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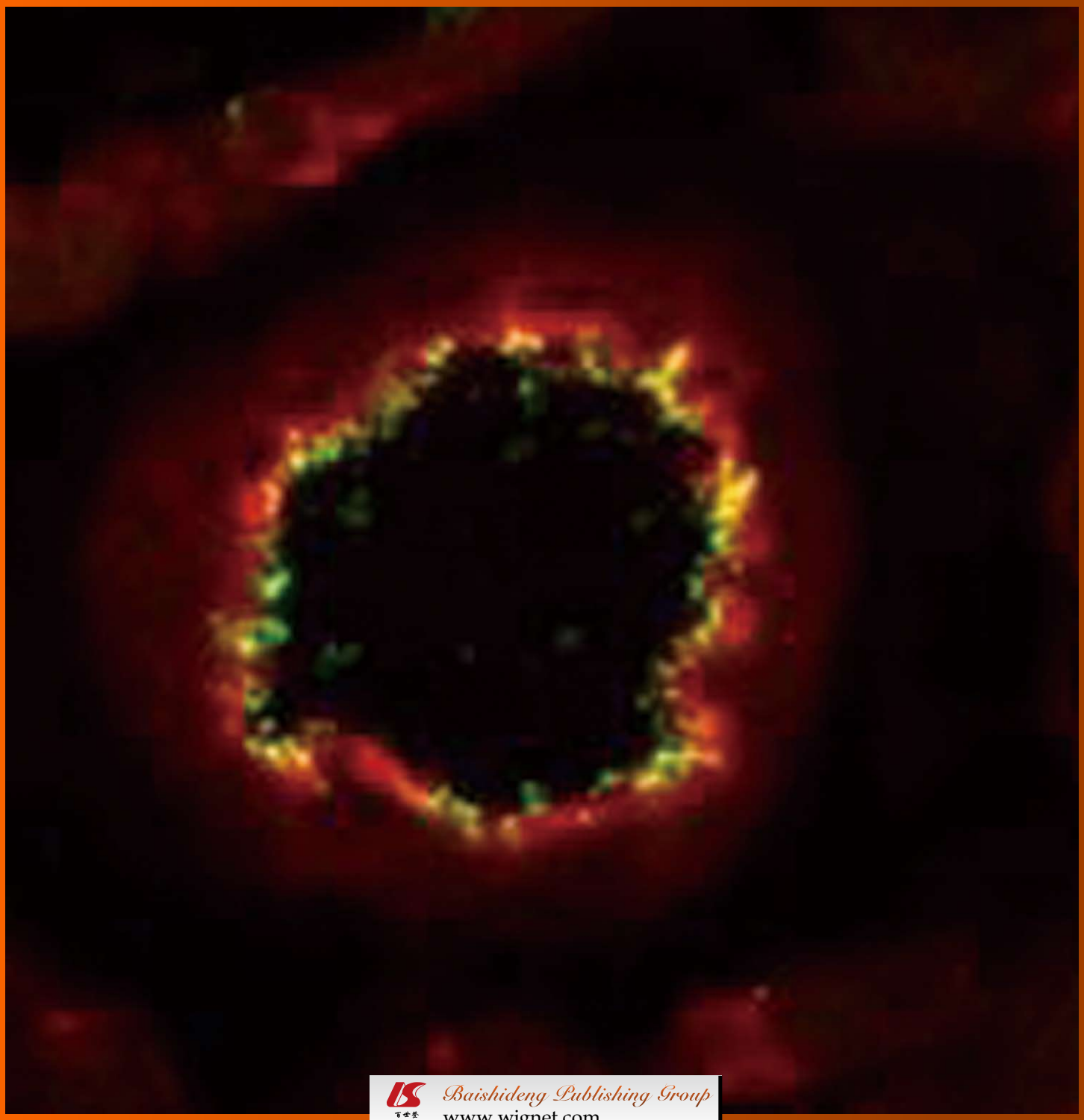

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EDITORIAL

Manual aspiration thrombectomy in acute ST elevation myocardial infarction: New gold standard?

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Abstract

Percutaneous coronary intervention (PCI) is the preferred method to treat ST segment myocardial infarction (STEMI). The use of thrombus aspiration (TA) may be particularly helpful as part of the PCI process, insofar as the presence of thrombus is essentially a universal component of the STEMI process. This article reviews evidence favoring the routine use of TA, and the limitations of these data. Based on current evidence, we consider TA to be an important maneuver during STEMI PCI, even in the absence of visible angiographic thrombus, and recommend it whenever the presence of thrombus is likely.

Key words: Aspiration thrombectomy; Myocardial infarction; Guidelines; Thrombus

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THROMBUS IN ACUTE MYOCARDIAL INFARCTION

A major component of the acute coronary syndrome, and especially ST segment myocardial infarction (STEMI), is thrombus. In treating STEMI with percutaneous coronary intervention (PCI), preventing distal embolization may be important in improving clinical outcomes by preventing "clogging" of the microvasculature and subsequent worsening of myonecrosis[1]. Previous studies have utilized devices to prevent distal embolization, including distal embolic protection devices and mechanical aspiration devices. Neither category of devices has demonstrated clinical efficacy[2,3]. This presentation reviews currently available data, utilizing full-length refereed publications, particularly randomized studies, (excluding abstracts and conference presentations) on manual aspiration thrombectomy, and addresses whether evidence is strong enough to recommend its use in all STEMI cases, even those without angiographically visible thrombus (Figure 1).

THE TAPAS STUDY: THE STRONGEST EVIDENCE IN FAVOR OF ROUTINE USE FOR MANUAL ASPIRATION THROMBECTOMY

The Thrombus Aspiration during Percutaneous Coronary

Table 1 One-year clinical outcomes in selected randomized ST segment myocardial infarction trials from 2000 to 2010

Study	Yr	Intervention	Control	*n*	All-cause death (%)		Cardiac mortality (%)		MI (%)	
					C	S	C	S	C	S
NORDISTEMI[16]	2010	All PCI	Selective	276	3.0	2.2	NA	NA	9.0	3.0
HORIZONS AMI[17]	2009	Bivalurudin	Hep/Gp	3602	4.8	3.5	3.8	2.1	NA	NA
TAPAS[5]	2008	TA + PCI	PCI/no TA	1071	7.6	4.7	6.7	3.6	4.3	2.2
DANAMI-2[18]	2008	PCI	Lytic	1424	1.3	1.4	NA	NA	0.9	1.3
Transfer with Tirofiban for PCI Thrombolysis with STEMI[19]	2007	Transfer/PCI	Lytic	401	NA	NA	12.5	7.0	7.5	3.5
SESAMI[20]	2007	DES	BMS	320	4.3	1.8	NA	NA	1.8	1.8
TYPHOON[21]	2006	DES	BMS	712	2.2	2.3	1.4	2.0	1.4	1.1
PASSION[22]	2006	DES	BMS	619	NA	NA	6.5	4.5	1.9	1.6
ADMIRAL[23]	2004	Abciximab + PCI	PCI	400	12.5	6.0	10.5	5.0	6.0	1.0
STENTIM-2[24]	2000	BMS	BA	211	1.9	3.0	NA	NA	5.5	4.0

BA: Balloon angioplasty; BMS: Bare metal stent; C: Control group; DES: Drug-eluting stent; Gp: Glycoprotein Ⅱb/Ⅲa inhibitors; Hep: Heparin; MI: Myocardial infarction; NA: Not applicable; S: Study (intervention) group; TA: Thrombus aspiration; PCI: Percutaneous coronary intervention.

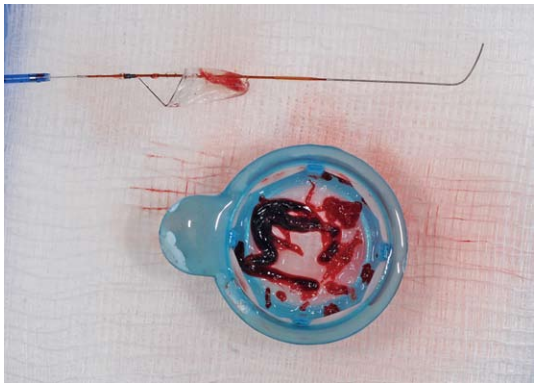

Figure 1 Findings from the use of both a distal embolic protection device and manual aspiration thrombectomy in a patient with ST segment myocardial infarction secondary to saphenous vein graft occlusion with visible angiographic thrombi. Please note the huge amount of thrombus removed and the relatively small amount of debris found in the filter.

Intervention in Acute Myocardial Infarction (TAPAS) Study randomized 1071 STEMI patients to manual aspiration thrombectomy (n = 535) prior to stenting using the Export device (Medtronic, Santa Rosa, CA, USA) or to PCI, usually with stenting, but without thrombus aspiration (TA) (n = 536). The primary endpoint was the myocardial blush grade (MBG) after intervention. Secondary endpoints included the degree of ST-segment elevation resolution, degree of persistent ST-segment elevation after PCI, and presence of pathological Q waves. Patients treated with TA showed a higher MBG ($P < 0.001$), less persistent ST segment elevation ($P < 0.001$), more resolution of the ST segment elevation ($P < 0.001$), and fewer pathological Q waves ($P = 0.001$). Patients with all of these characteristics of improved perfusion after thrombus aspiration showed a trend toward decreased death rates at 30 d ($P = 0.07$), decreased reinfarction ($P = 0.11$), and decreased combined major adverse cardiac events (MACE) ($P = 0.12$). The TAPAS results suggested that TA decreased microvascular obstruction and increased myocardial reperfusion[4]. At 1-year follow-up, there was a decrease in clinical events in the TA group *vs* the non-TA group: all-cause mortality (4.7% *vs* 7.6%, $P = 0.04$), cardiac death (3.6% *vs* 6.7%, $P = 0.02$), and rates of reinfarction (2.2 *vs* 4.3%, $P = 0.05$)[5]. The investigators did not measure either residual LV function and or infarct size.

