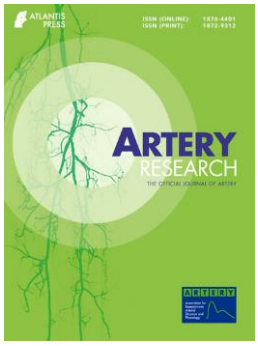

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5.3: INORGANIC NITRITE, CONDUIT ARTERIES & CENTRAL BLOOD PRESSURE

S. Omar, H. Fok, A. Nair, J. Hunt, B. Jiang, P. Chowienczyk, A.J. Webb

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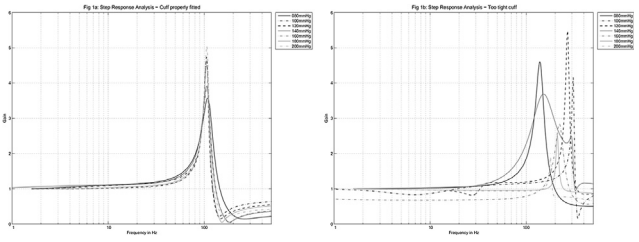
Conclusion. A higher level of PAEE is associated with lower levels of aortic stiffness indicating that the beneficial effects of PA on CVD are partially mediated by aortic stiffness.

4.5
FREQUENCY RESPONSE OF BLOOD PRESSURE CUFFS BASED ON STEP RESPONSE AND FORCED SINUSOIDAL HARMONIC EXCITATION

R. Lurf [1], R. Semerad [1], M. Meindl [1], C. Mayer [1], B. Hametner [1], T. Weber [2], S. Wassertheurer [1]
[1]*AIT Austrian Institute of Technology, Vienna, Austria*
[2]*Klinikum Wels-Grieskirchen, Wels, Austria*

Background. Pulse wave analysis (PWA) using cuff based methods emerged within the last years. Compared to traditional sensors used in PWA like catheters and piezo gauges very little is known on the frequency response of cuff based systems according to standard measurement and systems theory. Therefore the aim of this work is the investigation of the capability of blood pressure cuffs to register the dynamical behavior of the arterial pulse appropriately.
Methods. To evaluate the dynamic behavior of cuff based sensor chains we performed both tests on step response (similar to "pop test") as well as forced sinusoidal harmonic excitation by the means of a fully automated and standardized custom testing bench. The stepwise variation of cuff pressures and/or bladder volumes and cuff sizes was intended to account for various anatomical situations faced in clinical practice.
Results. The resonant frequencies of the evaluated systems are in the range of 110 Hz (Fig. 1a). Similar results have been obtained for both step response method and harmonic excitation. This behavior did not vary over a pressure range from 80 to 200 mmHg. Nevertheless we observed that pressure-volume relation had significant influence on the cuffs frequency response. In particular too tightly fitted cuffs lead to chaotic results (Fig. 1b). Too loosely fitted cuffs causes a loss in resolution.
Conclusions. Based on our actual data blood pressure cuffs provide acceptable capabilities to cope with the dynamics of the arterial pulse for PWA use. This is only valid for properly fitted and inflated cuffs.



Oral Session 5
Invited Lecture and Free Communication Oral Presentations
In association with the Pulse of Asia

5.1
VULNERABLE CAROTID PLAQUES ARE ASSOCIATED WITH THE DEVELOPMENT OF EARLY RESTENOSIS AFTER CAROTID ENDARTERECTOMY

E. A. Surkova, O. V. Tereshina, A. N. Vachev
Samara State Medical University, Samara, Russian Federation

Background. Carotid endarterectomy (CEA) is widely recognised as an effective surgical method in both symptomatic and asymptomatic patients with significant internal carotid artery stenosis. Although the association between vulnerable carotid plaques and stroke is well established, little is known about their role in development of myointimal hyperplasia after carotid surgery. In the current study we aimed to establish correlation between plaque morphology (as observed by ultrasonic scan) and the degree of myointimal hyperplasia after CEA.
Methods. A total of 567 patients with a median age of 65.0 $\pm$ 5,6 years who underwent CEA were examined using duplex ultrasound scanning prior to surgery and 12 months after. The morphology of plaques in terms of their echogenicity was graded as echolucent, predominantly echolucent, predominantly echogenic, echogenic, or calcified. The plaque surface was categorized as smooth, irregular, or ulcerated. Chi-square test and multivariate logistic regression were used for statistical analysis.
Results. Internal carotid artery restenosis due to intimal hyperplasia $\geq$50% were detected in 67 patients (11,82%). The incidence of carotid restenosis was significantly higher in patients with ulcerated carotid plaques ($P < 0.05$). There was no difference between rates of restenosis in patients who had plaques with smooth or irregular surface. Predominantly echolucent carotid plaque appeared to be an independent predictor of carotid restenosis in 12 months after CEA ($P < 0.05$).
Conclusion. The results of our study suggest that vulnerable carotid plaques can lead to myointimal hyperplasia after CEA and can be considered as an independent predictor of early restenosis after carotid surgery.

