Editorial Board
Page i

In Memoriam

Dr. Richard Bing (1909–2010)
Page 1

Point/Counterpoint

Too much or not enough of a good thing? Cardiac glucolipotoxicity versus lipoprotection
Pages 2-5
Heinrich Taegtmeyer, William C. Stanley

Editorials

Survivin signalling in the heart
Pages 6-8
Bodo Levkau

Innate immunity meets arteriogenesis: The versatility of toll-like receptors
Pages 9-12
Claudia Monaco

Primum non nocere: When will ryanodine receptor leak find its role in heart failure?
Pages 13-15
Sarah J. Briston, Andrew W. Trafford

Highlighted Articles

Survivin: A novel player in insulin cardioprotection against myocardial ischemia/reperfusion injury  Original Research Article
Pages 16-24

Research Highlights

►We found that myocardial SVV was up-regulated following I/R, possibly serving as a self-protective mechanism.
►Our data showed that treatment with insulin during reperfusion significantly increased myocardial SVV expression through a PI3K/Akt- and mTOR-dependent mechanism. ►RNAi-mediated SVV knockdown facilitated I/R-induced cardiomyocyte apoptosis whereas SVV overexpression reduced SI/R-induced cardiomyocytes from apoptosis.
Most importantly, SVV knockdown significantly blunted an insulin-induced anti-apoptotic effect. Our study demonstrates that SVV is a novel player in insulin-induced cardioprotection in MI/R.

**Arteriogenesis requires toll-like receptor 2 and 4 expression in bone-marrow derived cells**  
Original Research Article  
Pages 25-32  
Daphne de Groot, Imo E. Hoefer, Sebastian Grundmann, Arjan Schoneveld, René T. Haverslag, J. Karlijn van Keulen, Pieter T. Bot, Leo Timmers, Jan J. Piek, Gerard Pasterkamp, Dominique P.V. de Kleijn

**Research Highlights**

- Toll Like Receptor-2 and -4 are involved in arteriogenesis.
- The absence of TLR-2 and -4 deteriorates collateral formation and thereby tissue perfusion after arterial occlusion.
- The TLR-2 and -4 expression during arteriogenesis is mainly restricted to infiltrating leukocytes.
- Bone-marrow transplantation shows that TLRs on bone marrow derived cells are essential for arteriogenesis.

**Limitations of FKBP12.6-directed treatment strategies for maladaptive cardiac remodeling and heart failure**  
Original Research Article  
Pages 33-42  
Tim Seidler, Nils Teucher, Kristian Hellenkamp, Bernhard Unsöld, Cornelia Grebe, Petra Kramps, Hanna Schotola, Stefan Wagner, Friedrich A. Schöndube, Gerd Hasenfuss, Lars S. Maier

**Research Highlights**

- FKBP12.6$^{D37S}$ increased post-rest Ca transients and SR Ca content *in vivo*.
- FKBP12.6$^{D37S}$ decreased SR Ca leak in failing CaMKII TG mice.
- Contractility or hypertrophy did not improve with FKBP12.6$^{D37S}$.
- TAC-induced morphological remodelling was not susceptible to FKBP12.6$^{D37S}$.

**Review Article**

**Histidine-rich calcium binding protein: The new regulator of sarcoplasmic reticulum calcium cycling**  
Review Article  
Pages 43-49  
Demetrios A. Arvanitis, Elizabeth Vafiadaki, Despina Sanoudou, Evangelia G. Kranias

**Research Highlights**

- HRC and binding partners.
- Regulation of SR Ca-cycling by HRC.
- Genetic variants of HRC.

**Regular Articles**

**A KCR1 variant implicated in susceptibility to the long QT syndrome**  
Original Research Article  
Pages 50-57  
Kenshi Hayashi, Noboru Fujino, Hidekazu Ino, Katsuharu Uchiyama, Kenji Sakata, Tetsuo Konno, Eiichi Masuta, Akira Funada, Yuichiro Sakamoto, Toshinari Tsubokawa, Akihiko Hodatsu, Toshihiko Yasuda, Honin Kanaya, Min Young Kim, Sabina Kupershmidt, Haruhiro Higashida, Masakazu Yamagishi
**Research Highlights**

► A variant of KCR1 (E33D) was identified from a patient with VF and QT prolongation. ► The E33D variant does not protect KCNH2 from the effects of channel blockers. ► The E33D variant leads to a loss of enzymatic α-glycosyltransferase function.

