CD117, adult cardiac stem cell marker, is transiently expressed in methothelial epicardial cells  
Pages 711-712  
Fumiyuki Hattori

Digitalis and Na/Ca exchange: Old dog learns new mitochondrial tricks  
Pages 713-714  
Donald M. Bers

Static and dynamic properties of the HCM myocardium  
Pages 715-718  
Shannamar Dewey, Qian Xu, Aldrin Gomes

Highlighted Articles

Epithelial–mesenchymal transition of epicardial mesothelium is a source of cardiac CD117-positive stem cells in adult human heart  
Original Research Article  
Pages 719-727  
Franca Di Meglio, Clotilde Castaldo, Daria Nurzynska, Veronica Romano, Rita Miraglia, Ciro Bancone, Giuseppina Langella, Carlo Vosa, Stefania Montagnani

Role of mitochondrial dysfunction in cardiac glycoside toxicity  
Original Research Article  
Pages 728-736  
Ting Liu, David A. Brown, Brian O'Rourke

Research highlights

Background: ► Cardiac glycosides have been used for centuries to treat heart failure, yet their low therapeutic index and potential arrhythmogenic actions have limited their therapeutic potential. ► Glycosides work primarily by inhibiting the plasma membrane Na⁺ pump, which can help increase sarcoplasmatic reticular Ca²⁺ loading. However, high cytosolic Na⁺ also inhibits mitochondrial Ca²⁺ signaling, which can lead to a mismatch of energy supply and demand.

Results and significance: ► The present study shows that the cardiac glycoside ouabain increases cytosolic Na⁺, blunts mitochondrial Ca²⁺ accumulation during increased work (β-adrenergic stimulation and electrical pacing), causes net oxidation of the NAD(P)H pool, increases reactive oxygen species accumulation, and causes triggered arrhythmias. ► The mitochondrial dysfunction caused by ouabain could be prevented by enhancing mitochondrial Ca²⁺ uptake with an inhibitor (CGP37157) of the mitochondrial Na⁺/Ca²⁺ exchanger (mNCE). ► CGP37157 effectively preserved mitochondrial function during ouabain administration, potentiating the positive inotropic actions of the glycoside (and β-adrenergic agonists) and mitigating the toxic effects in cells, perfused hearts, or intact
animals. The results suggest that partial mNCE inhibition may represent a novel strategy for improving cardiac glycoside therapy in the context of heart failure.

Normal passive viscoelasticity but abnormal myofibrillar force generation in human hypertrophic cardiomyopathy

Pages 737-745


Research Highlights

► The passive stiffness of skinned HCM cardiac myocytes was similar to that of normal (donor) myocytes. ► Maximum Ca-activated force production was reduced by 40% in HCM vs donor myocytes. ► This loss of force could contribute to systolic dysfunction in HCM hearts. ► Myofibrillar Ca sensitivity was higher in HCM than in donor myocytes. ► The enhanced Ca sensitivity could compensate for the smaller maximum force but would tend to cause diastolic dysfunction. ► These characteristics were common to all HCM patients studied, suggesting the changes were secondary consequence of the underlying genetic variants.

HIV protease inhibitors elicit volume-sensitive Cl⁻ current in cardiac myocytes via mitochondrial ROS

Pages 746-752

Wu Deng, Lia Baki, Jun Yin, Huiping Zhou, Clive M. Baumgarten

Research Highlights

► HIV protease inhibitors acutely elicit volume-sensitive Cl⁻ current in cardiac cells. ► Corresponding effects on action potential duration were observed. ► Current activation depends on mitochondrial ROS production but not NADPH oxidase. ► Mitochondrial membrane potential also was reduced.

Allogeneic administration of fetal membrane-derived mesenchymal stem cells attenuates acute myocarditis in rats

Pages 753-761

Shin Ishikane, Kenichi Yamahara, Masaharu Sada, Kazuhiko Harada, Makoto Kodama, Hatsue Ishibashi-Ueda, Kazuhide Hayakawa, Kenichi Mishima, Katsunori Iwasaki, Michihiro Fujiwara, Kenji Kangawa, Tomoaki Ikeda

Research Highlights

► Previously, we reported that the autologous administration of bone marrow-derived mesenchymal stem cells (BM-MSC) significantly attenuated myocardial dysfunction and injury in a rat model of acute myocarditis. But BM aspiration procedures are invasive and can yield low numbers of MSC after processing. ► In this study, we focused on fetal membranes (FMs) as an alternative source of BM-MSC to provide a large number of cells. ► This study showed that the intravenous allogeneic administration of FM-MSC ameliorated cardiac dysfunction in a rat model of acute myocarditis. These beneficial effects may be mainly attributable to the suppression of T-lymphocyte activation rather than to angiogenesis and cardiomyocyte differentiation of the administrated allogeneic FM-MSC. ► These results suggest that allogeneic administration of FM-MSC might provide a new therapeutic strategy for the treatment of acute myocarditis.
Roles of phospho-GSK-3β in myocardial protection afforded by activation of the mitochondrial K\(_{\text{ATP}}\) channel

Yoshiaki Terashima, Tatsuya Sato, Toshiyuki Yano, Ole Maas, Takahito Itoh, Takayuki Miki, Masaya Tanno, Atsushi Kuno, Kazuaki Shimamoto, Tetsuji Miura

Research Highlights

► Activation of the mK\(_{\text{ATP}}\) channel is not sufficient for GSK-3β phosphorylation. ► In that GSK-3β phosphorylation, PKC-ε, PI3K and A2b receptor are involved. ► Phospho-GSK-3β contributes to cardioprotection by mK\(_{\text{ATP}}\) channel activation. ► Cyclophilin-D binding to ANT is inhibited by activation of the mK\(_{\text{ATP}}\) channel.

