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Dynamic Changes of Cardiac Biomarkers in Non-ST-elevation Myocardial Infarction

MARYAM NABATI,[1] BAHAREH GOLESTANI,[2] JAMSHID YAZDANI,[3] MOZHDEH DABIRIAN,[1] HOMA PARSAEE[4]

From [1]Department of Cardiology, Faculty of Medicine, Cardiovascular Research Center, Mazandaran University of Medical Sciences, Sari; [2]Student Research Committee, Faculty of Medicine, Cardiovascular Research Center, Mazandaran University of Medical Sciences, Sari; [3]Department of Biostatics, Faculty of Health, Mazandaran University of Medical Sciences, Sari; [4]Student Research Committee, Faculty of Medicine, Cardiovascular Research Center, Iran University of Medical Sciences, Tehran, Iran

NABATI ET AL: ***Dynamic Changes of Cardiac Biomarkers in Non-ST-elevation Myocardial Infarction:*** ***Objective:*** Creatine kinase-myocardial band (CK-MB) and troponin-I are the most specific and accurate indicators of myocardial infarction among different cardiac biomarkers. However, few studies have examined the correlation between temporal changes of these biomarkers and high risk echocardiographic and angiographic variables. The aim of our study was to assess the relationship between these variables. ***Methods:*** Our study was a prospective study of 113 patients with a diagnosis of non-ST-elevation myocardial infarction (NSTEMI) who were admitted within the first hours of the onset of chest pain. Troponin-I and CK-MB were measured serially at the time of hospital admission, at 6-9 hours and again at 12-24 hours. All patients underwent transthoracic echocardiography and coronary angiography and left ventricular ejection fraction (LVEF), mitral regurgitation and severity of coronary artery disease were determined. ***Results:*** Troponin-I level within 6-9 hours after admission was significantly associated with significant coronary artery disease among different variables (P-value=0.032, odds ratio=1.11, 95% confidence interval [1.01-1.22]). Also, patients younger than 65 years of age had higher levels of troponin-I within 6-9 and 12-24 hours after admission (P value 0.07 and 0.027, respectively). On the other hand, patients with LVEF<35% and hypertensive patients had higher levels of CK-MB within 6-9 and 12-24 hours, respectively (P value 0.042 and 0.023). ***Conclusion:*** Temporal changes of troponin-I and CK-MB after NSTEMI can be an important indicator for risk stratifying of these patients. *(J HK Coll Cardiol 2018;26:82-90)*

CK-MB, Myocardial infarction, Non-ST-elevation MI, Revascularization, Troponin-I

摘要

目的：肌酸激酶同工酶（CK-MB）和心肌鈣蛋白-I是心肌梗塞中最具特異性和準確性的心臟生物標誌物。然而，少有研究檢查這些生物標誌物的時間性變化與高風險超聲心動圖及血管造影變數之間的相關性。我們研究的目的是評估這些變數之間的關係。**方法：**我們的研究是一項前瞻性研究，對像是113名胸痛發作後數小時內入院，被診斷爲非ST上升型心肌梗塞（NSTEMI）患者，在入院後6-9小時及12-24小時持續測量患者的心肌鈣蛋白-I及肌酸激酶同工

Address for reprints: Ass. Prof. Maryam Nabati
Fellowship of Echocardiography, Artesh Boulevard, Fatemeh Zahra Teaching Hospital, Department of Cardiology, Faculty of Medicine, Cardiovascular Research Center, Mazandaran University of Medical Sciences, Sari, Iran

Email: Dr.mr.nabati@gmail.com

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酶水平。所有患者均接受經胸壁超聲心動圖、冠狀動脈造影及左心室射血分數（LVEF），確定二尖瓣關閉不全及嚴重冠狀動脈疾病。**結果：**入院後6 - 9 小時內心肌鈣蛋白- I 水平與冠狀動脈疾病之間的不同變量顯著相關（P 值=0.032，比值比=1.11，95%置信區間 [1.01-1.22]）。而且，年齡小於65歲的患者在入院後6-9小時及12-24小時內心肌鈣蛋白-I水平較高（P值分別爲0.07和0.027）。另一方面，左心室射血分數（LVEF）<35%患者及高血壓患者在6-9小時和12-24小時內的肌酸激酶同工酶出現較高水平（P值0.042和0.023）。**結論：**非ST上升型心肌梗塞後心肌鈣蛋白-I和肌酸激酶同工酶的時間變化可作爲這些患者風險分層的重要指標。

關鍵詞：肌酸激酶同工酶、心肌梗塞、非ST上升型心肌梗塞、重建血運、心肌鈣蛋白-I

Introduction

Cardiac markers and enzymes such as the cardiac troponin and creatine kinase-myocardial band (CK-MB) are central to the diagnosis of acute myocardial infarction (AMI). There is an association between magnitude of cardiac marker elevation and extent of myocardial necrosis and risk of adverse outcome in both ST-elevation myocardial infarction (STEMI) and non ST-elevation myocardial infarction (NSTEMI).[1] Even small rise in serum troponin concentration indicate cardiac muscle cell necrosis.[2] A dynamic changes in troponin concentration at 2-6 hours after admission should improve the diagnostic accuracy for AMI.[3] Few studies evaluated relations between cardiac biomarker changes along the time and other prognostic parameters such as echocardiographic variables and significant obstructive coronary artery disease in patients with NSTEMI. The aim of our study was to assess the correlation between changes in plasma concentrations of cardiac biomarkers along the time and these variables.

Methodology

Our study was a historical cohort study of 113 consecutive patients with a diagnosis of NSTEMI who were admitted to the coronary care unit of our hospital within the first hours of the onset of chest pain between 2017 and 2018. We obtained written informed consent from all participants and conducted the study according to the guidelines of the Helsinki Declaration. NSTEMI was diagnosed according to the guidelines of the European Society of Cardiology and was defined by the presence of angina pain and a dynamic elevation of cardiac biomarkers and the absence of ST-segment elevation ≥0.1 mv in leads other than aVR or V1 or left bundle branch block. Upper limit for troponin-I has been considered as <0.1 ng/ml.[4] Therefore, patients with troponin-I ≥0.1 ng/ml were considered as having myocardial infarction. According to the guidelines of the American College of Cardiology, troponin-I and CK-MB were measured serially over the time and blood samples were taken at the time of hospital admission, at 6-9 hours and again at 12-24 hours.[5] Patients with ST-segment elevation ≥0.1 mv in leads other than aVR or V1, left bundle branch block, preexcitation, cardiomyopathies, known valvular or congenital heart diseases and myocarditis were excluded from the study. We obtained demographic data from patients' medical records and a face-to-face questionnaire. Data were collected by one physician blinded to the study. Family history of coronary artery disease (CAD) was defined as having a first degree relative ≥55 years for men and ≥65 years for women with a history of CAD.[6] Hypertension (HTN) was defined as systolic blood pressure (BP) ≥140 mmHg, diastolic BP ≥90 mmHg or need for antihypertensive therapy.[7] Diabetes mellitus (DM) was defined according to the criteria of the American Diabetes Association or use of insulin or oral anti-diabetic drugs.[8] Patients with hyperlipidemia were defined as individuals with total cholesterol levels of ≥5.5 mmol/L, HDL-cholesterol levels of <1.0 mmol/L in men, or <1.1 mmol/L in women.[9]

Echocardiography

Transthoracic echocardiography was performed within 24 hours after admission by a Vivid S5 (GE Healthcare, Wauwatosa, WI, USA), 1-3 MHz transducer. The left ventricular ejection fraction (LVEF) was determined by a modified Simpson's technique that was defined as the left ventricular end diastolic volume

(LVEDV) minus the left ventricular end systolic volume (LVESV) divided by the LVEDV from apical four- and two-chamber views. Furthermore, mitral regurgitation severity was determined according to the guidelines of American society of echocardiography and was graded as mild, moderate and severe.[10]

Coronary Angiography

All patients underwent coronary angiography by a cardiac angiography system (Siemens AG, Medical Solutions, Erlangen, Germany) within 48-72 hours after admission. One experienced cardiologist blinded to the Patients' information, reviewed and reported all angiograms. Significant CAD was defined as 70% or greater coronary luminal stenosis of one or more of major epicardial arteries or 50% or greater luminal stenosis of left main coronary artery.[11] Significant CAD was determined quantitatively and was considered when one of the following conditions were presented: ≥50 stenosis of left main, significant (>70% diameter) stenosis in three major coronary arteries (with or without involvement of the proximal left anterior descending artery) or in the proximal left anterior descending artery plus one other major coronary artery or significant CAD in at least one major epicardial artery and having high-risk criteria on stress testing, abnormal intracoronary hemodynamic evaluation, or >20% perfusion defect by myocardial perfusion stress imaging or target vessels supplying a large area of viable myocardium.[12] The operators were blinded to the serial troponin-I results at the time of coronary angiography.

Statistical Analysis

Quantitative variables were expressed as median values and categorical variables were reported as frequency and percentage. The normality was determined for troponin-I and CK-MB using the Shapiro-Wilk test that showed these variables were not normally distributed. Therefore, the Mann-Whitney U test was used, and the data were reported as median values (25th and 75th percentiles). Also, Spearman's correlation was used to assess correlations between cardiac biomarkers and LVEF. A logistic regression model was used to determine confounding variables. A P Value <0.05 was considered statistically significant. All statistical analysis were done by SPSS/PASW (Predictive Analytics SoftWare) Statistics 18 (SPSS Inc., Chicago, IL, USA). Sample size was based on previous studies and following statistical formula:[13]

$$n=\frac{(z_{\frac{\alpha}{2}}+z_{\beta})^2}{\omega^2}+3=113,\omega=\ln(\frac{1+r}{1-r})=0.3\quad\alpha=0.05\quad\beta=0.1,r=0.3$$

Result

We included 113 patients who had been admitted to the hospital with NSTEMI between 2017 and 2018. The mean age was 60.81±9.85 years and mean body mass index was 26.65±3.41 kg/m^2. Sixty patients (52.2%) were male, 11 patients (9.6%) had prior coronary artery bypass graft and 2 (1.7%) had prior percutaneous coronary intervention. Among these patients, the most frequent CAD risk factor was HTN (56.5%) that was followed by DM (40.9%), HLP (39.1%) and smoking (24.3%). Cardiac troponin-I level at the time of admission was 2.80 [2.02-3.90] ng/ml, within 6-9 hours was 2.43 [1.99-3.73] ng/ml and 12-24 hours was 2.45 [2.05-3.60] ng/ml. Average CK-MB at the time of admission was 26 [23.33-28.62] ng/ml, within 6-9 hour was 26.28 [23.23-29.20] ng/ml and 12-24 hours was 22.75 [20.18-28.43] ng/ml. Correlation between serial levels of cardiac biomarkers and echocardiographic and angiographic variables of the study population are shown in Tables 1 & 2. Patients younger than 65 years of age had higher levels of troponin-I within 6-9 and 12-24 hours after admission compared with patients 65 years of age and older (P value 0.07 and 0.027, respectively). Also, there was significant correlation between troponin-I levels at the admission time and within 6-9 hours after admission with significant obstructive coronary artery disease (P value 0.03 and 0.012, respectively). On the other hand, we found that patients with LVEF <35% had higher CK-MB levels within 6-9 hours after admission compared with those with LVEF ≥35% (P value 0.042). Also, hypertensive patients had higher levels of CK-MB within 12-24 hours after admission (P value 0.023). Also,

Table 1. Correlation between serial levels of troponin-I with demographic, echocardiographic and angiographic variables of the study population