**Lysophosphatidylcholine enhances $I_{Ks}$ currents in cardiac myocytes through activation of G protein, PKC and Rho signaling pathways**

Original Research Article
*Pages 58-65*

Wei-Guang Ding, Futoshi Toyoda, Hisao Ueyama, Hiroshi Matsuura

**Research highlights**

► LPC-16) concentration-dependently and reversibly increased $I_{Ks}$ in atrial cells. ► Inhibitions of G protein, PKC and Rho pathways reduced LPC-16 action on $I_{Ks}$. ► G2A immunofluorescence was distributed in the plasma membrane of atrial myocytes.

**Rhythmic beating of stem cell-derived cardiac cells requires dynamic coupling of electrophysiology and Ca cycling**

Original Research Article
*Pages 66-76*


**Research Highlights**

► Inherent PKA activity drives basal Ca$^{2+}$ cycling in EC cell-derived cardiac cells. ► L-type Ca$^{2+}$ current synchronizes phases of local Ca$^{2+}$ oscillators. ► Synchronized diastolic Ca$^{2+}$ release activates Na$^{+}$/Ca$^{2+}$ exchanger current. ► Diastolic Na$^{+}$/Ca$^{2+}$ exchanger current strongly contributes cell automaticity. ► Rhythmic cell automaticity requires coupling of electrophysiology and Ca$^{2+}$ cycling.

**Hic-5 deficiency enhances mechanosensitive apoptosis and modulates vascular remodeling**

Original Research Article
*Pages 77-86*

Joo-ri Kim-Kaneyama, Naoki Takeda, Asami Sasai, Akira Miyazaki, Masataka Sata, Takahiro Hirabayashi, Motoko Shibanuma, Gen Yamada, Kiyoshi Nose

**PKA and Epac synergistically inhibit smooth muscle cell proliferation**

Original Research Article
*Pages 87-98*

Richard C. Hewer, Graciela B. Sala-Newby, Yih-Jer Wu, Andrew C. Newby, Mark Bond

**Research Highlights**

► PKA is required but not sufficient for the anti-mitogenic effects of cAMP in VSMC. ► cAMP-induced smooth muscle cell growth arrest is Epac-dependent but Rap1-independent. ► PKA and Epac synergise to inhibit smooth
muscle cell proliferation. ► cAMP inhibits ERK and JNK phosphorylation in a PKA- and Epac-dependent manner. ► cAMP-induced stellate morphology of SMC requires PKA and Epac.

Pravastatin normalises peripheral cardiac sympathetic hyperactivity in the spontaneously hypertensive rat

Original Research Article
Pages 99-106
Neil Herring, Chee Wan Lee, Nicholas Sunderland, Kathryn Wright, David J. Paterson

Research Highlights
► Pravastatin lowers resting heart rate (HR) in spontaneously hypertensive rats (SHR) ► Cardiac norepinephrine release & tachycardia are reduced by pravastatin in SHRs ► Neuronal NO signalling & NADPH oxidase expression are unchanged by pravastatin ► The effect of pravastatin on sympathetic neurotransmission is reversed by losartan. ► Pravastatin reduces cardiac angiotensin 2 & angiotensin converting enzymes 1 & 2.

Endoplasmic reticulum chaperon tauroursodeoxycholic acid alleviates obesity-induced myocardial contractile dysfunction

Original Research Article
Pages 107-116
Asli F. Ceylan-Isik, Nair Sreejayan, Jun Ren

Research highlights
►The ER chaperone tauroursodeoxycholic acid (TUDCA) alleviates obesity-induced ER stress and myocardial contractile dysfunction. ►TUDCA reconciles obesity-induced increase in diastolic diameter, cardiac hypertrophy, compromised fractional shortening, cardiomyocyte contractile and intracellular Ca\(^{2+}\) properties. ►TUDCA ablated palmitic acid-induced cardiomyocyte contractile dysfunction.

Impact of long-term caloric restriction on cardiac senescence: Caloric restriction ameliorates cardiac diastolic dysfunction associated with aging

Original Research Article
Pages 117-127
Ken Shinmura, Kayoko Tamaki, Motoaki Sano, Mitsushige Murata, Hiroyuki Yamakawa, Hideyuki Ishida, Keiichi Fukuda

Graphical Abstract
Research Highlights

► CR improves LV diastolic function without affecting LV systolic function. CR attenuates the decline in SERCA2 protein and its activity. ► CR ameliorates age-related deterioration of Ca^{2+} handling during myocyte relaxation. ► CR suppresses the mTOR pathway and enhances autophagic flux in the heart.

