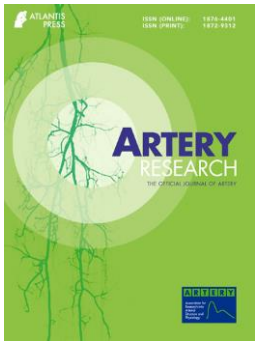

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5.4: A MONOCLONAL ANTIBODY TO AN ENDOGENOUS NA/K-ATPASE LIGAND, MARINOBUFAGENIN, REVERSES EXPRESSION OF PRO-FIBROTIC GENES AND REDUCES CARDIOVASCULAR FIBROSIS IN AGED RATS

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Conclusions. Contrary to expectation, inorganic nitrite is a normoxia-dependent selective conduit artery dilator with similar selectivity to nitroglycerin. A specific advantage of nitrite is that it lacks the problems of development of tolerance and endothelial dysfunction, which limit the efficacy of organic nitrates. The selective central BP-lowering effects of nitrite have therapeutic potential to reduce cardiovascular events.

5.4
A MONOCLONAL ANTIBODY TO AN ENDOGENOUS NA/K-ATPASE LIGAND, MARINOBUFAGENIN, REVERSES EXPRESSION OF PRO-FIBROTIC GENES AND REDUCES CARDIOVASCULAR FIBROSIS IN AGED RATS

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Cardiovascular fibrosis is a hallmark of aging. We had previously demonstrated, that a steroidal endogenous Na/K-ATPase inhibitor, marinobufagenin (MBG), plays a central role in cardiac fibrosis occurring in the context of experimental uremic cardiomyopathy (Hypertension 2007;49:215-24) via participation in Fli-1-dependent pro-fibrotic signaling. Here, we hypothesized, that MBG is implicated in aging-associated fibrosis, and that immunoneutralization of MBG in old rats will reverse pro-fibrotic signalling. To test our hypothesis, we measured plasma MBG in young (3-mo old) and aged (24-mo old) Sprague-Dawley rats, and in aged rats determined the effect of immunoneutralization of MBG on the expression of pro-fibrotic genes in left ventricular (LV) myocardium. One week following a single administration to aged rats of an anti-MBG monoclonal antibody ($n = 6$) or vehicle ($n = 6$), the expression of genes and levels of proteins implicated in pro-fibrotic signalling (qPCR) were assessed in LV myocardium.
Plasma MBG levels were elevated 2-fold ($p < 0.05$) in old vs. young rats, and was accompanied by up-regulation of genes implicated in TGFβ-signaling: TGFβ1 — 3-fold, CTGF1 — 6-fold, SMAD3 — 2-fold, collagen-1 — 2.6 fold. Expression of these genes was significantly suppresses following immunoneutralization of MBG in aged rats, although their expression remained higher than in young controls. The expression of a nuclear transcription factor Fli-1, a negative regulator of collagen-1 synthesis, was reduced by 3-fold in old vs. young rats, and anti-MBG antibody restored levels of Fli-1 in old rats to the level in young controls.
Thus, immunoneutralization of MBG produces an anti-remodeling effect associated with down-regulation of genes implicated in TGFβ-induced fibrosis. The age-associated increase in MBG participates in pro-fibrotic signaling linked to advancing age, and cross-talk between TGFβ-dependent and Fli-1-dependent pro-fibrotic pathways underlies this MBG effect.

5.5
ARTERIAL STIFFNESS IS INCREASED IN INFLAMMATORY BOWEL DISEASE, DEPENDENT UPON INFLAMMATION AND REDUCED BY IMMUNOMODULATORY DRUGS

