Results: Platelets in non-diabetic patients demonstrated miRNA expression profiles comparable to previously published data. The miRNA expression profiles of platelets in diabetics were similar. Statistical analysis unveiled only three miRNAs (miR-377-5p, miR-628-3p, miR-3137) with high reselection probabilities in resampling techniques, corresponding to signatures with only modest discriminatory performance. Functional annotation of predicted targets for these miRNAs pointed towards an influence of diabetes mellitus on mRNA processing.
Conclusions: We did not find any major differences in platelet miRNA profiles between diabetics and non-diabetics. Minor differences pertained to miRNAs associated with mRNA processing. Thus, previously described differences in plasma miRNAs between diabetic and nondiabetic patients cannot be explained by plain changes in the platelet miRNA profile.

P3252 | BENCH
The olive constituent oleuropein prevents cardiac doxorubicin-induced changes in eNOS expression, apoptotic mediators and energy metabonomics in rats

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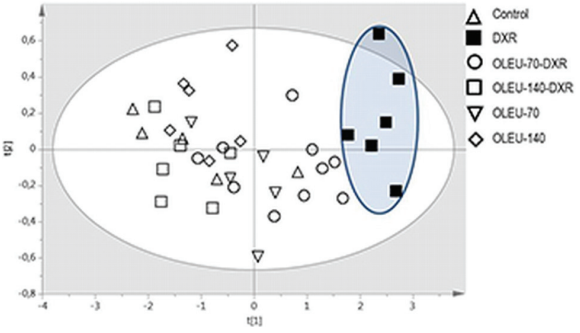
Purpose: Doxorubicin (DXR) causes cardiotoxicity through nitro-oxidative stress, but the exact pathogenesis is not fully elucidated. Oleuropein (OLEU), a polyphenolic constituent of olive and its products, prevents acute and chronic DXR-induced cardiotoxicity. We evaluated mechanisms potentially involved in chronic DXR cardiotoxicity, including eNOS, pro-apoptotic mediators and energy metabonomics as well as OLEU impact on these mechanisms.
Methods: Ninety rats were divided into 6 groups: Control group, no treatment; OLEU-70 and OLEU-140 groups, 70 and 140 mg/kg of OLEU, respectively, given intraperitoneally (ip) for 2 weeks; DXR group, 18mg/kg of DXR ip, divided into 6 equal doses and given over a period of 2 weeks; OLEU-70-DXR and OLEU-140-DXR groups, combined OLEU and DXR as previously described. The rats were finally sacrificed and the hearts were excised for tissue assessment of eNOS, Akt and AMPK by immunohistochemistry and Western-Blot. NMR spectra of tissue extracts was also recorded and analyzed further by multivariate statistics.
Results: DXR group had lower eNOS, Akt and AMPK activation compared to controls and all OLEU groups. The NMR-based metabonomic study depicted differences in the metabolic profile of DXR compared to all other groups (Figure) suggesting an impaired energy metabolism in this group and rehabilitation with OLEU administration. The inhibition of AMPK activation by DXR, correlated with the change in the profile of cardiac energy substrate utilization with a decrease in glucolysis and fatty acids oxidation.



Conclusion: Impaired eNOS, Akt and AMPK expression and cardiac energy metabolism disruption is involved in chronic DXR cardiotoxicity; OLEU prevented those changes, thus providing a potential protective agent against DXR-induced cardiomyopathy.

P3253 | BENCH
Effect of abrupt preload reduction on left atrial and ventricular pressures in a multi-scale mathematical model of the cardiovascular system

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Purpose: The time-varying elastance theory has been widely used to describe left atrial and ventricular behaviors. However, the applicability of this theory to the left atrium is not fully established. Therefore, we used a different type of model, based on a description of sarcomere contraction. We aim to observe if the model behaves similarly to experimental observations during inferior vena cava occlusion (IVCO) experiments.
Methods: We used a multi-scale model of the cardiovascular system in which left ventricular and atrial pressures are inferred from a sarcomere model. In this model, we reproduced IVCO experiments by a fourfold increase of the vena cava resistance. As in experimental settings, we observed the variation of measurements before and 5 heartbeats after modification of the resistance. These measurements were: maximum a and v wave pressures, minimum and end-diastolic ventricular pressures, slopes of a and v waves and maximum transmitral pressure gradients during early and late ventricular filling.
Results: Among the 8 measurements, in the model, 7 followed a similar decrease as experimentally observed. The only measurement that increased is the slope of the v wave. A possible reason for this discrepancy could be that in experimental protocols, vena cava is obstructed far from the heart. In our model, since the vena cava is only represented by a windkessel model, this geographical difference cannot be accounted for.

