Coronary Artery Disease

Effects of Coronary Intervention on Cardiopulmonary Exercise Testing in Men with Stable Coronary Artery Disease – A Pilot Observation

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Objective: To evaluate whether there is improvement of physiologic response in men with stable coronary artery disease (CAD) receiving percutaneous coronary interventions (PCI) compared to those with syndrome X by cardiopulmonary exercise test (CPX).

Method: We prospectively enrolled men with effort angina and ischemic treadmill exercise test or thallium-201 myocardial scan from outpatient department for coronary angiography (CAG) from 2007 to 2009. Patients with advanced valvular heart disease and poor ejection fraction by echocardiography were excluded. According to the result of CAG, they were divided into two groups: those receiving PCI (PCI group) and those without obvious stenosis syndrome X patients (syndrome X group). CPX was carried out before and after CAG with an interval of 4 weeks. A series of physiological parameters were obtained, including age, BMI, lipid profiles, biochemical tests, heart rate, blood pressure, VO_2max, VE/VCO_2, anaerobic threshold, exercise duration, cardiac output (CO), cardiac power output (CPO), and cardiac reserve.

Results: Totally, 20 men, mean age 51.9 year-old, were enrolled in the study. There were significantly lower levels in cardiac reserve and peak exercise CPO before CAG in the PCI patients, but no significant differences between age, BMI, biochemical tests or other parameters obtained from CPX before and after CAG between groups.

Conclusion: By CPX, only peak exercise CPO and cardiac reserve before PCI are significantly lower in men with stable CAD, as compared to those with syndrome X. Whether PCI is able to improve CPX remains unclear after this pilot study.

Key Words: Cardiopulmonary exercise test • Coronary artery disease • Syndrome X • Coronary angioplasty • Cardiac power output • Cardiac reserve

INTRODUCTION

There had long been debate regarding whether patients with stable coronary artery disease will benefit from coronary angioplasty until the results of the COURAGE study came out.[1] Those results showed that the outcome of cardiovascular events and all cause mortality were not reduced following coronary interventions (PCI) as compared to intensive medical treatment and life modifications in patients with stable angina. These findings were contrary to previous studies

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that coronary revascularization could substantially improve the poor prognosis and outcome in patients with acute coronary syndromes or severe coronary artery disease associated with markedly depressed left ventricular function.[2,3]

In stable coronary artery disease, symptom of effort angina results from imbalance between myocardial blood supply and oxygen demand based on two distinct mechanisms involving epicardial coronary artery stenosis and decreased microvascular circulation, both of which will attenuate coronary blood flow and reduce coronary reserve during exercise. Clinically, these two entities, known as epicardial coronary artery disease and syndrome X,[4] were difficult to differentiate until the availability of coronary anatomy imaging by invasive angiography.

Recently, evidence demonstrating the potential value of cardiopulmonary exercise testing (CPX) to accurately detect myocardial ischemia secondary to coronary artery disease has been beginning to emerge.[5] It is clear that the net physiologic effect of exercise-induced left ventricular dysfunction is common to both micro-vascular and macrovascular coronary artery disease. Therefore the abnormal physiologic response to CPX may be similar in patients with macro- and micro-vascular ischemia.[6] Since CPX has been used to predict the prognosis and outcomes of heart failure, peak aerobic exercise capacity was found to be the strongest independent predictor of mortality compared with other established risk factors among both healthy individuals and those with cardiovascular disease.[7] More specifically, peak aerobic exercise capacity directly measured as maximal oxygen consumption (VO_2max) was found to be the single best predictor of both cardiac and all-cause deaths among patients with established cardiovascular disease.[8] Other physiologic parameters that are related to prognosis include VE/VCO_2, peak systolic blood pressure, cardiac output, cardiac power output, and cardiac reserve,[9-13] in addition to exercise duration and VO_2max. Echocardiographic representation of left ventricular ejection fraction is perhaps the most widely used indicator of cardiac function. Although entrenched in cardiological practice and widely employed as an inclusion requirement into clinical trials, it is not a panacea. Usually measured at rest, left ventricular ejection fraction has previously been shown to correlate well with mortality,[14-16] but does not correlate with functional capacity as measured by exercise duration, METS achieved or VO_2max.[17-21] We conducted a prospective, unicenter, pilot study via CXP to evaluate whether PCI was beneficial for stable angina patients with significant epicardial coronary artery stenosis in improvement of physiologic response during exercise as compared to those patients who were without angioplasty or syndrome X.

