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Title	OJ-073 Fluctuation of Intracellular Ca2+ through Multiple Ca2+ Regulatory Proteins May Be Inevitable for Initiating Apoptosls in Adult Cardiac Myocytes(本文(Fulltext))
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Japanese Circulation Society

were assigned to additionally receive spironolactone (25 mg/day), while the remaining 15 patients continued their current drug regimen. Patients were studied before and 6 months after treatment. The delayed heart-to-mediastinum count (H/M) ratio, delayed total defect score (TDS), and washout rate (WR) were determined from 123I-meta-iodobenzylguanidine (MIBG) images. Left ventricular end-diastolic volume (LVEDV), and LVEF were determined by echocardiography. **Results:**Before treatment, TDS, H/M ratio, WR, LVEDV and LVEF were similar in both groups. In the spironolactone group, TDS decreased from 36±9 to 24±13($p<0.0001$), H/M ratio increased from 1.64±0.20 to 1.86±0.27($p<0.0001$), and WR decreased from 55±12 to 41±15($p<0.0005$). In addition, the LVEDV decreased from 187±26 to 154±41($p<0.005$), and LVEF increased from 33±6 to 39±6($p<0.005$). However, these parameters did not significantly change in the control group. Moreover, there was significant correlation between changes of the 123I-MIBG findings and changes of the echocardiographic LVEDV with spironolactone treatment (TDS, $r=0.684$, $p=0.0038$; H/M ratio, $r=-0.878$, $p<0.0001$; and WR, $r=0.737$, $p=0.0011$). **Conclusions:**Spironolactone improves cardiac sympathetic nerve activity and left ventricular remodeling in patients with DCM.

OJ-071

Relation between Acute Functional Response to Dobutamine and Late Functional Recovery by Beta-Blocker Therapy in Patients with Dilated Cardiomyopathy

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Objectives: Myocardial viability by dobutamine stress echocardiography(DSE) is reported to predict an improvement in global ejection fraction(EF) with beta-blockers in patients with heart failure(HF). To further verify the relation between myocardial viability and the reverse remodeling, we examined whether this relation is kept at the specific site of the left ventricle. **Methods:** Nineteen patients with stable mild to moderate HF due to dilated cardiomyopathy(EF=22±8%) were studied with DSE prior to, and 4 weeks after receiving treatment with carvedilol(20mg/day) or bisoprolol(5mg/day). 3 μg/kg/min and 6 μg/kg/min of dobutamine were used for DSE. Regional myocardial contractility was assessed by the peak velocity of systolic excursion(Vs) using tissue-Doppler-imaging. Vs was determined by averaging the values measured at medial and lateral portion of mitral annulus, respectively. **Results:** The improvement in Vs was observed as early as 4 weeks after the administration of beta-blockers (4.95±1.10 vs 6.10±1.52, $p=0.003$). Acute contractile response(%increase in Vs) to 3 μg/kg/min of dobutamine correlated with that to 6 μg/kg/min of dobutamine($r=0.75$, $p<0.0001$). %increase in Vs to 3 μg/kg/min correlated with %increase in resting Vs during 4 weeks($r=0.664$, $p<0.01$). %increase in Vs to 6 μg/kg/min also correlated with %increase in resting Vs during 4 weeks($r=0.647$, $p<0.01$). **Conclusions:** Regional functional recovery with beta-blockers is related with the grade of regional contractile reserve and suggests that reverse remodeling is related to myocardial viability.

Heart Failure Treatment (M)

OJ10

March 28 (Fri)

Room 3
(Fukuoka Sun Palace/B1F/Rehearsal Room)

16:00—17:36

OJ-072

Valsartan Restores Normal FKBP12.6-RyR Interaction by a Strong Inhibition of PKA-Mediated Hyperphosphorylation of RyR in Heart Failure

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We assessed the effect of angiotensinII receptor blocker valsartan on sarcoplasmic reticulum (SR) function, defectiveness of which is one of the major pathogenic mechanisms of heart failure. **Methods and Results:** SR vesicles were isolated from dog LV muscles {normal (N), n=7; 4-weeks rapid RV pacing with or without valsartan (V(+):0.1mg/kg/day, n=7; V(-), n=7). 1}In either V(-) or V(+), LV size was similarly enlarged with a reduced wall motion. However, the contractile response to dobutamine (8 μg/kg/min), assessed by peak +dP/dt of LV pressure, was significantly larger in V(+) than in V(-). 2) The density of β-adrenergic receptor was lower (-45%) in V(-) than in N, whereas it was restored in V(+) (- 9%). 3) In V(-), RyR was PKA-hyperphosphorylated, whereas it was completely reversed in V(+). 4) In V(-), a prominent Ca^{2+} leak was observed, whereas there was no appreciable Ca^{2+} leak in V(+). 5) Both SR Ca^{2+} uptake function and the amount of Ca^{2+}-ATPase were also decreased in V(-), whereas they were restored in V(+). **Conclusions:** Although valsartan did not improve cardiac function during the development of heart failure, it corrected SR function. This apparently discordant effect of valsartan may be due to surprisingly quite strong β-blockade-like action in this model.

