Purpose: Investigate whether association of PTX and MTX to LDE may reduce atheromas and vascular inflammation in rabbits with atherosclerosis.

Methods: 28 rabbits underwent induction of atherosclerosis by consuming high cholesterol diet for 8 weeks. After this period, 7 rabbits were euthanized and had their aortas analyzed (Controls). In the other 21 rabbits, high-cholesterol ingestion was continued, and were divided into 3 groups of 7 animals, according to different 8-week treatments: LDE-PTX, LDE-PTX+MTX and LDE-alone. Rabbits were then euthanized and aortas were analyzed for TNF-α gene expression. GAPDH gene was used to normalize the relative gene expression data. Lipid profile and hematological, hepatic and renal toxicities were also determined. This study followed the “Principles of laboratory animal care” (NIH Publication no. 85–23 revised 1985).

Results: See figure. LDE-PTX and LDE-PTX+MTX treatments showed marked reductions of plaque areas when compared to Controls: -64% (p < 0.01) and -71% (p < 0.01), respectively. Compared to LDE group, both treatments also presented gross regression of plaque areas: -49% in LDE-PTX (p < 0.01) and -59% for LDE-PTX+MTX (p < 0.01). Regarding TNF-α gene expression, both treatment groups presented markedly decreased TNF-α gene expression (p < 0.01). LDE-PTX had 0.31±0.10 and LDE-PTX+MTX 0.20±0.09 TNF-α values. No toxicity was observed during the protocol.

Conclusions: This study shows that the treatment with PTX+MTX associated to LDE reduced vascular plaque regression in rabbits with atherosclerosis. The anti-proliferative and anti-inflammatory effects observed and the absence of any toxicity of this treatment lead us to propose a new drug-targeting therapy based on lipid nanoparticles.

Acknowledgement/Funding: FAPESP, SBC

P5163 | BENCH
Hematopoietic PI3-kinase delta-deficiency aggravates atherosclerosis by promoting Th1 cells and regulatory T cells
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Introduction and purpose: Atherosclerosis is a chronic inflammatory disease of arteries and represents the main underlying cause of death worldwide. Although macrophages outnumber other leukocytes in atherosclerotic lesions, T-helper 1 (Th1) cells and regulatory T cells (Tregs) can shape the course of disease by possessing inflammatory and regulatory functions. T cells express the catalytic phosphoinositide 3-kinase isoform p110delta (PI3Kδ), exerting a key role in the regulation of immune responses including activation, proliferation, differentiation and effector function. Since Th1 cells and Tregs play a crucial role in atherosclerosis, we aimed to understand the role of PI3Kδ in T cells during atherogenesis. Moreover, we evaluated whether PI3Kδ represents a putative target for the treatment of atherosclerosis.

Methods and results: To investigate the role of PI3Kδ in T cells during atherogenesis, lethally irradiated LDLR−/− mice were transplanted with bone marrow from PI3Kδ−/− or PI3Kδ+/+ mice and were fed an atherogenic diet for 6 weeks. Hypercholesterolemic PI3Kδ−/− recipient LDLR−/− mice displayed strongly impaired CD4+ T-cell activation and proatherogenic Th1 responses as well as profoundly reduced numbers of atheroprotective Tregs in parasympathetic lymph nodes and spleen compared with PI3Kδ+/+ transplanted controls. Surprisingly, the net effect of PI3Kδ-deficiency was a substantial aggravation of atherosclerosis in LDLR−/− mice. Atherosclerotic lesion area at the aortic root and whole aorta of PI3Kδ−/− recipient LDLR−/− mice was significantly increased by 72% and 118% compared with PI3Kδ+/+ recipients, respectively (n=12–22; P < 0.001). Atherosclerotic lesion areas of PI3Kδ−/− transplanted LDLR−/− mice were characterised by a lower fraction of CD4+ T cells and an unaltered proportion of macrophages compared with controls. Accordingly, PI3Kδ-deficiency had only a modest impact on circulating monocytes and macrophage function including foam cell formation, effecytosis and polarization. However, PI3Kδ-deficient Tregs exhibited strongly reduced secretion of anti-inflammatory cytokines IL-10 and TGF-β as well as pro-atherogenic Th1 cytokines (IL-2, IFN-γ, TNF-α) and pro-inflammatory monocyte cytokines (IL-1α, IL-1β). Loss of PI3Kδ signalling in atheroprotective Treg responses outplays its impact on proatherogenic Th1 responses, thus leading to aggravated atherosclerosis. Hence, PI3Kδ appears to be inapplicable for the treatment of atherosclerosis.