MATERIALS AND METHODS

Setting

The study was performed at Tri-Service General Hospital, National Defense Medical Center, a 1700-bed tertiary center of cardiovascular disease in northern Taiwan.

Patients

We prospectively enrolled men with effort angina from the outpatient department whose treadmill exercise test (TET) or thallium-201 myocardial perfusion scan displaying myocardial ischemia after excluding advanced valvular heart disease and poor ejection fraction by echocardiography were admitted for coronary angiography in our hospital from 2007 to 2009. Everyone enrolled in this study had to sign informed consent before undergoing CPX and angiography with the Tri-Service General Hospital Institutional Review Board's approval (TSGHIRB095-05-082). According to the result of coronary angiography, we divided the patients into two groups, including those who had at least a target vessel over 2.0 mm in diameter with stenosis > 70% by QCA method receiving PCI (PCI group), and those without obvious vessel stenosis, syndrome X patients (syndrome X group). Medications such as aspirin, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, calcium channel blocker, beta-receptor blocker and statin were prescribed as standard treatment for coronary artery disease throughout the study period without any change. CPX was carried out before and after coronary angiography (CAG) with an interval of 4 weeks, and a series of physiologic variables were obtained as follows: age, BMI, cholesterol, HDL-C, LDL-C, triglycerides, plasma glucose, creatinine, rest/maximal heart rate (HR), reached percentage of predicted maximal HR (%PHRmax,

maximal HR/predicted maximal HR × 100%; predicted maximal HR = 220 − age), rest/peak systolic blood pressure (SBP) and diastolic blood pressure (DBP), peak oxygen consumption (VO_2max), ventilatory efficiency (VE/VCO_2), anaerobic threshold (AT), exercise duration, cardiac output (CO), cardiac power output (CPO), and cardiac reserve. The improvements of physiologic response were evaluated by the difference of the parameters between two times of CPX including %PMHR, rest/peak SBP, mean blood pressure (MBP), VO_2max, VE/VCO_2, AT/VO_2max, exercise duration, CO, CPO and cardiac reserve within individual group, so as the change ratios of each parameter between groups, Δvariant [variant after CAG($variant_{post}$) − variant before CAG ($variant_{pre}$)]/$variant_{pre}$. Echocardiography was not routinely repeated after coronary angioplasty in light of initial selection for patients with preserved left ventricular ejection fraction.

Cardiopulmonary exercise testing

Exercise testing was conducted on a TMX425CP TRACKMASTER™ treadmill (Full Vision Inc., KS, USA) using the standard Bruce protocol. Patients were excluded if a preliminary familiarization procedure identified them as not able to exercise for reasons other than cardiac limitation. The same supervisors (GM Lin and BH Tzeng) conducted the tests throughout the study. All patients performed symptom-limited exercise tests unless termination was indicated for safety reasons. Patients were exercised after a 2-hour postprandial period and were asked not to consume alcohol or caffeine in the preceding 12 hours. The room in which the tests were carried out was maintained at a constant temperature between 21° and 23 °C using an air conditioning system controlled by thermostat. Beta-blockers and other rate-slowing drugs (e.g. diltiazem) were stopped for 48 hours before the exercise test. The first stage consisted of an incremental exercise test with Bruce protocol. Twelve-lead ECG was monitored throughout with CardioPerfect™ workstation system (Welch Allyn, Inc., NY, USA). Blood pressure (BP) was measured by Tango™ stress test BP monitor (SunTech Medical Instruments Inc., NC, USA) at rest before exercise, with interval of 2 minutes during exercise and immediately just after exercise phase. Rates of oxygen consumption (VO_2), carbon dioxide production (VCO_2), end-tidal partial pressure of carbon dioxide ($PETCO_2$), tidal volume (Vt), and respiratory rate were recorded breath by breath using the Medgraphics CPX Ultima™ system with BreezeSuite software (Medgraphics, MN, USA). Respiratory exchange ratio (RER = VCO_2/VO_2), minute ventilation (VE = Vt × respiratory rate), and VO_2/kg were calculated from the above variables. The V-slope method[22] was used to calculate anaerobic threshold. The second stage began following 40 min of recovery. This stage was invented by Dr. Tan's group in the United Kingdom.[11] Briefly, the resting cardiac output was measured by using 10% CO_2 via the equilibrium CO_2 re-breathing technique of Collier[23] and calculated using the indirect Fick method. At least two measurements of cardiac output were taken in order to calculate an average. The patient then performed a constant maximum workload exercise test for at least 4 min to a VO_2 of at least 90% of the maximum level obtained during the incremental test. Peak cardiac output was measured in duplicate by using 4% CO_2 via the exponential CO_2 re-breathing technique of Defares.[24] Cardiac power output (CPO), in watts, was calculated from the equation: CPO = (CO × MBP) × K,[11,25] where MBP is the mean blood pressure in mmHg calculated by new formula: MBP = diastolic pressure + 0.412 (systolic pressure-diastolic pressure),[26] CO is the cardiac output in l/min and K the conversion factor 2.22 × 10^{-3}. Cardiac reserve = CPO at peak exercise (CPOmax) − CPO at rest (CPOrest), in watts.[11]

