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INFLUENCE OF THE NO/L-ARGININE-SYSTEM ON TACROLIMUS-INDUCED CHANGES OF RENAL HEMODYNAMICS

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Nitric oxide (NO) is involved in the regulation of renal hemodynamics in various pathophysiological conditions. Tacrolimus (Tac) is known for its nephrotoxic side effects which are believed to be partly due to acute vasoconstriction in the renal microvasculature. We examined if L-Arginine (Arg)-derived NO could improve renal microcirculatory changes in rat kidneys after acute renal failure due to clamping of both renal arteries for 40 min and infusion of Tac, Arg and L-monomethylarginine (MeArg) as unspecific antagonist of NO-synthases. We determined GFR, RPF, FF, MAP as functional parameters in 4 groups of 8 animals each during and after infusion of saline (Contr), Tac (0,05 mg / kg x h), Tac + Arg (500 mg / kg x h) and Tac + MeArg (1 mg / kg x h) for 120 min.. Clamping induced a significant fall in GFR during the whole experimental procedure from 1,37 ml/min to 0,08 ml/min in Contr. Tac even worsened the observed changes (1,39 ml/min → 0,038 ml/min), whereas simultaneous infusion of Arg with Tac improved GFR to 0,190 ml/min.. MeArg-coadministration showed non-significant changes compared to Tac. RPF fell in all groups (Contr 5,50 → 0,19 ml/min, Tac 6,56 → 0,04 ml/min; Tac + Arg 6,66 → 0,82 ml/min*; Tac + MeArg 6,11 → 0,19 ml/min). Filtration fraction rose in Contr, Tac and Tac+MeArg significantly higher than in Arg (86%, 94%, 72% and 59% respectively) indicating vasoconstriction of the efferent arteriole. During the infusion period we found no significant differences of MAP between the four groups. Administration of Tac leads to further deterioration of renal function after induction of acute ischemic renal failure. The NO-donator L-arginine could significantly alleviate the described changes most likely due to activation of NOS and consecutive endothelium-dependent vasorelaxation.

Key Words: NO/L-Arginine-system, Tacrolimus, Renal hemodynamics

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MYOCARDIAL ENDOTHELIN-1 EXPRESSION FOLLOWING HEART TRANSPLANTATION

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Endothelin-1 (ET-1), a potent vasoconstrictor, is released in response to several inflammatory cytokines following heart transplantation. In order to investigate the role of myocardial ET-1 expression (quantified by immunohistochemistry as weakly positive, +1, +2, +3 and +4) in cardiac allograft rejection (graded from 0 to 4 according to the International Society Heart Lung Transplantation criteria), myocardial fibrosis and subsequent coronary vasculopathy, endomyocardial biopsies were evaluated at 3 months post transplant in 31 heart transplant recipients. The 3-month interval was chosen because most of the episodes of rejection occur during this period. Transplant coronary vasculopathy was documented by cardiac catheterization at 1 year of follow up. Resulting data showed that vascular ET-1 expression was increased in the 3/31 patients experiencing acute cellular rejection from grade 2 (aggressive lymphocytic infiltration) to grade 3A (multifocal aggressive infiltrate). Interestingly, two patients had CMV viremia and hepatitis C at the time of biopsy and also showed positive vascular ET-1 in the absence of rejection. Interstitial ET-1 expression was positive in 18 and negative in 13 patients. The two groups had similar baseline characteristics (age, diabetes, hypertension, hyperlipidemia) and were on similar immunosuppressant medications. Positive interstitial ET-1 was significantly associated with the presence of post transplant myocardial fibrosis (12/18 vs 1/13, $p=0.001$), and increased incidence of coronary vasculopathy at 1 year of follow up (70.5% vs 7.7%, $p=0.001$). However, the average number of episodes of rejection (grade 2 and grade 3A) during the first 3 months of transplant was significantly reduced in the interstitial ET-1 positive patients (1.00 ± 0.68 vs 1.84 ± 1.77 episodes per patient, $p=0.03$). In conclusion, our study showed an evident association between acute rejection and vascular ET-1 expression. Further, it also demonstrated that interstitial ET-1 expression was present in patients manifesting post transplant myocardial fibrosis at 3 months and coronary vasculopathy at 1 year of follow up. Interestingly, positive interstitial ET-1 and fibrosis were also associated with a significantly lower incidence of rejection. Thus, interstitial ET-1 expression seems to play a significant role in the development of both myocardial fibrosis and coronary vasculopathy in heart transplant recipients, and thereby strongly influences post transplant prognosis. The low rate of rejection in patients with positive interstitial ET-1 expression and myocardial fibrosis is extremely interesting and merits further investigations.

Key Words: Endothelin-1, Cardiac Allograft Rejection, Heart Transplantation

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BLUNTED VASODILATORY RESPONSES IN THE CUTANEOUS MICROCIRCULATION OF CIGARETTE SMOKERS

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Background : To assess the vasodilatory response to acetylcholine (Ach, endothelium-dependent vasodilator) and Na nitroprusside (SNP, endothelium-independent vasodilator) in the skin microcirculation of habitual cigarette smokers.

Methods : Male healthy habitual smokers taking no medication acting on the cardiovascular system were included. They were divided in younger (Group 1, n = 10, age : 18 to 35 years; mean = 7 pack-years) and older (Group 2, n = 10, age : 40 to 60 years; mean =30 pack-years). Younger (Group 3, n = 10) and older controls (Group 4, n = 10) consisted of age-matched non-smokers. On the day of the experiment the subjects of Groups 1 and 2 were asked to smoke at least 15 cigarettes starting in the morning. At 4 p.m. they had to smoke within 5 min a filter cigarette containing 1 mg nicotine. Subjects of Groups 3 and 4 had a sham-smoking session at 4 p.m. Ach, 1%, and SNP, 0.1%, were administered transcutaneously for 7 min on the volar face of the right forearm using iontophoresis. This was done 15 min and 40 min after the end of the smoking session for Ach and SNP, respectively. The skin blood flow responses were evaluated using a laser-Doppler flowmeter allowing to scan the surface of Ach and SNP application (circular area, 1 cm diameter) .

Results : The following Table shows the peak changes induced by Ach and SNP (perfusion units, means±SD):

	Younger		Older	
	Ach	SNP	Ach	SNP
Non-smokers	505±65	425±99	473±91	392±71
Smokers	466±102	416±59	302±50**	301±104*

p<0.05;p<0.01, Smokers versus Non-smokers*

Conclusion : These data show that the vasodilatory response of the skin microvasculature is impaired in subjects having smoked cigarettes for many years. This abnormality involves both the Ach and the SNP responses, which implies a diminished relaxant capacity of vascular smooth muscle cells, even if an underlying endothelial dysfunction cannot be ruled out.

Key Words: Endothelial function, Cigarette smoking, Microcirculation