P5164 | BENCH
Protective roles of small GTP-binding protein GDP dissociation inhibitor stimulator against angiotensin II-induced thoracic aortic aneurysm formation and rupture in mice - A possible novel therapeutic target
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Background: Statins reduce the incidence and development of thoracic aortic aneurysm (TAA) and rupture. We have previously identified that small GTP-binding protein GDP dissociation inhibitor stimulator (SmgGDS) is a crucial mediator of the pleiotropic effects of statins.

Methods and results: To examine the role of SmgGDS in TAA formation, Apoe−/− and Apoe−/−/SmgGDS−/− (DKO) mice were infused with angiotensin II (AngII, 1,000 ng/min/kg) for 4 weeks. There was no significant difference in blood pressure between the 2 genotypes in response to the AngII treatment. However, during the final weeks of the study the systolic blood pressure of DKO mice (P < 0.05, n=14 each) was significantly lower than that of Apoe−/− mice (P < 0.05, n=14 each). Interestingly, while the abdominal aorta of Apoe−/− mice was comparable between the 2 genotypes, the abdominal aorta of DKO mice was significantly smaller (P < 0.05, n=14 each). Histological analysis of DKO mice showed dissections of major thoracic aorta in the early phase of AngII infusion (day 3–5). We performed ultrasound imaging every week to follow the serial changes in aortic diameters. A regressing aorta was progressively and significantly increased in DKO mice compared with Apoe−/− mice (1.6±0.06 vs. 1.4±0.05 mm at 4 weeks, P < 0.05, n=14 each), whereas that of the abdominal aorta was comparable between the 2 genotypes. Indeed, there was no significant difference in blood pressure between the 2 genotypes in response to the AngII treatment, whereas there was no TAA rupture in Apoe−/− mice (P < 0.05, n=14 each).

Conclusions: These results suggest that SmgGDS is a novel therapeutic target for the prevention and treatment of TAA.

P5165 | BEDSIDE
Impact of TAVI on great vessels functional characteristics

Purpose: We hypothesized that Transcatheter Aortic Valve Implantation (TAVI) will improve the aforementioned indices of PWV and augmentation, as well as total arterial impedance as expressed with Zva score.

Methods: We enrolled 29 patients (82±6 years) who underwent TAVI. All measurements were performed before and 3 days after TAVI. Echocardiography was used to estimate effective aortic valve area (AVA), mean transvalvular gradient, and left ventricular ejection fraction (LVEF). Arterial impedance was evaluated by Zva (AVA÷Mean gradient+Systolic blood pressure)/Stroke Volume indexed). Additionally, PWV and augmentations index of the aortic pressure waveforms were measured at both time periods.

Results: Compared to baseline measurements, we found that after TAVI, the achieved significant improvements in Zva score (P < 0.01). We also found a statistical significant decrease in Zva (9.7±3.9 mmHg/m2 vs. 7.8±2.2 mmHg/m2, p=0.01). Aix was significantly reduced (29.6±10.22% vs. 25.22±9.01%, p=0.02). In line with this evidence central aortic systolic pressure had a trend for reduction after...
TAVI (117±15mmHg vs. 112±12mmHg, p=0.08), while peripheral systolic arterial pressure did not significantly change after TAVI (p=0.28). In addition, we observed an increase in PWV (12.59±5.33 mm/sec vs. 10.66±2.85 mm/sec, p=0.04)

Conclusion: Successful TAVI improves central arterial reflected waves, decreases total arterial impedance (Zva) and augments pulse wave velocity probably by improving flow through the aortic valve.

P5165 | BEDSIDE
Electronic cigarette smoking increases of arterial stiffness and oxidative stress to a lesser extent than a single normal cigarette: an acute and chronic study
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Background: Electronic cigarette is proposed as a bridge to smoking cessation. In this study we examined its effects on aortic elasticity, exhaled CO concentration, and oxidative stress both acutely and after 1 month of use.