Statistical analysis

All continuous variables included in the analysis are presented as means ± standard deviations (SD). Statistical significance was set at the 5% level, and analysis of all variables was carried out using SPSS statistical software version 16.0 (SPSS Inc., Chicago, IL, USA). Each variable (pre vs. post) is compared by using the paired-samples Student's *t* test in each group separately (PCI group alone and syndrome X group alone) to examine whether the intervention was associated with any improvement in those variables, followed by comparing the change ratios of all variables between PCI and syndrome X groups by using the independent-samples Student's *t* test. Fisher exact probability test was used for categorical data. Wilcoxon signed rank test was used for the evaluation of ST improvement in the 12-lead ECGs by TETs before and after PCI, with the exclusion of no sig-

nificant ST depression before CAG initially.

RESULTS

Patient characteristics

A total of 20 patients who fulfilled the inclusion criteria of stable coronary disease were admitted to the hospital within the study period. The baseline characteristics of 12 patients with significant epicardial coronary artery stenosis (PCI group) and 8 with syndrome X (Syndrome X group) are shown in Table 1. The age of the 20 patients who enrolled the study was 51.9 ± 9.0 year-old (range 38-67), and all patients were male. No statistically significant differences were observed between the two groups with respect to age, BMI, diabetes, hypertension, smoking, lipid profiles, plasma glucose, creatinine, kinds of cardiovascular medications, left ventricular ejection fraction and pulmonary artery systolic pressure estimated by transthoracic echocardiography. Their medications were kept the same during the study period.

Angiographic and the treadmill exercise test ECG findings

The angiographic findings, listed in Table 2, revealed 5 subjects with single-vessel coronary disease, 6 with double-vessel and only 1 with triple-vessel disease. Percutaneous coronary interventions (PCI) including balloon angioplasty or stenting were regularly performed in patients if a coronary lesion narrowing was more than 70% of the target vessel with a diameter at least 2.0 mm in reference. The distal lumens and branches of main coronary arteries with small diameter or minor stenosis were left alone. All the target lesions had TIMI III flow and below 20% residual stenosis after PCI. As shown in Table 2, the TET ECG performed during CPX showed that there were no more ST depression after PCI in 3 patients, improvement in ST depression in 6 patients, and not any ST depression both before and after CAG in 3 patients whose myocardial ischemia were diagnosed by thallium-201 myocardial perfusion scan. There was a significant improvement in the ST depression after PCI, excluding the three cases with no any ST depression initially. In the syndrome X patients, their TET ECGs