Angiotensin II induces afterdepolarizations via reactive oxygen species and calmodulin kinase II signaling  Original Research Article
Pages 128-136
Zhenghang Zhao, Nadezhda Fefelova, Mayilvaahanan Shanmugam, Peter Bishara, Gopal J. Babu, Lai-Hua Xie

Research Highlights

► Ang II induces early afterdepolarizations (EADs) and triggered activities in rabbit myocytes. ► The NADPH oxidase-ROS-calmodulin kinase II (CaMKII) pathway is involved. ► The Ang II-induced EADs are caused by the activation of both I_{Ca,L} and late I_{Na} mediated by CaMKII. ► These results support a link between renin-angiotensin system and cardiac arrhythmias.

Loss of the AE3 anion exchanger in a hypertrophic cardiomyopathy model causes rapid decompensation and heart failure  Original Research Article
Pages 137-146

Research Highlights

► Loss of AE3 Cl^{-}/HCO_3^{-} exchanger increased death rate in hypertrophic cardiomyopathy. ► Loss of AE3 had no effect on cardiac hypertrophy or NHE1 Na^{+}/H^{+} exchanger levels. ► Increased death rate was due to more rapid decompensation and heart failure. ► Decompensation was due to impaired Ca^{2+} handling and β-adrenergic responses. ► Impaired Ca^{2+} handling and β-adrenergic responses led to reduced cardiac reserve.

Loss of interstitial collagen causes structural and functional alterations of cardiomyocyte subsarcolemmal mitochondria in acute volume overload  Original Research Article
Pages 147-156

Research highlights

► Loss of interstitial collagen is a hallmark of volume overload (VO). ► Acute VO generates oxidative stress in rat left ventricle (LV). ► Acute VO results in LV subsarcolemmal mitochondrial (SSM) dysfunction. ► Observed degradation of SSM in acute VO is reversed by MMP inhibitor.
Elevated levels of activated NHE1 protect the myocardium and improve metabolism following ischemia/reperfusion injury

Research Highlights

► Expression of activated NHE1 induced cardioprotection with myocardial ischemia/reperfusion. ► Activated NHE1 increased fatty acid oxidation and glycolysis following ischemia reperfusion. ► Transgenic hearts with activated NHE1 had elevated ATP levels following ischemia/reperfusion.

Calcium binding kinetics of troponin C strongly modulate cooperative activation and tension kinetics in cardiac muscle

Research Highlights

► Cooperative cardiac thin filament activation depends on cTnC Ca\(^{2+}\) binding kinetics. ► cTnC Ca\(^{2+}\) dissociation rate (k\text{off}) affects acto-myosin binding but not cycling. ► Altering k\text{off} affects Ca\(^{2+}\) sensitivity of isometric tension development. ► Increasing k\text{off} can decrease the rate of contractile activation. ► Decreasing k\text{off} can increase the duration of isometric relaxation.

Presence of tubular and reticular structures in the nucleus of human vascular smooth muscle cells

Research Highlights

► Nucleoplasmic reticulum is present in nuclei of human vascular smooth muscle cells. ► Nuclear T-tubules are present in human vascular smooth muscle cells. ► Angiotensin II type 2 receptors are found on the nuclear T-tubules of human vascular smooth muscle cells. ► Lamin A/C is associated with the nuclear T-tubules of human vascular smooth muscle cells. ► Functional IP3 and Ryanodine receptors in nucleoplasmic reticulum.

Ca efflux via the sarcolemmal Ca ATPase occurs only in the t-tubules of rat ventricular myocytes

Research Highlights

► In rat cardiac ventricular myocytes, Ca extrusion via the sarcolemmal Ca ATPase is localised to the t-tubules. ► Ca extrusion via sarcolemmal Ca ATPase is not regulated by PKA. ► Tonic PKA-induced stimulation of Ca extrusion via NCX occurs at the t-tubules but not the surface membrane.
Expression and roles of Ca\textsubscript{v1.3} (\(\alpha_{1D}\)) L-Type Ca\textsuperscript{2+} Channel in atrioventricular node automaticity

Qian Zhang, Valeriy Timofeyev, Hong Qiu, Ling Lu, Ning Li, Anil Singapuri, Cyril L. Torado, Hee-Sup Shin, Nipavan Chiamvimonvat

Research Highlights

► AV node provides the physiological delay between atrial and ventricular contraction. ► Presence of Cav1.3 Ca\textsuperscript{2+} channels in AV node in addition to Cav1.2. ► Cav1.3 plays an important role in AV node automaticity. ► Cav1.2 channel cannot functionally substitute for Cav1.3 channel in AV node. ► Identification of AV node-specific ion channels may provide a new therapeutic target.

