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P6279 | BENCH
SGK1 controls vascular smooth muscle cell calcification via NF-kB signaling

J.G.J. Voelkl[1], R. Tuffaha[2], K. Musculus[2], T. Auer[2], M. Sacherer[3], B. Metzler[4], D.N. Mueller[5], B. Pieske[1], F. Lang[2], I.S. Alesutan[6]. *[1]Charite - Campus Virchow-Klinikum (CVK), Cardiology, Berlin, Germany; [2]Dpt. Physiology I, Tuebingen, Germany; [3]Medical University of Graz, Graz, Austria; [4]Innsbruck Medical University, Innsbruck, Austria; [5]Max Delbruck Center for Molecular Medicine, Berlin, Germany; [6]Charité - Universitätsmedizin Berlin, BIH, Cardiology CVK, Berlin, Germany*

Introduction: Medial vascular calcification is an active process mainly regulated by vascular smooth muscle cells. In chronic kidney disease, hyperphosphatemia triggers vascular calcification, which underlies the high cardiovascular mortality of these patients.
Purpose: Investigate the role of the serum- and glucocorticoid-inducible kinase 1 (SGK1) during vascular calcification.
Methods/Results: In primary human aortic smooth muscle cells (HAoSMCs), triggers of vascular calcification increased SGK1 expression. SGK1 expression was increased in aortas from animal models of vascular calcification and in coronary artery biopsies of patients with renal disease. Silencing and pharmacological inhibition of SGK1 ameliorated phosphate-induced osteo-/chondrogenic reprogramming and vascular calcification in-vitro. Similarly, genetic Sgk1-deficiency blunted phosphate-induced calcification in primary mouse aortic smooth muscle cells. Transfection of a constitutively active SGK1, but not inactive SGK1, was sufficient to induce osteo-/chondrogenic reprogramming in HAoSMCs. Constitutively active SGK1 increased NF-kB nuclear translocation and transcriptional activity. Pharmacological NF-kB inhibition or silencing of IKK prevented the osteoinductive effects of constitutively active SGK1. Vascular calcification and osteo-/chondrogenic reprogramming was blunted in aortas of Sgk1-deficient mice after cholecalciferol-overload. Renal failure by 5/6 nephrectomy triggered vascular calcification and osteo-/chondrogenic reprogramming in ApoE-deficient mice, effects ameliorated by Sgk1-deficiency.
Conclusions: SGK1 is a key regulator of vascular calcification by regulating NF-kB activity. Inhibition of SGK1 may be a clinically feasible strategy to prevent vascular calcification in chronic kidney disease.
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Impact of chronic outward force on the arterial responses of proximal and distal of long superficial femoral artery stent: combined clinical and preclinical study

S.W. Rha[1], H. Li[1], S.-H. Park[2], J.Y. Park[3], A.-Y. Her[4], Y.H. Kim[4], T.S. Park[5], B.G. Choi[1], S.Y. Choi[1], J.K. Byun[1], C.U. Choi[1], E.J. Kim[1], C.G. Park[1], H.S. Seo[1], D.J. Oh[1]. *[1]Korea University Guro Hospital, Seoul, Korea Republic of; [2]Soonchunhyang University Cheonan Hospital, Cheonan, Korea Republic of; [3]Eulji General Hospital, Seoul, Korea Republic of; [4]Kangwon National University Hospital, Chuncheon, Korea Republic of; [5]Virginia Commonwealth University, Richmond, United States of America*

Background: Self-expanding nitinol stent (SENS) implantation are commonly oversized in the superficial femoral artery (SFA). SENS oversizing leads to chronic outward force (COF). COF by SENS is an important factor for the restenosis. COF would cause continuous mechanical stimulation toward arterial wall chronically, would increase neointimal hyperplasia and subsequent in-stent restenosis (ISR).
Methods: This study was conducted either by clinical and preclinical studies to prove the impact of COF on arterial wall. For the clinical evaluation, we evaluated the degree of intimal hyperplasia especially between proximal segment and distal segment of implanted SENS in SFA using Quantitative Angiography (QA). The impact of COF on mid-term angiographic outcomes was investigated. For the preclinical study, porcine model and SENS (CV Bio, seoul, korea) was used to evaluate the impact of COF on angiographic outcomes and histopathologic outcomes at 1 month. Excised stented arteries were prepared for the histopathologic analysis.
Results: In this study, we analyzed 65 SENS in 61 patients' SFA. Follow-up angiography was done at 6 months to 1 year. The baseline stent diameter of 6.8±0.71 mm and a length of 97.0±33.8 mm. The ratio of the diameter of the stent to the reference vessel was 1.3±0.24 at the proximal portion and 1.53±0.27 at the distal portion ($P<0.001$). In the long stent, stent-to-vessel ratio was significantly higher in the distal stent than in the proximal stent (1.3±0.2 vs. 1.55±0.25, P=0.001). ISR was statistically significant at the distal site (37.3% vs 52.6%, P=0.029).
All 11 animals survived for 4 weeks. After the procedure, QA and morphological analysis were performed. In the QA before stenting, the vessel diameter was 4.04±0.40 vs 4.45±0.63, and there was no significant difference between the two groups (P=0.12). The stent diameter was 5.27±0.46mm vs. 7.18±0.4mm (P=0.001). The stent-to-vessel diameter ratio was 1.31±0.12 versus 1.63±0.20 ($P<0.001$). After 4 weeks, restenosis % was 29.5±12.9% versus 46.8±21.5% (P=0.016). In the histopathologic analysis, the neointimal area was 5.37±1.15 mm^2 vs. 8.53±5.18 mm^2 (P=0.05). The restenosis % was 39.34±8.53% versus 63.97±17.1% (P=0.001).
Conclusions: COF is an important cause of restenosis in the distal portion of the SFA stent. Optimal sizing of the SFA stent is important in daily clinical practice, and the development of a tapered type stent in longer lesions and smaller diameter SENS suitable for vessel size would be necessary.