Table 1. Clinical characteristics in groups of PCI and syndrome X

Group	PCI (N = 12)	Syndrome X (N = 8)	P-value
Age (years)	50.0 ± 8.1	54.8 ± 10.0	0.22
BMI (kg/m^2)	27.5 ± 0.5	27.0 ± 0.6	0.10
Total cholesterol (mg/dl)	184.9 ± 40.4	186.6 ± 15.4	0.91
HDL cholesterol (mg/dl)	50.0 ± 8.5	50.5 ± 3.7	0.68
LDL cholesterol (mg/dl)	115.1 ± 14.5	115.6 ± 6.4	0.92
Triglycerides (mg/dl)	200.8 ± 70.0	200.8 ± 29.4	1.00
Glucose (mg/dl)	120.3 ± 10.6	116.3 ± 9.0	0.40
Creatinine (mg/dl)	1.0 ± 0.3	1.0 ± 0.1	0.81
LVEF (%)	55.4 ± 4.6	57.5 ± 5.8	0.38
PASP (mmHg)	30.8 ± 2.4	31.8 ± 2.7	0.43
Diabetes	4 (33.3%)	3 (37.5%)	0.61
Hypertension	10 (83.3%)	6 (75%)	0.53
Smoking	9 (75.0%)	6 (75%)	0.69
Aspirin/Clopidogrel	12 (100%)	8 (100%)	1.00
ACEI/ARB	10 (83.3%)	7 (87.5%)	0.66
CCB	7 (58.3%)	5 (62.5%)	0.61
Beta-blocker	8 (66.7%)	5 (62.5%)	0.61
Statin	8 (66.7%)	5 (62.5%)	0.61

Data are presented as mean ± SD and number (%) unless otherwise indicated. PCI: percutaneous coronary intervention group; BMI: body mass index; HDL: high-density lipoprotein; LDL: low-density lipoprotein; LVEF: left ventricular ejection fraction; PASP: pulmonary artery systolic pressure. ACEI/ARB: angiotensin-converting enzyme inhibitor/ angiotensin II receptor blocker; CCB: calcium channel blocker; Beta-blocker: beta-receptor blocker.

Table 2. Angiographic results, managements and treadmill exercise test results of the PCI group

	Coronary involvement	PCI > 2.0 mm diameter	Lesions without PCI	ST depression pre-PCI	ST depression post- PCI
Case 1	3 vessels	LAD, RCA	LCx, DB1	2-3 mm	1-2 mm
Case 2	1 vessel	LAD	DB1	NSTD	NSTD
Case 3	2 vessels	LCx, RCA	PL	2.0 mm	1.0 mm
Case 4	2 vessels	LAD, LCx	OM1	1.5 mm	NSTD.
Case 5	1 vessel	RCA	Nil.	NSTD	NSTD
Case 6	2 vessels	LCx	LAD	2-3 mm	1-2 mm
Case 7	1 vessel	LAD	Nil.	1.0 mm	NSTD
Case 8	1 vessel	LAD	Nil.	NSTD	NSTD
Case 9	2 vessels	RCA	LCx	2.0 mm	1.0 mm
Case 10	2 vessels	LCx, RCA	Nil.	1.0 mm	NSTD
Case 11	1 vessel	RCA	Nil.	2.0 mm	1.0 mm
Case 12	2 vessels	LAD, LCx	DB1	1.5 mm	1.0 mm
				Median: 2.0 mm	1.0 mm
					P-value (exact): 0.004

PCI: percutaneous coronary intervention; LAD: left anterior descending coronary artery; LCx: left circumflex coronary artery; RCA: right coronary artery; DB1: first diagonal branches; PL: postero-lateral branch; OM1: first obtuse marginal branch; NSTD: no significant ST depression; Case 2, 5, and 8: no significant ST deviation in both pre- and post-angiographic treadmill exercise test ECGs, and their myocardial ischemia was diagnosed by thallium-201 myocardial perfusion scan. We excluded Cases 2, 5, and 8 for the statistical analysis.

before and after CAG showed no change.

Results of cardiopulmonary exercise testing

As seen in Table 3, there were no statistically significant differences between the before and the after CAG CPX results in both groups regarding exercise duration, HRmax, %PHRmax, peak exercise SBP, peak MBP, VO_2max/kg, AT/VO_2max, VE/VCO_2, rest CO, peak CO, CPO at rest and peak exercise, and cardiac reserve. Comparing between the two groups, there were no statistically significant differences regarding exercise duration, HRmax, peak exercise SBP, peak MBP, VO_2max/kg, AT/VO_2max, VE/VCO_2, rest CO, peak CO, and rest CPO both before and after CAG, nor of the levels of the changes (ΔVariant = $\text{Variant}_{pre} - \text{Variant}_{post}$) or the change ratios ($\Delta\text{Variant}/\text{Variant}_{pre}$) of the above parameters. However, significant differences were found in the CPOmax and cardiac reserve before PCI, but both they became insignificant differences after PCI between the two groups.