		Troponin-I (The first time) ng/ml	P value	Troponin-I (The second time) ng/ml	P value	Troponin-I (The third time) ng/ml	P value
Age (years) No. (percent)	Less than 65: 78 (69%)	3.24 [2.22-4.50]	0.1	3.15 [2.17-4.34]	0.07	2.90 [2.23-4.10]	0.027
	More than 65: 35 (31%)	1.89 [0.84-3.22]		1.90 [1.38-3.15]		1.98 [1.44-3.30]	
Sex No. (percent)	Male 60 (53.1)	2.23 [1.20-3.70]	0.655	2.17 [1.55-3.90]	0.477	2.19 [1.53-3.67]	0.689
	Female 53 (46.9)	3.25 [1.95-4.75]		2.80 [2.10-4.03]		2.55 [2.02-4.17]	
DM No. (percent)	No: 66 (58.4%)	3.97 [2.10-5.16]	0.140	3.55 [2.17-5.00]	0.106	3.17 [2.22-4.33]	0.131
	Yes: 47 (41.6%)	2.22 [0.89-3.27]		2.12 [1.36-3.27]		2.18 [1.16-3.44]	
HLP No. (percent)	No: 68 (60.2%)	3.90 [1.40-6.30]	0.212	3.40 [2.22-5.65]	0.223	2.55 [1.94-4.94]	0.265
	Yes: 45 (39.8%)	2.27 [1.59-3.32]		2.14 [1.58-3.33]		2.43 [1.90-3.49]	
HTN No. (percent)	No: 48 (42.5%)	2.93 [1.87-4.10]	0.644	2.37 [1.90-3.98]	0.621	2.54 [2.03-4.20]	0.305
	Yes: 65 (57.5%)	2.40 [1.37-4.37]		2.55 [1.60-4.00]		2.33 [1.50-3.58]	
Smoking No. (percent)	No: 85 (73.9)	2.43 [1.47-3.70]	0.159	2.32 [1.73-3.40]	0.134	2.38 [1.86-3.58]	0.142
	Yes: 28 (24.3)	3.40 [2.11-6.33]		3.40 [1.80-5.99]		3.03 [2.14-5.22]	
LVEF No. (percent)	Less than 35%: 57 (50.5%)	3.10 [2.16-7.90]	0.204	3.15 [2.27-6.05]	0.139	2.40 [2.05-5.50]	0.317
	More than 35%: 56 (49.5%)	2.50 [1.38-3.80]		2.26 [1.65-3.67]		2.49 [1.90-3.80]	
MR No. (percent)	No or mild: 77 (68.1%)	2.76 [2.02-3.96]	0.980	2.37 [1.88-3.78]	0.556	2.50 [2.08-3.90]	0.970
	More than mild: 36 (31.9%)	2.70 [1.05-5.76]		2.85 [1.64-5.90]		2.35 [1.54-5.20]	
Significant CAD No. (percent)	No: 60 (53.1%)	1.78 [0.65-2.97]	0.03	1.90 [1.50-2.52]	0.012	2.19 [1.61-3.20]	0.110
	Yes: 53 (46.9%)	3.50 [2.60-5.70]		3.50 [2.40-5.90]		3.58 [2.10-4.44]	

CAD: Coronary artery disease; LVEF: Left ventricular systolic function; MR: Mitral regurgitation; DM: Diabetes mellitus; HTN: Hypertension; HLP: Hyperlipidemia; troponin-I (The first time): Level of troponin-I at the time of admission, troponin-I (The second time): Level of troponin-I within 6-9 hours after admission; troponin-I (The third time): Level of troponin-I within 12-24 hours after admission; Continuous variables (troponin and CK-MB) are expressed as median values (25th and 75th percentiles) and dichotomous variables (rows) are expressed by number (percent)

Table 2. Correlation between serial levels of CK-MB with demographic, echocardiographic and angiographic variables of the study population

		CK-MB (The first time) ng/ml	P value	CK-MB (The second time) ng/ml	P value	CK-MB (The third time) ng/ml	P value
Age (years) No. (percent)	Less than 65: 78 (69%)	26.20 [23.86-29.20]	0.965	25.86 [22.14-29]	0.462	21.43 [19.75-28.11]	0.213
	More than 65: 35 (31%)	24.50 [18.75-33.40]		29.00 [17.00-33.00]		28.67 [14.00-35.00]	
Sex No. (percent)	Male 60 (53.1)	27.17 [22.67-29.71]	0.908	26.40 [23.00-30.33]	0.865	22.00 [19.50-29.43]	0.977
	Female 53 (46.9)	24.50 [22.50-29.66]		26.00 [20.40-30.25]		24.00 [18.57-29.40]	
DM No. (percent)	No: 66 (58.4%)	26.80 [22.80-30.25]	0.385	29.28 [24.00-31.33]	0.134	28.71 [21.50-31.00]	0.076
	Yes: 47 (41.6%)	25.67 [21.40-29.00]		24.71 [19.50-28.11]		20.78 [17.40-26.19]	
HLP No. (percent)	No: 68 (60.2%)	27.00 [20.67-32.33]	0.538	28.25 [20.33-31.99]	0.519	21.75 [18.00-28.66]	0.907
	Yes: 45 (39.8%)	25.67 [22.91-28.50]		25.50 [21.00-29.28]		23.50 [19.75-29.73]	
HTN No. (percent)	No: 48 (42.5%)	26.00 [23.00-30.33]	0.306	28.57 [23.6031.60]	0.077	28.67 [20.83-32.39]	0.023
	Yes: 65 (57.5%)	29.00 [21.33-29.20]		24.50 [20.13-28.43]		20.57 [17.17-25.00]	
Smoking No. (percent)	No: 85 (73.9)	25.14 [22.60-28.60]	0.292	25.25 [21.30-29.18]	0.126	23.00 [19.83-29.00]	0.417
	Yes: 28 (24.3)	28.25 [23.01-31]		28.67 [22.60-34]		23.00 [18.00-30.19]	
LVEF No. (percent)	Less than 35%: 57 (50.5%)	30.33 [20.00-45.19]	0.198	32.00 [22.80-48.00]	0.042	29.00 [19.40-44.31]	0.098
	More than 35%: 56 (49.5%)	25.75 [23.00-28.33]		25.28 [21.00-28.40]		21.83 [19.43-28.12]	
MR No. (percent)	No or mild: 77 (68.1%)	26.25 [22.63-29.75]	0.836	27.50 [23.00-30.14]	0.546	26.50 [20.50-30.67]	0.290
	More than mild: 36 (31.9%)	25.75 [21.40-29.20]		25.33 [20.33-29.67]		20.50 [17.33-27.57]	
Significant CAD No. (percent)	No: 60 (53.1%)	25.71 [22.00-29.00]	0.486	26.50 [22.29-29.62]	0.695	24.00 [19.01-28.75]	0.713
	Yes: 53 (46.9%)	26.67 [22.83-31.00]		26.00 [20.63-31.20]		21.33 [19.14-31.00]	

CAD: Coronary artery disease; LVEF: Left ventricular systolic function; MR: Mitral regurgitation; DM: Diabetes mellitus; HTN: Hypertension; HLP: Hyperlipidemia; CK-MB (The first time): Level of CK-MB at the time of admission, CK-MB (The second time): Level of CK-MB within 6-9 hours after admission; CK-MB (The third time): Level of CK-MB within 12-24 hours after admission; Continuous variables (troponin and CK-MB) are expressed as median values (25th and 75th percentiles) and dichotomous variables (rows) are expressed by numbers (percent)

Table 3. Correlation between cardiac biomarkers and left ventricular systolic function (LVEF)

			LVEF	CK-MB (The first time)	CK-MB (The second time)	CK-MB (The third time)	Troponin-I (The first time) ng/ml	Troponin-I (The second time) ng/ml	Troponin-I (The third time) ng/ml
Spearman's rho	LVEF	Correlation Coefficient	1.000	-0.167	-0.248**	-0.215*	-0.050	-0.052	-0.048
		Sig. (2-tailed)	–	0.077	0.008	0.022	0.604	0.584	0.613
		N	113	113	113	113	112	113	113
	CK-MB (The first time)	Correlation Coefficient	-0.167	1.000	0.908**	0.841**	0.439**	0.425**	0.405**
		Sig. (2-tailed)	0.077	–	0.000	0.000	0.000	0.000	0.000
		N	113	113	113	113	112	113	113
	CK-MB (The second time)	Correlation Coefficient	-0.248**	0.908**	1.000	0.912**	0.392**	0.395**	0.442**
		Sig. (2-tailed)	0.008	0.000	–	0.000	0.000	0.000	0.000
		N	113	113	113	113	112	113	113
	CK-MB (The third time)	Correlation Coefficient	-0.215*	0.841**	0.912**	1.000	0.308**	0.325**	0.403**
		Sig. (2-tailed)	0.022	0.000	0.000	–	0.001	0.000	0.000
		N	113	113	113	113	112	113	113
	Troponin-I (The first time) ng/ml	Correlation Coefficient	-0.050	0.439**	0.392**	0.308**	1.000	0.947**	0.891**
		Sig. (2-tailed)	0.604	0.000	0.000	0.001	–	0.000	0.000
		N	112	112	112	112	112	112	112
	Troponin-I (The second time) ng/ml	Correlation Coefficient	-0.052	0.425**	0.395**	0.325**	0.947**	1.000	0.913**
		Sig. (2-tailed)	0.584	0.000	0.000	0.000	0.000	–	0.000
		N	113	113	113	113	112	113	113
	Troponin-I (The third time) ng/ml	Correlation Coefficient	-0.048	0.405**	0.442**	0.403**	0.891**	0.913**	1.000
		Sig. (2-tailed)	0.613	0.000	0.000	0.000	0.000	0.000	–
		N	113	113	113	113	112	113	113

*Correlation is significant at the 0.05 level (2-tailed); **Correlation is significant at the 0.01 level (2-tailed)

LVEF: left ventricular systolic function; troponin-I (The first time): Level of troponin-I at the time of admission, troponin-I (The second time): Level of troponin-I within 6-9 hours after admission; troponin-I (The third time): Level of troponin-I within 12-24 hours after admission; CK-MB (The first time): Level of CK-MB at the time of admission, CK-MB (The second time): Level of CK-MB within 6-9 hours after admission; CK-MB (The third time): Level of CK-MB within 12-24 hours after admission

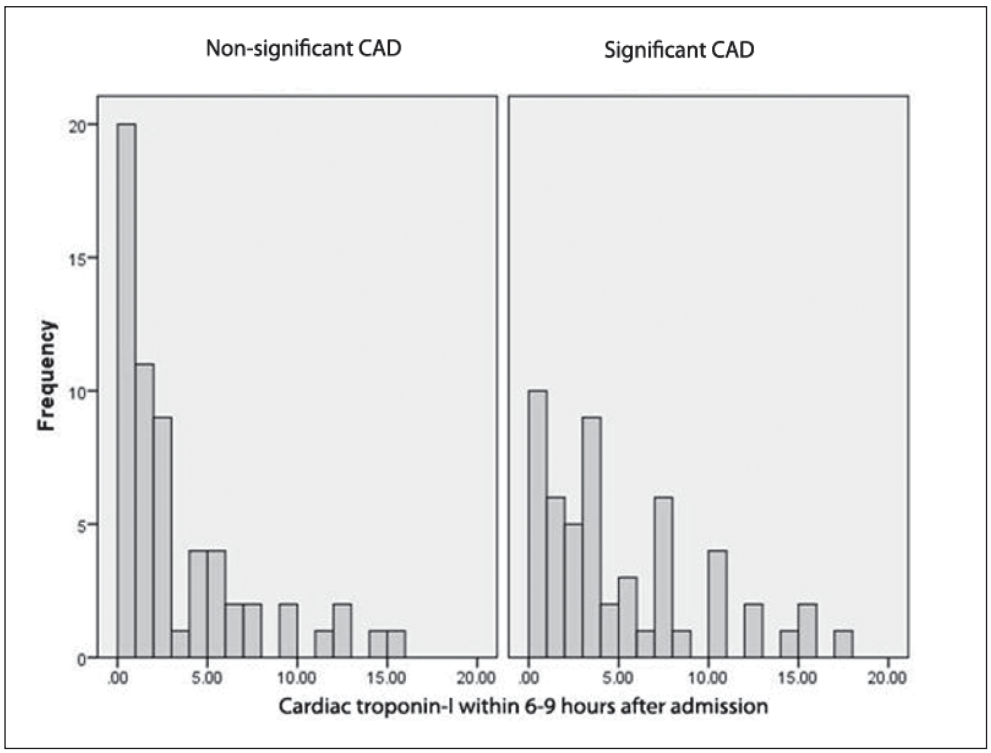

Figure 1. *Correlation between levels of cardiac troponin-I within 6-9 hours after admission and involving at least one major epicardial artery (P value 0.036).*

Table 4. Predictors of having significant CAD

Variables in the equation									
		B	**S.E.**	**Wald**	**df**	**Sig.**	**Exp(B)**	**95% C.I. for EXP(B)**	
								Lower	**Upper**
Step 1[a]	Sex	0.293	0.409	0.511	1	0.475	1.340	0.601	2.989
	HTN	0.323	0.403	0.645	1	0.422	1.382	0.628	3.043
	DLP	0.109	0.409	0.071	1	0.790	1.115	0.500	2.484
	DM	0.228	0.414	0.302	1	0.583	1.256	0.557	2.828
	ct1nd	-0.093	0.146	0.0406	1	0.524	0.911	0.685	1.213
	ct2nd	0.105	0.049	4.585	1	0.032	1.111	1.009	1.223
	LVEF	-0.114	0.534	0.046	1	0.830	0.892	0.313	2.539
	Constant	-1.764	1.640	1.158	1	0.282	0.171		

DM: Diabetes mellitus; HTN: Hypertension; HLP: Hyperlipidemia; ct1nd: Level of troponin-I at the admission time; ct2nd: Level of troponin-I within 6-9 hours after admission; LVEF: Left ventricular ejection fraction

Spearman's correlation showed levels of CK-MB within 6-9 and 12-24 hours after admission were inversely correlated with LVEF (P value 0.008 and 0.022, respectively; Table 3). We conducted a logistic regression analysis to determine whether cardiac Troponin-I is an independent predictor of significant coronary artery disease. Troponin-I level within 6-9 hours after admission was significantly associated with significant coronary artery disease among different variables (Table 4).