One year mortality in both the control and treatment arms of the TAPAS trial is relatively high compared with other contemporary STEMI studies such as HORIZONS-AMI (Table 1). It is uncertain whether the high mortality in the control group may have accounted for the significant difference in clinical outcomes, i.e. a chance occurrence *vs* a true effect of TA.

WHAT OTHER EVIDENCE SUGGESTS A CLINICAL BENEFIT OF TA IN ACUTE MYOCARDIAL INFARCTION?

Several randomized trials have evaluated the use of different aspiration thrombectomy devices in STEMI (Table 2). Primary endpoints were typically related to angiographic and electrocardiographic findings.

The Randomized Evaluation of the effect of MEchanical reduction of Distal embolization by thrombus aspiration In primary and rescue Angioplasty (REMEDIA) trial[6] has shown improvement in the primary endpoints of ST-segment resolution (STR) ⩾ 70% and MBG ⩾ 2 (STR: 44.9% *vs* 36.7%, $P = 0.02$; MBG: 68.0% *vs* 58.0%, $P = 0.034$) using the Diver CE device (Invatec, Brescia, Italy). In a 50-patient myocardial contrast echocardiography substudy, TA reduced microvascular obstruction acutely and demonstrated a trend to a decrease in 6-mo adverse left ventricular remodeling[7].

In a similar study design, De Luca and colleagues[8] have shown, in 76 anterior STEMI patients, STR in 81.6% of TA *vs* 55.3% of non-TA patients ($P = 0.02$), and MBG 3 of 36.8% for TA and 13.1% for non-TA patients ($P = 0.03$).

Kaltoft *et al*[9] have randomized 215 STEMI patients to PCI with or without TA using a 4.5 Fr Rescue extraction catheter (Boston Scientific/Scimed, Maple Grove, MN, USA). This study did not show improvement in the primary endpoint of scintigraphic myocardial salvage at

Table 2 Randomized studies utilizing manual aspiration devices in ST segment myocardial infarction and primary percutaneous coronary intervention[1]

Study	Yr	*n*	Device	Primary endpoint(s)	Outcomes[1]
EXPIRA[14]	2009	175	Export (Medtronic, Minneapolis, MN, USA)	MBG > 2, STR	Improvement
VAMPIRE[11]	2008	355	TVAC (Nipro, Osaka, JP)	SR or NR	Trend to improvement
TAPAS[5]	2008	1071	Export (Medtronic, Minneapolis, MN, USA)	MBG	Improvement
De Luca et *al*[8]	2006	76	Diver CE (Invatec, Brescia, IT)	MBG > 2, STR	Improvement
Kaltoft *et al*[9]	2006	215	Rescue (BSC, Maple Grove, MN, USA)	Myocardial salvage	No improvement
DEAR-MI[10]	2006	148	Pronto (Vascular Solutions, Minneapolis, MN, USA)	STR, MBG 3	Improvement
REMEDIA[6]	2005	99	Diver CE (Invatec, Brescia, IT)	MBG > 2, STR	Improvement

[1]Please see text for study data. MBG: Myocardial blush grade; NR: No reflow; SR: Slow reflow; STR: ST segment resolution.

30 d, based on the difference between myocardium at risk and final infarct size[9]. In fact, the final infarct size was significantly larger in the TA group (15% *vs* 8%, P = 0.004). Although the reason for this latter finding is not certain, the device used in this study was relatively bulky (4.5 Fr), and possibly provoked embolization during its passage.

In the Dethrombosis to Enhance Acute Reperfusion in Myocardial Infarction (DEAR-MI) study, 148 patients with STEMI were randomized to primary PCI without or with TA using the Pronto extraction device (Vascular Solutions, Minneapolis, MN, USA)[10]. There was a significant improvement in the primary endpoints of complete STR (68% *vs* 50%, $P < 0.05$) and MBG 3 (88% *vs* 44%, $P < 0.0001$). In addition, there was improvement in no reflow (3% *vs* 15%, $P < 0.05$), angiographic embolization (5% *vs* 19%, $P < 0.05$%) and peak creatine kinase MB ($P < 0.0001$). This study was not powered to evaluate long-term clinical events[10].

The VAcuuM asPIration thrombus REmoval (VAMPIRE) Trial randomized 355 patients to a single lumen aspiration catheter device (TVAC; Nipro, Osaka, Japan) attached to a motorized vacuum system (n = 180) or conventional PCI without TA (n = 175). The primary endpoint was slow or no-reflow defined as thrombolysis in myocardial infarction (TIMI) flow grade < 3 not attributable to occlusive thrombus, dissection or epicardial spasm. There was a trend to improvement with TA (12.4% *vs* 19.4%, P = 0.07). MBG grade 3 was higher in TA patients (46.0% *vs* 20.5%, $P < 0.001$). Although there was no significant difference in 30-d outcomes, there was a 38% decrease incidence in MACE at 8 mo ($P < 0.05$), with less target lesion revascularization (TLR) ($P < 0.05$) and repeat PCI ($P < 0.05$), but no significant difference in mortality. A subgroup analysis of patients presenting < 6 h from symptom onset showed the most benefit with TA. These patients showed a decrease incidence in no reflow (P = 0.01), improved MBG (P = 0.04), improved TIMI flow (P = 0.01), decreased TLR (P = 0.03), and decreased MACE (P = 0.04)[11].

The age of the aspirated thrombus in STEMI and its relationship to outcome was analyzed in 1315 consecutive patients[12]. Fresh thrombus (< 24 h) was characterized mostly by erythrocytes, granulocytes, platelets, and fibrin. Older thrombus was defined as showing necrotic areas from red and white blood cells, as well as smooth muscle growth potentially with neovascularization and connective tissue deposition. No material was aspirated in 326 patients (24.7%). Fresh thrombus was found in 552 patients (42.0%), whereas older thrombus was found in 372 patients (28.2%). Patients with older thrombus had significantly higher risk of all-cause mortality at 4 years (16.0% *vs* 7.4%; hazard ratio 1.82, 95% CI: 1.17-2.85, P = 0.008). These data are consistent with STEMI being the culmination of an iterative thrombus-producing event in many patients.

It is well established that timely reperfusion is crucial for restoration of myocardial blood flow during acute infarction to preserve left ventricular (LV) function. In a retrospective cohort (n = 195) with 109 patients receiving TA with stenting and 86 receiving conventional angioplasty without TA, left ventriculography was performed pre- and post-procedure, and patients were followed up for 6 mo to determine the effect of TA on LV remodeling (defined as an increase in LV end-diastolic volume index by > 20%). Adverse LV remodeling was significantly lower at 6 mo follow-up in the group treated with TA (22%) compared with the conventional group (44%, P = 0.01)[13].

In a recent randomized trial of 175 patients with STEMI with PCI, with or without TA, investigators evaluated LV function by contrast-enhanced magnetic resonance imaging (CE-MRI), 3-5 d after PCI and again at 3 mo[14]. The two groups showed no difference in infarct size, end-systolic and diastolic volumes, or ejection fraction 3-5 d after PCI. However, the TA group had significantly greater MBG (P = 0.0001), and ST-segment resolution (P = 0.0001). CE-MRI showed significantly greater microvascular obstruction in the conventional PCI group as compared with the TA group. At 3 mo, the TA group had a significantly smaller infarct size than the conventional PCI group. At 9 mo, the TA group had a lower incidence of cardiac death (0% *vs* 4.6%, P = 0.02)[14].

A Bayesian meta-analysis in STEMI patients randomized to PCI with or without aspiration thrombectomy (both manual and mechanical methods) identified 21 eligible trials with 4299 patients. Adjunctive thrombectomy was shown to improve early markers of reperfusion, but had no effect on reinfarction, 30-d post-MI mortality, or stroke[15]. This study was limited in evaluating manual aspiration because it included mechanical aspiration device

studies, which have not been shown to be effective in individual studies in improving clinical outcomes.

CONCLUSION

In STEMI, primary PCI is the standard of care[1]. It is extremely effective in rapidly recanalizing an occluded vessel. However, it may also provoke distal embolization of soft thrombus that may be removed easily by manual aspiration. Routine TA, even in the absence of a large thrombus burden, has been shown to be a quick and simple method of improving, in an MI cohort, early markers of reperfusion including MBG, TIMI flow, and ST-segment resolution. There may be design and operational issues that favor certain systems over others, but at present, there is a paucity of data to identify the preferred manual aspiration device. TA may also improve TLR, MACE and LV remodeling[3,5]. Routine TA may also have a mortality benefit as shown in the TAPAS study, particularly if employed early[5,12,14]. The American College of Cardiology/American Heart Association guidelines update has recognized these data by making it a Class Ⅱa indication for STEMI[1]. Additional data are required to confirm the salutary effects of routine TA on long-term outcomes of mortality and MACE in order that it be a Class Ⅰ indication, i.e. the standard of care.