DISCUSSION

Coronary artery disease is caused by a narrowing of the blood vessels that supply blood and oxygen to the heart. Under stress condition, the narrowing vessels will be insufficient to supply enough blood and oxygen to the myocardium, which may cause angina pectoris and heart function impairment. Exercise test, such as TET, is a more natural physiologic index of stress, and is routinely used to induce cardiac ischemia in our daily practice. Exercise capacity, expressed as exercise duration or workload achieved, has been recognized for several decades as an important prognostic marker in cardiac disease.[27] Peak exercise capacity was shown to be the strongest predictor of all-cause mortality among both normal subjects and those with cardiovascular disease.[7] CPX, with the addition of respiratory gas analysis to standard exercise testing, has become increasingly important over the years, especially in the assessment of heart failure. The use of peak oxygen consumption (VO_2max) in prognostic assessment and monitoring of heart function has become, and continues to be, a standard practice.[28] VO_2max is a more reliable index of exercise capacity than exercise duration or workload as it represents a more precise, reproducible and physiological measure of cardiopulmonary function.[29] Numerous studies published in the last couple decades demon-

Table 3. Comparison of cardiopulmonary exercise test results before and after angiography between groups of PCI and Syndrome X

Group	PCI	Syndrome X	P-value
	N = 12	N = 8	
Exercise duration (min)			
Pre-CAG	8.7 ± 2.8	9.0 ± 2.9	0.82
Post-CAG	9.5 ± 1.9	9.4 ± 1.9	0.88
ΔExercise duration	0.8 ± 1.3	1.1 ± 2.4	0.75
ΔExercise duration (%)	15.5 ± 30.1	18.5 ± 33.8	0.84
Rest SBP (mmHg)			
Pre-CAG	134 ± 4.9	136 ± 5.1	0.33
Post-CAG	133 ± 4.5	135 ± 5.8	0.37
Rest DBP (mmHg)			
Pre-CAG	77.1 ± 5.7	74.0 ± 4.3	0.21
Post-CAG	76.2 ± 5.2	73.5 ± 3.6	0.23
Rest heart rate (beats/min)			
Pre-CAG	71.5 ± 2.8	72.2 ± 2.3	0.53
Post-CAG	71.2 ± 2.3	71.6 ± 2.1	0.65
Peak SBP (mmHg)			
Pre-CAG	171.1 ± 32.0	191.6 ± 28.2	0.16
Post-CAG	180.8 ± 29.1	202.4 ± 30.3	0.13
ΔPeak SBP	9.7 ± 32.6	10.8 ± 17.9	0.93
ΔPeak SBP (%)	8.2 ± 23.0	6.0 ± 10.7	0.81
Peak MBP (mmHg)			
Pre-CAG	126.8 ± 23.9	136.9 ± 21.0	0.34
Post-CAG	132.1 ± 17.5	140.8 ± 21.3	0.33
ΔPeak MBP	5.3 ± 24.5	3.8 ± 13.2	0.88
ΔPeak MBP (%)	7.0 ± 21	3.1 ± 9.6	0.63
Peak heart rate (beats/min)			
Pre-CAG	147.7 ± 21.0	159.6 ± 29.1	0.30
Post-CAG	153.0 ± 12.4	156.5 ± 26.9	0.70
ΔPeak heart rate	5.3 ± 12.4	-3.1 ± 17.3	0.22
ΔPeak heart rate (%)	4.6 ± 9.1	-1.0 ± 11.1	0.23
% of PHRmax (%)			
Pre-CAG	86.1 ± 10.2	96.4 ± 15.3	0.09
Post-CAG	89.4 ± 5.7	94.8 ± 16.0	0.39
Δ% of PHRmax	4.4 ± 11.0	-1.6 ± 10.5	0.24
Δ% of PHRmax (%)	6.2 ± 13.3	-1.0 ± 11.1	0.22
VO_2 max/Kg (ml/min/kg)			
Pre-CAG	22.4 ± 6.0	25.9 ± 5.6	0.20
Post-CAG	24.7 ± 4.4	27.3 ± 4.0	0.21
ΔVO_2 max/Kg	2.4 ± 5.3	1.4 ± 3.2	0.64
ΔVO_2 max/Kg (%)	15.3 ± 28.1	7.4 ± 14.3	0.48
AT/VO_2max (%)			
Pre-CAG	63.3 ± 9.1	61.5 ± 12.8	0.72
Post-CAG	62.0 ± 5.2	60.8 ± 7.5	0.68
ΔAT/VO_2max	-1.3 ± 9.3	-7 ± 12.9	0.90
ΔAT/VO_2max (%)	-0.5 ± 14.5	1.3 ± 18.5	0.81