Discussion

Our study showed that patients with higher level of cardiac troponin-I at the time of admission and within 6-9 hours were more likely to have significant involvement of at least one major epicardial coronary artery. Also, CK-MB levels within 6-9 and 12-24 hours after admission were inversely correlated with LVEF after AMI. On the other hand, Patients younger than 65 years of age had higher levels of troponin-I within 6-9 and 12-24 hours and hypertensive patients had higher levels of CK-MB within 12-24 hours. The increased values for cardiac troponin-I and CK-MB are defined as the values that exceed the 99th percentile of reference values. Cardiac troponins are the preferred cardiac biomarkers for myocardial damage. This is due to their high sensitivity and specificity that can detect even micro infarcts. On the other hand, CK-MB appears in the blood more rapidly and has a greater clinical specificity for irreversible injuries. Blood samples are recommended to be obtained at the time of admission, 6-9 hours and 12-24 hours after admission.[5] Dynamic changes in cardiac enzyme concentration can distinguish between structural heart disease and myocardial ischemia. An abnormal but stable elevation of cardiac troponin in serial sampling is more commonly due to structural heart disease. However, significant dynamic pattern over 2 to 6 hours is strongly suggestive of AMI.[3] Elevated cardiac troponin can be detectable within 2 to 4 hours. The sensitivity reaches its highest level at 6 hours or more after onset of infarction.[14] It may not be detectable for up to 3 hours after onset of injury.[15] In addition to its diagnostic value, elevated cardiac troponin is associated with adverse angiographic characteristics and risk of death.[16,17] This is consistent with our study that cardiac troponin-I level at 6 to 9 hours was independently associated with significant involvement of at least one major epicardial coronary artery. Increase of CK-MB occurs within 3 to 4 hours. However, it has a rapid decline that returns to normal range after 48 to 72 hours.[15] Elevated CK-MB level correlates with a lower than normal LVEF, higher incidence of ventricular tachyarrhythmia and a poor prognosis.[18] The LVEF is one of the most important predictors of mortality in patients with established CAD, and LVEF <35% is associated with significantly increased risk for arrhythmic mortality.[19,20] In our study, elevated CK-MB levels at 6 to 9 hours was significantly associated with reduced LVEF. Chronic HTN is the most common risk factor and a major predictor of short and long term adverse outcome among patients with NSTEMI.[21] In our study, hypertensive patients had higher levels of CK-MB at 12 to 24 hours, suggesting that irreversible myocardial necrosis can contribute to adverse outcome of these patients. Furthermore, troponin-I within 6-9 and 12-24 hours was significantly higher in our younger patients that can be due to statistical chance or a lower development of collateral circulation.[22]

Conclusion

Dynamic changes of cardiac biomarkers within 24 hours is helpful for stratifying of patients with acute coronary syndrome in spite of not being a surrogate for clinical assessment e.g. TIMI risk score or GRACE score.

Limitation

A limitation of our study is small sample size. Also, we did not follow the patients to assess the adverse outcome and novel markers of myocardial ischemia such as cystatin C and soluble CD-40 ligand and another imaging modalities such as cardiac magnetic resonance

imaging were not included in our study. Furthermore, the absence of prospective follow up for clinical events (e.g. major adverse cardiac events) would limit the prognostic value of serial troponin.

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Coronary Arcade Visualized in 256 Sliced Multi-Detector Cardiac Computed Tomography

THOMAS ANGER,[1] PATRICIA PABST,[1] SVENJA LINNEMANN,[1] ECKHARDT SCHOLTZ,[2] CONSTANTIN MÄNZ,[2] MARTIN OBERHOFF[1]

From [1]Department of Internal Medicine; [2]Department of Radiology, Klinikum Calw-Nagold, Germany

THOMAS ANGER ET AL: ***Coronary Arcade Visualized in 256 Sliced Multi-Detector Cardiac Computed Tomography:*** A 52-year-old male patient presented to our Department of Internal Medicine with severe sustained chest pain for at least 18 hours, for ruling out acute myocardial infarction. We performed a cardiac 256 multi-sliced computed tomography to document a coronary arcade as the coronary abnormality. *(J HK Coll Cardiol 2018;26: 90-93)*

Arcade, Coronary artery disease, Multi-sliced cardiac-ct

摘要

爲了排除急性心肌梗塞，一名至少持續嚴重胸痛18小時的52歲男病人被送到內科，我們進行了256切面多斷層心臟電腦掃描，證明爲因冠狀動脈異常而致冠狀動脈拱廊。

關鍵詞：冠狀拱廊、冠狀動脈疾病、多斷層心臟電腦掃描

Case Report

A 52-year-old male patient presented to our Department of Internal Medicine with severe sustained chest pain for at least 18 hours, for ruling out acute myocardial infarction. He had no definite cardiovascular risks, nor any history of any disease. He is in healthy conditions except the acute pain symptom in his upper chest spreading to the left arm / shoulder regions. Drugs or any oral medications were denied. There were no allergies nor any known intolerances.

We performed a 12-channel electrocardiogram (ECG) and blood tests, to demonstrate normal ECG tracing and normal levels for troponin T and creatinin kinase initially, as well as after 1h, in respect to rule out acute myocardial infarction. Further, we ruled out any structural heart disease using transthoracic echocardiography. We decided to perform a cardiac CT and send the patient to the Department of Radiology in our Hospital, as he still had severe chest pain although his circulatory conditions were stable.

The Cardiac-CT scan was performed using a Philips Brilliance 256 MDCT iCT system (0,6 mm x 256 collimation). The patient's heart rate was optimized (50-60/min) with administration of metoprolol succinat.[1,2] Contrast-enhanced scans were performed during held-inspiration, after an intravenous infusion of 80 ml contrast medium Iomeprol 350 mgI/mL (Imeron 350, Bracco Imaging Deutschland GmbH, Germany), using a tracking bolus system to commence scanning.[3] A cardiac step and shoot protocol was performed to reduce X-ray intensity for the patient (Philips, Amsterdam, The Netherlands©), and retrospective data

Address for reprints: Dr. Thomas Anger
Department of Internal Medicine, Klinikum Calw-Nagold, Germany

Email: th.anger@arcor.de

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collection was used in 0.6 mm slice thickness to establish coronary artery status. In order to create different reconstructions: (i) a 65% RR interval was chosen regardless of heart rhythm,[4] (ii) a 3D model was reconstructed (Figure 1), (iii) a curved analysis for the coronary arteries (Figure 2), and (iv) a linearized maximum intensity projection for specific coronary arteries (Figure 3) were assessed for coronary analyses.

Focusing primarily on the coronary arteries,[5] we ruled out any coronary calcifications (Agatston Score 0, data not shown) and moreover, no further non-calcified plaque formations in all demonstrated coronary arteries (Figure 1). In contrast, we visualized an accessory vessel with origin as the side branch of the right coronary artery connecting to the circumflex artery (Figures 2 and 3). To confirm this observation, we repeated the diagnosis-finding by a different observer with the same result.

What we found was a coronary arcade, a non-physiological coronary vessel collateralizing the right coronary artery to the circumflex artery.

Intercoronary communication or coronary arcade is a rare congenital coronary anomaly. The functional importance of this variant is not clear, but it may cause myocardial ischemia by coronary steal, or function as a natural bypass**.** In which case it may play a protective role in the myocardium if significant coronary atherosclerosis will develop.[6] Little information is known about coronary arcades and only few case reports have been reported.

In general, coronary arcades are documented using invasive coronary catheter examinations in the Cath.-Lab focusing on patients with unstable symptoms (angina pectoris[6]). Additionally, coronary fistula, or severe coronary artery disease are also documented by coronary angiography, both being ruled out here non-invasively by multi-sliced computed tomography.

Coronary artery fistulae are primarily congenital bypass abnormalities connecting coronary arteries with the pulmonary artery[7] or with the right ventricle,[8] will be commonly visualized by invasive angiography or by non-invasive cardiac computed tomography.[9] Coronary artery fistula may be late complications of coronary artery perforation during primary percutaneous coronary intervention.[10] Coronary artery fistula may also connect

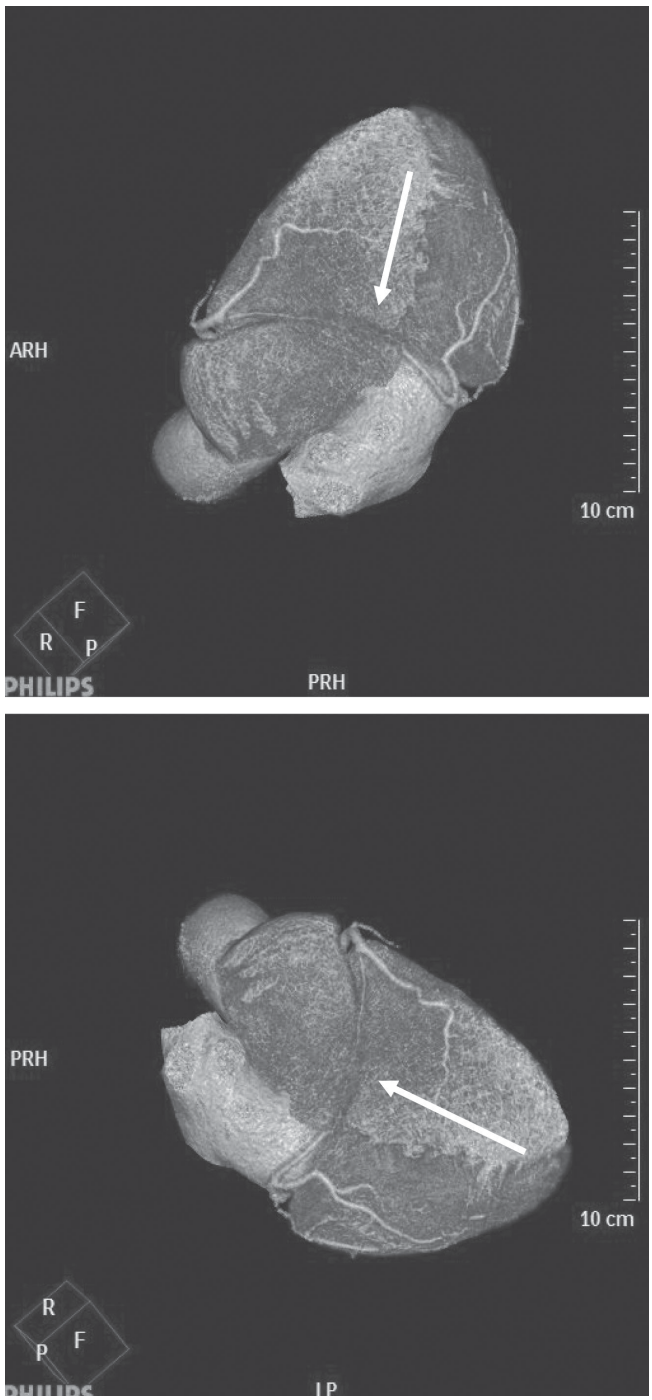

Figure 1. *Cardiac 3D Scans of the Coronary Abnormality: The Coronary Arcade. Demonstrated here the 3D scans of the accessory arteriosus vessel with origin as side branch from the right coronary artery connecting with approach to the circumflex artery as marked with arrows.*

to the coronary venous sinus.[11] The treatment of giant coronary fistula is the specific closure through different cardiac device approaches.[12,13] There are case reports cited offering co-existence of coronary artery disease with coronary artery fistula.[14]

Here, we are focusing on non-invasive cardiac computed tomography which indeed documented a congenital coronary arcade. Since there is no further therapeutic approach to follow, we decided not to attach a coronary specific angiography in the Cath.-Lab. The cardiac CT revealed the aetiology his symptoms.

Conclusion / Learning Objectives

Cardiac multi-sliced computed tomography documents coronary abnormalities as coronary arcades in patient with unstable angina pectoris. Unfortunately, on exploring the existing literature, no specific treatment options have been offered so far for these coronary abnormalities.

