C13


Chemotherapy and radiotherapy represent the two principal therapeutic axes in the management of cancers. Several clinical investigations have already highlighted the increased risk of cardiac damage when combining thoracic irradiation with doxorubicin (DDX), each generating specific cardiotoxic effects. Our study was performed to assess the cardiac responses of rats hearts submitted to DDX or local cardiac irradiation or the combined therapies. Mice were treated intraperitoneally with saline or DDX (1 mg/kg/day for 10 days). 24 hours after the end of the drug treatment, half of the animals received a local cardiac irradiation consisting of a single dose of 20 Gy. Functional cardiac parameters were measured using the isolated heart model perfused according to the Langendorf's technique. Additional biochemical data investigating the systems antioxidant system were also determined. Antioxidant vitamin E (PVC) levels, the ascorbyl radical vitamin C ratio (ACR) and indices of lipid peroxidation. Experiments were performed 24 hours and one month after the end of the radiation exposure. 24 hours after irradiation, rat hearts mechanical performance evaluated at rest were not affected by both therapies but after an ischemia-reperfusion sequence, the postischemic coronary flow (Col) was higher in hearts treated with DDX. During the ischemic period, diastolic pressure (Pd) was slightly higher in hearts treated with DDX, but the postischemic increase was not significant compared to hearts receiving saline. Moreover, rats treated with DDX displayed lower PVC level (p<0.01), associated with a slightly higher ACR and lower plasmatic MDA contents. These results suggest a solicitation of some components of the antioxidant system associated with the preservation of cardiac functions. One month after the cardiac irradiation, Col of rats prealably treated with DDX was significantly lower. But after the ischemia-reperfusion, hearts behaviour was homogeneous between the different groups of rats. No difference were observed in PVC levels, neither in the ACR between the 4 populations, whilst plasmatic MDA contents increased gradually in irradiated, DDX treated and DDX+irradiated rats. Thus, changes long after irradiation did not affect the same targets as in the early stage of irradiation, suggesting different mechanisms of alterations. In conclusion, the combination of chemotherapy and radiotherapy was not associated with increased cardiotoxicity in the early stage of radiation exposure, whilst more significant changes appeared with time.

Key Words: irradiation, free radicals, hearts, rats

C14

REDUCED RESPONSE OF ISOLATED PAPILLARY MUSCLES TO ISOPROTERENOL IN OBESE RABBITS.

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Obesity is an independent predictor of congestive heart failure but there are limited data on mechanisms whereby obesity leads to abnormal systolic cardiac function. Therefore, the purpose of this study was to determine the contractile response to β-stimulation in rabbits that had been fed either a control (n=6) or 10% fat diet (n=7) for 12 weeks. Contractile responsiveness was determined using right ventricular papillary muscles to evaluate the dose-response relationship between isoproterenol (ISO) and peak developed tension (T/mm²) cross sectional area (CSA) and maximal rate of tension development (dT/dt/CSA). ISO doses were 10⁻⁷, 3x10⁻⁷, 10⁻⁶, 3x10⁻⁶,10⁻⁵, and 3x10⁻⁵. Log dose-response data were fit to a sigmoidal function for analysis. After 12 weeks, rabbits fed the high fat diet developed obesity (5.59±0.06 vs 3.77±0.04 kg, p<0.05), hypertension (103±4 vs 85±1 mmHg, p<0.05) left ventricular hypertrophy (0.59±0.18 vs 0.49±0.16 g, p<0.05), and greater right papillary muscle CSA (1.06±0.13 vs 0.56±0.05 mm², p<0.05). Obese rabbits had reduced maximum (0.41±0.04 vs 1.00±0.12 g/mm², p<0.05) and maximum (1.99±0.21 vs 2.97±0.18 g/mm², p<0.05) T/CSA values, as well as reduced minimum (0.64±0.27 vs 1.12±0.33 g/mm², p<0.05) and maximum (367±40 vs 483±45 g/mm², p<0.05) dT/dt/CSA values. Potency of ISO as reflected by the EC₅₀ did not differ between lean and obese but for T/CSA the EC₅₀ tended to be increased in obese rabbits (p=0.06); the slope of the log dose-response curve did not differ between groups for either variable. These results demonstrate a decreased contractility in the obese rabbit associated with a reduction in efficacy of β-agonists and suggest that a decreased response to β-stimulation may be a factor in the systolic dysfunction of obesity. (Supported by NIH grant HL-51971 and AHA grant-in-aid 93-1485.)

