

Heart failure prognosis and the options to improve

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The impact of anthropometric measures of obesity on heart failure outcomes in Asia

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Funding Acknowledgements: Boston Scientific Investigator Sponsored Research Program, National Medical Research Council of Singapore, A*STAR BRC ATTRaCT and Bayer

Background: The inverse association between obesity, traditionally classified by body mass index (BMI), and mortality among patients with heart failure (HF) is well-reported in Western nations but confined to a few small single-centre studies across Asia. Given the reservations against using BMI to measure obesity and the predisposition of Asian patients to a lean HF phenotype we assessed whether this obesity paradox exists in this region when different anthropometric measures are used.

Purpose: To examine a) the associations of BMI with clinical characteristics (b) the relationships of BMI, waist circumference (WC) and waist-to-height ratio to outcomes among Asian patients with HF.

Methods: Using the prospective multinational Asian Sudden Cardiac Death in HF (ASIAN-HF) Registry, the relationship between BMI (WHO-recommended Asian cut-offs: < 18.5, 18.5–23.0, 23.0–27.5, = 27.5 kg/m² for underweight, normal, overweight and obese respectively) with clinical characteristics and outcomes was assessed. In a subset of patients with available measurements of WC, the associations of BMI, WC, waist-to-height ratio with 1-year all-cause mortality and composite outcomes (HF hospitalisation or 1-year mortality) were examined.

Results: Among 5954 subjects (mean age 61.7years, 26.3% women) 6.1, 30.3, 37.5 and 26.2% were underweight, normal, overweight and obese respectively. Positive correlations were observed between increasing BMI and blood pressure, WC, prevalence of hypertension, diabetes, myocardial infarction, and peripheral oedema (p-trend < 0.001).

A linear inverse trend in crude all-cause mortality at 1-year was observed across BMI subgroups (16.5%, 11.5%, 9.5%, 6.9%, p < 0.001), with the lowest rates in the obese category. Compared to obese patients, underweight patients had the highest hazards of 1-year all-cause mortality (adjusted hazards ratio [aHR] = 2.38; 95% CI 1.64–3.44) and composite outcomes (aHR = 1.53; 95% CI 1.16–2.00), followed by patients in normal and overweight categories.

Among subjects with available WC measures (n = 2051), every 1kg/m² increase in BMI was associated with reduced crude and adjusted risk of mortality (5% and 8% respectively, p < 0.003). WC and waist-to-height ratio did not affect the crude hazards of death. Interestingly, BMI (per 1kg/m²) and waist-to-height ratio (per 0.1 increment) was respectively associated with 6% lower and 55% higher adjusted risk of composite outcomes (p < 0.01).

Conclusion: Among Asian patients with HF, those with high BMI had more prevalent comorbidities yet better outcomes, compared to low BMI. This obesity paradox was observed, only when obesity was defined by BMI and not WC or waist-to-height ratio. A direct correlation was observed between central obesity and poor composite outcomes in HF. These findings carry implications for the clinical application of anthropometric parameters in risk stratification of patients with HF.

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S2PLIT Score: a simple risk score predicting post-discharge 1-year mortality in patients with acutely decompensated heart failure

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Background: The acutely decompensated heart failure (ADHF) is a condition associated with poor outcomes, especially during the first year after hospitalization.

Purpose: To assess the performance of the S2PLIT scoring model in predicting a 1-year all-cause mortality in ADHF patients.

Methods: Clinical and laboratory data of 340 patients admitted for ADHF at a single-center ICCU were retrospectively examined. Variables that were significantly associated with 1-year mortality in multivariate regression analysis adjusted for age, sex, NYHA class, post-discharge medications, and comorbidities were included in the risk stratification model. Hosmer-Lemeshow test and C-statistic were used to determine the validity and predictive power of the model. Kaplan-Meier survival analysis was used to assess survival among risk groups.

Results: The average age of the studied population was 74 ± 9.8 years and 50.6% were women. Seventy-eight patients (22.9%) were NYHA II, 162 (47.8%) were NYHA III while 100 patients (29.5%) belonged to NYHA IV functional class. The average left-ventricular ejection fraction (LVEF) was 42.2 ± 9.5% while average systolic blood pressure (SBP) was 137.4 ± 27.4 mm Hg. Serum creatinine, uric acid, and sodium levels averaged 142.3 ± 96.2 µmol/L, 489 ± 172.9 µmol/L, and 138.2 ± 4.4 mmol/L, respectively. Significant independent predictors for 1-year all-cause mortality in our sample were LVEF, SBP, prior history of ADHF hospitalization(s) and serum creatinine, uric acid, and sodium levels. According to calculated S2PLIT score (Table 1), 153, 78 and 109 patients were stratified into a low-, intermediate- and high-risk groups with the observed mortality rates of 9.8% (15/153), 33.3% (26/78) and 91.7% (100/109), respectively. The obtained area under the curve (AUC) for the proposed score model was 0.900 (95% CI 0.864–0.937, SE 0.019, p < 0.001) (Figure 1A) with clear separation among respective risk groups in terms of cumulative survival (Figure 1B).