Human progenitor cells derived from cardiac adipose tissue ameliorate myocardial infarction in rodents

Antoni Bayes-Genis, Carolina Soler-Botija, Jordi Farré, Pilar Sepúlveda, Angel Raya, Santiago Roura, Cristina Prat-Vidal, Carolina Gálvez-Montón, José Anastasio Montero, Dirk Büscher, Juan Carlos Izpisúa Belmonte

Research Highlights

► A dimer of the N-terminal domain of RFX5 forms the binding site for RFXAP. ► Multiple contacts from RFX5 promote folding of the C-terminal domain of RFXAP. ► A leucine-rich region of RFX5 is required for dimerization and complex formation. ► Folding of RFXAP results in the formation of a potential binding site for RFXB.

Inhibition of Rho–ROCK signaling induces apoptotic and non-apoptotic PS exposure in cardiomyocytes via inhibition of flippase


Graphical Abstract

Our data point to a role for Rho–ROCK signaling in the maintenance of phospholipid transbilayer asymmetry (a). Impaired Rho signaling through TcdB or C3 leads to both apoptotic (caspase 3 activation) and non-apoptotic PS exposure (probably via impaired ROCK signaling) (b). Impaired ROCK signaling through direct inhibition by Y27632 or H1152 indeed leads to non-apoptotic PS exposure via impaired flippase activity (c).
Research Highlights

► Impaired Rho-ROCK signaling leads to phosphatidylserine (PS) exposure. ► Impaired Rho-ROCK signaling leads to inhibition of flippase. ► Impaired Rho-ROCK signaling leads to inhibition of Akt. ► Inhibition of Rho leads to both apoptotic and non-apoptotic PS exposure. ► Inhibition of ROCK leads to non-apoptotic PS exposure only.

VAMP-1, VAMP-2, and syntaxin-4 regulate ANP release from cardiac myocytes  
Original Research Article  
Pages 791-800  
Marcella Ferlito, William B. Fulton, Mohamed A. Zauher, Eduardo Marbán, Charles Steenbergen, Charles J. Lowenstein

Research Highlights

► ANP is released from cardiac myocytes by exocytosis. ► Cardiac myocytes express a subset of SNARE proteins. ► SNARE proteins VAMP-1, VAMP-2, and syntaxin-4 regulate ANP exocytosis.

An association between gene expression and better survival in female mice following myocardial infarction  
Original Research Article  
Pages 801-811  
Quanhai Chen, Roy Williams, Chastity L. Healy, Casey D. Wright, Steven C. Wu, Timothy D. O’Connell

Research Highlights


Angiotensin II inhibits the electrogenic Na⁺/HCO₃⁻ cotransport of cat cardiac myocytes  
Original Research Article  
Pages 812-818  
Verónica C. De Giusti, Alejandro Orlowski, Ernesto A. Aiello

Graphical Abstract

Schematic diagram showing the proposed mechanisms involved in the angiotensin II (Ang II)-induced actions on cardiac Na⁺/HCO₃⁻ cotransport (NBC).
Research Highlights

► Ang II, binding to AT1 receptors, exerts an opposite effect on NBC isoforms. ► nNBC stimulation is mediated by ROS and ERK 1/2. ► p38 kinase mediates the Ang II-induced eNBC inhibition. ► nNBC stimulation may induce intracellular calcium overload. ► eNBC inhibition could lead to action potential prolongation.

ROCK1 plays an essential role in the transition from cardiac hypertrophy to failure in mice
Original Research Article
Pages 819-828
Jianjian Shi, Yi-Wei Zhang, Yu Yang, Lumin Zhang, Lei Wei

Research highlights

► ROCK1 deletion abolished peripartum mortality, prevented the development of heart failure, and inhibited cardiomyocyte apoptosis while preserving cardiomyocyte hypertrophy in the peripartum Gaq mice. ► ROCK1 deficiency improved survival, inhibited cardiomyocyte apoptosis, and preserved LV dimension and function in old Gaq mice at 12 months. ► Transgenic overexpression of ROCK1 increased cardiomyocyte apoptosis and accelerated hypertrophic decompensation in Gaq hearts in the absence of pregnancy stress. ► The present study demonstrated the long-term beneficial effects of ROCK1 deficiency in hypertrophic decompensation.

