tween OPG and OPN serum levels, vascular function and inflammation in CAD patients. These findings suggest another possible mechanism linking OPG and OPN serum levels with CAD progression through arterial wall stiffening and inflammation.

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Effects of the DPP-4 inhibitor saxagliptin on early vascular changes in the retinal and systemic circulation

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In type-2 diabetes early vascular changes (among others) are hyperperfusion in the retinal circulation (like in the kidney) and increased pulse wave reflection leading to increased aortic pressure. We analyzed whether the DPP4-inhibitor saxagliptin reverses early vascular and haemodynamic changes in type-2 diabetes.
In this double-blind randomized controlled clinical cross-over trial 42 patients with type-2 diabetes (age 60.3, 13 were females, BMI 30.6 kg/m^2, mean duration of diabetes 4 years, HbA1c 7.0%, blood pressure 132/79 mmHg) were consecutively [PB1] included and randomized to placebo or saxagliptin 5 mg for 6 weeks each. Retinal capillary flow (RCF) was assessed at baseline and after flickerlight exposure (as a vasodilatory test) by scanning laser Doppler flowmetry. Central (aortic) systolic blood pressure (SBP), central pulse pressure (PP), augmentation index and pulse wave velocity were determined with the SphygmoCor device.
Following treatment with saxagliptin (as opposed to placebo) saxagliptin effected a better glycemic control, a reduced retinal capillary flow (p=0.033) and, in parallel, reduced central systolic augmentation and pulse pressure (see table). In accordance, Flicker light induced increment of RCF (indicative of vasodilatory capacity of the retinal circulation) was numerically 2-fold greater, although not significant.

Table 1

X ± SEM	Placebo	Saxagliptin 5 mg	p-value
Glucose concentrations			
Fasting (mg/dl)	135±5.9	130±5.3	0.097
Postprandial (mg/dl)	182±7.7	167±7.5	0.001
Retinal capillary flow (RCF)			
RCF basal (Arbitrary Unit)	314±14.1	288±13.2	0.033
RCF Flicker (Arbitrary Unit)	331±13.6	323±16.8	0.462
Delta (%)	6.6±2.2	11.4±2.5	0.176
Systemic haemodynamic parameters			
Central aortic SBP	124±2.3	119±2.3	0.038
Central augmentation pressure	12.4±0.9	11.0±1.0	0.094
Central pulse pressure	45.3±2.0	41.9±2.0	0.058

Our data suggest that treatment with saxagliptin for 6 weeks normalizes retinal capillary flow and improves central haemodynamics in type 2 diabetes.

P608 | SPOTLIGHT 2013
Bone marrow derived cells with defective c-Myb activity protect against neointimal remodeling following injury

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Purpose: We previously showed that the transcription factor c-myb regulates the differentiation of contractile vascular smooth muscle cells in embryonic stem cell-derived embryoid bodies. While we also showed that c-Myb regulates the expansion of a specific embryonic hemangiogenic progenitor, it is unclear if this population has a role in the adult animal. However, the role of c-Myb in the proliferation and potential (trans)differentiation of bone marrow (BM)-derived vs. vessel-resident cells in arterial remodelling in the adult has eluded genetic examination due to the embryonic lethality of c-myb-/- mice from hematopoietic failure. To examine the role of c-myb in BM-derived vs. vessel-resident cells, we have used a mouse harboring a non-lethal point mutation resulting in a hypomorphic (h) allele of c-myb with defective c-Myb activity.
Methods and results: Histology of common carotid arteries of 12 wk-old male c-mybh/h and c-mybwt mice was performed 14 days after carotid artery wire denudation injury. Uninjured vessels from wt and h/h mice did not differ in lumen, intima, and media morphometry or I/M ratio. Following wire injury, h/h mice showed reduced intima formation (16,723±2,550 vs. 31,402±49,890 μm^2; $p<0.05$; N=6-7/group) and I/M ratio (0.313±0.044 vs. 0.565±0.089; $p<0.01$) than wt controls. To determine the relative contribution of BM-derived vs. vessel cells in arterial remodeling, reciprocal BM transplants were performed in 5wk old wt and h/h mice, which were allowed to reconstitute their BM for 7 wks before wire injury. Compared to wt→wt mice, injured arteries from h/h→wt mice had decreased intima formation (19,222±2,622 vs. 8,080±1,337 μm^2; $p<0.0001$; N= 7/group) and I/M ratio (0.491±0.068 vs. 0.217±0.01; $p<0.0001$). However, injured arteries from wt→h/h mice had no differences in intima formation as compared to h/h→h/h mice (14,519±486 vs. 13,437±1,175 μm^2; p=NS; N= 7/group), with no differences observed in uninjured BM-transplanted control arteries.
Conclusions: The blunted arterial remodelling response observed in h/h→wt mice is due to a c-Myb dependent defect in BM-derived cell populations that participate in the pathogenesis of neointimal proliferation following arterial injury.