Key Words: Obesity, systolic function, β-adrenergic stimulation

C15

THE EMOTIONAL VASODILATION IS IMPAIRED IN HYPERINSULINEMIC VERY MILD HYPERTENSIVES.

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Hyperinsulinemia was found during hypertension but few studies investigated the relationship between insulin levels and hemodynamic stress response in very mild hypertensives. A cohort of 13 non-smokers, (8 lean, 5 (HI.htn) and 19 (HI.2htn) hypertensives, underwent a stress session (mental arithmetic, handgrip and cold pressor). Muscular contraction (EMG), systolic (SBP) and diastolic (DBP) blood pressure, heart rate (HR), stroke volume (SV), cardiac output (CO) and total vascular resistance (TVR) were taken non-invasively. The stress response parameters were: systolic, diastolic (SBP, DBP), HR, SV, CO, TVR, and history of hypertension (age, sex), diabetes, hypertension, and vascular resistance total (mmHg). The baseline capillary flow was reduced in hypertensives while the postischemic test, which was used as measure of the regional (MFAVR) and microvascular (msLDF) vasodilating reserve and structural damage (mFAVR), did not point out any difference.

Key Words: Blood pressure, diabetes, hypertension, insulin, obesity, stress reactivity (area-under-the-curve) was significantly higher in hypertensives and associated to a restrained capillary flow.

C16

VERY MILD SYSTOLIC HYPERTENSIVES MANIFEST AN ALTERED MICROVASCULAR AND REGIONAL HEMODYNAMIC.

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Hypertension is an independent predictor of congestive heart failure but there are limited data on mechanisms whereby obesity leads to abnormal systolic cardiac function. Therefore, the purpose of this study was to determine the contractile response to β-stimulation in rabbits that had been fed either a control (n=6) or 10% fat diet (n=7) for 12 weeks. Contractile responsiveness was determined using right ventricular papillary muscles to evaluate the dose-response relationship between isoproterenol (ISO) and peak developed tension (T/mm²) cross sectional area (CSA) and maximal rate of tension development (dT/dt/CSA). ISO doses were 10⁻⁷, 3x10⁻⁷, 10⁻⁶, 3x10⁻⁶,10⁻⁵, and 3x10⁻⁵. Log dose-response data were fit to a sigmoidal function for analysis. After 12 weeks, rabbits fed the high fat diet developed obesity (5.59±0.06 vs 3.77±0.04 kg, p<0.05), hypertension (103±4 vs 85±1 mmHg, p<0.05) left ventricular hypertrophy (0.59±0.18 vs 0.49±0.16 g, p<0.05), and greater right papillary muscle CSA (1.06±0.13 vs 0.56±0.05 mm², p<0.05). Obese rabbits had reduced maximum (0.41±0.04 vs 1.00±0.12 g/mm², p<0.05) and maximum (1.99±0.21 vs 2.97±0.18 g/mm², p<0.05) T/CSA values, as well as reduced minimum (0.64±0.27 vs 1.12±0.33 g/mm², p<0.05) and maximum (367±40 vs 483±45 g/mm², p<0.05) dT/dt/CSA values. Potency of ISO as reflected by the EC₅₀ did not differ between lean and obese but for T/CSA the EC₅₀ tended to be increased in obese rabbits (p=0.06); the slope of the log dose-response curve did not differ between groups for either variable. These results demonstrate a decreased contractility in the obese rabbit associated with a reduction in efficacy of β-agonists and suggest that a decreased response to β-stimulation may be a factor in the systolic dysfunction of obesity. (Supported by NIH grant HL-51971 and AHA grant-in-aid 93-1485.)

Key Words: Obesity, systolic function, β-adrenergic stimulation

Key Words: Blood pressure, diabetes, hypertension, insulin, obesity, stress reactivity (area-under-the-curve) was significantly higher in hypertensives and associated to a restrained capillary flow.

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Key Words: Blood pressure, diabetes, hypertension, insulin, obesity, stress reactivity (area-under-the-curve) was significantly higher in hypertensives and associated to a restrained capillary flow.

The findings show that an impaired functional regional and microvascular response characterize - in spite of age, fasting insulin, cholesterol and structural damage - the systolic hypertensive patients at the very early stages of the disease. Therefore, a slight blood pressure increase should be maintained under strict medical control even in the possible related metabolic and functional consequences.

Key Words: Hypertension, functional regional and microvascular response.