Methods: Seventy current smokers (mean age 48 years±5) without cardiovascular disease participated in the study. In the acute phase the subjects were randomized to smoke either a single normal or an electronic cigarette for 7 min (simulating the duration of a normal cigarette smoking), and after a 40 minute washout period were crossed over to the alternative cigarette. Of the 70 subjects 35 used a nicotine-free electronic cigarette fluid during the acute phase protocol and the remaining 35, an electronic cigarette fluid with a nicotine concentration of 12 mg/dL. All 70 subjects smoked an electronic cigarette with nicotine concentration of the fluid of 12 mg/dL for one month. Measurements were performed at baseline and after 1 month of electronic cigarette smoking. In both acute and chronic phases, we measured a) the aortic PWV (PWV) and augmentation index (Aix) by Arteriograph and Compilor; b) the exhaled CO level (parts per million-ppm) as a smoking status marker; and c) the plasma malondialdehyde (MDA) levels as an oxidative stress burden index.

Results: In the acute phase, compared to baseline, PWV, exhaled CO, and MDA levels were lower after the electronic compared to the normal cigarette smoking (9.3±0.2 vs 10.3±0.2 vs 10.8±0.2 m/s, p=0.05; 12.9±0.7 vs. 12.0±0.6 vs 14.9±0.7 ppm, p=0.001; 1.17±0.1 vs 1.28±0.1 μmol/L, p=0.001, respectively). In addition, nicotine-free electronic cigarette caused a significantly smaller increase of arterial stiffness, compared to the nicotine containing fluid (ΔPWV=+0.3 vs +0.9/m, p=0.05, respectively). In the chronic phase we observed a significant improvement of Aix, as well as of MDA compared to baseline (25.6±2% vs 29.5±2%, p=0.01; 1.09±0.1 vs 1.22±0.1 μmol/L, p=0.05 respectively).

Conclusions: Electronic cigarette smoking causes a smaller increase of arterial stiffness and oxidative stress, compared to a single normal cigarette in an acute setting. Replacement of normal cigarettes by a moderate nicotine concentration electronic cigarette results in improved aortic elasticity and oxidative stress within 1 month.

P5167 | BEDSIDE
Influence of the Sievers type and aortic valveular dysfunction on the bicuspid aortic valve associated aortopathy
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Objective: Bicuspid aortic valve (BAV) is associated with high risk of developing ascending aortic aneurysm. In sporadic form of BAV, changes in outflow’s hemodynamic secondary to the valvular morphology are said to play a prominent role in the development of aortic dilatation. However, the influence of valve morphology as described by Sievers on aortic diameter increase remains controversial, we aimed to compare the different ascending aorta segment diameters according to the morphotype and function of the BAV.

Methods: We evaluated 174 patients with sporadic BAV by transthoracic echo-cardiography. The valvular morphology was assessed in parasternal short-axis view and classified according to Sievers’ classification. The valvular function was defined as either Aortic Insufficiency (AI) if Grade ≥ 2, Aortic Stenosis (AS) if mean gradient > 20mmHg. Both in presence of the 2 criteria, or Normal in absence of both criteria. Aortic diameters were measured at the Valsalva sinus and the ascending tubular aorta after longitudinal alignment. Aortic arch diameter was measured from a supra-sternal view. Kruskal-Wallis, Mann-Whitney and Spearman tests were used for comparisons.

Results: Among the non-operated patients, Sievers’ morphotype was type 1LR for 63%, type 1NR for 18%, and other types counted for 19%. The Valsalva sinus diameter did not differ according to the Sievers’ type (p=0.78). The type 1LR type compared to the type1NR one appeared to have a wider tubular aorta, but not significantly (p=0.47; 37.3mm; p=0.001 respectively). Aortic valve area was also distributed as follows: AI: 39%; AS: 20%; Both: 9%; Normal: 32%. Comparison of the different valve dysfunctions revealed a difference between the groups at the Valsalva (p=0.04) and the tubular aorta (p=0.001) but not at the aortic arch level (p=0.62). AI was highly associated with an increase of the aortic diameters of any segment, excepting for the arch, while patients were younger than those with an AS (53.7±18.0 vs. 46.7±14.6 years; p=0.02). In addition, aortic diameters increased with age in case of AI (Valsalva: r=0.28; p=0.02; Tubular aorta: r=0.27; p=0.02) and not in case of AS (r=0.06; p=0.73 and r=-0.03; p=0.84 respectively) (Figure).