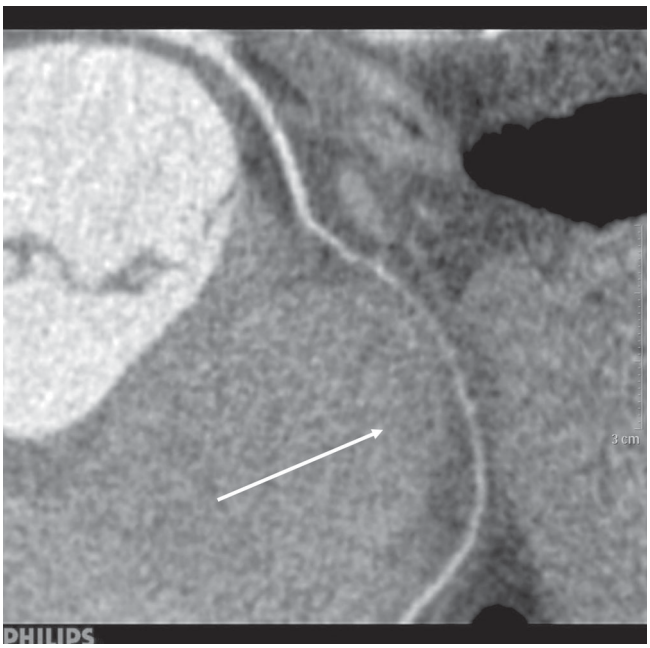

Figure 2. *Cardiac Curved Scans of the Coronary Arcade. Demonstrated here the curved scans of the accessory arteriosus vessel with origin as side branch from the right coronary artery and connecting with the circumflex artery as marked with the white arrow. No significant calcification or non-calcified plaque was demonstrated (Agatston Score 0).*

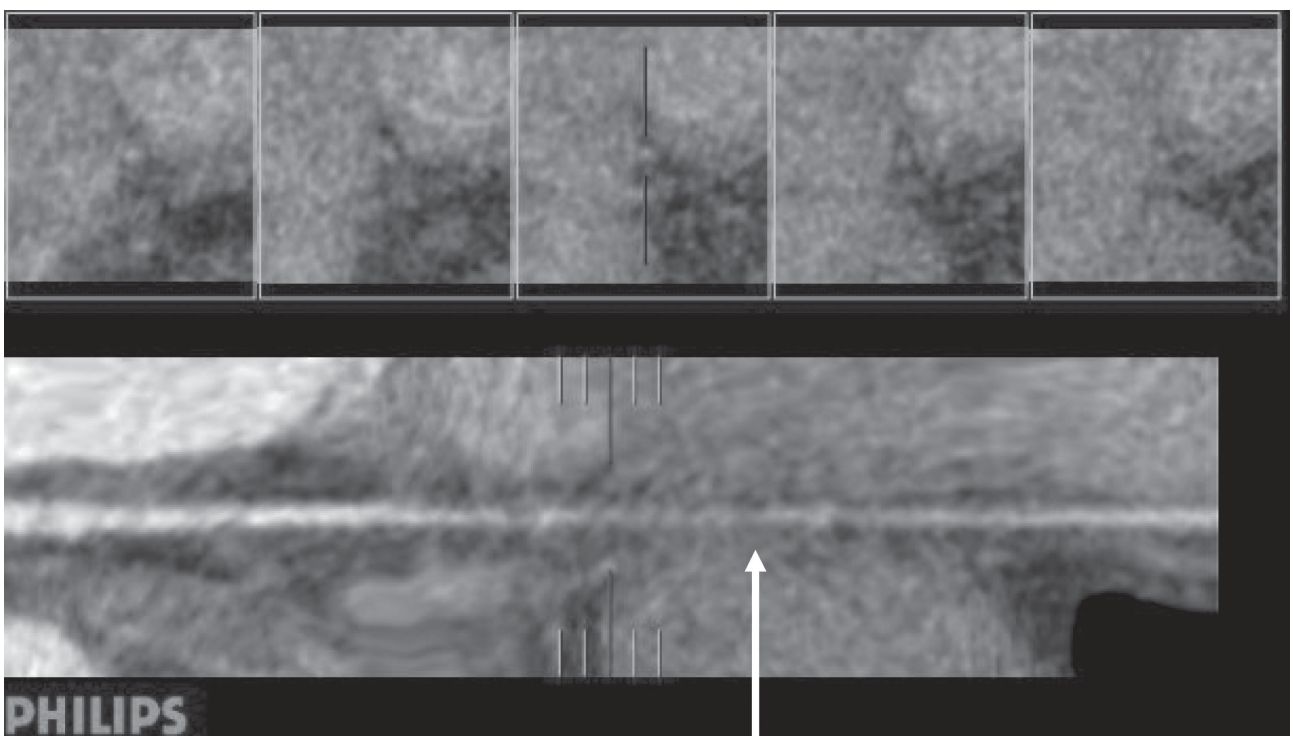

Figure 3. *Maximum Intensity Projection to the Coronary Arcade. Demonstrated here the scans reconstructed to the maximum intensity projection of the accessory arteriosus vessel as marked with the white arrow.*

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SCIENTIFIC PROGRAMME

10 NOVEMBER 2018 (SATURDAY)

0830 **Registration**

0900-1030 **Oral Presentations for Young Investigator Award (I)** ***(Sponsored by Sun Chieh Yeh Heart Foundation)*** **cum 7th APCCRC Abstract Presentation**
Chairpersons: Dr. Ching-Lung Cheung and Dr. Li-Wah Tam
Judges for Young Investigator Award:
Prof. Xiao-Qiang Yao, Dr. Heather J. Ballard and Dr. Susan Leung

1040-1115 Tea Break / Exhibition / Poster Presentation

1115-1245 **Oral Presentations for Young Investigator Award (II)**
(Sponsored by Sun Chieh Yeh Heart Foundation)
Chairpersons: Dr Judith Mak and Dr Xiao-Yu Tian
Judges for Young Investigator Award:
Prof. Xiao-Qiang Yao, Dr. Heather J. Ballard and Dr. Susan Leung

1245-1400 Lunch Break

1400-1445 **Opening Ceremony with 7th APCCRC**

1445-1530 **Invited Lectures**
Chairpersons: Prof. Bernard Cheung and Prof. Yu Huang
1. TRPM2 channels promote neointimal hyperplasia in vascular wall
Prof. Xiao-Qiang Yao, The Chinese University of Hong Kong, HKSAR
2. Crosstalk between bone and cardiovascular systems: implication in drug treatment
Dr. Ching-Lung Cheung, The University of Hong Kong, HKSAR

1530-1600 Tea Break / Exhibition / Poster Viewing

1600-1730 **Invited Lectures**
Chairpersons: Dr. Kelvin Yiu and Dr. Carmen Chan
1. Clinical experience in using ARNI in managing heart failure
Dr. Kelvin Yiu, The University of Hong Kong, HKSAR
2. Screening asymptomatic diabetics with non-invasive imaging
Dr. Ming-Yan Ng, The University of Hong Kong, HKSAR
3. Topic TBC
Speaker TBC

1730-1800 **Closing ceremony and Young Investigator Award Ceremony**
Dr. Kelvin Yiu, The University of Hong Kong, HKSAR

1800 **Annual General Meeting**

ABSTRACTS

Abstracts for Invited Lectures:

IL01.

TRPM2 CHANNELS PROMOTE NEOINTIMAL HYPERPLASIA IN VASCULAR WALL

X Yao, X Ru, QN Zhao, L Sun
The Chinese University of Hong Kong, Hong Kong

A hallmark of atherosclerosis is progressive intimal thickening (or neointimal hyperplasia), which leads to occlusive vascular diseases such as coronary heart disease and stroke. Over-production of reactive oxygen species (ROS) and alteration of Ca2+ signaling are among the key factors contributing to neointimal growth in atherosclerosis. In the present study, we investigated the role of TRPM2, a ROS-sensitive Ca2+ entry channel, in neointimal hyperplasia. We first established a vascular injury-induced atherosclerosis model in mice. Immunostaining showed numerous TRPM2-positive smooth muscle cells in neointimal regions. ROS were over-produced and PCNA-positive proliferating cells were numerous in the neointimal regions. The neointimal hyperplasia was substantially reduced in TRPM2 knockout mice compared with wild-type mice. In addition, we generated a rabbit anti-TRPM2 antibody, named TM2E3, that can inhibit TRPM2 activity. TM2E3 can effectively inhibit the activity of TRPM2 channels in patch clamp recording. Importantly, TM2E3 treatment caused a marked reduction in neointimal hyperplasia in a human model of vascular wall hyperplasia. We also explored the mechanism of TRPM2 involvement in atherosclerostic development. The results demonstrated that TRPM2 participates in several key steps of atherosclerotic development; 1) it promotes the proliferation and migration of vascular smooth muscle cells; 2) it enhanced autophagic and apoptotic cell death of vascular cells. Taken together, our data suggest a critical functional role of TRPM2 in the progression of neointimal hyperplasia and atherosclerosis. The study also highlights the possibility of targeting TRPM2 as a potential therapeutic option for the treatment of atherosclerosis.

Acknowledgment: This work was supported by grants from Hong Kong Research Grant Committee [AoE/M-05/12, 14118516]; Hong Kong ITF [ITS/096/18], and National Natural Science Foundation of China [31470912].

IL02.

CROSSTALK BETWEEN BONE AND CARDIOVASCULAR SYSTEMS: IMPLICATION IN DRUG TREATMENT

CL Cheung
Department of Pharmacology and Pharmacy, Centre for Genomic Sciences, The University of Hong Kong, Hong Kong

Emerging evidences have suggested a link between osteoporosis and cardiovascular diseases (CVD), such relationship could be contributed by the shared pathophysiology and common risk factors. Calcium-parathyroid hormone-vitamin D axis plays an important role in bone and mineral metabolism, multiple studies have indicated their involvements in both diseases. In addition to this axis, vitamin K also plays a role in bone mineralization, and it is also a target of the anticoagulant warfarin. Our recent study showed that, compared with dabigatran, warfarin use is associated with increased risk of fracture in patients with nonvalvular atrial fibrillation. In terms of treatment of osteoporosis, nitrogen-containing bisphosphonates (N-BP) is usually regarded as the first line medication. Pharmacological study of N-BP showed that N-BP possesses the anti-inflammatory and immune-modulatory property, therefore N-BP is potentially beneficial for cardiovascular events. Using a large propensity score matched population, we recently showed that N-BP use in hip fracture patient was associated with reduced cardiovascular events, including 48% reduction in myocardial infarction. Notably, a recent unpublished randomized controlled trial in 3000 osteopenic postmenopausal women has also demonstrated a similar effect (42% reduction) of N-BP in myocardial infarction. Notably, N-BP reduces bone resorption by targeting the mevalonate pathway, which is the same molecular pathway that statin targets. We therefore evaluated the role of LDL-cholesterol in bone metabolism and found that it is inverse and causally associated with bone mineral density, whereas statin use is associated with better bone mass (submitted for publication). In conclusion, there is a substantial crosstalk between bone and cardiovascular systems, thus special attention is required in the treatment of bone and cardiovascular diseases, as the use of drug may affect both systems.

IL03.

SCREENING ASYMPTOMATIC DIABETICS WITH NON-INVASIVE IMAGING

MY Ng[1,2]
[1]Department of Diagnostic Radiology, The University of Hong Kong, Hong Kong, [2]HKU-Shenzhen Hospital, China

Current American Diabetes Association guidelines (2015) currently does not recommend the use of widespread screening with non-invasive imaging despite cardiovascular complications being the main cause of death and morbidity in patients with diabetes. This talk goes through the research literature backing this statement. The talk will also go through knowledge gaps and possible future developments in identifying a suitable non-invasive imaging strategy to identify at risk patients.

ABSTRACTS

Abstracts for Oral Presentation:

OP01.

FACTORS ASSOCIATED WITH PERSISTENT SMOKING IN PATIENTS WITH ESTABLISHED CARDIOVASCULAR DISEASES (CVD) AND INDIVIDUALS AT HIGH RISK FOR CVD: POST-HOC ANALYSIS OF THE EUROACTION PLUS VARENICLINE STUDY

N Primaditta, C Jennings
Imperial College London, London, United Kingdom

Background: Intensive smoking cessation intervention in conjunction with a comprehensive preventive cardiology programme increases the rate of a successful quit attempt. However, the interaction of a multitude of other relevant factors surrounding care influences the attainment of abstinence at the end of treatment.
Objective: To examine the factors associated with persistent smoking among smokers within the intervention arm of the EUROACTION plus varenicline (EA+) trial.
Methods: A dataset consisted of 342 smokers (271 at high CVD risk and 71 with vascular disease) within the intervention arm of the EA+ trial was analysed using a post-hoc multivariate regression analyses. The primary outcome of the main trial was smoking abstinence as defined by a self-reported seven-day point prevalence abstinence (PPA), validated with a breath carbon monoxide (CO) measurement. Persistence of smoking as the outcome of the present study was compared with explanatory variables in a bivariate analysis using stepwise logistic regression to examine the association between them. Variables showing significant association in the analysis were subsequently included into the multivariate analysis.
Results: The result of the multiple logistic regression revealed that anxiety is positively associated with an unsuccessful quit attempt at 16-week follow-up, with an odds ratio (OR) of 1.07 [95% confidence interval (CI) 1.01-1.13, p=0.01], following a nurse-led, comprehensive, multifactorial preventive cardiology programme with the focus on intensive smoking cessation. In non-quitters, every one-point increase in anxiety score was associated with an increase of 7% chance of continuing to smoke.
Conclusion: The findings of this study highlighted the influence of psychosocial factors on smoking abstinence. Intensive smoking cessation emphasised within a preventive cardiology programme improved the likelihood of persistent smokers to stop smoking.

OP02.