5.2
CENTRAL PULSE PRESSURE: A POSSIBLE ROBUST MARKER OF THE CARDIAC HEMODYNAMIC LOAD

M. Odaira, H. Tomiyama, A. Yamashina
Tokyo Medical University, Tokyo, Japan

Background. No prospective study has examined whether markers of the central hemodynamics, e.g., central pulse pressure, might be a more robust marker of change in the cardiac hemodynamic load, estimated by the change during the study period of the serum levels of N-terminal fragment B-type natriuretic peptide (NT-proBNP), as compared to markers of the arterial stiffness or brachial blood pressure variables in subjects with preserved cardiac function.
Methods. The brachial-ankle pulse wave velocity, radial augmentation index (rAI), second peak of the radial pressure waveform, systolic and pulse pressure of the second peak of the radial pressure waveform (SP2 and PP2) and serum NT-proBNP level were measured at the start (first examination) and at the end (second examination) of this 3-year study in middle-aged healthy Japanese men ($n = 1851$).
Results. A stepwise multivariate linear regression analysis demonstrated that only PP2, among the parameters related to arterial stiffness and central hemodynamics and also brachial blood pressure variables, was significantly associated with the serum NT-pro BNP levels in the subjects. Furthermore, only the changes of the PP2 during the study period, among the parameters related to arterial stiffness and central hemodynamics, were significantly correlated with those of the serum NT-pro BNP levels during the study period (beta $= 0.131$, $p < 0.001$).
Conclusion. Central pulse pressure, as reflected by PP2, may be a robust marker of the cardiac hemodynamic load and reflect changes in the cardiac hemodynamic load even in persons with preserved cardiac function.
Keywords. Natriuretic peptides, Central blood pressure, Cardiac hemodynamic load

5.3
INORGANIC NITRITE, CONDUIT ARTERIES & CENTRAL BLOOD PRESSURE

S. Omar [1,2], H. Fok [1,2], A. Nair [1,2], J. Hunt [1,2], B. Jiang [1,2], P. Chowienczyk [1,2], A. J. Webb [1,2]
[1]*King's College London, London, United Kingdom*
[2]*Guy's & St. Thomas' NHS Foundation Trust, London, United Kingdom*

Background. Organic nitrates (e.g. nitroglycerin) are highly selective dilators of muscular conduit arteries. By contrast, the endogenous inorganic nitrite anion (NO_2^-) is thought to be a hypoxia-dependent dilator of small resistance arterioles, via its reduction to vasodilating nitric oxide (NO) by deoxyhaemoglobin.
Objective. To establish selectivity of nitrite for resistance versus conduit arteries.
Methods and Results A series of forearm blood flow (FABF) studies were performed in healthy volunteers. Intra-brachial sodium nitrite (8.7 μmol/min) markedly increased radial artery diameter (assessed using ultrasound) by 37.6 $\pm$ 9.7% ($P < 0.001$), with HbO_2 ~99%. Furthermore, nitrite (0.087-87 μmol/min) displayed similar selectivity as nitroglycerin (0.003-1 μg/min) for conduit arteries, compared to resistance arterioles (FABF). Intravenous administration of sodium nitrite (8.7 μmol/min) dilated the contralateral radial artery by 10.7 $\pm$ 1.8% ($P < 0.01$) and lowered central systolic blood pressure (BP) by ~12mmHg from 98.3 $\pm$ 12.3 to 86.7 $\pm$ 15.1 mmHg ($P = 0.02$) without any change in peripheral BP; nitrite also reduced augmentation index and pulse wave velocity. In contrast to nitrite's effects on FABF, induction of hypoxia (breathing 12% O_2) paradoxically inhibited nitrite-induced dilatation of the radial artery to a similar extent as hyperoxia/breathing 100% O_2 (both $P < 0.001$ compared to normoxia).

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

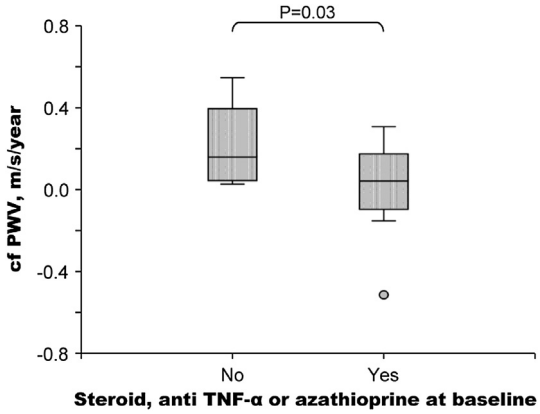
O. V. Fedorova, V. Shilova, V. Zernetkina, Y. Zhang, E. Lehrmann, K. G. Becker, E. G. Lakatta, A. Y. Bagrov
National Institute on Aging, NIH, Baltimore, United States

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

L. Zanoli [1], S. Rastelli [1], G. Inserra [1], P. Boutouyrie [2], S. Laurent [2], P. Castellino [1]
[1]*Internal Medicine, University of Catania, Catania, Italy*
[2]*Department of Pharmacology, Hôpital Européen Georges Pompidou, Assistance Publique — Hôpitaux de Paris, INSERM U970, Paris, France*

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

C. Agabiti Rosei [1], C. De Ciuceis [1], C. Rossiini [1], E. Porteri [1], R. Rezzani [1,2], L. F. Rodella [2], S. B. Withers [3], A. M. Heagerty [3], G. Favero [2], D. Rizzoni [1], E. Agabiti Rosei [1]
[1]*Clinica Medica, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy*
[2]*Chair of Human Anatomy, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy*
[3]*Cardiovascular Research Group, School of Biomedicine, University of Manchester, Manchester, United Kingdom*

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.