Paclitaxel accelerates spontaneous calcium oscillations in cardiomyocytes by interacting with NCS-1 and the InsP₃R
Original Research Article
Pages 829-835
Kun Zhang, Felix M. Heidrich, Brenda DeGray, Wolfgang Boehmerle, Barbara E. Ehrlich

Research highlights

► Paclitaxel accelerates calcium oscillations in cardiomyocytes. ► Paclitaxel binds to neuronal calcium sensor 1 (NCS-1). ► NCS-1 enhances the activity of the InsP₃R. ► The extra InsP₃R activity modulates the calcium oscillation frequency. ► The effects of paclitaxel in cardiomyocytes is opposite that seen in neurons.

Partial rescue of the Tbx1 mutant heart phenotype by Fgf8: Genetic evidence of impaired tissue response to Fgf8
Original Research Article
Pages 836-840
Francesca Vitelli, Gabriella Lania, Tuong Huynh, Antonio Baldini

Research Highlights

► Fgf8 is required in Tbx1-expressing cells for heart development. ► Forced expression of Fgf8 in Tbx1 null embryos failed to rescue the heart phenotype. ► Fgf8, in the presence of low Tbx1 expression partially rescues the heart phenotype. ► Tbx1 null cells are unable to respond to Fgf8 in culture.

Synergistic effects of the GATA-4-mediated miR-144/451 cluster in protection against simulated ischemia/reperfusion-induced cardiomyocyte death
Original Research Article
Pages 841-850
Xiaowei Zhang, Xiaohong Wang, Hongyan Zhu, Cheng Zhu, Yigang Wang, William T. Pu, Anil G. Jegga, Guo-Chang Fan
Research Highlights

►The miR-144/451 cluster is directly regulated by cardiac transcription factor GATA-4. ►Increased levels of miR-144 and miR-451 protect adult cardiomyocytes against simulated ischemia/reperfusion-induced cell death, and overexpression of miR-144/451 reveals additive effects on cardioprotection. ►Both miR-144 and miR-451 target CUGBP2, an RNA-binding protein, which interacts with COX-2 3′UTR and inhibits its mRNA translation. ►COX-2 is upregulated in miR-144-, miR-451-, and miR-144/451-overexpressing cardiomyocytes. ►Inhibition of COX-2 partially abrogates miR-144/451-mediated cardioprotection.

Proteomic and metabolomic analysis of atrial profibrillatory remodelling in congestive heart failure

Ayesha I. De Souza, Sophie Cardin, Robin Wait, Yuen-Li Chung, Meeraa Vijayakumar, Ange Maguy, A. John Camm, Stanley Nattel

Natriuretic peptide pharmacogenetics: Membrane metallo-endopeptidase (MME): Common gene sequence variation, functional characterization and degradation

Naveen L. Pereira, Pinar Aksoy, Irene Moon, Yi Peng, Margaret M. Redfield, John C. Burnett Jr., Eric D. Wieben, Vivien C. Yee, Richard M. Weinshilboum

Research highlights

►Membrane metallo-endopeptidase (MME), also known as neutral endopeptidase 24.11 is involved in the metabolism of natriuretic peptides that play a key role in modulating cardiac structure and function. ►MME was resequenced in three ethnic groups resulting in identification of 90 polymorphisms of which 65 were novel, including 8 nonsynonymous single nucleotide polymorphisms (nsSNPs) of which 7 were not described before. ►The functional effects of the nsSNPs on expressed protein levels and enzyme activity was studied in an in-vitro cell based system leading to the identification of a significant reduction in enzyme activity (21% of wild-type) and immunoreactive protein (29% of wild-type) for the Met73Val variant allozyme ►Proteasome-mediated degradation and autophagy participated in the degradation of the Met73Val allozyme and was associated with increased expression of the chaperone proteins, BiP and GRP94 suggesting protein misfolding, compatible with conclusions based on the MME X-ray crystal structure. ►The Met73Val variant allozyme could have a significant effect on the metabolism of natriuretic peptides.

Q site of mitochondrial complex III is the source of increased superoxide after transient exposure to hydrogen peroxide

Helena M. Viola, Livia C. Hool

Evidence that the acute phase of ischemic preconditioning does not require signaling by the A2B adenosine receptor

Jason E. Maas, Tina C. Wan, Robert A. Figler, Garrett J. Gross, John A. Auchampach

Research Highlights

►Protection by early preconditioning can be elicited in A2B receptor knock-out mice. ►Preconditioning in rats is also present during A2B receptor blockade with ATL-801. ►Giving the A2B receptor agonist BAY 60-6583, however, reduces infarct size in rats.
Rapid Communications

Cardiovascular determinants and prognostic significance of CC Chemokine Ligand-18 (CCL18/PARC) in patients with stable coronary artery disease
Pages 894-896
J. De Sutter, S. Struyf, N.R. Van de Veire, J. Philippé, M. De Buyzere, J. Van Damme

Myocardial stress remodelling after regional infarction is independent of glycogen synthase kinase-3 inactivation
Pages 897-900
Ian G. Webb, Pierre Sicard, James E Clark, Simon Redwood, Michael S. Marber

Announcement

Call for Nominations: ISHR Outstanding Investigator Award
Pages I-II