EFFECTIVENESS OF PROCESS OPTIMIZING AND MOBILE APP MONITORING ON DOOR-TO-BALLOON TIME IN ST-ELEVATION MYOCARDIAL INFARCTION PATIENTS

JG Yang,[1] JJ Su,[2] G Zhou,[1] XF He[1]
[1]Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [2]The Nethersole School of Nursing, The Chinese University of Hong Kong, Hong Kong

Objective: To determine the impact of optimizing the primary percutaneous coronary intervention (pPCI) process and monitor the process by a mobile app for door-to-balloon time among ST-elevation myocardial infarction patients.
Methods: A quasi-experimental before-and-after study. Consecutive ST-elevation myocardial infarction patients who visited the hospital emergency department between January 2016 and December 2016 were included. An intervention program was designed that incorporated an expert panel root cause analysis, a patient transfer protocol, a pPCI education scheme, standard preoperative preparation guidelines, and time monitoring via a mobile app.
Results: Of the 180 patients examined, 22 were examined prior to the intervention; 55 immediately after the intervention, which was implemented to determine the short-term effect; and 103 at five months after the intervention was initiated. The D2B time was significantly shortened immediately after the intervention was implemented (108.26 [47.23] minutes) than before the intervention (162.56 [100.74] minutes) but was not as short as the D2B time at the end of the follow-up period (97.76 [44.02] minutes) ($p<0.001$). Achievement of D2B time within 90 min was 27.8% before intervention, 43.4% immediately after the intervention, and 48.5% during follow up ($p=0.26$). Before the intervention, two patients died before catheterization, while after the intervention, no patients died ($p<0.05$). A monthly time series analysis demonstrated a sustained improvement following the intervention.
Conclusion: The process-optimizing intervention and monitoring by a mobile app significantly shortened the D2B time and reduced mortality. The rate of achieving a D2B time within 90 minutes has improved although not statistically significant.

ABSTRACTS

Abstracts for Oral Presentation:

OP03.

CLINICAL PATHWAY IN HEART FAILURE EFFECTIVELY INCREASES THE UTILIZATION OF EVIDENCE BASED HEART FAILURE MEDICATIONS RESULTING IN BETTER PATIENT OUTCOME

YH Cheng, YH Chan, CW Wong, CS Lam
Pok Oi Hospital, Hong Kong

Background: The burden of congestive heart failure (CHF) in the modern society of Hong Kong is increasing annually. A local study in 1997 estimated the overall incidence rate per 1000 men and women was 5.7 and 4.8 respectively. Patients would benefit from a standardized guideline oriented inpatient hospital care. Clinical pathways for heart failure have been developed, but these models have not been evaluated in the local community setting. Here, we sought to assess the effectiveness of implementation of a clinical heart failure pathway by evaluating the use of heart failure medications, length of stay, rate of readmission in patients with congestive heart failure.
Methods: Heart failure pathway was implemented in Pok Oi Hospital since December 2015. We retrospectively studied a total of 185 patients (mean age 66.5 ±10.1) with diagnosis of congestive heart failure in a community hospital between January 2015 and December 2016. Patients were divided into two groups, 93 patients who were mainly managed by the general medical team and 92 patients who were recruited into the pathway, all reviewed by the cardiac team with suggested management. We conducted detailed reviews to determine and compare the use of evidence based heart failure medications, risk factors control status, length of stay and rate of readmission.
Results: There were significantly more heart failure medications prescribed including angiotensin converting enzyme inhibitor or angiotensin receptor blocker (ACEI / ARB) (59% vs 78%, $p<0.01$), betablocker (44% vs 68%, $p<0.01$), aldactone (8% vs 14%, $p<0.01$), digoxin (7% vs 9%, $p=0.03$) and warfarin (17% vs 24%, $p= 0.01$) after patients were recruited into the pathway. And lower rate of readmissions was observed after the launch of heart failure pathway with 22% vs 11% in 30-day readmission ($p=0.03$) and 45% vs 30% in 6-month readmission ($p=0.04$) for those not enrolled and enrolled respectively.
Conclusion: Use of heart failure pathway in the local hospital setting was associated with an increase in use of heart failure medications as well as reduction in heart failure readmission.

OP04.

EXERCISE TRAINING PROGRAM IN PATIENTS WITH NYHA III CLASS SYSTOLIC HEART FAILURE – PARALLEL COMPARISON TO THE EFFECTS OF RESYNCHRONIZATION THERAPY

E Smolis-Bak, T Chwyczko, I Kowalik, A Borowiec, A Maciag, H Szwed, R Dabrowski
Institute of Cardiology, Warsaw, Poland

Background: The aim of this study was to assess exercise capacity and echocardiographic parameters in patients with systolic heart failure (HFrEF) in NYHA III functional class, after cardiac resynchronization therapy (CRT) or cardioverter-defibrillator (ICD) implantation followed by 6 months of supervised rehabilitation in ICD patients.
Methods: The study included 61 patients (53 male, aged 49-77 years) in NYHA III class with HFrEF and impaired left ventricle systolic function (LVEF ≤35%), divided into two groups: CRT group, > six weeks after CRT-D implantation, and ICD-rehab group: patients after ICD implantation > six weeks, followed by 6 months of supervised aerobic interval training and the conditioning exercises. At baseline and after 6 months in all the patients cardiopulmonary exercise tests (CPX) and standard echocardiographic examinations were performed.
Results: The study included 61 patients (49-77 years) with HFrEF. At baseline, the values of CPX parameters were similar in both groups. After completing training almost all CPX parameters in the ICD-rehab group significantly improved, except for anaerobic threshold (AT). In the CRT group significant improvements were found in 2 parameters: peak oxygen uptake (VO_2) and exercise tolerance (metabolic equivalents, METs). Significant reductions in left and right ventricle diameters and an increase in LVEF were observed in both groups after 6 months.
Conclusions: Significant improvement in exercise tolerance capacity and increase of LVEF were observed in the similar extent both in heart failure patients with CRT and with ICD undergoing rehabilitation program. Regular, controlled exercise trainings provided additional, safe and easy to conduct therapeutic option for heart failure patients with no indications for CRT.

ABSTRACTS

Abstracts for Oral Presentation:

OP05.

HIGH SERUM URIC ACID IS ASSOCIATED WITH DYSLIPIDEMIA, OVERWEIGHT/OBESITY AND ELEVATED ARTERIAL STIFFNESS: A CROSS-SECTIONAL STUDY IN A COASTAL CHINESE POPULATION

Y Yuan, F Huang, F Lin, M Lin, P Zhu
Department of Geriatric Medicine, Fujian Provincial Hospital, Fujian Provincial Institute of Clinical Geriatrics, Provincial Clinical Medical College of Fujian Medical University, Fuzhou, China

Background: Hyperuricemia is more prevalent in populations with high seafood intake. Although the relationships between serum uric acid (SUA) and metabolic disorders had been recognized in patients with various clinical conditions such as hypertension or CKD, the association of SUA and dyslipidemia or overweight/obesity among community-based coastal individuals remains not comprehensively assessed.
Methods: In the current cross-sectional study, we evaluated the relationship between SUA and dyslipidemia, overweight/obesity as well as arterial stiffness in a coastal population of China. The study included a questionnaire survey, physical exam and lab test, and was conducted in 7 coastal villages. High SUA was defined as SUA at ≥420 μmol/L in men and ≥360 μmol/L in women. Elevated arterial stiffness was defined as brachial-ankle pulse wave velocity (baPWV) at >1400 cm/s.
Results: Among the 3,343 subjects who completed the study (1,335 men and 2,008 women, mean age 53.79±13.18 years), hyperuricemia was detected in 673 subjects (20.13%). The age-standardized prevalence was 18.85%. Subjects with high SUA had higher levels of blood lipids, blood pressure, BMI (p<0.05) and higher rate of overweight/obesity (49.03% vs. 43.33%), dyslipidemia (63.60% vs. 43.40%), hypertension (47.40% vs. 40.00%), diabetes (16.20% vs. 12.96%), as well as elevated arterial stiffness (50.07% vs. 44.34%). Multivariate linear regression analysis revealed higher SUA was associated with higher BMI, TG, LDL-C, baPWV, and lower HDL-C, eGFR (p<0.05 for all). Multivariate logistic regression analysis revealed that after adjusting confounding factors, the probability of dyslipidemia, overweight/obesity and elevated arterial stiffness was significantly increased with the SUA quartiles (5.182 times for high TG, 2.418 times for high LDL-C, 1.454 times for low HDL-C, 1.336 times for high BMI, 1.421 times for elevated baPWV, all p<0.01 for Q4 vs. Q1).
Conclusion: High SUA is an independent factor of dyslipidemia, overweight/obesity, or elevated arterial stiffness in this costal Chinese population.

OP06.

OUTCOME OF PHASE II CARDIAC REHABILITATION ON 6 MWT AND PHYSICAL FITNESS CHANGES IN PATIENTS AFTER PERCUTANEOUS CORONARY INTERVENTION (PCI)

R Zhang, EHK Yeung, C Chen, F Huang, G Li, KH Yiu
The University of HongKong-Shenzhen Hospital, Shenzhen, China

Objectives: Cardiac rehabilitation (CR) was recommended to be an effective and safe therapy in management of clinically stable people following PCI. However, limited information is available on the methodology and design of exercise based CR program, especially the result of phase II CR in patients after PCI. The aim of our study was to evaluate the outcome of supervised aerobic and resistance exercise on patients after PCI by assessing the result of 6 MWT and physical fitness test.
Methods: We reviewed the treatment records of patients who received PCI at Hong Kong University-Shenzhen Hospital cardiac rehabilitation center in 2016 and 2017. Fifty-five patients were chosen, who had completed supervised 45 minutes aerobic exercise and 15min resistance exercise twice a week for two months. Six minutes walk test has been shown to provide a clinical useful index of functional capacity and clinical change following heart rehabilitation. Accordingly, initial measurements of 6 minutes walk distance and physical fitness test including skin sebum test, sit and reach test, single leg stand test with eye open and eye close were performed. All measurements were repeated after the treatment program. Changes of 6 minutes walk distances physical fitness parameters were analyzed using pair t-test.
Results: 55 participants (52 males and 3 females) aged between 30 and 73 years old (mean 53.02±9.61) were included. As expected, a better exercise capacity was proved after two months phase II cardiac rehabilitation. Outcome of 6 minutes walk distances increased from 536.42±80.42 meters to 593.85±66.41 meters (P<0.01). However, no obvious change of skin sebum (P>0.01) was found. Other physical fitness parameters (result of sit and reach test, single leg stand test with eye open and eye close) had a significant improvement for both left and right side from baseline to the end of rehabilitation program (P<0.01).
Conclusion: In conclusion, a supervised aerobic and resistance exercise based cardiac rehabilitation program is feasible, as it improves patients' exercise capacity and physical fitness to perform a better life quality following PCI.

ABSTRACTS

Abstracts for Oral Presentation:

OP07.

DELETION OF TELOMERE-Rap1 AGGRAVATES ADVERSE CARDIAC REMODELING DURING AGING

H Liu,[1,2] Y Cai,[2] F Ying,[2] M Irwin,[2] S Liu,[1] Z Xia[2]

[1]Guangzhou Institute of Cardiovascular Disease, the Second Affiliated Hospital, Guangzhou Medical University, Guangzhou, China; [2]Department of Anesthesiology, The University of Hong Kong, Hong Kong

Background: The heart undergoes multiple functional and structural declining with aging, including impaired fatty acid metabolism, systolic/diastolic dysfunction and compensative myocardial hypertrophy. Repressor activator protein 1 (Rap1), telomere-associated protein, is essential for the maintenance of telomere length and structure integrity. Our preliminary work showed that Rap1-/- mice exhibited more pronounced phenotypes of aging, including massive hair loss, earlier hair greying and lower body weight. However, it is still unclear whether deletion of Rap1 aggravates aging-related adverse cardia remodeling. Thus, the present study was designed to investigate the role of Rap1 in cardiac aging and the underlying mechanism.

Methods: Transthoracic echocardiography was performed noninvasively to determine the cardiac structure and function of Rap1+/+ and Rap1-/- mice [36-weeks-old]. Size of cardiomyocytes were detected by WGA (Wheat germ agglutinin) staining. Cardiac senescence and the level of heart lipids were evaluated by β-Galactosidase (SA-β-gal) and Oil Red O staining. The ultrastructure of mitochondria was detected by electron microscope with samples from apex cordis of mice. Protein expression of p53, PPARα, Acetyl-CoA carboxylase (ACC), carnitine palmitoyl transferase I (CPT1) and Acyl-CoA dehydrogenase long chain (ACADL) in the heart were measured by Western blotting.

