abdominal aorta constriction, and confirmed with echocardiographic and hemodynamic measurements. The rabbits in the Sham group (n=14) received the same procedure without abdominal aorta constriction. Eight weeks after the index procedure, ex vivo electrophysiological parameters were determined. The protein expression levels of RYR2, phosphorylated RYR2 (iRYR2), and FKBP2 were determined using western-blot. The level of RYR2 phosphorylation was defined as the ratio of RYR2p to RYR2.

RESULTS Compared to the sham group, the LVH group had a significantly shorter left ventricular effective refractory period (127.75 ± 10.31 ms vs 95.57 ± 16.31 ms, P < 0.001). Six isolated hearts (6/8) in the LVH group occurred inducible ventricular tachycardia or ventricular fibrillation under program stimulation, while none (0/8) in the Sham group occurred arrhythmia (P < 0.007). All hearts (6/8) in the HF group occurred spontaneous ventricular fibrillation, while the other two groups didn’t have. Compared to the Sham group, the LVH group had significantly higher protein expression of RYR2, iRYR2, and FKBP2 (P < 0.05), while the level of RYR2 phosphorylation didn’t differ significantly between these two groups. Compared to the sham group, the HF group had significantly lower protein levels of RYR2 and FKBP2, but higher levels of RYR2p and RYR2 phosphorylation ratio (P < 0.05).

CONCLUSIONS The present study showed that despite of the altered expression levels of RYR2 in both LVH and HF, the ratio of RYR2 phosphorylation only increased in HF rather than in LVH, suggesting RYR2 hyperphosphorylation may play an important role in the development of hypertensive HF. Furthermore, the altered RYR2 expression and phosphorylation level might be translated into more vulnerable electrophysiological characteristics.

**GW26-e4566**

Loss of Osteoglycin Promotes Angiogenesis in Limb Ischemia Mouse Model via Modulation of VEGF-VEGFR2 Signaling Pathway

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**OBJECTIVES** Osteoglycin (OGN) plays important roles in cardiovascular disease. However, the relationship between OGN and angiogenesis remains unknown. Therefore, we sought to investigate the effect of OGN on ischemia-induced angiogenesis and address the underlying mechanisms.

**METHODS** Expression of OGN on endothelial cells (ECs) in angiogenic tissue was detected. Limb ischemia model was established in OGN knockout (KO) (n=12) and wild type (WT) (n=12) mice. Laser Doppler imaging was used to estimate perfusion recovery. Meanwhile, 6th orders was used as an evaluation model of angiogenesis. Small interfering RNA was used to knock down OGN expression in culturing human umbilical vein endothelial cells (HUVECs), and cell functions were assessed in subsequent study. Protein-protein interaction was revealed by co-immunoprecipitation assay. And molecular docking was performed to predict the binding site of OGN to VEGFR2.

**RESULTS** OGN was down regulated in intermuscular endothelial cells during angiogenesis in patients of peripheral artery disease and mice model of limb ischemia. OGN knockout promoted perfusion as femoral artery ligation. The blood flow recovery of WT mice after ischemia induction was 24.8%, 44.6% and 63.5% respectively at day4, day7 and day14, while that of KO mice was 46.5%, 71.5%, and 83.0% coordinate. Capillary density indicating by CD31 positive staining was significantly high in OGN KO mice in the gastrocnemius muscle of the ischemia limb. But no difference of inflammatory cells infiltration between two groups was observed. Aortic rings isolated from OGN KO mice had stronger sprouting than those from WT ones. In vitro study revealed tube formation, proliferation, and migration of HUVECs were enhanced in OGN knockdowm group, compared with negative control group. OGN knockdown did not alter protein level of VEGF or VEGFR2, but changed activation of VEGFR2 and its downstream signaling pathways as Akt or ERK1/2. Co-immunoprecipitation assay revealed association of OGN and VEGFR2 both in vitro and in vivo. And OGN was found to modulate interaction of VEGF and VEGFR2. Molecular docking showed OGN docked into the binding pocket of VEGFR2 on the extracellular domain2 and domain3, which is the exact binding site of VEGF.