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BRIEF ARTICLE

Global left ventricular performance in non-diabetic non-hypertensive metabolic syndrome adults

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Abstract

AIM: To evaluate the left ventricular structure and function in isolated metabolic syndrome.

METHODS: One hundred and fifty six consecutive adults with metabolic syndrome were enrolled in the study. Fifty nine had isolated metabolic syndrome (group A) and 97 had metabolic syndrome with hypertension and/or diabetes (group B). There was a control group of 34 healthy adults. In addition to classic echocardiographic assessment of myocardial structural and functional changes, the Tei index was used to evaluate global left ventricular performance.

RESULTS: There were no statistically significant differences between group A and controls in all parameters of left ventricular structural, systolic, and diastolic function except global myocardial performance (Tei index). On the other hand, significant differences were observed between group B and the control group in most of the parameters of left ventricular structural and global performance.

CONCLUSION: The early identification of isolated metabolic syndrome in non-diabetic, non-hypertensive adults may be an indication that aggressive preventive measures should not be postponed until overt obesity, hypertension or diabetes mellitus has developed.

Key words: Metabolic syndrome; Tei-index; Heart function tests

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INTRODUCTION

Metabolic syndrome is a condition characterized by the accumulation of multiple risk factors (insulin resistance, hyperglycemia, dyslipidemia, hypertension, visceral obesity) for cardiovascular disease (CVD) in an individual with a background of obesity and/or lack of exercise[1]. However, it is not known whether isolated metabolic syndrome (hyperglycemia or elevated blood pressure but not diabetes mellitus or hypertension)[2] is also associated with abnormal cardiac structure and function. If isolated metabolic syndrome indicates persons who have already developed abnormal left ventricular (LV) structure and

function, early recognition of isolated metabolic syndrome would be important.

The new International Diabetes Federation (IDF) definition of metabolic syndrome, when compared to the National Cholesterol Education Program Adult Treatment Panel III (ATPIII) criteria, allows for better applicability to different ethnic groups, because of ethnic-specific cutoffs for identification of visceral obesity[3,4].

The Tei index was introduced by Tei *et al*[5] as a Doppler-derived index that combines both systolic and diastolic function to separate those with normal ventricular function from those with ventricular dysfunction. This index has been found to correlate well with invasive measures of systolic and diastolic LV function[6]. Measurement of the Tei index is non-invasive and easily obtained, does not require the presence of an experienced echocardiographer, and it does not significantly prolong the time required for the examination[7].

The goal of the current study was to examine the echocardiographic parameters of LV structural and global performance using the Tei index in metabolic syndrome patients with and without hypertension and/or diabetes and in healthy controls.

MATERIALS AND METHODS

Subjects and methodology

A case-control study was performed. One hundred and fifty six consecutive adults with metabolic syndrome were enrolled in the study. All were recruited from the outpatient cardiology, diabetes and general medicine clinics of Suez Canal University Hospital from November 2007 to April 2010. Fifty nine patients fulfilling the hyperglycemia or elevated blood pressure criteria for metabolic syndrome, but not the criteria for diabetes mellitus or hypertension, were considered as having isolated metabolic syndrome (group A). Ninety seven patients had metabolic syndrome with hypertension and/or diabetes, (group B). Thirty four healthy adults with no metabolic syndrome and matched for age and gender comprised the control group. Metabolic syndrome was diagnosed according to the International Diabetes Federation (IDF) definition: waist circumference ⩾ 94/80 cm (men/women) plus any 2 of the following 4 factors: increased triglyceride level ⩾ 150 mg/dL or a specific treatment for this lipid abnormality; reduced high density lipoprotein cholesterol < 40/50 mg/dL (men/women) or a treatment specific for this lipid abnormality; raised blood pressure (BP): systolic BP ⩾ 130 or diastolic BP ≥ 85 mm Hg or treatment of previously diagnosed hypertension; raised fasting plasma glucose ⩾ 100 mg/dL or treatment of previously diagnosed type 2 diabetes[3].

Exclusion criteria were the following: chronic kidney disease; a history or findings of cardiovascular disease including heart failure symptoms or systolic dysfunction; coronary artery disease; significant valvular heart disease (i.e. greater than mild valvular insufficiency, or stenosis) and/or hypertrophic cardiomyopathy; pregnancy or lactation; and/or major systemic illness.

All groups had a full medical history and clinical examination including BP measurement, anthropometric measures, systemic examination, biochemical tests including lipid profile, fasting plasma glucose (FPG), glycosylated hemoglobin (Hb) A1c, and echocardiographic studies. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2) and was used as an estimate of overall adiposity. Waist circumference, a validated estimate of visceral adiposity, was measured to the nearest 0.5 cm[8]. Systemic hypertension was defined according to the Joint National Committee VII (JNC VII) criteria, as a BP > 140/90 mmHg and/or under current antihypertensive therapy[9]. Diabetes was defined according to revised American Diabetes Association criteria as (a) fasting serum glucose level ⩾ 126 mg%, or HbA1c ⩾ 6.5 and/or (b) current medical therapy with an oral hypoglycemic agent and/or insulin[10].

Echocardiographic evaluation

M-Mode and 2D echocardiographic studies were performed with a Hewlett-Packard phased array ultrasonoscope (Sonos 1800, USA, model: DR 53 15) using a 2.5 and 3.5 MHz transducer.

Parameters of LV structure: LV dimensions (systolic diameter (SD) and diastolic diameter (DD), LV diameter (LVD), interventricular septum (IVS) and posterior wall (PW) thicknesses were measured at end diastole (R wave of electrocardiogram) and end systole (maximum posterior motion of septum) and were indicated by d and s, respectively. All were detected in the parasternal long-axis view during M-mode tracing according to the recommendation of the American Society of Echocardiography[11]. LV mass (LVM) was calculated according to the modified cube formula of Mayosi *et al*[12] as follows: LVM = $1.01[(IVS_d + PW_d + DD)^3 - (DD)^3] - 13.6$ g.

LVM index (LVMI) was then calculated as follows: LVMI=LVM/m^2, where m was the height of the patient in meters. Relative wall thickness (RWT) was calculated as the ratio $(IVS_d+PW_d)/LVD_d$. LV geometric pattern was considered normal if LVMI was < 50 g/m^2 and RWT was < 0.44. Concentric remodeling was diagnosed when LVMI was < 50 g/m^2 and RWT was > 0.44; concentric hypertrophy was defined as LVMI > 50 g/m^2 and RWT > 0.44; eccentric hypertrophy was diagnosed when LVMI was > 50 g/m^2 and RWT was < 0.44.

Parameters of systolic function: LV end-diastolic and end-systolic volumes (EDV and ESV) were calculated according to Abraham *et al*[13]; stroke volume was calculated as the difference between EDV and ESV; cardiac output (CO) was obtained as the product of stroke volume and heart rate (HR). Ejection fraction (EF) was calculated as EF% = 100 × (EDV–ESV)/EDV[14].

Parameters of diastolic function: assessment of diastolic function was obtained by pulsed-wave Doppler of both transmitral and pulmonary venous flow patterns recorded in the apical 4-chamber view. Peak flow velocity

Table 1 Clinical and biochemical characteristics of both case and control groups (mean ± SD)

Characteristics	Controls (n = 34)	Group A (n = 59)	Group B (n = 97)	P	P^1	P^2
Age (yr)	46.9 ± 7.4	44.4 ± 7.3	49.9 ± 8.3	NS	NS	NS
SBP (mmHg)	117.5 ± 6.1	134.4 ± 5.6	140.1 ± 8.1	NS	0.01	< 0.05
DBP (mmHg)	78.9 ± 6.4	85.3 ± 4.3	91.9 ± 7.9	NS	0.05	< 0.05
BMI (%)	22.2 ± 1.2	28.7 ± 3.6	31.8 ± 4.7	< 0.5	< 0.01	NS
W. Circum. (cm)	82.2 ± 4.6	98.1 ± 6.5	105.1 ± 7.1	< 0.05	< 0.05	NS
HDL (mg/dL)	45.7 ± 6.9	40.8 ± 6.5	43.2 ± 7.6	NS	NS	NS
Triglyceride (mg/dL)	138.9 ± 16.1	174.7 ± 23.3	181.9 ± 24.1	< 0.05	< 0.05	NS
FPG (mg/dL)	91.7 ± 10.6	98.6 ± 15.2	118.4 ± 43.6	< 0.05	< 0.01	< 0.05
HbA1c (%)	5.10 ± 0.41	6.20 ± 0.30	7.40 ± 1.10	< 0.05	< 0.01	< 0.05

Group A: Isolated metabolic syndrome patients; Group B: Metabolic syndrome patients; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic BP; W. Circum: Waist circumference; HDL: High density lipoprotein cholesterol; FPG: Fasting plasma glucose; HbA1c: Glycosylated hemoglobin; NS: Non significant; P: Comparison between group A (isolated metabolic syndrome) and control; P^1: Comparison between group B (metabolic syndrome) and control; P^2: Comparison between group A and B.