Results: Deletion of Rap1 in mice significantly increased the myocardial performance index (MPI), left ventricular internal dimension end diastole (LVIDd), LV mass and LV mass index, when compared with the age-matched wildtype mice, indicating that Rap1 deficiency led to aging-related cardiac structural changes and dysfunction. Furthermore, deletion of Rap1 increased the cardiomyocytes size, which further reinforced the conclusion that Rap1 deficiency led to dilated cardiac hypertrophy in mice. In addition, there adverse changes were associated with increased cardiac senescence (elevated SA-β-gal) in Rap1-/- mice. Taken together, these findings suggested that Rap1 deficiency precipitate cardiac aging in mice. The severe cardiac aging in aged Rap1-/- mice was paralleled by greater abnormalities in mitochondrial ultrastructure (cristae fragmentation, vacuolization and disrupted external membranes) along with impaired fatty acid oxidation (reduced PPARα, A CADL, CPT1 level and increased ACC expression), supporting that Rap1 deficiency led to mitochondrial structural injury and dysfunction. Of note, p53, a trigger of cellular senescence and mitochondrial defects, was significantly elevated in the heart of aged Rap1-/- mice, indicating that Rap1 deficiency might precipitate cardiac aging and mitochondrial defects via p53.

Conclusions: Deletion of Rap1 may impair mitochondrial function including fatty acid oxidation via p53, leading to more severe cardiac dysfunction and compensative structural changes during aging.

OP08.

ASSOCIATION OF ALENDRONATE AND RISK OF CARDIOVASCULAR MORTALITY IN PATIENTS WITH HIP FRACTURE

CW Sing,[1] AY Wong,[2] DP Kiel,[3] EY Cheung,[4] JK Lam,[5] TT Cheung,[5] EW Chan,[1] AW Kung,[5] IC Wong,[1,6] CL Cheung[1]

[1]Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong; [2]Department of Non-communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom; [3]Institute for Aging Research, Hebrew Senior Life and Department of Medicine Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, United States; [4]Department of Medicine and Geriatrics, United Christian Hospital, Hong Kong; [5]Department of Medicine, The University of Hong Kong, Hong Kong; [6]Research Department of Practice and Policy, UCL School of Pharmac, London, United Kingdom

Background: The risk of cardiovascular mortality with alendronate use in real-world hip fracture patients is unknown. This study aimed to investigate the risk of cardiovascular mortality with and without use of alendronate in patients with hip fracture.

Method: We conducted a retrospective cohort study using a population-wide database managed by the Hong Kong Hospital Authority. Patients newly diagnosed with hip fracture from 2005 through 2013 were followed until November 6, 2016. Alendronate and other anti-osteoporosis medications use during the study period were examined. We matched treated and non-treated patients based on time-dependent propensity score. The risks of 1-, 3-, 5- and 10-year cardiovascular mortality between treatment groups were evaluated using conditional Cox regression stratified by match pairs.

Results: Among 34,991 patients with newly diagnosed hip fracture, 4,602 (13.2%) received anti-osteoporosis treatment during follow-up. Physical functioning or survival prospect was not significantly different between treated and non-treated patients. 4,594 treated patients were matched with 13,568 non-treated patients. Results of Cox-regression analysis revealed that alendronate was associated with a significantly lower risk of one-year cardiovascular mortality (HR: 0.33; 95% CI: 0.17-0.65). The strength of the association declined over time but remained significant. Similar results were observed when all nitrogen-containing bisphosphonates were analyzed together. These findings were robust in multiple sensitivity analyses.

Conclusion: The use of alendronate was associated with a reduced risk of cardiovascular mortality. Additional studies in other population samples and randomized clinical trials may be warranted to further understand the relationship between use of various anti-osteoporosis medication and risk of cardiovascular events in patients with hip fracture.

ABSTRACTS

Abstracts for Oral Presentation:

OP09.

KLF2 SUPPRESSES VASCULAR CALCIFICATION THROUGH INHIBITION OF ENDOTHELIAL BMP/SMAD PATHWAY

J Huang, J Luo, Y Huang
Institute of Vascular Medicine, The Chinese University of Hong Kong, Hong Kong

Vascular calcification is a common vascular complication of diabetes, fibrotic renal diseases and atherosclerosis, and is associated with an increased risk of cardiovascular mortality. The bone morphogenetic proteins (BMPs) have been implicated as mediators of calcification in the vascular wall. However, the regulatory mechanism of BMP/Smad pathway in the progression of vascular calcification is largely unknown. Here, we show that KLF2, a transcription factor induced by athero-protective shear stress, negatively regulates BMP/Smad pathway. Specifically, KLF2 knockdown in human umbilical vein endothelial cells (HUVECs) increases expression levels of BMP2/4/6, total and phosphorylated Smad1 and Smad5, and decreases expression of Smad6 (an inhibitory Smad). By contrast, KLF2 overexpression downregulates expression of BMP2/4/6 and Smad1, and upregulates Smad6 expression. In addition, KLF2 overexpression also induces the expression of BMPER that functions as an endothelial BMP antagonist. Endothelial cells are constantly exposed to mechanical forces generated by blood flow. Different flow patterns induce distinct cellular responses. Disturbed flow (DF) induces vascular inflammation and promotes atherogenesis, while laminar shear stress (LSS) produces anti-inflammatory and athero-protective effects. We found that LSS decreases expression of BMP4 and increases expression of BMPER and Smad6, suggesting an inhibition of BMP/Smad signaling. Moreover, KLF2 silencing using shRNA abolishes the inhibitory effect of LSS on the expression of BMP4, BMPER and Smad6, suggesting that KLF2 is likely to mediate the suppressive effect of LSS on BMP pathway. On the other hand, DF decreases BMPER and increases BMP4 and p-Smad1/5, suggesting an activation of BMP/Smad signaling. KLF2 overexpression reverses the activation BMP/Smad signaling induced by DF. Taken together, our present study suggests that targeting the KLF2-BMP/Smad signaling cascade may hold promise as a novel drug target against vascular calcification.

OP10.

AMPK-ACTIVATION REDUCES EDH-TYPE RELAXATIONS IN RAT SMALL ARTERIES

H Chen, PM Vanhoutte, SWS Leung
The University of Hong Kong, Hong Kong

Introduction: The role of adenosine monophosphate-activated protein kinase (AMPK) in controlling the vascular tone, especially in small arteries which contribute majorly to the regulation of peripheral resistance and arterial blood pressure, is still unclear. Endothelium-dependent hyperpolarization (EDH) is an important vasodilator signal in small arteries; it is triggered by the opening of endothelial calcium-activated potassium channels (KCa), resulting in the release of potassium ions and hyperpolarization of the endothelial cells. The endothelial hyperpolarization is transmitted to the underlying vascular smooth muscle cells, leading to their relaxation. The present study aimed to examine whether or not AMPK affects EDH-mediated relaxations in small arteries of the rat.
Methods: Male Sprague-Dawley rats (12 weeks old) were used. Superior mesenteric arteries were isolated and suspended in conventional organ chambers for isometric tension recording. In some preparations, the endothelium was removed by perfusing the lumen of the arteries with 0.5% Triton X-100. To study EDH-type relaxations, the preparations were incubated with L-NAME (nitric oxide synthase inhibitor; 10-4 M) and indomethacin (cyclooxygenase inhibitor; 10-5 M) during 40 minutes before they were contracted with phenylephrine followed by exposure to vasodilator agents. The activity and protein presence of AMPK were measured by ELISA and Western blotting, respectively.
Results: AICAR (10-4 M) and A769662 (10-4 M), two AMPK activators with different structures and binding sites on the enzyme (the active metabolite of the former binds to the γ subunit, leading to conformational change of the complex and exposure of the α subunit while the latter is a β1-selective activator), significantly reduced EDH-type relaxations in response to acetylcholine and those to SKA-31 (KCa channels opener). The inhibitory effects of AICAR and A769662 were prevented by compound C (AMPK inhibitor; 10-5 M). AMPK activity assays confirmed that at 10-4 M, AICAR and A769662 increased the kinase activity in rings with endothelium; however, in rings without endothelium, only A769662 did so. A769662, but not AICAR, significantly inhibited relaxations to potassium ions and levcromakalim (opener of ATP-sensitive potassium channel) in rings without endothelium. The relaxations to the nitric oxide-donor DETA NONOate were not affected by A769662. The protein levels of α subunit and β subunit of AMPK in preparations with endothelium were comparable to those without endothelium.
Conclusions: AMPK-activation causes reduction of EDH-type relaxations in rat superior mesenteric arteries. While AICAR appears to reduce the generation of the endothelial signal, A769662 prevents the signaling downstream of hyperpolarization of the vascular smooth muscle cells.

ABSTRACTS

Abstracts for Oral Presentation:

OP11.

FoxO1-INDUCED INFLAMMATION AND ARTERIAL SMOOTH MUSCLE CELLS PHENOTYPIC SWITCHING CONTRIBUTE TO THE DEVELOPMENT OF DIABETIC VASCULAR REMODELING

X Xie, J Liu, D Yan, Z Xia
The University of Hong Kong, Hong Kong

Diabetes is associated with vascular structural and functional alterations both in large and small-resistance arteries. The forkhead transcription factor 1 (FoxO1) is a key angiogenic regulator and plays a pathologic role in progression of diabetes. The present study was designed to investigate the involvement of FoxO1 in impaired vascular smooth muscle cells phenotypic and vascular remodeling modulation in diabetes. Experiments were carried out in WT versus FoxO1-selective inhibitor AS1842856 (AS) gavaged rats at 8 weeks after STZ injection and in human umbilical arterial smooth muscle cells (HASMCs). We found that AS prevented the morphological changes of the aortic wall in the STZ-induced diabetic rats and recruited SMCs in the media of carotid arteries. Treatment with AS abrogated elevation of the expression of matrix metalloproteinases 2 (MMP2) and matrix metalloproteinases 9 (MMP9) in diabetic rats. AS reduced the cellular phenotypic switching as well as cell death, suggesting that FoxO1 promotes vascular remodeling as the result of cellular phenotypic modulation. Moreover, administration of AS in STZ induced-diabetes rats causes a dramatic decrease of proinflammation factors and NRLP3 inflammasome, suggesting that a low level of FoxO1 in quiescent SMCs may be necessary for inactivation of inflammatory response. FoxO1 knockdown significantly attenuated the HASMCs proinflammatory phenotype and cell survival in the treatment of hyperglycemia and TNF-α in vitro. Furthermore, we demonstrated that 3-phosphoinositide-dependent protein kinase 1 (Pdk1) is the key molecule that regulates the FoxO1 translocation into the nuclear for the subsequent transcriptional regulation during hyperglycemia. Taken together, our data suggest that FoxO1 is a novel promoter of vascular remodeling in STZ-induced diabetes and may have important therapeutic implications for cardiovascular diseases caused by diabetes.

OP12.

DETERMINING THE OPTIMAL LEVEL OF SYSTOLIC BLOOD PRESSURE FOR HYPERTENSIVE PATIENTS: A NETWORK META-ANALYSIS

Y Fei, MF Tsoi, BMY Cheung
The University of Hong Kong, Hong Kong

Background: Lowering systolic blood pressure (SBP) to <120 mmHg was reported to reduce cardiovascular events and mortality in the large clinical trial. Whether this should be the clinical target is controversial. We therefore study the relationship between the level of SBP attained and outcomes using network meta-analysis in order to determine the optimal target SBP.
Methods: We searched MEDLINE, the Cochrane database and ClinicalTrials.gov up to 1 May 2018 for randomised controlled trials comparing different SBP targets. Those reported cardiovascular events and mortality were eligible to be included. The mean SBP attained was classified into five groups (110-119, 120-129, 130-139, 140-149 and 150-159 mmHg). The primary variables of cardiovascular mortality, stroke and myocardial infarction were assessed using R.
Results: Fourteen trials with altogether 44015 patients over 50 years old were included. Lowering SBP to 120-129 mmHg significantly reduced stroke and major adverse cardiovascular events when compared to 130-139 mmHg (OR 0.83, 95% CI 0.69-0.99 and OR 0.84, 95% CI 0.73-0.96), 140-149 mmHg (OR 0.73, 95% CI 0.55-0.97 and OR 0.74, 95% CI 0.60-0.90), and 150-159 mmHg (OR 0.43, 95% CI 0.26-0.71 and OR 0.41, 95% CI 0.30-0.57), respectively. The risk of stroke was further lowered with more intensive control to <120 mmHg (OR 0.58, 95% CI 0.38-0.87, OR 0.51, 95% CI 0.32-0.81, and OR 0.30, 95% CI 0.16-0.56, respectively). In contrast, the risk of cardiovascular mortality and myocardial infarction was significantly higher with SBP ≥150 mmHg when compared to 120-129 mmHg (OR 2.18, 95% CI 1.32-3.59 and OR 1.73, 95% CI 1.06-2.82) and 130-139 mmHg (OR 1.71, 95% CI 1.11-2.61 and OR 1.53, 95% CI 1.01-2.32). No significant association between SBP and all-cause mortality was found.
Conclusions: Lowering SBP to <130 mmHg reduces major adverse cardiovascular events and stroke. Further lowering to <120 mmHg can be considered to reduce stroke if the treatment is tolerated. Long-term SBP should not exceed 150 mmHg because of the increased risk of cardiovascular events and deaths.