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Reversal of age-related vascular dysfunction through dietary nitrate supplementation

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Physiological aging is accompanied by alterations in the vasculature due to impaired Nitric Oxide (NO) bioavailability leading to gradual loss of vascular homeostasis. Dietary nitrate can be bioactivated in vivo to form nitrite and NO. We hypothesized that chronic dietary nitrate supplementation increases endogenous nitrite levels and that this reverses age-related vascular dysfunction.
Methods: Young (6 months, YN) and old (22 months, ON) C57Bl6 WT mice were treated with dietary nitrate (1 g/l) for 8 weeks with age-matched mice as controls (YC and OC). Systolic blood pressure (SBP) was determined using a pressure catheter and aortic stiffness was assessed in vivo by pulse-wave velocity (PWV). Endothelial function was determined in isolated aortic rings. Nitrite and nitrate were measured by HPLC technique, gene-expression microarray profiling and qPCR were performed.
In a clinical approach n=21 healthy elderly volunteers were treated with dietary nitrate (150μmol/kg BW) for 4 weeks and compared to placebo. Arterial (Augmentation index, AIX) and aortic stiffness were determined using applanation tonometry. Endothelial function was assessed by flow-mediated dilation (FMD) and nitrite and nitrate measurements were determined.
Results: SBP was reduced in old mice receiving nitrate (75±2 mmHg vs. 60±3 mmHg, n=7, p=0.01). Aortic stiffness showed an age-related increase (YC 3.15±0.8 m/s vs. OC 4.32±0.8 m/s, n=6, $p<0.001$), which was reversed by nitrate treatment (ON 3.20±0.8 m/s, $p<0.001$). Endothelial function was reduced in old mice (AcH-dependent dilation OC 60±2% vs. YC 76±3%, n=6, $p<0.05$) restored by nitrate treatment (ON 74±4% $p<0.05$). Plasma nitrite increased only in old mice (0.8±0.5 μM to 4.2±1.4 μM, n=5, $p<0.05$). Gene expression revealed n=270 differentially expressed age-related genes altered by dietary nitrate related to TGF-beta and calcium signalling, ECM remodelling, and vascular smooth muscle contraction.
In humans, dietary nitrate led to reduced SBP (134±4 mmHg to 126±5 mmHg, p=0.016), reduced arterial (AIX@75hr: 23.7±2 to 19.7±3, p=0.005) and aortic stiffness (PWV: 10.2±1 m/s to 8.5±1 m/s, p=0.03) and increased FMD (5.8±0.2% to 6.7±0.2%, p=0.007). Nitrite levels were increased 4 fold (80±1 nM to 310±40 nM, p=0.001).
Conclusions: We show that a chronic dietary nitrate supplementation reversed age-related vascular stiffness and endothelial dysfunction, remarkably in mice and humans. Gene expression profiling revealed novel pathways through which nitrate exerts its beneficial effects. Dietary nitrate could be a promising agent against senescence associated cardiovascular disorders.

P610 | BEDSIDE
Circulating microRNAs in patients with myocardial bridging

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Rationale: MicroRNAs are released by cultured cells and can be detected in the blood. Recent studies reported that circulating microRNAs profile could be the biomarker of coronary artery disease.
Objective: To address the regulation of circulating microRNAs in patients with myocardial bridging.
Methods and results: To determine the regulation of microRNAs, we performed a microRNA profile using RNA isolated from n=15 healthy volunteers and n=33 patients with myocardial bridging that diagnosed by the invasive coronary angiography. Low density chip initially screened the almost 30 suspected microRNAs differentially expressed in the mixed serum from patients and volunteers. To prospectively confirm these data, we detected selected microRNAs in serum among each donator by quantitative PCR. Staticstical analysis demonstrated that seven microRNAs' expression level were significantly different between the myocardial bridging patients and healthy volunteers. Consistent with the data obtained by the profile, microRNA-92a/487a/503/201/126 were obviously higher, while microRNA-29b/339 were remarkably lower in the patient group compared with healthy control. These results were demanded to be validated by more cohort of patients with documented myocardial bridging from other cardiological centers. Likewise, bioinfromatics database shown that microRNA-92a/503/126 were involved in the cellular hypoxia/ischemia, miR-29b may regulated the process of angiogenesis, collagen remodelling. In addition miR-339 takes part in the mesenchymal cell differentiation and embryonic development, while miR-487a is associated with vascular constriction/dilation. The specific regulatory function and mechanism are required further research in the future.
Conclusions: Circulating levels of vascular development and cellular hypoxia/ischemia -associated microRNAs are significantly detectable in serum and discrepantly expressed in patients with myocardial bridging.