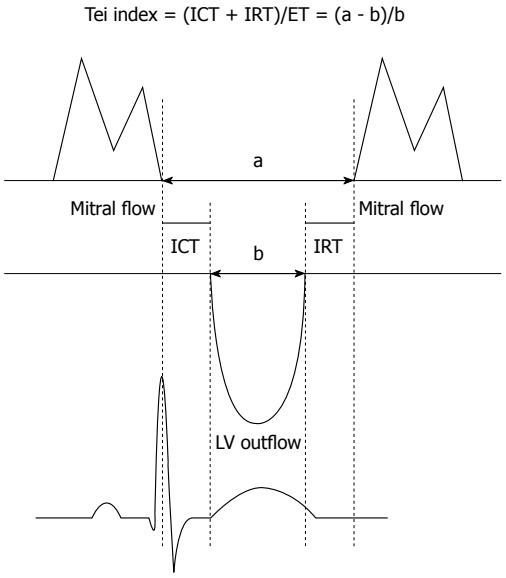

Figure 1 Doppler time intervals included in the Tei index[16]. Measurement of Doppler intervals. The index is defined by the equation (a-b)/b, where a represents the interval between cessation and onset of mitral inflow and b represents the ejection time (ET) of the left ventricular outflow. Isovolumic relaxation time (IRT) is measured by subtracting d, the interval from the peak of the R wave on the ECG to the end of ejection time, from the interval c between the R wave and the onset of mitral inflow. Isovolumic contraction time (ICT) is obtained by subtracting IRT from a-b.

in early diastole (E wave) and during atrial contraction (A wave) and peak E/A ratio were measured. LV isovolumetric relaxation time (IRT) was also measured in ms as the interval between the aortic valve closure click and the start of mitral flow[15].

The following time intervals were measured for Tei index calculation: IRT (ms: from the end of the S wave to the beginning of the E wave); isovolumetric contraction time (ICT ms: from the beginning of the first positive deflection after the Q wave to the onset of the S wave; ejection time (ET) ms: From the beginning to the end of the S wave. The Tei index was calculated as (ICT+IRT)/ET (Figure 1)[16]. A Tei index < 0.40 is considered normal. Higher index values correspond to more pathological states with overall cardiac dysfunction[17].

Ethics

Informed consent was obtained from all adults. The aim and the value of the work were explained in a simplified manner for them. There was no harm inflicted on them. On the contrary all showed a benefit in the follow-up and in the final results of the study. The study was approved by the Ethics Committee of Faculty of Medicine, Suez Canal University. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the institution's Human Research Committee.

Statistical analysis

According to the type of data, the Student unpaired t test and the χ^2 test were used for statistical comparisons between 2 groups. Descriptive statistics were obtained including mean, standard deviation, mode and median for quantitative variables and frequency and percent for qualitative variables. The analysis was carried out by a computer program (SPSS Version 11). The P value was set at < 0.05 for statistically significant results and at < 0.0001 for highly significant results.

RESULTS

Baseline characteristics of 59 patients (33 male, 26 female, mean age 44.4 years) with isolated metabolic syndrome (group A), 97 patients (51 male, 46 female, mean age 49.9 years) with metabolic syndrome (group B) and 34 healthy controls (19 male, 15 female, mean age 46.9 years) are shown in Table 1. In group B, 20 patients had diabetes mellitus, 36 patients had hypertension, and 41 patients had both. The average durations of diabetes and hypertension were 5.4 and 7.2 years, respectively. The majority of diabetics were taking secretogogues, 75% of the hypertensive patients were taking angiotensin converting enzyme inhibitors, but only 40% of patients with dyslipidemia were taking statins. No patient in group A was taking any medications for elevated blood sugar or high blood pressure.

Table 2 Echocardiographic data in both case and control groups (mean ± SD)

Characteristics	Controls (n = 34)	Group A (n = 59)	Group B (n = 97)	P	P^1	P^2
End SD (mm)	28.8 ± 1.5	29.1 ± 1.4	28.8 ± 1.4	NS	NS	NS
End DD (mm)	48.7 ± 4.6	50.6 ± 4.4	49.9 ± 4.5	NS	NS	NS
EF (%)	63.9 ± 7.9	63.5 ± 6.5	62.7 ± 7.4	NS	NS	NS
IVS thickness (mm)	8.6 ± 0.5	8.4 ± 0.6	9.2 ± 0.7	NS	< 0.05	NS
PW thickness (mm)	8.6 ± 0.7	8.6 ± 0.6	9.3 ± 0.9	NS	< 0.05	NS
RWT (%)	36.3 ± 3.6	37.9 ± 3.8	47.7 ± 5.8	NS	< 0.05	< 0.05
LVMI (g/m^2)	88.2 ± 7.4	93.2 ± 4.1	120.8 ± 26.8	NS	< 0.05	< 0.01
E/A ratio	1.41 ± 0.19	1.26 ± 0.12	1.17 ± 0.08	NS	< 0.01	< 0.05
Tei index	0.36 ± 0.07	0.64 ± 0.17	0.87 ± 0.12	< 0.01	< 0.001	NS

End SD: End systolic diameter; End DD: End diastolic diameter; EF: Ejection fraction; IVS: Interventricular septum; PW: Posterior wall; RWT: Relative wall thickness; LVMI: Left ventricular mass index; E: E velocity; A: A velocity; P: Comparison between group A and control; P^1: Comparison between group B and control; P^2: Comparison between group A and B.

No significant difference was observed among the groups regarding age. There were significant differences in BMI, waist circumference, BP, FBS, and triglycerides between group B and the control group. There were significant differences between group A and group B regarding BP, FPG and HbA1c.

Echocardiographic and Doppler data are shown in Table 2. There were no statistically significant differences between group A and controls in all parameters of LV structural, systolic, and diastolic function except the global myocardial performance (Tei index). On the other hand, significant differences were observed between group B and the control group in most of the parameters of LV structural and global performance. Comparing echocardiographic parameters between group A and B, no significant differences were observed except for LVMI, RWT, and E/A ratio.

DISCUSSION

The value of a diagnosis of metabolic syndrome has been challenged because it includes persons with established hypertension and diabetes mellitus, components already known to be CVD risk factors. Metabolic syndrome also includes persons with mild hyperglycemia, but not diabetes, who are at an increased risk of developing overt diabetes[18]. Established hypertension is a powerful risk factor for CVD, but those with pre-hypertension may already manifest detrimental changes in cardiac structure and function[19]. To investigate this further, the current study was undertaken to evaluate whether isolated metabolic syndrome is also associated with abnormal cardiac structure and function. If isolated metabolic syndrome identifies persons who have already developed abnormal LV structural and functional changes, the importance of early recognition of isolated metabolic syndrome would be enhanced.

In the current study, we found structural modifications of the heart in patients with metabolic syndrome. The associated established hypertension and/or diabetes could be thought to be responsible factors in the induction of the structural cardiac changes. Analysis of the current data revealed that concentric hypertrophy appears to be the most obvious morphological change (LVMI > 50 g/m^2 and RWT > 44). Similar results were recorded in various studies[2,20-22]. However, in the current study we observed that, in the metabolic syndrome group, the increase in LVM could be attributed to an increase in septal and posterior wall thickness without changes in LV diastolic diameters, compared with no increase in LVM in the isolated metabolic syndrome group. The concentric hypertrophy may be the result of a lack of increase in LV end-diastolic dimensions, whereas wall thickness increases under the stimulus of the elevated total vascular resistance.

The E/A ratio exhibited a stepwise decrease from the control group to the isolated metabolic syndrome group to the metabolic syndrome group, primarily as a result of increased A-wave velocity. The deceleration time and isovolumic relaxation time were significantly longer in the metabolic syndrome group. These findings suggest that there is a progressive impairment in LV relaxation depending on the component of the metabolic syndrome. The present data showed a significant decrease in diastolic function for group B *vs* control, indicating impairment in diastolic function with the increasing burden of metabolic syndrome.

The results of the present study are consistent with those of prior studies that identified hypertension, diabetes mellitus, and obesity as independent predictors of impaired LV structure and function[23-29]. Increased LV mass, RWT, and deceleration time have been reported in hypertensive subjects with metabolic syndrome compared with a hypertensive cohort without metabolic syndrome[22]. In the Strong Heart Study, those with metabolic syndrome had greater LVM and RWT and significantly lower E/A ratio[21]. Similarly, in the current study, LV diastolic function was not found in the isolated metabolic group but was present in the metabolic syndrome group.

The above altered geometric pattern was associated in the current study with a non significant depressed systolic function in both groups, and significantly altered diastolic function in the metabolic syndrome group. These different findings might be due to the variability in metabolic diagnostic criteria and subsequently the total vascular resistance.

Tei Chuwa devised and published an index of myo-

cardial performance (the Tei index) in 1995 that evaluated LV systolic and diastolic function in combination[16]. The index has proved to be a reliable method for the evaluation of LV systolic and diastolic performance, with clear advantages over older established indexes and has prognostic value in many kinds of heart disease[30,31].

In the current study LV global function was assessed using the Tei index. The Tei index exhibited a stepwise increase from the control group to the isolated metabolic syndrome group to the metabolic syndrome group. In spite of the apparent normal LV systolic function (as shown by a normal EF), the high Tei index predicted the presence of early combined systolic and diastolic function in isolated metabolic syndrome.

Other studies have previously shown that visceral obesity is associated with diastolic dysfunction, an effect that may be mediated by an obesity-related pro-inflammatory state and/or by suppression of adiponectin expression[24,26]. In the current study, even in the isolated metabolic group who were non-diabetic and non-hypertensive and had a BMI significantly lower than that the metabolic syndrome group, the altered global ventricular performance may be mediated by other potential mechanisms. This may contribute to insulin resistance, hypertriglyceridemia with subsequent impaired endothelial dysfunction, abnormalities in myocardial perfusion and/or metabolic substrate utilization, inflammation and oxidative stress, interstitial fibrosis, impaired ventricular–vascular interaction, *etc*.