ABSTRACTS

Abstracts for Oral Presentation:

OP13.

Bmal1 DELETION IN MACROPHAGES ENHANCES HYPERTENSION AND HYPERTENSION-ASSOCIATED VASCULAR REMODELING IN MICE

M Huo,[1] CW Lau,[1] Y Wu,[1] A Chawla,[2] Y Huang,[1] XY Tian[1]
[1]The Chinese University of Hong Kong, Hong Kong; [2]University of California San Francisco, San Francisco, United States

Background: Peripheral circadian clock plays an important role in regulating cardiovascular function and immune responses through rhythmic expression of clock-controlled transcripts and their biological functions. Our recent study has shown that Bmal1 deletion in monocytes and macrophages promotes atherosclerosis in ApoE knockout mice by enhancing monocyte trafficking to plaques (Huo et al., 2017). In the present study, we aim to study whether deletion of Bmal1 in macrophages and monocytes promotes vascular inflammation and immune cell infiltration in the adventitia, thus accelerating hypertension involving upregulation of matrix metalloproteinases (MMPs) and increased vascular stiffness.
Materials & Methods: We use the Bmal1FloxP/FloxP (Bmal1MWT) as control mice and Bmal1FloxP/FloxP;LysMCre/+ (Bmal1MKO) as myeloid-specific Bmal1-deficient mice housed under 12 hour light/dark cycle at 22°C Hypertension was induced by angiotensin II (Ang II) infusion via osmotic pump for 28 days and blood pressure was measured using implantable radio telemetry. Bone marrow derived macrophages (BMDMs) were isolated from bone marrow of tibia and femur and differentiated in DMEM containing serum and macrophage colony-stimulating factor (M-CSF). Serum shock was used to synchronize BMDMs before various treatments.
Results: The systolic blood pressure was higher in Bmal1MKO compared to Bmal1MWT mice (131.5±7.2 vs 117.8±9.7 mmHg) after 4-week Ang II infusion. Stretch experiments and Masson's trichrome staining of arteries from Ang II-treated Bmal1MKO mice showed increases in vascular stiffness, reduced vascular compliance in functional testing, as well as morphological features showing increased vascular smooth muscle thickness, adventitial collagen deposition, and the number of infiltrated macrophages. Flow cytometry analysis showed the elevated number of pro-fibrotic macrophages with upregulation of M2 marker CD301 in aortic and its adventitia. The expressions of M2 markers (Arg1 and Fizz1), MMP2/9/13 and collagen-related genes all increased in aorta in Ang II-treated Bmal1MKO mice. In addition, MMP9/13 mRNA expression in M2-polarized BMDMs was further enhanced with deletion of Bmal1. MMP13 protein expression and activity also increased in M2-polarized BMDMs with Bmal1 deletion.
Conclusions: The present study provides new evidence that myeloid Bmal1 deletion exacerbates Ang II-induced hypertension and related vascular remodeling. Bmal1 deletion induces MMP9/13 expressions in BMDMs. Thus, myeloid Bmal1 deletion in Ang II-induced hypertension leads to pro-fibrotic responses in the vascular wall.
(This study is supported by NSFC 91739103, HMRF-RFS 01150057, 05162906.)

OP14.

CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR (CFTR) INDUCES ATP FORMATION AND RELEASE BY REGULATING ACID-BASE TRANSITION AND MITOCHONDRIAL OXIDATIVE PHOSPHORYLATION IN THE HEART

Y Wang, H Ballard
The University of Hong Kong, Hong Kong

ATP is released in the heart during hypoxia, ischaemia or catecholamine stimulation. Both ischaemia and hypoxia lower intracellular pH. However, little is known about the signaling pathways involved in CFTR regulated ATP formation and release in heart. Lactic acid infusion, the mimic of ischaemia, increased left ventricular wall interstitial ATP in anaesthetized rats, which was blocked by inhibitors of CFTR. The signaling mechanism was studied in cardiomyocytes isolated from adult rat heart: lactic acid increased intracellular cAMP, Ca in the near membrane area, and ATP release. Acidosis-induced ATP release was abolished by CFTR inhibitors or CFTR siRNA. The CFTR potentiator, apigenin, or cAMP-elevating agents, forskolin and IBMX (F&I), also increased ATP release, confirming the role of CFTR. Inhibition of either the Na+/H+ exchanger (NHE) with amiloride or the Na+/Ca2+ exchanger (NCX) with SN6 abolished acidosis-induced ATP release. Acidosis or F&I failed to activate ATP release with either BAPTA, an intracellular calcium chelator, or calcium free incubation medium. Thus, both cAMP and calcium activated CFTR opening during acidosis. Forskolin or acidosis-stimulated ATP release from cardiomyocytes was abolished in bicarbonate free incubation medium, suggesting that the role of CFTR is to permit bicarbonate entry. Bicarbonate increased mitochondrial cytochrome C expression and release of both ATP and cytochrome C from isolated mitochondria; these were inhibited by KH7, a soluble adenylyl cyclase (sAC)-specific inhibitor, suggesting that mitochondrial cyclic AMP activates mitochondrial PKA, which phosphorylates mitochondrial proteins resulting in increased mitochondrial oxidative phosphorylation and accumulation of cytochrome-C. Cyclosporin A or V5, mitochondrial permeability transition pore/Bax inhibitors, induced accumulation of cytochrome-C in mitochondria, whereas they inhibited ATP release from cardiomyocytes, suggesting that cytochrome-C leaves the mitochondria through mPTP. Pannexin1 inhibitors, caspase inhibitors or pannexin1 siRNA, attenuated the ATP release during acidosis or forskolin treatment, suggesting that Pannexin1, activated by caspase cleavage, functions as the ATP release channel. Immunofluorescence imaging suggested that CFTR was co-localized with Pannexin1. Hence, we demonstrate for the first time that the CFTR channel is activated by calcium/cAMP signaling during acidosis, allowing the movement of bicarbonate into the cell. The bicarbonate activates the HCO3-mito-sAC-cAMP-PKA signaling cascade, which serves as a metabolic sensor modulating ATP generation, and subsequently modulates Pannexin1 gating (for ATP release) by activation of caspase.

ABSTRACTS

Abstracts for Oral Presentation:

OP15.

GLP-1R AGONIST EXENATIDE PROTECTS AGAINST HYPERHOMOCYSTEINEMIA-INDUCED ENDOTHELIAL DYSFUNCTION BY REDUCING ENDOPLASMIC RETICULUM STRESS THROUGH AMPK ACTIVATION

CK Cheng,[1,2] CW Lau,[1,2] XY Tian,[1,2] Y Huang[1]

[1]School of Biomedical Sciences, The Chinese University of Hong Kong; [2]Institute of Vascular Medicine, Shenzhen Research Institute and Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Hong Kong

Background: Hyperhomocysteinemia (HHcy) is an independent risk factor for both cardiovascular diseases (CVDs) and type 2 diabetes mellitus (T2DM). Homocysteine (Hcy) can induce endoplasmic reticulum (ER) stress to injure endothelial cells, resulting in endothelial dysfunction. Although glucagon-like peptide-1 (GLP-1) protects endothelial function in CVDs-related vascular events and improves postprandial glucose metabolism, its beneficial effects are limited by rapid dipeptidylpeptidase 4 (DPP4)-mediated degradation. GLP-1 analogue exenatide was previously shown to ameliorate ER stress but the detailed mechanism remains debated. We therefore propose to further investigate on how enzymatically stable exenatide could reduce ER stress against HHcy-induced endothelial dysfunction.

Materials and Methods: Isolated aortae of wild-type Sprague-Dawley (SD) rats and C57BL/6 mice, and circumflex arteries of swine were pre-treated with exendin-4 (Ex4, a form of exenatide), followed by the acute impairment by Hcy (300 μmol/L). High methionine Low Folate (HMLF) diet-induced HHcy C57BL/6 mice were subjected to chronic Ex4 injection (1 nmol/kg) subcutaneously for 4 consecutive weeks. Vascular functions of arteries were evaluated either by organ bath or myograph, depending on the size of arteries. The reactive oxygen species (ROS) level in arteries was determined by both confocal microscopy of dihydroethidium (DHE) staining and lucigenin-enhanced chemiluminescence approach. Meanwhile, protein and mRNA expression levels of the signaling pathway were determined by Western blotting and RT-PCR respectively in human umbilical vein endothelial cells (HUVECs) and diet-induced HHcy mice.

Results: Ex4 treatment improved acetylcholine (ACh)-induced endothelium-dependent relaxations (EDRs) in both acutely and chronically impaired arteries. Ex4 down-regulated the levels of ER stress markers such as phosphorylated eIF2α, ATF6 and spliced XBP-1. In addition, exenatide was also shown to improve proper protein folding in ER to limit Hcy-induced ER stress, via the activation of AMP-activated protein kinase (AMPK).

Conclusions: Both acute and chronic treatment with exenatide showed promising protective effects against Hcy-induced endothelial dysfunction among different species, shedding light on the therapeutic potential of exenatide against CVDs and/or T2DM associated with HHcy.

OP16.

ASSOCIATION BETWEEN BLOOD LEAD LEVEL AND HYPERTENSION: THE UNITED STATES NATIONAL HEALTH NUTRITION AND EXAMINATION SURVEY: 1999-2016

MF Tsoi,[1] K Lui,[1] T Cheung,[1] B Cheung[1,2]

[1]Department of Medicine, The University of Hong Kong; [2]Institute of Cardiovascular Science and Medicine, The University of Hong Kong, Hong Kong

Introduction: Lead is a heavy metal without a biological role in human. High level exposure is known to be associated with hypertension. However, their association at low levels of exposure is uncertain.

Methods: Adult participants with blood lead measurements and blood pressure measurements, or self-reported hypertension diagnosis, were included in this analysis. If not already diagnosed, hypertension was defined according to AHA/ACC 2017 hypertension guideline. Results were analysed using R statistics version 3.5.1 with package 'survey' and sample weight adjustment. Logistic regression was used to study the association between blood lead level and hypertension. Odds ratio (OR) and 95% confidence interval (95%CI) were estimated.

Results: 39477 participants were included in this analysis. Every doubling in blood lead level was associated with hypertension (OR [95%CI]: 1.45 [1.40-1.50]). This association remained significant after adjusting for age, gender, ethnicity, waist circumference and smoking. Using quartile 1, blood lead level <0.89 μg/dL, as reference, higher blood lead levels were associated with increased adjusted odds of hypertension (Quartile 4 vs. Quartile 1: 1.22 [1.09-1.36]; Quartile 3 vs. Quartile 1: 1.15 [1.04-1.28]; Quartile 2 vs. Quartile 1: 1.14 [1.05-1.25]).

Conclusion: Blood lead level is associated with hypertension in the general population. Most of them did not have elevated blood lead level. Our findings suggest that reducing present levels of environmental lead exposure may benefit adults by reducing blood pressure and its attendant cardiovascular risk.

ABSTRACTS

Abstracts for Oral Presentation:

OP17.

CAUSAL ASSOCIATION BETWEEN PHOSPHATE METABOLISM AND GLYCEMIC TRAITS IN CHINESE AND US POPULATION

PCM Au, GHY Li, CL Cheung
The University of Hong Kong, Hong Kong

Introduction: Randomized trials showed that colestilan and sevelamer, a phosphate binder, reduced glycated hemoglobin and LDL-cholesterol. However, the relationship and underlying mechanism between serum phosphate, glycemic control, and lipids, especially in people without diabetes and chronic kidney disease, remains unknown. We therefore evaluated the relationship of serum phosphate with glycated hemoglobin (HbA1c) and LDL-cholesterol in the National Health and Nutrition Examination Survey III (NHANES III) and the Hong Kong Osteoporosis Study (HKOS).
Materials and Methods: We used data from 4,369 participants from the NHANES III and 284 participants from the HKOS. We studied the relationship of serum phosphate with HbA1c, fasting glucose, and LDL-cholesterol using multivariable linear regression with adjustment for confounding factors. Mendelian Randomization (MR) was used to infer causality. Untargeted metabolomic profiling was performed to evaluate if metabolite plays a role in the relationship.
Results: Serum phosphate was significantly associated with increased HbA1c levels in both cohorts and reduced fasting glucose in the NHANES III. A significant interaction (P=0.003) was observed between phosphate and fasting glucose on HbA1c. The beta estimate between fasting glucose (natural-log unit) and HbA1c (natural-log unit) increased from 0.151 to 0.227 in the lowest quartile and highest quartile of phosphate levels, respectively. MR analysis showed that serum phosphate was causally associated with serum A1c (IVW: +0.033% per 1 SD of serum phosphate, P=0.009). Seven metabolites were found to be significantly associated with phosphate and HbA1c, with branched-chain amino acids being the most associated metabolic pathway.
Conclusion: Serum phosphate is causally associated with increased HbA1c, and this implicated that serum phosphate may be a confounder in glycemic trait measurement. Cautious interpretation of HbA1c in patients with elevated phosphate levels is required.