VE/VCO_2			
Pre-CAG	29.6 ± 5.2	26.8 ± 3.4	0.19
Post-CAG	28.9 ± 3.5	26.8 ± 2.6	0.16
$\Delta VE/VCO_2$	-0.7 ± 4.7	0.0 ± 1.4	0.68
$\Delta VE/VCO_2$ (%)	-0.8 ± 12.9	0.4 ± 5.0	0.80
Rest CO (L/min)			
Pre-CAG	4.7 ± 0.7	4.6 ± 1.0	0.81
Post-CAG	4.6 ± 1.0	4.5 ± 1.1	0.92
ΔRest CO	-0.1 ± 1.3	-0.1 ± 1.0	0.94
ΔRest CO (%)	-0.3 ± 30.2	1.2 ± 29.8	0.91
Peak CO (L/min)			
Pre-CAG	14.0 ± 3.4	16.1 ± 1.5	0.08
Post-CAG	14.9 ± 2.5	17.0 ± 2.4	0.07
ΔPeak CO	0.9 ± 3.1	0.9 ± 2.5	0.98
ΔPeak CO (%)	9.9 ± 22.7	6.1 ± 15.5	0.69
CPOrest (watts)			
Pre-CAG	1.0 ± 0.1	1.0 ± 0.2	0.91
Post-CAG	0.9 ± 0.3	1.0 ± 0.3	0.77
ΔCPOrest	-0.1 ± 0.3	0.0 ± 0.3	0.77
ΔCPOrest (%)	-3.2 ± 32.9	3.0 ± 35.9	0.70
CPOmax (watts)			
Pre-CAG	3.7 ± 1.4	5.0 ± 1.2	0.04
Post-CAG	4.2 ± 0.9	4.8 ± 1.2	0.16
ΔCPOmax	0.5 ± 1.0	-0.1 ± 1.3	0.26
ΔCPOmax (%)	21.3 ± 33.9	0.3 ± 27.3	0.16
Cardiac reserve (watts)			
Pre-CAG	2.7 ± 1.3	4.0 ± 1.1	0.04
Post-CAG	3.2 ± 1.0	3.8 ± 1.2	0.21
ΔCardiac reserve	0.5 ± 1.0	-0.1 ± 1.3	0.23
ΔCardiac reserve (%)	35.6 ± 56.4	0.6 ± 31.0	0.13

Data are presented as mean ± SD unless otherwise indicated. PCI: percutaneous coronary intervention group; CAG: coronary angiography; SBP: systolic blood pressure; MBP: mean blood pressure; % of PHRmax: reached % of predicted maximal heart rate; VO_2max: peak exercise oxygen consumption; AT: anaerobic threshold; VE/VCO_2: minute ventilation/carbon dioxide slope; CO: cardiac output; CPO: cardiac power output; CPOrest: CPO at rest; CPOmax: CPO at peak exercise; Δstands for post-angiographic CPX result subtracts pre-angiographic CPX result; (%) means the change ratio after angiography [(post-angiographic CPX result subtracts pre-angiographic CPX result)/pre-angiographic CPX result × 100%].