Measurements before and after IVCO

Measurement	Units	Experiments		Model simulations	
		Baseline	IVCO	Baseline	IVCO
Maximum a wave pressure	mmHg	6.6	4.3	9.64	4.95
Maximum v wave pressure	mmHg	5.6	2.9	14.31	14.08
Minimum ventricular pressure	mmHg	1	–0.4	7.04	14.08
End-diastolic ventricular pressure	mmHg	6.5	3.8	10.24	4.95
Slope of the a wave	mmHg/s	60	37	54.88	29.16
Slope of the v wave	mmHg/s	21	13	18.74	41.05
Maximum early pressure gradient	mmHg	2.8	2.4	1.50	1.08
Maximum late pressure gradient	mmHg	1.2	0.9	2.43	1.70

Conclusion: The developed multi-scale model inferring ventricular and atrial contraction from a sarcomere model correctly represents the left atrial behavior and responds to IVCO experiments as physiologically expected.

P3254 | BENCH
Structural modifications of apelin-12 molecule differently affect cardiac function

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Purpose: Apelin-12, the short active fragment of natural apelin-77, and its synthetic analog apelin-12-2 have been shown to exert beneficial effects in experimental heart failure. The aim of this study was to explore effects of other analogs of apelin-12 molecule.
Methods: The cardiac function of ketamine-anesthetized Wistar rats has been studied using catheterization of the left ventricle (LV) with Millar micromanometer and thoracic electrical impedance. Electric and pressure signals were sent to a computer via an analog-to-digital converter. Bolus injections of apelins were applied with subsequently increasing rate (0.05-5.0 mg/kg) at 10-min intervals.
Results: Substitution of methionine in apelin-12 molecule on norleucine (apelin-12-1 analog) shortened duration of hypotensive effect due to more rapid recovery of LV systolic pressure and LV dP/dtmax associated with an increase dP/dtmax/P index and the shortening of duration of preejection time. Further modifications were made on the basis of apelin-12-1 molecule. Replacement of arginine at N-end on methylarginine (apelin-12-2 analog) was associated with removal of hypotensive effect, increased enddiastolic and systolic LV pressures as well as the rate of increment of impedance signal suggesting increased ejection speed. Replacement of hydroxyl group at C-end of this molecule by amide group (apelin-12-3 analog) reduced the extent of positive inotropic effect, but increased the relaxation constant. Finally, replacement in the latter molecule of methylarginine at the N-end by nitroarginine (apelin-12-4 analog) while retaining relaxation acceleration, exerted hypotensive effect with a reduction of LV systolic pressure, but slightly increased ejection speed and dP/dtmax/P index.
Conclusions: Hypotensive effect of apelin analogs is associated with the presence of arginine and not methylarginine at N-end of molecule. The combination of methylarginine at N-end and OH-group at C-end facilitate positive inotropic effect of an analog. The presence of NH2-group instead of OH-group at C-end results in fastened relaxation. Thus, these modifications are capable to influence different targets in myocardial and vascular cells.

P3255 | BENCH
Potential etiology of diabetic cardiomyopathy

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The objective of the current study was to determine whether the negative effects of diabetes on the adult heart are dictated by defects in resident cardiac stem cells (CSCs) growth and lineage commitment.Type I insulin-dependent diabetes mellitus (IDDM) was induced in mice by streptozotocin administration. The kinetics of CSCs and cardiomyocytes was measured 1, 3, 5, 10, 20, 30, 60, and 90 days after the onset of diabetes, by analyzing 14C birth dating of cardiac cells by Accelerator Mass Spectrometry, which gives the information of the turnover of cardiomyocytes and CSCs in the presence and absence of diabetes. Additionally, the number of cardiomyocytes dying by apoptosis and necrosis were measured