Conclusions: The S2PLIT scoring model performed well and demonstrated high predictive power for all-cause mortality in ADHF patients during the 1-year period following discharge.

Table 1

Variable collected at admission	Points
Left-ventricular ejection fraction ≤ 45%	1
Serum creatinine of 125–160 µmol/L (1 point) or > 160 µmol/L (2 points)	1 OR 2
Serum sodium ≤ 135 mmol/L	1
Serum uric acid > 440 µmol/L	1
Systolic blood pressure < 130 mm Hg	1
History of prior hospitalization(s) due to exacerbation of the heart failure	1

Clinical and laboratory parameters incorporated into the S2PLIT score.

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Relationship between polymorphism of Connexin40 gene and primary sick sinus syndromeA Anna Chernova¹; S YU Nikulina¹¹Krasnoyarsk State Medical University named prof. V. F. Voino-Yasenevsky, Krasnoyarsk, Russian Federation

Background: Sick sinus syndrome refers to a collection of disorders marked by the heart's inability to perform its pacemaking function. Predominantly affecting older adults, sick sinus syndrome comprises various arrhythmias, including bradyarrhythmias with or without accompanying tachyarrhythmias. Intrinsic causes include degenerative fibrosis, ion channel dysfunction, and remodeling of the sinoatrial node.

Material and Methods: A family examination was performed in 67 patients with sick sinus syndrome (SSS). The control group consisted of 615 patients without clinical ECG manifestations of cardiac diseases. All the examinees have undergone ECG, echocardiography, electrophysiological examination of the heart.

Results: by results of research it is established that the frequency of carriers of a homozygous genotype on rare allele (44AA) among patients with SSS ($35,8 \pm 5,9$) was higher in comparison with control selection ($4,7 \pm 0,9$). The obvious tendency to decrease in carriers of a homozygous genotype on extended allele (44GG) among patients with SSS ($22,4 \pm 5,1$) in comparison with group of control ($57,1 \pm 2,0$) is also noted.

Conclusions: In this work we for the first time revealed on clinical - genetic material association between hereditary SSS and polymorphism of Connexin40 gene.

Genotypes:	SSS (n = 67)	Control group (n = 615)	?
n	%±m	n	%±m
44AA	24	35,8±5,9	29 4,7±0,9 ? <0,0001
44AG	28	41,8±6,0	235 38,2±2,0 ? >0,05
44GG	15	22,4±5,1	351 57,1±2,0 ? <0,0001
Allels:			
Allel 44A	76	56,7±4,3	293 23,8±1,2 ? <0,0001
Allels 4?	58	43,3±4,3	937 76,2±1,2 ? <0,0001
?R; 95% CI OR	4,19;2,906-6,043		
Genotype 44AA	24	35,8±5,9	29 4,7±0,9 ? <0,0001
Genotypes 44AG+44GG	43	64,2±5,9	586 95,3±0,9 ? <0,0001
?R; 95% CI OR	11,278;6,048-21,033		

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Effect of gender on myocardial reverse remodeling in a rat model of banding and debanding of the abdominal aortaM Mihaly Ruppert¹; T Radovits¹; S Korkmaz-Icoz²; S Loganathan²; W Jiang²; LH Lehmann³; A Olah¹; BA Barta¹; B Bodi⁴; Z Papp⁴; B Merkely¹; M Karck²; G Szabo²¹Semmelweis University Heart Center, Budapest, Hungary; ²University of Heidelberg, Department of Cardiac Surgery, Heidelberg, Germany; ³University Hospital of Heidelberg, Department of Cardiology, Angiology and Pulmonology, Heidelberg, Germany; ⁴University of Debrecen, Division of Clinical Physiology, Faculty of Medicine, Debrecen, Hungary**Funding Acknowledgements:** UNKP-17-3-I-SE-6; NKFI; NVKP-16-1-2016- 0017

Background: Gender differences have been intensively investigated during the development of pressure overload-induced left ventricular (LV) myocardial hypertrophy (LVH). However, it is less clear whether female sex also affects the regression of LVH after pressure unloading therapy.

Purpose: In the present study we aimed to investigate the effect of gender on myocardial reverse remodeling following pressure unloading in male and female rats utilizing a rat model of banding and debanding of the abdominal aorta.

