Cardiac function in an experimental model of the metabolic syndrome through pressure conductance analysis and cine MRI

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INTRODUCTION

The prevalence and consequences of diabetes mellitus type 2 and the metabolic syndrome contribute to the increasing morbidity and mortality from ischemic heart disease. Experimental animal models allow us to evaluate disease progression and new treatment options. We used cardiac cine MRI (cMRI) and left ventricular (LV) pressure conductance (PC) analysis to study cardiac function in an experimental model of the metabolic syndrome (DKO mice [1], both leptine and LDL receptor deficient, leading to obesity, diabetes mellitus type 2 and dyslipidemia). The aims of our study were: (1) to compare PC and MRI volumetric information and (2) to determine which contractility parameters were altered in the DKO mice at 24 weeks.

METHODS

Wild-type (WT) C57Bl/6J mice (24 weeks, n=11, body weight 27**±**5g) and age-matched DKO mice (n=6; 59**±**3g), were analyzed first with cMRI and the next day with PC analysis. Rectal temperature was maintained at 37**±1**°C using a warm water circuit under the abdomen.

MRI acquisition and processing

ECG and respiratory gated cMRI was performed under isoflurane anesthesia (induction 2%; maintenance 1.2-1.7% in pure O_2) . MR images were acquired with a 9.4T Biospec system (Bruker Biospin, horizontal bore, 20 cm) equipped with an actively shielded gradient (600mT/m) and using a 7 cm volume resonator and a actively decoupled 2x2 phased array coil (Rapid Biomedical, GE). For localization purposes 2D ecg-triggered pseudo short axis and long axis T_1-weighted images were recorded (FLASH, TE=1.3ms, TR=7.7ms, flip angle= 15deg, matrix 256x56, FOV 30x30mm, slice thickness= 500um). A stack of short axis images was then recorded from base to apex (at end-systole) (12-15 frames depending on heart rate). Volumes and ejection fraction (EF) were calculated using home-written software [2]. The papillary muscles were included in the volume analysis.

LV pressure conductance analysis

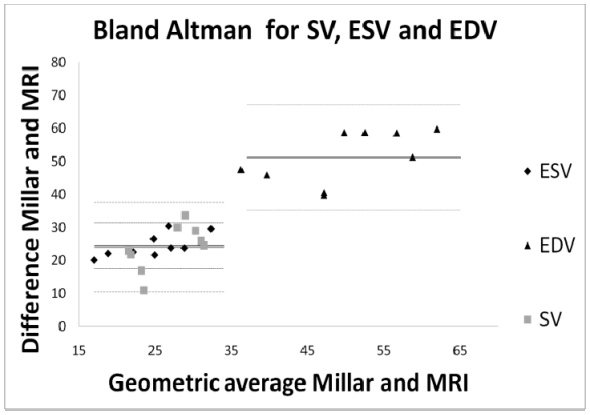
One day later, mice were intubated and ventilated (Minivent 845; Hugo Sachs/Harvard Apparatus, March-Hugstetten, GE) under isoflurane anesthesia and after administration of pancuroniumbromide (1mg/kg). A 1.4 Fr high fidelity pressure-conductance catheter (SPR-839; Millar Instruments, Houston, TX) was inserted through the right carotid artery into the LV and baseline PC loops were recorded (Powerlab/4SP ADInstruments, Castle Hill, AU). The inferior caval vein was compressed between liver and diaphragm with a cotton swab for temporary preload reduction. Load dependent contractility parameters and the load independent parameter preload recruitable stroke work (PRSW) were assessed subsequently. Parallel volume was determined by a bolus injection of 3 µl of 30 % sodium chloride solution in the jugular vein. Finally, specific blood conductivity was determined in 3 precalibrated cuvets to allow recalculation of conductance into volume. All data are expressed as mean ± standard deviation.

Statistical significance was determined with a break-down one way ANOVA.

RESULTS AND DISCUSSION

To verify our methodology, a comparison of PC versus MRI was first performed in WT C57Bl/6J mice. A consistent volume underestimation was found with PC in comparison with MRI: enddiastolic volume (EDV)= 70±16 µl in MRI while 25±7 µl in PC, endsystolic volumes (ESV)= 33±10 µl in MRI and 13±4 µl in PC and stroke volume (SV)= 36±8 µl in MRI and 15±3 µl in PC analysis. The Bland Altman curves for EDV, ESV and SV measured by MRI and PC (figure 1) show a volume dependent offset between the two techniques. We found a ratio between MRI and PC of 3.0±1.0, 2.8±0.8 and 2.5±0.8 for EDV, ESV and SV, respectively). No differences in EF were found (MRI: 52±6% vs PC: 57±7%). These findings are in good agreement with previous comparative studies on WT mice (3,4).

Fig1 Comparison of MRI vs. PC derived volumes in WT mice



In a second part of the study both techniques were applied to the DKO mice. Heart rates (HR) during PC analysis were lower in DKO mice (537±23 bpm) vs. WT animals (640±46 bpm, p<0.001).The DKO data showed a similar volumetric underestimation by PC analysis (volume ratio MRI/PC = WT: 2.6±0.6 ; DKO: 2.7±0.9). HR in both DKO and WT mice were significantly higher during PC vs. cMRI measurements (p<0.01). EF was comparable in both phenotypes both with MRI and PC analysis (WT: 52±6% with cMRI vs 57±7% with PC; DKO: 54±6% with MRI vs. 58±8% with PC). The more robust [5] and load independent PRSW was however lower in DKO than in WT animals (WT: 99±19 mmHg DKO: 74±9 mmHg, p=0.02).

Differences in HR could be due to longer anesthesia times and low local chest temperature even though rectal temperature was monitored during scanning. Moreover positive pressure ventilation during PC could result in a more pronounced reduction of EDV, ESV and SV vs. spontaneously breathing animals. Assumptions concerning geometrics and LV shape in the applied calculations, could also play a role in the differences in reported absolute values.

CONCLUSIONS

In summary, our data show that PC analysis systematically underestimates intracardiac volumes, but difference in HR and methodology could play a role. The underestimation is reproducible for EDV, ESV and SV. This underestimation was similar for both WT and DKO mice, and thus can be compensated for mathematically. Both MRI and PC analysis did not reveal load dependent contractility changes in the adult DKO phenotype. Only the load independent PRSW, measured with PC analysis was able to show a significant difference in contractility in DKO mice at 24 weeks.

References

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