OP18.

RIGHT VENTRICULAR APICAL PACING VS.NON-RIGHT VENTRICULAR APICAL PACING INDUCED TRICUSPID REGURGITATION: IMPLICATION OF 3D ECHOCARDIOGRAPHIC LOCATION OF LEADS

Y Yu, YJ Yu, Y Chen, MZ Wu, CP Lau, HF Tse, KH Yiu
The University of Hong Kong, Hong Kong

Objectives: We sought to evaluate: (1) Tricuspid regurgitation (TR) degree in patients with right ventricular apical (RVA) pacing vs. non-RVA pacing; (2) the relationship of lead-position between RVA vs. non-RVA pacing associated with TR undergo 3-dimensional echocardiography (3DE).
Methods: Conventional echocardiography performed in 434 patients after pacemaker implantation. In addition, 249 patients with pre-pacemaker implantation echocardiography available were included to evaluate the development of significant TR prospectively.
Results: RVA pacing patients had a higher frequency of significant TR (degree>=2) compared to non-RVA pacing (62.5% vs. 34.7%, p value <0.001). For RVA pacing, the lead was more likely to positioned at the anterior, posterior and septal compared to non-RVA pacing (51.5% vs. 28.8%). Importantly, leads were more likely to be positioned in the central portion with non-RVA pacing compared to RVA pacing (34.7% vs. 13.3%). Among 249 patients with pre&post-implantation echocardiography, RVA pacing is associated with the development of significant TR compared to non-RVA pacing (62.6% vs. 35.7%, P<0.001).
Conclusions: The study demonstrates that RVA pacing is more likely to develop significant TR compared to non-RVA pacing. Significantly, this study is the first to demonstrate that lead impingement is one of the possible mechanisms that could explain the higher frequency of TR in RVA pacing compared to non-RVA pacing by 3DE.
Acknowledgment: This research is supported by UDM Departmental Research Grant, The University of Hong Kong.

ABSTRACTS

Abstracts for Posters:

P01.

miR-590-3P RESTORES AUTOPHAGY IN HUMAN GLOMERULAR ENDOTHELIAL CELLS, BUT NOT IN AORTIC ENDOTHELIAL CELLS

W Liu,[1] M Meng,[1] SWS Leung,[2] Y Shi[1]
[1]Biomedical Research Center, Zhongshan Hospital Fudan University, Shanghai, China; [2]Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong

Background: Autophagy is an important mechanism to maintain homeostasis under physiological condition. Previous data mining indicated that miR-590-3p was involved in diabetes-induced endothelial dysfunction. The present study was designed to investigate the role of microRNA-590-3p (miR-590-3p) in the regulation of autophagy in endothelial cells.
Methods: Human aortic endothelial cells (HAEC) and glomerular endothelial cells (HGEC) were incubated in medium containing normal (5.5 mM) or high glucose (44.4 mM) level. They were transfected with or without miRNA-590-3p mimic using lipofectamine RNAiMAX. Cells were collected for quantitative real-time polymerase chain reaction and western blotting.
Results: After six hours incubation with high glucose, expressions of miR-590-3p were significantly reduced in HGEC, but not in HAEC, while the expressions of miR-590-5p were not changed. After 48 hours of incubation with high glucose, in HGEC, but not in HAEC, the protein expressions of microtubule-associated proteins 1A/1B light chain 3B-II (LC3B-II), autophagy-related genes (ATG) 5, and beclin-1 were reduced, while those of SQSTM1/p62 were increased; such impairment of autography was prevented in HGEC with miR-590-3p overexpression. Moreover, incubation of HGEC with high glucose reduced the phosphorylation of AMP-activated protein kinase (AMPK) and increased that of mammalian target of rapamycin (mTOR), the upstream signaling of autophagy. Overexpressing miR-590-3p restored the phosphorylation levels of AMPK and mTOR in HGEC treated with high glucose. High glucose did not alter the expressions of apoptosis proteins, including bcl-2, pBAD, and caspase-3, in HGEC or HAEC.
Conclusion: High glucose incubation reduces autophagy in HGEC which is prevented by overexpressing miR-590-3p through AMPK/mTOR signaling pathways.

P02.

COMBINED TREATMENT OF CYCLOSPORINE AND MYCOPHENOLATE IMPROVES ENDOTHELIAL FUNCTION IN AORTA OF LDLR-/- MICE

M Meng, Z Li, PM Vanhoutte, SWS Leung, Y Shi
Biomedical research center, Zhongshan Hospital Fudan University, Shanghai, China

Background: Chronic inflammation is a key player in the process of atherosclerosis. The present study was designed to investigate effects of immunosuppressive agents on endothelial dysfunction in a mouse model of atherosclerosis.
Methods: To induce atherosclerosis, 6-week old LDLR knockout mice were fed with western diet for two months. Clinically used immunosuppressive agents, cyclosporine and mycophenolate, were mixed in chow. Aortic rings were fixed in the organ chambers for isometric tension measurement. Atherosclerotic plaques in aortic arch were visualized using Oil red O (ORO) staining. Presences of CD68 and COX-2 protein were measured by Immunofluorescence assay. Serum samples were collected for biochemistry tests.
Key results: After two months, acetylcholine induced relaxations at low concentrations, but contractions at high concentrations in the aorta of LDLR knockout mice. The acetylcholine-induced contractions, but not the relaxations, were significantly reduced in mice treated with immunosuppressive agents. In the presence of indomethacin (non-selective inhibitor of cyclooxygenase), acetylcholine-induced contractions were restored to relaxations in both groups. ORO staining showed that atherosclerosis plaques in the aortic arch were reduced in mice fed with immunosuppressive drugs, compared with those fed with western diet. Expressions of CD68 in plagues, a marker of macrophage, were comparable in the two groups. Expressions of COX-2 in plagues, an indicator of plaque vulnerability, were reduced in the immunosuppressants treated group. Combined treatment of immunosuppressive agents did not change serum levels of cholesterol, lipid proteins, glutamic oxalacetic transaminase, glutamic-pyruvic transaminase, or creatinine.
Conclusion: Immunosuppressive treatment reduces atherosclerotic plaque and prevents endothelial dysfunction in LDLR knockout mice. The underlying mechanisms may involve cyclooxygenase pathway; further studies are warranted to confirm, or not, the postulation.

ABSTRACTS

Abstracts for Posters:

P03.

GINKGO BILOBA LEAF EXTRACT ATTENUATES ATHEROSCLEROSIS IN STREPTOZOTOCIN-INDUCED DIABETIC APOE-/- MICE BY INHIBITING ENDOPLASMIC RETICULUM STRESS VIA RESTORATION OF AUTOPHAGY THROUGH MTOR SIGNALING PATHWAY

J Tian,[1,2] MS Popal,[2] Y Liu,[3] R Gao,[4] S Lyu,[2] K Chen,[1] Y Liu[1]

[1]Cardiovascular Disease Centre, Xiyuan Hospital of China Academy of Chinese Medical Sciences; [2]Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing Institute of Heart, Lung and Blood Vessel Diseases; [3]Graduate School, Beijing University of Chinese Medicine; [4]Institute of Clinical Pharmacology of Xiyuan Hospital, China Academy of Chinese Medical Sciences, Beijing, China

Background: There is a crosstalk between endoplasmic reticulum stress (ERS) and autophagy, and autophagy could attenuate endoplasmic reticulum stress-mediated apoptosis. Ginkgo biloba leaf extract (GBE) exerts vascular protection functions. The purpose of the present study is to investigate the role of autophagy in diabetic atherosclerosis (AS) and the effect of GBE on autophagy and ERS.

Methods: Network pharmacology was utilized to predict the targets and pathways of the active chemical compounds of Gingko biloba leaf attenuate AS. ApoE-/- mice were rendered diabetic by intraperitoneally ingested with streptozotocin combined with high-fat diet. The diabetic mice were divided into five groups: model group, atorvastatin group, rapamycin group, low and high dose of GBE groups. Serum and tissue markers of autophagy or ERS markers, including the protein expression were examined.

Results: mTOR and NF-κB signaling pathway were targeted by the active chemical compounds of GBE to attenuate AS predicted by Network pharmacology. GBE reduced the plaque area/lumen area and the plaque lipid deposition area/intimal area, and inhibited the expression of CD68, MMP2, and MMP9. Rapamycin and GBE inhibited the expression of mammalian target of rapamycin and SQSTM1/p62 which increased in the aorta of diabetic mice. In addition, GBE reduced the expression of ERS markers in diabetic mice. GBE reduced the serum lipid metabolism levels, blood glucose, and inflammatory cytokines.

Conclusion: Impaired autophagy and overactive endoplasmic reticulum stress contributed to diabetic atherosclerosis. mTOR inhibitor rapamycin and GBE attenuated diabetic atherosclerosis by inhibiting ERS via restoration of autophagy through inhibition of mTOR.

P04.

RESVERATROL STIMULATES NA+-Ca2+ EXCHANGER ON THE PLASMA MEMBRANE TO REDUCE CYTOSOLIC Ca2+ IN RAT AORTIC SMOOTH MUSCLE CELLS

F Yan,[2] Y Zhang,[1] X Yao[1]

[1]The Chinese University of Hong Kong, Hong Kong; [2]Department of Physiology, Guangzhou University of Chinese Medicine, Guangzhou, China

Background: Resveratrol has well-documented vascular relaxant and anti-hypertensive effect. Here we studied the action of resveratrol in modulating cytosolic [Ca2+] level and ATP-induced Ca2+ release from sarcoplasmic reticulum (SR) in rat aortic smooth muscle cells (ASMCs) and explored the underlying mechanisms.

Method and result: Cytosolic [Ca2+] and SR [Ca2+] in ASMCs were determined by Fluo-4/AM or Mag-Fluo-4/AM, respectively. Resveratrol (20, 50 and 100 μM) caused a rapid and substantial reduction in cytosolic [Ca2+] in ASMCs bathed either in the normal Hank's Balanced Salt Solution (HBSS) or in a Ca2+-free HBSS. Resveratrol pretreatment reduced ATP-induced SR Ca2+ release and also lowered SR Ca2+ content. In cells bathed in a Na+-free physiological saline, which favors reverse mode of Na+-Ca2+ exchanger (NCX), resveratrol induced rises in cytosolic [Ca2+] and SR [Ca2+]. The effect of resveratrol on cytosolic [Ca2+] and SR [Ca2+] were inhibited by a selective NCX inhibitor, SEA0400.

Conclusion: Resveratrol stimulates NCX to reduce cytosolic [Ca2+] and SR [Ca2+] in ASMCs in normal physiological saline.

ABSTRACTS

Abstracts for Posters:

P05.

THE ROLE OF MITOCHONDRIA IN CIGARETTE SMOKE-INDUCED INFLAMMATION AND APOPTOSIS IN CARDIOMYOCYTES

Y Liang, MSM Ip, JCW Mak
The University of Hong Kong, Hong Kong

Background: Smoking has been regarded as the major risk factor for cardiovascular diseases (CVD). Reactive oxygen species (ROS) production has been implicated in promoting inflammation and inducing apoptosis in pathogenesis of cigarette smoke (CS)-induced CVD. The mitochondria are important sources of ROS in the heart. Therefore, it is necessary to investigate the role of mitochondria in smoking-related cardiac injury and whether the therapeutic strategies specifically targeting mitochondrial ROS may have benefits. This study was aimed to investigate the role of mitochondria in cigarette smoke medium (CSM)-exposed human AC16 cardiomyocytes and to examine the effects of mitochondria-targeted antioxidant Mito-TEMPO in vitro.

Materials and methods: The AC16 cell line was cultured in DMEM/F12 containing 12.5% fetal bovine serum, in a CO_2 incubator at 37°C. CSM was prepared by bubbling smoke from two cigarettes into 20ml serum-free medium, which was regarded as 100%. After serum starvation with 1% fetal bovine serum for 24h, cells were pretreated with Mito-TEMPO (1 μM) for 30 mins before 4% CSM was added and incubated for an additional 24h. Supernatant was collected for determination of interleukin (IL)-8 by ELISA. Cells were collected to perform MitoSox Red assay to determine mitochondrial superoxide by flow cytometry. Apoptotic cells were measured with Annexin V apoptosis detection kit. Cell lysates were prepared for Western blot analysis.

Results: Exposure of AC16 cells to CSM for 24h significantly induced mitochondrial superoxide production, which was prevented by Mito-TEMPO. Treatment with Mito-TEMPO inhibited CSM-induced IL-8 release and decreased cell apoptosis in cardiomyocytes. Mechanistic study revealed that the beneficial effect of Mito-TEMPO were associated with inhibition of NF-κB phosphorylation.

Conclusions: Inhibition of mitochondrial ROS by Mito-TEMPO reduced CSM-induced inflammation and apoptosis via NF-κB pathway in cardiomyocytes in vitro. Thus, mitochondria-targeted antioxidants may be an effective therapy for smoking-related cardiac complications.

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