Methods: Pressure overload of the left ventricle was induced in male (M) and female (F) Sprague-Dawley rats by abdominal aortic banding (AB) for 6 or 12 weeks. Sham

operated animals served as controls. Pressure unloading was evoked by removing the aortic constriction after week 6 (debanding). Serial echocardiography and LV pressure-volume analysis was performed to assess the morphological and functional alterations. In addition, histological and molecular biological measurements were also carried out.

Results: In male (M) and female (F) AB groups, development of LVH at a similar extent was confirmed by increased left ventricular mass, heart weight-to-tibial length ratio (HW/TL) and cardiomyocyte diameter (CD). On the functional level, LVH was associated with diastolic dysfunction in both genders. However, impairment of systolic function could be only detected in male aortic-banded rats. In contrast to the sex-dependent differences in LVH, removal of the aortic constriction resulted in a similar morphological (HW/TL: $0,38 \pm 0,01$ debanded-M vs. $0,47 \pm 0,01$ AB-M, $p < 0,05$; $0,28 \pm 0,01$ debanded-F vs. $0,36 \pm 0,02$ AB-F, $p < 0,05$), histological (CD: $16,4 \pm 0,5$ debanded-M vs. $18,2 \pm 0,6$ AB-M, $p < 0,05$; $14,7 \pm 0,4$ debanded-F vs. $17,7 \pm 0,6$ AB-F, $p < 0,05$) and functional reverse remodeling in both genders.

Conclusion: Our results provide evidence that pressure unloading therapy at a relatively early time point leads to myocardial reverse remodeling at a comparable degree in male and female rats.

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Gse1, a new player in cardiac developmentF Alnour¹; X Xu¹; E Baier¹; M Drignath¹; M Zeisberg²; EM Zeisberg¹¹University Medical Center Goettingen, Cardiology department, Goettingen, Germany; ²University Medical Center Goettingen, Nephrology department, Goettingen, Germany

Purpose: Hypoplastic left heart syndrome (HLHS) is one of the most severe congenital heart diseases. KIAA0182 gene (Gse1 in mouse) was found to be de novo mutated in HLHS. While the function of this gene has not been elucidated yet, Gse1 is known to produce one circular RNA isoform that is highly abundant. Gse1-knockdown in zebrafish revealed a cardiac phenotype. We therefore aimed to explore the biological role of Gse1 gene using a newly generated Gse1 knockout mouse.

Methods: By using targeted gene-trapping strategy we established Gse1-knockout-first mice with the mutated allele (Gse1-tm1a(EUCOMM)Wtsi) as a knockout model for Gse1 on expression level. In these mice the trapping cassette is located just downstream from the second exon of Gse1 that generates its circularized isoform.

Results: After confirming the correct targeting of Gse1 by the trapping cassette, offspring of matings between heterozygous (Gse1 tm1a/+) parents was analyzed, and within 134 newborn mice no homozygous (Gse1 tm1a/tm1a) mice were detected, indicating embryonic lethality. Systematic embryological analysis revealed that the time of lethality spans over the last trimester of pregnancy. Histological analysis revealed cardiac abnormalities comprising hypoplastic and non-compacted myocardium and ventricular septum defect in the majority of homozygous embryos. Gse1 linear mRNA was surprisingly downregulated by less than 50% in homozygous embryos compared to wild type, without any clear difference on protein level. To exclude the possibility of off-target effects due to the trapping cassette in Gse1-tm1a allele, the genes upstream and downstream from Gse1 were tested and none of them was found to be dysregulated in the homozygous embryos. We found, however, a significant upregulation of Gse1 circular RNA in homozygous as compared to wild type embryos, suggesting that the trapping cassette affects the backsplicing process within the circular RNA forming region, and that this circular RNA may be responsible for the observed abnormalities. We next used miRBase database to identify 12 miRNAs that can be bound by Gse1 circular RNA, and the online database miRDB to identify more than 4000 genes potentially affected by these miRNAs. Among these genes, we focused on 5 candidates (WT1, Mef2c, Tfp2b, Hey2 and GATA4), which were previously linked to cardiac development. We found upregulation of WT1 and downregulation of GATA4 in heart samples from homozygous embryos as compared to wild type. This potentially reflects two known functions of circular RNA to either sequester or to protect miRNAs, providing a possible link between Gse1-circular RNA and the cardiac phenotype.

Conclusions: Homozygosity of Gse1-tm1a allele causes embryonic lethality. The observed cardiac phenotype may be caused, at least in part, by the upregulated circular RNA isoform of Gse1. The biological mechanisms behind our results and the exact functions of Gse1 and its circular RNA are still to be further elucidated.