Finally, as the Tei index is capable of estimating combined systolic and diastolic performance, it could be more advantageous than the isolated measurement of either systolic or diastolic parameters in the early evaluation of global LV function in isolated metabolic syndrome patients. It is simple, noninvasive, easy to use and reproducible. Moreover, the calculation of the Tei index is independent of age, arterial pressure, heart rate, ventricular geometry, atrioventricular valve regurgitation, afterload, and preload in patients who are in a supine position[5,17,28,31,32].

In conclusion, the current study shows that metabolic syndrome groups (those with or without hypertension and or/diabetes) have an associated abnormal LV global performance. The functional changes are independent of and precede the structural changes. In metabolic syndrome the increase in LVMI is physiologically consistent with an increase in LV diastolic dysfunction. The identification of isolated metabolic syndrome in non-diabetic, non-hypertensive adults may be an indication that aggressive preventive measures should not be postponed until overt obesity, hypertension or diabetes mellitus have developed.

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CASE REPORT

Right coronary artery from the left sinus of valsalva: Multislice CT and transradial PCI

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Abstract

A 42-year-old-woman presented with *de novo* crescendo angina. Thallium-scintigraphy showed inferior ischemia. Coronary angiogram revealed a right coronary artery (RCA), originating from the left sinus of Valsalva with a severe proximal systolic compression. She underwent successful transradial percutaneous coronary intervention with stent implantation. Multislice-computed tomography (MSCT) is usually used to evaluate coronary artery anomalies and can effectively show the anomalous RCA and the inter-arterial trajectory between the aorta and pulmonary arteries. Anomalies of the origin of the coronary arteries are rare, but can produce specific clinicopathological entities that should be diagnosed with accuracy. This case report illustrates the role of MSCT in the detailed description of an abnormal coronary artery and the use of stenting for symptoms relief.

INTRODUCTION

Coronary artery anomalies occur in approximately 1% of the population, often without other congenital cardiac malformations[1]. The abnormal origin of the right coronary artery (RCA) from the left aortic sinus of Valsalva is a very rare congenital anomaly, frequently coursing between the aorta and the pulmonary artery[2].

CASE REPORT

A 42-year-old woman presented with a history of *de novo* crescendo angina. The patient decided to enter the National Army Services. Following standard procedures, she began progressive and very stringent exercise training. During intense exercise sessions, she started to complain of typical angina. Despite no previous chest pain episodes, nor any cardiovascular risk factors, she underwent a complete workout to rule out atherosclerotic coronary

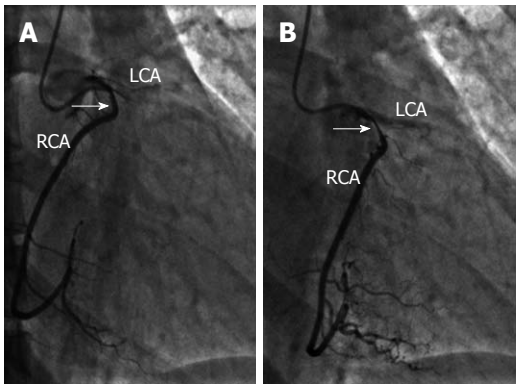

Figure 1 Coronary angiogram of the right coronary artery. Coronary angiography showing a significant compression of the proximal right coronary artery (RCA) due to an inter-arterial trajectory between the pulmonary artery and the aorta during systole (arrows). A: Diastole; B: Systole. LCA: Left coronary artery.

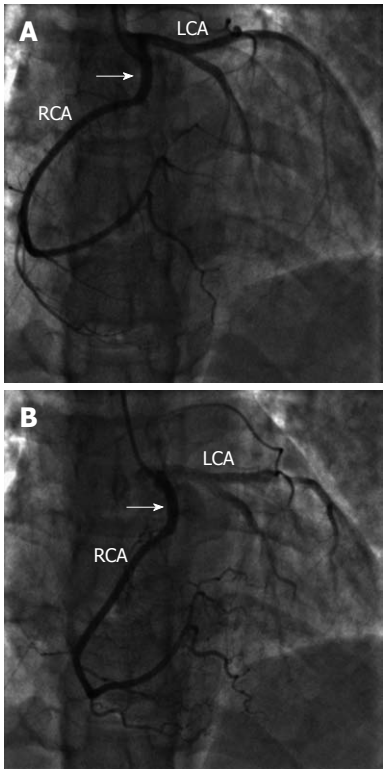

Figure 2 Coronary angiogram following successful transradial percutaneous coronary intervention. Coronary angiography showing no compression effect (arrows) after successful stent implantation in the proximal right coronary artery (RCA). A: Diastole; B: Systole. LCA: Left coronary artery.

artery disease. Thallium scintigraphy showed inferior ischemia. Therefore she was referred to our tertiary care center for diagnostic coronary angiography and possible revascularization therapy. The coronary angiogram showed a left coronary artery from the left sinus of Valsalva without significant lesion. The right coronary artery (RCA) originated from the left sinus and demonstrated a severe systolic compression (Figure 1A and B). Several injections/projections were performed after the injection of intracoronary nitroglycerine, and no changes nor improvement were observed. She underwent right radial percutaneous coronary angioplasty using a 6 Fr Amplatz Left 2 guiding catheter, and a 3.5 mm × 16 mm bare-metal stent (Liberté®, Boston Scientific Corporation, Natick, MA, US) was successfully implanted (Figure 2A and B).

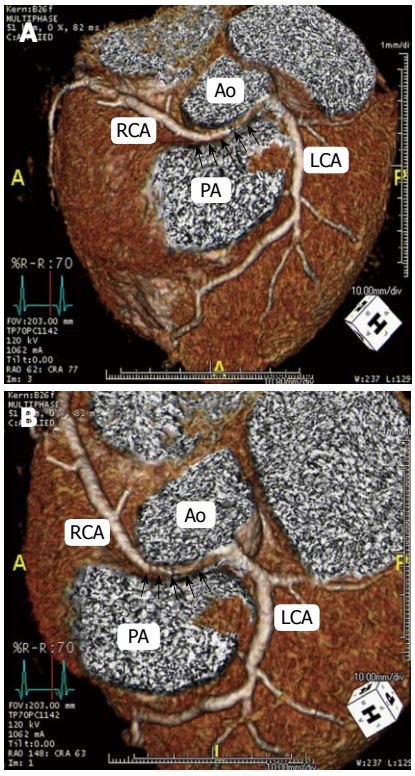

Figure 3 Three-dimensional volume rendered multislice computed tomography (A and B). Computed tomography image showing the right coronary artery (RCA) arising from the left sinus of Valsalva, and an inter-arterial trajectory (black arrows) between the pulmonary artery (PA) and the aorta (Ao). LCA: Left coronary artery.

Multi-slice computed tomography (MSCT) is usually used and can effectively show the RCA arising from the left sinus of Valsalva and its inter-arterial trajectory (Figure 3A and B, arrows) between the aorta and the pulmonary arteries. After 1 year follow-up, the patient has remained asymptomatic with a negative stress test.

DISCUSSION

In this case report, we describe the case of a young woman without cardiovascular risk factors who presented with typical effort angina and inferior ischemia. Angiography revealed dynamic compression of an abnormally arising right coronary artery and she was treated by transradial bare-metal stent implantation.

Anomalies of the origin of the coronary arteries are rare, but can provide specific clinicopathological entities that should be diagnosed with a high degree of accuracy. The origin of both coronary arteries from the left sinus of Valsalva is a very rare (0.28%) anomaly[3]. Manifestations vary from asymptomatic patients to those who present with angina pectoris, myocardial infarction, heart failure, syncope, arrhythmias, and also sudden death[1]. Myocardial ischemia in association with this anomaly is thought to be

caused by an abnormal slit-like RCA ostium, acute angulations, and compression of the RCA between the aorta and pulmonary trunk during exercise[3]. Extrinsic compression of the left main coronary artery can occur in patients with severe pulmonary hypertension and enlarged pulmonary artery trunk[4,5]. It has usually been described in the setting of congenital defects such as atrial septal defect, ventricular septal defect, and, more rarely, isolated persistent ductus arteriosus[4,5]. MSCT allows 3-dimensional visualization of the coronary arteries with high spatial resolution, and may be the most promising imaging modality for diagnosing these anomalies[4-6].

Surgical correction or coronary artery bypass grafting can be carried out with minimal risk and good anatomic and functional results[7,8]. Although the risks of surgical intervention are low in young subjects, surgery requires opening the chest and may be complicated by aortic valve damage or neurological emboli.

This case-report illustrates the role of MSCT in the detailed description of an abnormal coronary artery and the use of stenting symptoms relief. In the presence of a symptomatic patient with an isolated RCA anomaly and no other atherosclerotic coronary disease, transradial percutaneous intervention could be an effective and safe option.