Fibronectin increases the force production of mouse papillary muscles via \(\alpha_{5}\beta_1\) integrin

Xin Wu, Sanjukta Chakraborty, Cristine L. Heaps, Michael J. Davis, Gerald A. Meininger, Mariappan Muthuchamy

Research Highlights

► Fibronectin (FN) acts via \(\alpha_{5}\beta_1\) integrin to increase force production in myocardium. ► The force enhanced by FN relates to an increase in intracellular Ca\textsuperscript{2+} concentration. ► FN increases L-type Ca\textsuperscript{2+} channel currents in cardiomyocytes. ► FN-treated myocardium exhibits an increase in myofilament Ca\textsuperscript{2+} sensitivity. ► FN enhances contractility via PKA activation and phosphorylation of phospholamban.

Calmodulin kinase II inhibition prevents arrhythmias in RyR2\textsuperscript{R4496C+/-} mice with catecholaminergic polymorphic ventricular tachycardia

Nian Liu, Yanfei Ruan, Marco Denegri, Tiziana Bachetti, Yang Li, Barbara Colombi, Carlo Napolitano, William A. Coetzee, Silvia G. Priori

Research Highlights

► CaMKII inhibition prevents arrhythmogenesis in a mouse model of catecholaminergic polymorphic ventricular tachycardia. ► CaMKII inhibition enhances the threshold for spontaneous Ca\textsuperscript{2+} release. ► CaMKII inhibition attenuates SERCA function.

Inhibition of nonsense-mediated mRNA decay by antisense morpholino oligonucleotides restores functional expression of hERG nonsense and frameshift mutations in long-QT syndrome

Qiuming Gong, Matthew R. Stump, Zhengfeng Zhou

Research Highlights
The expression of hERG nonsense and frameshift mutations is prevented by nonsense-mediated mRNA decay (NMD) in long QT syndrome. Inhibition of NMD by antisense morpholino oligonucleotides restores functional expression of hERG nonsense and frameshift mutations. Blocking downstream intron splicing is a potential strategy to prevent NMD and rescue some hERG nonsense and frameshift mutations.

SR-targeted CaMKII inhibition improves SR Ca\(^{2+}\) handling, but accelerates cardiac remodeling in mice overexpressing CaMKII\(^{δC}\)

Sabine Huke, Jaime DeSantiago, Marcia A. Kaetzel, Shikha Mishra, Joan H. Brown, John R. Dedman, Donald M. Bers

Research Highlights

- SR-targeted CaMKII inhibition decreases activity of SR-associated CaMKII.
- Inhibition of SR-CaMKII decreases diastolic SR Ca leak.
- Inhibition of SR-CaMKII improves Ca handling in mice with increased CaMKII
- Non-SR targets contribute to heart failure progression in mice with increased CaMKII

Thioredoxin 1 enhances neovascularization and reduces ventricular remodeling during chronic myocardial infarction: A study using thioredoxin 1 transgenic mice

Ram Sudheer Adluri, Mahesh Thirunavukkarasu, Lijun Zhan, Yuzo Akita, Samson Mathews Samuel, Hajime Otani, Ye-Shih Ho, Gautam Maulik, Nilanjana Maulik

Research Highlights

- Trx1 attenuates oxidative stress, apoptosis, fibrosis and increases neovascularization during myocardial infarction (MI).
- Trx1 reduces the expression of TXNIP and AKAP12 during MI.
- Trx1 increases the expression of p-Akt, p-GSK-3beta, Beta-catenin, HIF-1alpha, VEGF, p-eNOS, Bcl-2 and survivin during MI.
- Trx1 reduces/prevents the post-infarction mediated ventricular remodeling.

Immune-inflammatory dysregulation modulates the incidence of progressive fibrosis and diastolic stiffness in the aging heart

Katarzyna A. Cieslik, George E. Taffet, Signe Carlson, Jesus Hermosillo, JoAnn Trial, Mark L. Entman

Research Highlights

- Immune dysregulation causes myocardial fibrosis and diastolic dysfunction in aging mice.
- Diastolic dysfunction is associated with an increased infiltration of CD45\(^{+}\) fibroblasts.
- Progressive fibrosis is accompanied by elevated mRNA level for MCP-1 and IL-13.
- In vitro studies demonstrate that IL-13 enhances monocyte to fibroblast transformation.