. Our data suggest that ACE and aminopeptidases are involved in the basal and TGF-beta1-stimulated soluble collagen production in cardiac fibroblasts.

Key Words: ACE-Inhibition, Aminopeptidase-Inhibition, Cardiac Fibroblasts

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EFFECT OF LISINOPRIL ON ANGIOTENSIN I- AND TRANSFORMING GROWTH FACTOR-BETA1-STIMULATED COLLAGEN PRODUCTION IN CARDIAC FIBROBLASTS


The aim of this study was to investigate whether the angiotensin converting enzyme inhibitor lisinopril could affect the angiotensin I (Ang I) stimulated collagen production in cardiac fibroblasts. The effect of lisinopril was compared to that of the chymase inhibitor chymostatin, the calpain (serine protease) inhibitor E64-d and the dipeptidyl peptidase IV inhibitor diprotin A. Cardiac fibroblasts (from 6 normal male adult rats) were cultured to confluence, incubated with (600 pmol/L TGF-beta1 for 2 days in serum-free Dulbecco’s Modified Eagle’s Medium and further incubated with the tested products (lisinopril, Ang I, chymostatin, diprotin A and E64-d) for 1 day in this serum-free medium with ascorbic acid, beta-aminopropionitrile and tritiated proline. Soluble collagen was measured in the conditioned medium. Ang I (1 microM) stimulated (p<0.001) soluble collagen production in cardiac fibroblasts from 680±72 (mean±SEM) to 972±82 dp/mg DNA and lisinopril (10 microM) suppressed (p<0.05) it further to 811±74 dp/mg DNA Chymostatin, diprotin A and E64-d (100 microM) also reduced the basal and Ang I-stimulated collagen production by 26±3% (p<0.05) and 27±5% (p<0.01), 35±2% (p<0.01) and 40±5% (p<0.05), 21±2% (p<0.01) and 24±3% (p<0.01) respectively. TGF-beta1 stimulated (p<0.01) soluble collagen production from 684±59 to 1267±148 dp/mg DNA and Ang I plus TGF-beta1 increased soluble collagen production to 1354±93 dp/mg DNA compared to the basal values. Lisinopril reduced (p<0.01) Ang I-plus TGF-beta1-stimulated soluble collagen production to 1009±71 dp/mg DNA. Our data suggest that angiotensin converting enzyme together with other peptidases are involved in the basal and Ang I- and TGF-beta1-stimulated soluble collagen production in cardiac fibroblasts.

Key Words: Collagen Production, Angiotensin I, Transforming Growth Factor-beta 1

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CAPTOPRIL TEST IDENTIFIES SEVERITY OF RESIDUAL PRESSURE GRADIENT IN RECOARCTATION


Blood pressure abnormalities after correction for aortic coarctation are very well described. How much these abnormalities are renin-dependent, and how much captopril test is important to identify recoarctation is the aim of our present study.

Twenty three young patients (6 female/17 male) with a mean age of 17 years old and blood pressure equal or lower than P95 were prospectively submitted to a captopril test as it is currently performed in our department. Arm-leg systolic blood pressure gradient was also measured at that time. Catheterization with aortic angiography, and visualization of renal arteries, was performed in those patients whose captopril test was positive.

In all the patients, except two, active renin rise significantly after captopril (P<0.001). From these, in 11/21 (52%) the test was positive but aortic angiography excluded renal artery stenos. Otherwise a linear correlation could be established between the multiple of renin rise and the arm-leg systolic blood pressure gradient for all patients (R^2=0.485).

These results indicate that blood pressure abnormalities in post-coarctation patients might be related to residual pressure gradient. However, a renin-dependent mechanism is also important to stratify severity of the condition and could explain why hypertension is often a late complication of the aortic disease. Recoarctation can also be identified by means of the captopril test.

Key Words: Coarctation, Renin, Captopril

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EFFECTS OF ADRENOMEDULLIN (AM) ON RENIN-ANGIOTENSIN-ALDOSTERONE (RAA) SYSTEM AND OXIDATIVE STRESS IN RATS WITH ACUTE MYOCARDIAL INFARCTION (MI)

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Previous studies have suggested that AM counteracts the systemic or local RAA system and oxidative stress in vitro and in vivo. AM is expressed in cardiac tissue, and plasma AM levels increased in patients with acute MI. This study was performed to examine the effects of AM on the RAA system and oxidative stress in rats with MI. Rats with MI induced by left coronary ligation were intra-peritoneally infused with 1.0 µg/h of recombinant human AM or saline by osmotic mini-pump. Then, the MI rats were examined during and at the end of the AM infusion period for 7 days. Tissue angiotensin-converting enzyme (ACE) mRNA levels were measured by a Real-Time-quantitative PCR method, and urinary isoprostane, a marker of oxidative stress, by an enzyme immunoassay. When compared with the saline infusion in the control, the AM infusion had no effect on organ weights, blood pressure, left ventricular (LV) end-diastolic pressure, plasma renin activity and aldosterone concentration, but significantly reduced ACE mRNA level in non-infarct LV (~31%, P<0.05) and urinary excretion of isoprostane (~61%, P<0.01). To investigate the effects of these AM actions on long-term outcome of MI, another series of rats infused with AM for one week immediately after MI induction were sacrificed at 9 weeks. When compared with the control, the AM infusion significantly improved the survival (59 vs. 81%, P<0.05) and body weight gain (2.8±0.2 vs 3.7±0.1 g/day, mean±SEM, P<0.01), and reduced heart weight (4.7±0.2 vs 3.4±0.1 g/kg BW, P<0.01), lung weight (6.5±0.6 vs. 4.8±0.5 g/kg BW, P<0.01), LV end-diastolic pressure (11.4±2.0 vs 4.0±0.6 mmHg, P<0.05), collagen volume fraction of non-infarct LV (~39%, P<0.05) and plasma level of endogenous rat AM (~38%, P<0.05), without affecting the infarct size. AM administration during the early period of MI reduced left ventricular ACE expression and oxidative stress in rats. These AM actions may...