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Interrelation between arterial inflammation in acute coronary syndrome and circadian variation

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Abstract

At present, the study into inflammatory markers has become a new tool which is most useful for establishing the prognosis of patients with acute coronary syndrome. The inflammatory substrate involved is acute coronary syndrome is extremely complex, with a large number of factors involved both in its activation and its modulation. It is known that C-reactive protein play a key role in the physiopathology of the atherosclerosis. Furthermore, scientific literature reports that the existence of a circadian rhythm in the triggering of cardiovascular accidents can suggest the implication of, or association with these physiological rhythms that show activity peaks at particular times of the day or night. Keeping in mind the potential association between inflammation and circadian rhythm, a better understanding of the kinetics of said markers could lead to improvements in their use in cardiovascular diseases. Considering the diversity of the diurnal variations in the intrinsic properties of the cardiovascular system, these should be kept in mind during the design of in vivo experimental studies. As such, the information available reinforces our opinion when suitably validating the biomarkers and the need to demonstrate their reliability, stability, and lack of variability and standardise the methodology of their measurement.

Key words: Inflammatory markers; Acute coronary syndrome; Circadian rhythm

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TO THE EDITOR

In his scholarly article, Fay[1] reviewed the effects of C-reactive protein (CRP) on hemostasis, platelet function, and fibrinolysis. However, we would like to point out an important aspect of the significance of light-dark variations in CRP in acute coronary syndrome (ACS).

Cardiovascular parameters such as heart rate, blood pressure, endothelial function and fibrinolytic activity exhibit variations consistent with a circadian rhythm[2]. Likewise, circulating biomarkers are subjected to variability arising from sampling procedures and biologic variation, which must be determined and adjusted for the interpretation of laboratory results[3]. Diurnal variation may be an important source of heterogeneity or bias, and standardization for sampling time may be important in population-based studies, as well as in using these variables for additional coronary heart disease risk prediction in individuals[3].

CRP represents the most extensively studied proinflammatory molecule, but additional effort is required

on the part of investigators to manage standardization of methodology, to establish cut-off points that separate populations with different risks, and to determine cost-effective timing and frequency of measurements[3]. Conflicting clinical data exist with respect to its prognostic value, probably a reflection of the different times when samples were taken and the wide variation in the results obtained[4]. Sánchez *et al*[5] have demonstrated a variation in CRP kinetics in patients with ACS. The scientific literature has described circadian variations in the circulating concentrations of some cytokines and acute phase reactants[3]. In a recent report, Rudnicka *et al*[6] described one of the largest cross-sectional studies on seasonal and diurnal fluctuations in fibrinogen, CRP, fibrin d-dimer, tissue plasminogen activator antigen, and von Willebrand factor in 9377 men and women aged 45 years. These investigators demonstrated that diurnal variations exist for these biomarkers. Likewise, work by our group among patients with ACS has shown daytime variations in serum CRP concentrations, which displayed that the serum CRP values are significantly higher in the light phase (9:00 am) than in the dark phase (2:00 am)[7,8].

Several lines of evidence suggest that an understanding of the chronobiological implications for cardiovascular therapy may prove fruitful. The kinetics of CRP is interesting, since a variation in the inflammatory functions during the 24-h period may hypothetically allow identification moments of the day or the night in which "inflammatory bursts" are most likely to occur and, accordingly, increase the incidence of cardiovascular events. Thus, the timing of drug administration can be altered to improve therapeutic efficacy[3].

In conclusion, preanalytic conditions, such as diurnal variation on CRP levels, are of paramount importance.

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Cardiovascular physiology at the bench for application in the clinic

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Abstract

Our research focuses on microphysiological aspects of the cardiovascular system, with an emphasis on what is occurring in heart tissues, to learn more about how various diseases arise and how they can be avoided or cured. These diseases include atherosclerosis, diabetes, myocardial infarction, obesity and ischemia/reperfusion (I/R). We use animal models, particularly mice, to aid us in these studies. A key feature of our work centers on dissection of coronary arterioles and examining their functionality using drugs, electrophysiology, fluoroscopy, genomics, proteomics, and standard chemical analyses to determine their physiological status, and compare it with other treated animals. My laboratory is focusing on anti-inflammatory and antioxidative stress therapeutic effects, the roles of sodium salicylate, exercise and resveratrol in type 2 diabetes, I/R injury, obesity, and atherosclerosis. Recently, we began investigations of the effects of stem cells and gastric bypass surgery on vascular dysfunction in obesity and diabetes. Our work identifies how diet, exercise, surgical interventions and drugs can be considered to combat these diseases in a clinical setting.

Key words: Coronary artery disease; Cytokines; Inflammation; Microcirculation; Nitric oxide; Reactive oxygen species

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INTRODUCTION AND EDUCATIONAL EXPERIENCE

Dr. Cuihua Zhang received her medical degree in 1985 from Jin Zhou Medical College (Liaoning, China) and her PhD in 1995 from the Chinese Academy of Medical Science and Peking Union Medical College (Beijng, China), where she studied endothelium-derived relaxation factor and nitric oxide in hypertension[1,2]. Dr. Cuihua did her postdoctoral work beginning with a research fellowship in Dr. Benidito Machado's laboratory in the Department of Physiology School of Medicine of Ribeirão Preto University, São Paulo, Brazil. She investigated the roles of blockade of neurokinin-1 receptors in the nucleus tractus solitarii of awake rats in the cardiovascular responses to chemoreflex activation[3]. She continued with postdoctoral work in Dr. Lih Kuo's laboratory in the Department of Medical Physiology in the Medical College at Texas A&M

University (TAMU)[4-12] (Figure 1, Mentor Dr. Lih Kuo and Cuihua Zhang), then accepted appointments in the Departments of Anesthesiology, Surgery, and Physiology in the School of Medicine at Louisiana State University Health Sciences Center in New Orleans as an Assistant Professor (Figure 2, 1st Zhang Laboratory), and then returned to TAMU as an Assistant Professor in Veterinary Physiology and Pharmacology, and affiliated with the Michael E. DeBakey Institute and the Cardiovascular Research Institute in the College of Medicine Health Science Center at TAMU, until coming to the University of Missouri-Columbia in January 2008. She currently is an Associate Professor of Medicine, Medical Pharmacology and Physiology, and Nutrition and Exercise Physiology in the Division of Cardiovascular Medicine in the University of Missouri-Columbia (Figure 3).

Figure 1 Dr. Cuihua Zhang and her postdoctoral mentor Dr. Lih Kuo in 2003 at an Experimental Biology meeting.

Figure 2 The team at Louisiana State University Health Sciences Center, New Orleans. Front Row: Souad Belmadani, Cuihua Zhang, Marta Focardi, Jinjiang Peng, Xue Gao. Back Row: Eric T Guilbeau, Andrea Picchi, Xiangbin Xu.

Figure 3 Cuihua Zhang, MD, PhD, FAHA, Division of Cardiovascular Medicine in the Departments of Internal Medicine, Medical Pharmacology and Physiology, Nutrition and Exercise Physiology, Dalton Cardiovascular Research Center, University of Missouri-Columbia, 134 Research Park Drive, Columbia, MO 65211, United States.

ACADEMIC STRATEGY AND GOALS

During the past decade, Dr. Cuihua has developed a successful independent research program conducting basic research in coronary microcirculation, which is aimed at understanding the underlying mechanisms responsible for the pathophysiological manifestations of ischemic heart disease. Specifically, her laboratory primarily studies natural and genetically modified murine strains to understand the role of specific genes in the pathophysiological sequelae of cardiovascular disease, i.e. atherosclerosis, hypertension, ischemia/reperfusion (I/R) injury, and diabetes at the molecular, cellular and intact tissue levels. Dr. Cuihua serves on the American Heart Association and National Institutes of Health study sections, editorial boards (*American Journal of Physiology-Heart and Circulatory Physiology*, *Basic Research in Cardiology*, *Circulation Research*, *Frontiers in Vascular Physiology* and *World Journal of Cardiology*), and organizes and moderates sessions in professional meetings (Experimental Biology Meetings, American Heart Association Scientific Sessions, Arteriosclerosis, Thrombosis, and Vascular Biology Annual Conference and World Congress for Microcirculation). Her research has resulted in the publication of approximately 70 peer-reviewed publications and has generated more than $4 million in grant support. Progress has been made in finding therapeutic remedies for the above-mentioned diseases as a result of her work.

ACADEMIC ACHIEVEMENTS

Dr. Cuihua's research focuses on basic investigations in vascular biology, especially in coronary microcirculation and cardiovascular physiology (Figure 4, vasculature image). Heart malfunctions are at the root of many diseases and include risk factors such as atherosclerosis, I/R injury, and diabetes. Obtaining detailed knowledge of the mechanisms that lead to heart dysfunction can: (1) identify therapeutic targets for new and more effective drugs; (2) provide new protocols to reduce risks associated with surgical procedures; (3) suggest improvements in diet and exercise therapies; and (4) aid in discovering new remedies for cardiovascular disease. Her ongoing projects in the laboratory include studying the role of inflammatory cytokines in vascular dysfunction in type 2 diabetes. Another research interest is aimed at understanding a contributing factor to the pathophysiological manifestations of ischemic heart disease by assessing a potential role of the