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A DLG1 polymorphism shortens the action potential duration and the QT interval

E. Delpon[1], D. Tinaquero[1], S. Alfayate[1], P. Nieto-Marin[1], R.G. Utrilla[1], M. Matamoros[1], M. Perez-Hernandez[1], M. Tamargo[2], J. Toquero[3], F.G. Cosio[4], R. Peinado[5], J. Perez-Villacastin[6], J.A. Bernal[7], J. Tamargo[1], R. Caballero[1]. *[1]Complutense University of Madrid, Madrid, Spain; [2]University Hospital Gregorio Maranon, Cardiology, Madrid, Spain; [3]University Hospital Puerta de Hierro Majadahonda, Cardiology, Madrid, Spain; [4]University Hospital of Getafe, Cardiology, Getafe, Spain; [5]University Hospital La Paz, Cardiology, Madrid, Spain; [6]Hospital Clinic San Carlos, Cardiology, Madrid, Spain; [7]National Centre for Cardiovascular Research (CNIC), Madrid, Spain*

Introduction: SAP97 is an scaffolding protein encoded by the DLG1 gene that interacts with several cardiac ion channels including those underlying the fast Na (INa), the inward rectifier (IK1) and the transient outward (Ito) currents, respectively. By next generation sequencing we identified a common [5.3% in the European (non Finnish) population] DLG1 polymorphism (rs34492126) in a man and two sisters diagnosed with Brugada Syndrome, two siblings with familial atrial fibrillation, a man with idiopathic ventricular fibrillation and another with early repolarization syndrome.
Purpose: This work aimed to determine the electrophysiological consequences of the SAP97 p.P888L polymorphism and whether they can contribute to the phenotype of the patients.
Methods: Native (WT) and p.P888L SAP97 tagged with ds-red were cotransfected or not together with the cDNA encoding the alpha and beta subunits underlying human INa, ICa, Ito, and IK1 currents, respectively, in Chinese hamster ovary (CHO) cells. Two cardiac–specific transgenic-like mouse models on the basis of adeno-associated virus gene transfer were created expressing WT and p.P888L SAP97, respectively. Currents and action potentials (APs) were recorded using patch-clamp.
Results: Co-expression of WT SAP97 significantly increased the IK1, INa, and Ito in CHO cells (by 181%, 44%, and 77% respectively, $n\geq20$, $P<0.05$). These results were confirmed in ventricular myocytes from SAP97 overexpressing mice. Conversely, overexpression of WT SAP97 halved the ICaL densities recorded in both CHO cells and mouse ventricular myocytes. The effects produced by p.P888L SAP97 over the INa and the ICaL were undistinguishable from those produced by the WT form, results that were confirmed in p.P888L cardiomyocytes. Conversely, in both CHO cells and mouse myocytes, overexpression of p.P888L SAP97 markedly reduced the IK1, i.e, the opposite effect to that produced by SAP97 WT. Regarding the Ito, p.P888L also increased the Ito peak density, but, more importantly, it doubled the time constant of current inactivation. The slowing of the inactivation process increased the Ito charge density (133%) in both CHO cells and mouse myocytes. As a consequence, the AP duration (APD) measured at 20% and 50% of repolarization of the APs recorded in p.P888L SAP97 myocytes was significantly shortened. Electrocardiographic recordings in transgenic-like mice demonstrated that p.P888L overexpression shortened the QT interval compared with WT SAP97 overexpressing mice.
Conclusions: The SAP97 p.P888L polymorphism shortens the QT interval and the APD as a consequence of a marked increase of the Ito charge. Therefore, this polymorphism could exacerbate the phenotypic manifestations in patients affected by arrhythmogenic syndromes characterized by the repolarization acceleration.
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Angiotensin II-mediated oxidative stress increased the vulnerability of ventricular arrhythmia in cardiac hypertrophy rabbit model, which is suppressed by CaMKII inhibitor

Y.S. Lee[1], H.W. Park[2], B.Y. Joung[2], B.C. Jung[3], D.G. Shin[4]. *[1]Catholic University of Daegu, Daegu, Korea Republic of; [2]Yonsei University College of Medicine, Cardiology, Seoul, Korea Republic of; [3]Fatima General Hospital, cardiology, Daegu, Korea Republic of; [4]Yeungnam University, cardiology, Daegu, Korea Republic of*

Objectives: Angiotensin system is a major cause of heart failure and arrhythmia. Despite a lack of direct evidence that oxidative stress causes ventricular arrhythmia, reversal of oxidative stress is considered a plausible therapy. This study evaluated the Ca2+/calmodulin-dependent protein kinase II (CaMKII) inhibitor could suppress arrhythmia in cardiac hypertrophy rabbit model.
Methods: Angiotensin II (Ang II) or saline was administrated for 2 weeks via osmotic minipumps implanted subcutaneously in the midclavicular region. Hearts were perfused, mapped optically to analyze action potential durations (APD), and restitution kinetics, and tested for VF vulnerability. The intracellular calcium dynamics were measured in cardiomyocyte treated with Ang II (10 ng/ml) for 1 hours.
Results: In Ang II rabbit groups, 2 (30%) rabbits died and had ventricular ar-