OJ-073

Fluctuation of Intracellular Ca^{2+} through Multiple Ca^{2+} Regulatory Proteins May Be Inevitable for Initiating Apoptosis in Adult Cardiac Myocytes

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Adult cardiac myocytes shows a dynamic and unique process during execution of apoptosis; they exhibit beating just before and at the early phase of apoptosis (Am J Pathol. 2001;159:683), suggesting important roles of intracellular Ca^{2+} concentration ($[Ca^{2+}]i$) and Ca^{2+} regulatory proteins for initiating apoptosis in those cells. In the present study, we examined the regulatory mechanisms of Ca^{2+} regulatory proteins for initiating apoptosis in adult cardiac myocytes, which was induced by activation of β-adrenergic receptor by isoproterenol (10-5 M). Apoptosis was evident, as documented by activated caspase-3, DNA fragmentation based on in situ nick end-labeling (TUNEL) and DNA ladder pattern, and apoptotic ultrastructure. These apoptotic features were found strongly inhibited by nifedipine (L-type Ca^{2+} channel antagonist), thapsigargin (SERCA antagonist), and ryanodine (ryanodine receptor antagonist) in a dose-dependent manner. According to serial observation under a real-time videomicroscope, those antagonists also inhibited beating before and at the early stage of apoptosis. Thus, those

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protected adult cardiac myocytes from apoptosis induced by activation of β-adrenergic receptor. These findings suggest an important role of, not only an increase of $[Ca^{2+}]i$ through L-type Ca^{2+} channel or ryanodine receptor but also a decrease of it through SERCA, for initiating apoptosis; a fluctuation of $[Ca^{2+}]i$ may be inevitable for it, and imply an exquisite regulation of initiating apoptosis in adult cardiac myocytes by multiple Ca^{2+} regulatory proteins.

OJ-074

Inhibitory Effect of Natriuretic Peptides on Aldosterone Synthase Gene Expression in Cultured Neonatal Rat Cardiocytes

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Background: Previously thought to be synthesized solely in adrenal cortex, we have recently showed that aldosterone is produced and the expression of CYP11B2 mRNA was induced in the failing or hypertensive human ventricle. Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are cardiac hormones with a wide biological effect, including inhibition of renin and aldosterone synthesis in the adrenal gland. We hypothesized that natriuretic peptides reduce the expression of CYP11B2 mRNA produced in the heart as well as in the adrenal gland. **Methods and results:** To test this hypothesis, we examined whether endogenous or exogenous natriuretic peptides reduce the expression of CYP11B2 mRNA using real-time reverse transcription-polymerase chain reaction. By using HS 142-1, a functional guanylyl cyclase (GC)-A type receptor antagonist , we showed that angiotensin II (Ang II) pretreated with HS-142-1 increased CYP11B2 mRNA expression (1.62±0.12-fold, HS142-1 + Ang II 10-7M versus Ang II 10-7M alone, $p<0.0001$). The treatment with exogenous (10-6M) ANP and BNP reduced CYP11B2 mRNA expression (ANP, p=0.0042, BNP, P=0.0012). **Conclusions:** We showed that endogenous and exogenous natriuretic peptides reduced CYP11B2 mRNA expression in cultured neonatal rat cardiocytes. This may inhibit the cardiac renin-angiotensin-aldosterone system by suppressing the gene expression of CYP11B2 and restrains cardiac hypertrophy and fibrosis.