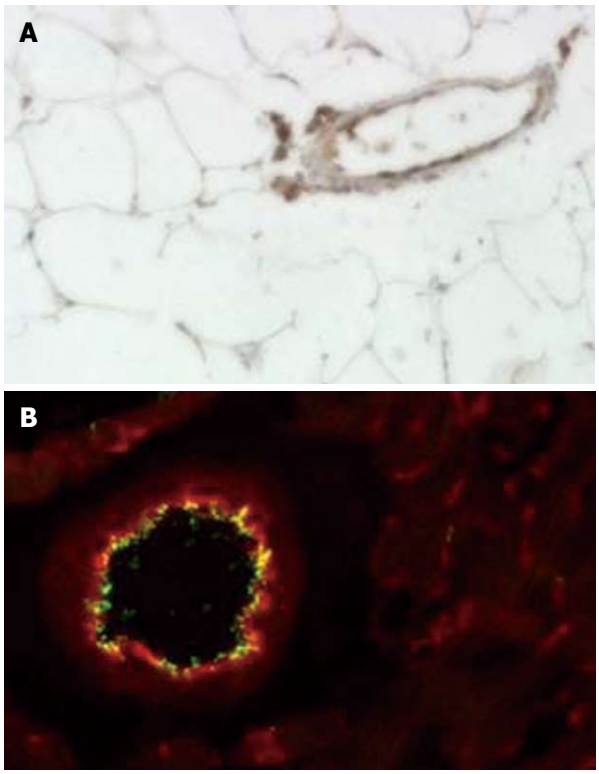

Figure 4 The magic of blood vessels in "A" shows that Mac3 positive macrophages infiltrate the adventitia of small vessels in the mesenteric adipose tissue of diabetic mice. The magic of blood vessels in "B" shows adiponectin is co-localized with endothelial layers of a small artery in the heart tissue of mice with genetic detection of tumor necrosis factor.

inflammatory cytokine, tumor necrosis factor (TNF)-α in I/R injury. A murine genetic model (TNF over-expression, TNF++/++ mice) is used for these studies. The TNF++/++ transgenic model offers a unique approach that allows assessment of the role played by TNF in many cardiovascular diseases. This work is supported by National Institutes of Health (NIH) funding (RO1) of the program. This was recognized with the 2007 Werner Risau New Investigator Award in Vascular Biology[13] by American Heart Association Journal, stemming from the Zhang Laboratory 2006 publication in *Arteriosclerosis*, *Thrombosis*, *and Vascular Biology*.

Discovery of a new paradigm for vascular inflammation in I/R injury

The basic factors leading to microvascular dysfunction in the pathophysiology of I/R injury involve a series of events that begin with ischemia, characterized by reduction of blood flow, inadequate oxygen supply, reduction in cellular energy stores, and accumulation of noxious metabolites. These conditions begin to improve when blood flow is restored, but reperfusion injury occurs when blood flow carries reactive oxygen species (ROS), including peroxynitrite, which is derived from reactions between nitric oxide (NO) and superoxide anions, into the affected tissue. Differentiation of the contributions of ischemia from those of reperfusion to microvascular dysfunction is difficult, and the current focus is on documentation of the degree and manner in which reperfusion exacerbates cellular damage that is initiated during ischemia. The reason for this focus is that ischemia is usually a pre-existing condition that the patient presents to the clinician, and the quickest remedy is for the clinician to induce reperfusion. If we understand the exact process of damage that accompanies reperfusion, then useful remedies can be developed and applied by the clinician when reperfusion is induced.

The formation of oxygen-derived free radicals depends on the generation of superoxide anions through endothelium- and leukocyte-stimulated biochemical reactions. This understanding is based on the facts that endothelial cells contain xanthine oxidase, whereas leukocytes feature membrane-bound NADPH oxidase. Although leukocyte-endothelium interactions are nearly universally established in inflammatory processes and in the increased microvascular permeability to macromolecules in I/R[14-16], the results of Zhang *et al*[14] and Gao *et al*[15,16] have demonstrated that their activation is not a relevant mechanism of action for TNF-induced derangement of vasodilation. We have shown that TNF enhances generation of superoxide, and the same deleterious microcirculatory effects in control and leukopenic animals; an observation that supports an important direct action of TNF on microvascular cells, which leads to the generation of ROS and a decrease in the vasodilatory capacity of coronary arterioles. We also hypothesize that neutralization of TNF at the time of reperfusion exerts a beneficial effect on endothelial function and reduces the production of ROS. We have employed a murine model of myocardial I/R (30 min/90 min) and administered TNF-neutralizing antibodies at the time of reperfusion. I/R elevated TNF expression (mRNA and protein), whereas administration of anti-TNF prior to reperfusion attenuated TNF expression. We have detected TNF expression in vascular smooth muscle cells, mast cells and macrophages, but not in endothelial cells. I/R induces endothelial dysfunction and superoxide production. Administration of anti-TNF at the onset of reperfusion partially restores NO-mediated coronary arteriolar dilation and reduces superoxide production. I/R increases the activity of NADPH oxidase and xanthine oxidase, and enhances the formation of nitrotyrosine residues in untreated mice compared to sham-treated animals. Administration of anti-TNF prior to reperfusion blocks the increase in activity of these enzymes. Inhibition of xanthine oxidase (allopurinol) or NADPH oxidase (apocynin) improves endothelium-dependent dilation and reduces superoxide production in isolated coronary arterioles following I/R. I/R enhances superoxide generation and reduces endothelial function in neutropenic animals, and in mice treated with a neutrophil NADPH oxidase inhibitor, which indicates that the effects of TNF are not through neutrophil activation. We conclude that myocardial ischemia initiates TNF expression, which induces vascular oxidative stress, independent of neutrophil activation, and leads to coronary endothelial dysfunction.

Molecular mechanisms and therapies in diabetic microvasculopathy

Recent evidence suggests that inflammation plays a role in the development of insulin resistance, and predicts the development of type 2 diabetes mellitus. Type 2 diabetes mellitus is often anticipated by the development of the metabolic syndrome, which is a clustering of atherosclerotic cardiovascular risk factors characterized by visceral adiposity, insulin resistance, low high-density lipoprotein cholesterol, and a systemic proinflammatory state. The diagnosis of the metabolic syndrome appears to identify substantial additional risks beyond the individual risk factors. Inflammation is a condition that underscores much cardiovascular pathology, including endothelial dysfunction, but no link has yet been established between the vascular pathology of the metabolic syndrome and a particular inflammatory cytokine. We hypothesized that impairments in coronary endothelial function in obesity, the prediabetic metabolic syndrome, is caused by TNF overexpression. Our results have demonstrated that endothelial dysfunction in obesity is the result of effects of the inflammatory cytokine TNF and subsequent production of superoxide. Our work is supported by an AHA award (SDG) to our program, and some results were published in *Circulation Research* in 2006[17], and have been reported at national and international meetings.

Our work also examines the mechanisms underlying the endothelial dysfunction of the coronary artery in pathological conditions such as coronary artery disease and other cardiovascular-related health problems of particular importance in the United States. We utilize genetic models for obesity and type 2 diabetes ($Lepr^{db}$ mouse), the heterozygote lean controls (m $Lepr^{db}$), and $Lepr^{db}$ mice null for TNF (db^{TNF-}/db^{TNF-})[18]. We have chosen to focus on TNF because this cytokine is one of the key inflammatory mediators that are expressed during a variety of inflammatory conditions. Furthermore, TNF initiates the expression of an entire spectrum of inflammatory cytokines ranging from many interleukins to interferon. Our hypothesis regarding diabetes diverges when considering the enzyme system responsible for this pathophysiological disease. Diabetes is one of the leading risk factors for the development of coronary artery and peripheral vascular diseases. Before vascular disease develops in diabetes, endothelial dysfunction occurs. In fact, endothelial dysfunction appears to be a hallmark that underlies many vascular diseases with differing etiology. We believe that understanding endothelial dysfunction is crucial because the progression of vascular disease may be halted if endothelial dysfunction is rectified. Our goal has been to delineate a potential cause of endothelial dysfunction by testing the hypothesis that TNF induces the inflammation that is responsible for endothelial dysfunction in type 2 diabetes. Our data have revealed that endothelial function is normal in diabetic mice that lack TNF (TNF knockout in the $Lepr^{db}$ diabetic mouse). Moreover, we have observed that diabetic mice have elevated expression of TNF, which suggests that this inflammatory cytokine produces, or at least contributes to, endothelial dysfunction in diabetes[19-26]. We also have found that the endothelial dysfunction induced by TNF in diabetes is related to excess production of the free radical, superoxide. Finally, we have observed that advanced glycosylation end products (AGEs) and their receptors (RAGEs) seem to amplify TNF expression in diabetes; thus, TNF and AGE/RAGE signaling play pivotal roles in endothelial dysfunction in type 2 diabetes. The work is supported by an NIH grant (RO1) to our program, and some results have been published in *Circulation*[18] and *American Journal of Physiology - Heart and Circulatory Physiology*[27]. Our current studies on the role of lectin-like oxidized low-density lipoprotein receptor (LOX)-1 in atherosclerosis have documented the first direct evidence that endothelial dysfunction in atherosclerosis is mediated, at least in part, *via* the interaction of oxidized low-density lipoprotein (Ox-LDL) with its receptor, LOX-1, which in turn stimulates endothelial generation of superoxide radicals by activation of NADPH oxidase. The results of this study may contribute to the development of novel adjunctive therapies using anti-Ox-LDL and/or anti-LOX-1 antibodies or soluble receptors to prevent endothelial dysfunction following atherosclerosis[28].