**CONCLUSIONS** This study demonstrates the crucial role of OGN in the setting of ischemia-induced angiogenesis. Down regulation of OGN promoted endothelial cell functions and angiogenic pathways. In mechanism, this phenomenon can be attributed to OGN binding to VEGFR2 and modulation of VEGF-VEGFR2 signaling pathway.

**GW26-e4567**

The role of Hippo signal transduction pathway in the development of hypertrophic cardiomyopathy

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**OBJECTIVES** This research will explore the expression of Hippo signal transduction pathway in the patients with hypertrophic cardiomyopathy and the regulation of this pathway and its related gene in the development of cardiac hypertrophy, and explore the possible role of Hippo signal transduction pathway in hypertrophic cardiomyopathy.

**METHODS** Myocardial tissues of 32 patients with hypertrophic cardiomyopathy, who accept the Marrow’s surgery in Beijing Anzhen Hospital from September 2011 to April 2013 and 4 cases of normal myocardial tissue were harvested and then protein and RNA of these tissues were also extracted and tested to detect the expression of Hippo signal transduction pathways in the protein and the mRNA level, pathological specimen was pathologically diagnosed as YAP positive mice, as well as the Isoprotenerol (ISO) cardiomyocyte hyperplasia model, are used to explore the possible molecular mechanism of Hippo signal transduction pathway in the process of promoting cardiac hypertrophy. Using mouse primary cultured cardiomyocytes explore the mechanism of this pathway in vitro.

**RESULTS** The expression of protein and mRNA of MST in tissues of hypertrophic cardiomyopathy is less than normal myocardial tissue, the expression of protein and mRNA of YAP in tissues of hypertrophic cardiomyopathy is more than normal myocardial tissue and the expression of YAP-S127 declines. Same results are obtained in HCM model mice.

**CONCLUSIONS** The abnormal expression of Hippo signal transduction pathways regulates myocardial cell hyperplasia and proliferation and promotes the occurrence of hypertrophic cardiomyopathy. Low expression of MST in Hippo pathway can upregulate the activity of the pathway downstream gene (YAP) and the other specific genes to regulate the proliferation of myocardial cells, which affects the myocardial hypertrophy and participates in the development of hypertrophic cardiomyopathy.

**GW26-e4571**

DIM attenuates TGF-β1-induced myofibroblast differentiation in neonatal cardiac fibroblasts through AKT/GSK-3β signaling pathways

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**OBJECTIVES** 3,3'-Diindolylmethane (DIM) is a natural component of cruciferous plants. Previous studies have shown that DIM has multiple physiological effects including anti - angiogenic, anti-inflammatory and anti-cancer effect. However, little is known about the role of DIM on myofibroblast differentiation and extracellular matrix (ECM) production. This study aimed to investigated the effect of DIM on myofibroblast differentiation and ECM production in neonatal rat cardiac fibroblasts induced by transforming growth factor β1 (TGF-β1).

**METHODS** The neonatal rat cardiac fibroblasts in vitro were stimulated with TGF-β1 (1 μmol/L) for 48 h to induce myofibroblast differentiation. Cell viability was examined by CCK8, the percentage of positive cardiac fibroblasts was measured with immunofluoresence staining. The mRNA expression levels of fibrotic markers were measured with Real-time PCR and the protein expression levels of AKT and glycogen synthase kinase-3β (GSK-3β) were examined with Western Blotting analysis.

**RESULTS** Our data showed that DIM could dramatically blunt the percentage of positive cardiac fibroblasts which express α-smooth muscle actin (α-SMA) protein induced by TGF-β1, and reduced the mRNA and protein expressions of α-SMA. Moreover, DIM also significantly decreased the mRNA expression of fibrotic markers (Collagen I,