OJ-075

The Therapeutic Effect of Mitochondrial K_{ATP} Opener in Chronic Myocardial Ischemia in Rats

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Although mitochondrial KATP (mitKATP) opener attenuates acute ischemia-reperfusion (I-R) injury, it is not known whether it is also effective in chronic myocardial ischemia. To assess it, firstly, we administered vehicle, diazoxide (a mitKATP opener, n=8) or 5-hydroxydecanoate (5-HD, a mitKATP blocker, n=8) to rats with coronary stenosis (CS)(Circulation, 2002). Four weeks later, we assessed cardiac function by echocardiography. In the vehicle-group (n=32), LV end-diastolic (LVEDD) and end-systolic diameter (LVESD) increased compared to the sham (n=8)(7.6*±0.2 vs 6.5±0.2mm, 4.8*±0.3 vs 3.6±0.2mm, *$p<0.05$), LVEF decreased (72±4* vs 83±2%). Diazoxide did not modify, and 5-HD rather increased LVEDD and LVESD, and decreased LVEF compared to the vehicle (8.9±0.4*and 6.5±0.6*mm, and 61±6*%). Secondly, when the same doses to the first experiment were pretreated, myocardial infarct size (infarct area/risk area) by 30min-ischemia and 24hr-reperfusion (30I-24R) were attenuated (67±4; sham, 45±6; diazoxide, 64±8%; 5-HD). Thirdly, we performed 30I-24R in 7 rats 7 days after creating CS, and the infarct size (51±6*%) was lower than the sham. Thus, the dose of the mitKATP opener effective in acute I-R was not effective in attenuating CS-induced heart failure. These results suggest that in CS-induced chronic ischemia, mitKATP may be already opened to some degree possibly as an intrinsic protection, leading to hypo-responsiveness to diazoxide in CS-induced chronic ischemia.

OJ-076

Aldosterone Induces Angiotensin-Converting-Enzyme Gene Expression through Both Mineralcorticoid- and Glucocorticoid-Receptors in Cultured Neonatal Rat Cardiocytes

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The cardiac renin-angiotensin-aldosterone system (RAAS) is activated in heart failure in proportion to the severity. Aldosterone has been widely accepted as an unfavorable hormone in pathophysiology of heart failure; aldosterone provides excessive sodium retention, oxidative stress and cardiac fibrosis in heart failure. In cultured neonatal rat cardiocytes, we also reported that aldosterone induces angiotensin-converting-enzyme (ACE) gene expression, reinforcing a circular cascade of cardiac RAAS. However, the mediated receptor(s) of aldosterone to ACE gene expression has not been clearly demonstrated. We hypothesized that not only mineralcorticoid receptor (MR) but also glucocorticoid receptor (GR) would play a role for the signal transduction, and then planned this study. For detection and quantification of expression of ACE mRNA, we used RT-PCR in cultured neonatal rat cardiocytes. Exposing cardiocytes to aldosterone (10-5M) for 24 hour showed a significant increase in ACE mRNA expression (25.5± 5.8-fold vs. control, $p<0.01$). The effect of aldosterone (10-5M) to ACE mRNA expression was significantly but not completely inhibited by RU486 (10-5M), a specific GR antagonist (90% reduction, $p<0.01$); ACE mRNA expression still remained to be increased even in pretreatment by RU486 (1.91±1.0-fold vs. control, $p<0.01$). In conclusion, aldosterone up-regulates ACE mRNA expression via both MR and GR. This study suggests a possible relationship of aldosterone not only to MR but also to GR in heart failure.

OJ-077

Possible Cardioprotective Effect of Dehydroepiandrosterone Produced in the Human Heart

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Background: Recently extra-adrenal synthesis of aldosterone has been demonstrated in the human heart. In this study, we examined whether dehydroepiandrosterone(DHEA) or cortisol is produced in the human heart and their significance. **Methods and Results:** Samples of left ventricular tissue were obtained at autopsy from seven patients free of cardiovascular disease. Using RT-PCR, the expression of CYP11A, 3β-HSD2, CYP21 and CYP17, required to produce DHEA and cortisol, were detected in these samples. By measuring the plasma DHEA and cortisol levels at the coronary sinuses and aortic roots of subjects without cardiovascular disease during cardiac catheterization, we found that DHEA levels were significantly higher at the coronary sinus than at the aortic root. By contrast, there was no significant difference in the cortisol levels in the two regions. In order to examine the significance of DHEA, we measured the gene expression of B-type natriuretic peptide (BNP), a marker of cardiac hypertrophy, using a neonatal rat cardiocyte culture system. We found that DHEA (10^{-8} and 10^{-5} mol/L) significantly reduced upregulation of BNP levels induced by 10^{-7} mol/L endothelin-1 (P=0.001 and P=0.0001 respectively, compared with the levels stimulated by endothelin-1 alone). **Conclusion:** We demonstrated the production of CYP17and DHEA but not that of CYP11B1 and cortisol in the human heart. We postulate that DHEA exerts a cardio-protective action by its anti-hypertrophic effects.

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