Basic factors in vascular dysfunction

We have experience with measuring transmural differences in coronary arteriolar dilation in response to adenosine[6]; pathophysiological disturbances in hypertension[11] and I/R[7]; endothelial regulation of vascular function; heterogeneous coronary arteriolar dilation in response to β2-adrenergic receptor activation[5], and the role of NO and K-ATP channels[4]; divergent roles of angiotensin II AT1 and AT2 receptors[8] in modulating coronary microvascular function, and the effect of TNF-induced production of superoxide on endothelium-dependent, NO-mediated dilation of coronary arterioles; and the role of ceramide signaling and xanthine oxidase[29]. This experience combined with newly available murine genetic models has allowed rapid progress in understanding cardiovascular pathophysiology in our laboratory.

CONCLUSION

In summary, we believe that activation of inflammatory cytokines, especially TNF, leads to the interaction of AGEs/RAGEs and Ox-LDL/LOX-1, which causes progression of inflammatory disorders and initiates endothelial dysfunction, which culminates in coronary microcirculation in type 2 diabetes, I/R injury, obesity, and atherosclerosis. The excessive production of TNF[30] has a deleterious downstream effect by augmentation of ROS production[31] and limiting NO bioavailability in endothelial cells, which results in reducing NO-dependent vasodilation in vascular smooth muscle cells. Our laboratory is focusing on anti-inflammatory and antioxidative stress therapeutic effects, and the roles of sodium salicylate[22], exercise and resveratrol[24,25] in type 2 diabetes[18,19,21-23,27], I/R injury[13-16], obesity[17] and atherosclerosis[28,32]. Recently,

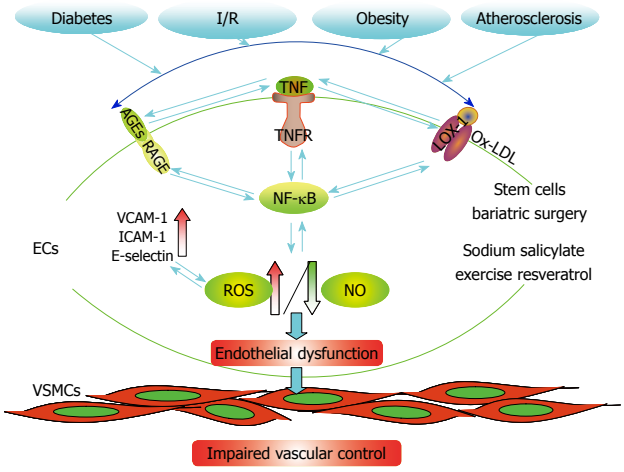

Figure 5 Activation of inflammatory cytokines leads to the interaction of advanced glycosylation end product and their receptor and oxidized low-density lipoprotein/lectin-like oxidized low-density lipoprotein receptor-1, which causes progression of inflammatory disorders which initiates endothelial dysfunction and culminates in coronary microcirculation in type 2 diabetes, ischemia/reperfusion injury, obesity, and atherosclerosis. The excessive production of tumor necrosis factor (TNF)-α has a deleterious downstream effect by augmentation of superoxide production and limiting nitric oxide (NO) bioavailability in endothelial cells, which results in reduction of NO-dependent vasodilation. My laboratory is focusing on anti-inflammatory and antioxidative stress therapeutic effects, and the roles of sodium salicylate, exercise and resveratrol in type 2 diabetes, ischemia/reperfusion (I/R) injury, obesity, and atherosclerosis. Recently, we have started looking at the effects of stem cells and bariatric surgery on vascular dysfunction in obesity and diabetes. ROS: Reactive oxygen species; NF-κB: Nuclear factor κB; Ox-LDL: Oxidized low-density lipoprotein; LOX-1: Lectin-like oxidized low-density lipoprotein receptor-1; AGEs: Advanced glycosylation end products; RAGE: Advanced glycosylation end products receptor; ECs: Endothelial cells; VSMCs: Vascular smooth muscle cells.

we have started looking at the effects of stem cells and gastric bypass surgery[33] on vascular dysfunction in obesity and diabetes (Figure 5).

Dr. Cuihua credits her postdoctoral success to her many mentors that include training by Drs. Yongfeng Zheng, Benedito Machado, Lih Kuo, Michael Davis, and William Chilian; administrators in many institutions that had sufficient faith in her abilities to employ her; receptivity of funding agencies to her proposals; collaborators, postdoctoral workers and committed graduate students that have shared fresh ideas and added new approaches of mutual interest; dedicated technical personnel in the laboratory and administrative personnel at the institutional level whose hard work keeps projects on track; and opportunities for involvement with scientific organizations, where one can make the transition from education achieved by pursuing a formal degree to a lifetime of continuing education, which are supported by the meetings, publications and other activities that they support. A scientific career can be much more than a job, and it can, under the best of circumstances, become a way of life. Success, Dr. Cuihua believes, is not an individual accomplishment, but rather a collective outcome that results from the interactions that take place between the individual and other persons in their everyday lives. Alacrity is the best trait to cultivate in oneself to have the best chance of success. Dr. Zhang has trained and interacted with > 10 postdoctoral fellows and > 5 graduate students in the past 8 years. It is a joy to see young scientists using their training and becoming successful.

Our future plans are to build and expand this research program along the lines outlined above for the next few years. We also expect new animal models, diagnostic techniques and therapeutic agents to be developed and delivered to reduce the risks and ravages of cardiovascular disease. I am excited that our laboratory can participate in that future to improve human health through science.

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Meetings

Events Calendar 2011

January 25
Moving towards a national strategy for Chronic Obstructive Pulmonary Disease
London, United Kingdom

Februrary 24-26
Abdominal Obesity 2011 - 2nd International Congress on Abdominal Obesity
Buenos Aires, Argentina

Februrary 25-27
CardioRhythm 2011
Hong Kong, China

March 19-26
Cardiology Update: Caribbean Cruise
San Diego, CA, United States

March 25
Cardiology for General Practice
London, United Kingdom

April 1-2
11th Annual Spring Meeting on Cardiovascular Nursing
Brussels, Belgium

April 14-16
EuroPRevent 2011
Genova, Switzerland

April 30-May 4
ATC 2011 - 2011 American Transplant Congress
Philadelphia, United States

May 11-14
3th Radiochemotherapy and Brachitherapy Congress & 6th Medical Physycs Meeting
Córdoba, Argentina

May 15-18
ICNC10 - Nuclear Cardiology and Cardiac CT
Amstedan, The Netherlands

May 19-20
Adult Cardiovascular Pathology
London, United Kingdom

May 20-22
XXIX NATIONAL CARDIOLOGY CONGRESS
Córdoba, Argentina

May 20-22
4th Meeting Uremic Toxins and Cardiovascular Disease
Groningen, The Netherlands

May 21-24
Heart Failure Congress 2011
Gothenburg, Sweden

June 2-5
CODHy 2011 - The 1st Asia Pacific Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension
Shanghai, China

June 26-29
EHRA EUROPACE 2011
Madrid, Spain

June 29-July 1
Hands-on Cardiac Morphology - Summer Edition
London, United Kingdom

August 27-31
ESC 2011 - European Society of Cardiology Congress 2011
Paris, France

October 23-26
9th International Congress on Coronary Artery Disease
Venecia, Italy

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Instructions to authors

GENERAL INFORMATION

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The columns in the issues of *WJC* will include: (1) Editorial: To introduce and comment on major advances and developments in the field; (2) Frontier: To review representative achievements, comment on the state of current research, and propose directions for future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To review systemically progress and unresolved problems in the field, comment on the state of current research, and make suggestions for future work; (8) Original Articles: To report innovative and original findings in cardiology; (9) Brief Articles: To briefly report the novel and innovative findings in cardiology; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJC*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of cardiology; and (13) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on the research in cardiology.

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stepwise), correlation, analysis of variance, analysis of covariance, *etc*. The reviewing points include: (1) Statistical methods should be described when they are used to verify the results; (2) Whether the statistical techniques are suitable or correct; (3) Only homogeneous data can be averaged. Standard deviations are preferred to standard errors. Give the number of observations and subjects (*n*). Losses in observations, such as drop-outs from the study should be reported; (4) Values such as ED50, LD50, IC50 should have their 95% confidence limits calculated and compared by weighted probit analysis (Bliss and Finney); and (5) The word 'significantly' should be replaced by its synonyms (if it indicates extent) or the *P* value (if it indicates statistical significance).

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Department, Korgialenio-Benakio Red Cross Hospital, Athens 15451, Greece

Author contributions: The format of this section should be: Author contributions: Wang CL and Liang L contributed equally to this work; Wang CL, Liang L, Fu JF, Zou CC, Hong F and Wu XM designed the research; Wang CL, Zou CC, Hong F and Wu XM performed the research; Xue JZ and Lu JR contributed new reagents/analytic tools; Wang CL, Liang L and Fu JF analyzed the data; and Wang CL, Liang L and Fu JF wrote the paper.

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Key words

Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

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Data that are not statistically significant should not be noted. $^{a}P < 0.05$, $^{b}P < 0.01$ should be noted ($P > 0.05$ should not be noted). If there are other series of *P* values, $^{c}P < 0.05$ and $^{d}P < 0.01$ are used. A third series of *P* values can be expressed as $^{e}P < 0.05$ and $^{f}P < 0.01$. Other notes in tables or under illustrations should be expressed as ^{1}F, ^{2}F, ^{3}F; or sometimes as other symbols with a superscript (Arabic numerals) in the upper left corner. In a multi-curve illustration, each curve should be labeled with ●, ○, ■, □, ▲, △, *etc.*, in a certain sequence.

Acknowledgments

Brief acknowledgments of persons who have made genuine contributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

REFERENCES

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1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

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Italics
Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
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