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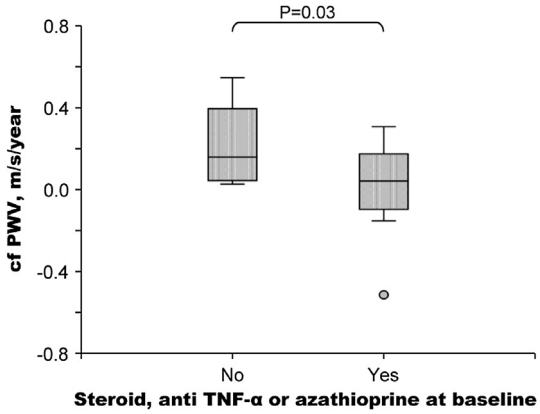
Background. Inflammatory bowel disease (IBD) is associated with an increased cardiovascular risk that is not explained by traditional cardiovascular risk factors, as well as an increased arterial stiffness. In this study, we investigated the relationship between inflammation and arterial stiffening and tested the hypothesis that aortic stiffening is reduced by immunomodulatory therapy in IBD.
Methods. Pulse wave velocity (PWV) was measured in 80 IBD patients and 80 matched controls. Both acute and chronic inflammatory measures were determined. The effect of therapy on PWV was measured at 0 and 3.3 ± 0.3 years in 13 IBD patients treated with immunomodulating drugs (steroids, anti TNF-α or azathioprine) and in 10 IBD patients treated only with salicylates.
Results. IBD patients, compared with controls, have higher carotid-femoral PWV (7.9 ± 1.6 vs. 7.0 ± 1.1 m/s, respectively; $P < 0.001$) and carotid-radial PWV (8.8 ± 1.3 vs. 7.2 ± 0.9 m/s, respectively; $P < 0.001$). Age was a determinant of carotid-femoral PWV in both groups and of carotid-radial PWV in IBD patients. In fully adjusted models performed on IBD subjects, carotid-femoral PWV was positively associated with disease duration, and carotid-radial PWV was positively associated with a history of IBD reactivation and high-sensitivity C-reactive protein. For a comparable value at baseline, the variation of carotid-femoral PWV during follow-up was significantly reduced in subjects treated with immunomodulating drugs compared with those treated only with salicylates (+0.03 ± 0.22 vs. +0.23 ± 0.19 m/s/year of follow-up, respectively; $P < 0.05$; Fig. 1).
Conclusions. IBD is associated with increased arterial stiffness, which correlates with markers of chronic and acute inflammation. Aortic stiffening is reduced by immunomodulating drugs.



5.6
LONG-TERM TREATMENT WITH MELATONIN MAI IMPROVE ANTICONTRACTILE ACTIVITY OF PERIVASCULAR FAT IN OBESE MICE

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Background. The anticontractile effect of perivascular adipose tissue(PVAT) is lost in obese patients due to adipocyte hypertrophy, leading to hypoxia, inflammation, and oxidative stress(Circulation 2009; 119(12):1661-1670).We recently demonstrated that the property of PVAT, partially maintained in an animal model of genetic obesity, seems to be related to the activity of BK_{CA} channels, since is selectively blocked by iberiotoxin. We aimed to investigate functional responses of small mesenteric arteries in an animal model of genetic obesity after chronic treatment with melatonin, an endogenous hormone with antioxidant and vasculoprotective properties.
Methods. Obese mice ($n = 9$) (B6.V-Lep ob/OlaHsd, Harlan Laboratories S.r.l.) (ob/ob) and control lean mice ($n = 8$) (CLM) were treated with melatonin (MEL)100 mg/kg per day for 8 weeks (from the5th to the 13th week of age).Data were compared from untreated ob/ob ($n = 15$) and CLM ($n = 10$) animals. Mesenteric small resistance arteries were dissected and mounted on a wire myograph. Concentration-response to norepinephrine was evaluated in vessels with intact PVAT (WF) and in vessels in which PVAT was removed (NoF) under normoxic and hypoxic (30'95% N_2/5%CO_2) conditions. Norepinephrine concentration-response curve was repeated with iberiotoxin(30'preincubation 100 nm/L).
Results. MEL significantly reduced the contractile response in NoF ob/ob and CLM vessels (ANOVA $P = 0.014$ and $P = 0.049$ respectively).The improvement after MEL was also seen in CLM NoF vessels during hypoxia(ANOVA $p < 0.05$) and following preincubation with iberiotoxin($P < 0.05$), with no significant improvements in ob/ob. Increases in contractility following hypoxia and iberiotoxin treatment were restored byMEL in Ob/Ob WF vessels ($P = 0.013$ and $P = 0.036$ respectively),whereas MEL only rescued the effects of hypoxia($P = 0.045$) in CLM WF arteries. In conclusion, MEL exerts a protective effect in small vessels with and without PVAT from both ob/ob and CLM, counteracting the adverse effect of hypoxia and iberiotoxin in vessels with PVAT and in CLM vessels whitout PVAT. However, in Ob/Ob animals MEL rescues the effects only in the presence of PVAT indicating the importance of PVAT oxidative stress in vascular dysfunction observed in Ob/Ob animals.