strate peak VO_2 to be an independent predictor of mortality.[7,28-30] Other parameters such as the blood pressure response to exercise,[31,32] VE/VCO_2[33-35] and oxygen recovery post exercise[36] have emerged in recent years as independent predictors of outcome. However, these variables are only indirectly related to cardiac function, and therefore can only be considered as markers of severity of organ failure, with direct means to improve these values not necessarily indicating an improvement in cardiac function. More direct measurements of cardiac work, represented by peak stroke work index,[37,38] cardiac output (CO) response to exercise[39] or cardiac power output, CPO,[12,40] have emerged as powerful independent predictors of prognosis over VO_2max. CPO, the product of cardiac output and arterial pressure, represents the overall function, equivalent to the rate of hydraulic energy imparted by the cardiac pump into the circulation to facilitate the perfusion of various metabolizing tissues.[41] By virtue of containing the arterial pressure term, CPO measurement, especially at maximal exercise, may well

represent the best way of detecting and monitoring primary cardiac pump inadequacy in heart failure patients, complementing the natural detection of inadequate BP levels already afforded through natural evolution.[42] In addition, recent studies showed peak cardiac power out (CPOmax), measured noninvasively, is an independent predictor of outcome that can enhance the prognostic power of peak VO_2 in the evaluation of patients with heart failure.[9,12] In this study, we used not only the traditional parameters of CPX, but also CO, CPO and cardiac reserve to evaluate cardiac physiologic responses after PCI in coronary artery disease patients. To evaluate the effect of PCI, we divided stable angina patients to two groups, PCI and non-PCI group, and compared with the parameters from CPX before and after CAG. All the procedures between the two groups were the same, except one had PCI. The patients without PCI could not simply be defined as normal patients only by normal CAG. The diagnosis of syndrome X may be more suitable for them, because all of them had positive stress test, thallium-201 myocardial perfusion scan or TET, and typical symptom of effort angina. We firstly evaluated the PCI effect by comparing the CPX results before and after PCI in the PCI group. However, there were no significant changes in all of the results, including exercise duration, HRmax, %PHRmax, peak exercise SBP, peak MBP, VO_2max/kg, AT/VO_2max, VE/VCO_2, COrest, COmax, CPOrest, CPOmax, and cardiac reserve. In the Syndrome X group, there were also no significant changes in all of the above parameters before and after CAG. Exercise capacity depends on physical and psychological factors,[41] although the bulk of it is determined by aerobic capacity (peak oxygen consumption, VO_2max). To elicit the influence of cardiac catheterization on the patients' psychological and physical impacts on exercise, we next compared the CPX results between the two groups, only with the difference of PCI procedure. We compared all of the above CPX parameters before and after CAG, the changes of each parameter before and after CAG, and the changes in ratios to the parameter before CAG between the two groups. There were significant differences only in CPOmax and cardiac reserve before CAG between groups, but still no significant differences in all the other ones, including all the changes and change ratios of each parameter (Table 3). However, although insignificant statistically, there seems to be tendency toward improvement of CPOmax and cardiac reverse after PCI, because the CPOmax and cardiac reserve after CAG between groups became insignificant differences, not like the ones before CAG. Compared to the previously published papers in Medline, our study revealed novel results of CPX regarding patients with stable epicardial coronary disease and syndrome X.[6,43] Here, we demonstrate that CPOmax and cardiac reserve are more powerful parameters than others to reflex the differences between the two groups. However, we also show similar CPX results in most of the parameters before and after coronary interventions in patients of either macro- or micro-vascular ischemia in our study. Since CPX is usually used for the prognostic stratification,[44,45] these findings might be compatible to the conclusions of the COURAGE study that coronary interventions would not reduce cardiovascular and all-cause mortality in patients with stable coronary disease compared to intensive medical treatment.[1] To prove that, a large-scale trial is needed.

Micro-vascular ischemia is becoming increasingly recognized as a significant cause of morbidity in patients with angiographically normal coronary arteries.[46] Because standard exercise stress testing in women is frequently associated with appreciable rates of false-positive results, it has limited diagnostic accuracy in detecting microvascular ischemia, and hence female gender was precluded in our study.[47] Another reason for this preclusion is that there are obviously less women going for PCI around the age of 50 years old. This may have had a great influence on our statistics. As we know, abnormalities in coronary vasomotor can contribute to the precipitation and maintenance of ischemia in humans. Endothelial dysfunction may impair microvascular adaptation to ischemia, and cause constrictor responses to reduced intraluminal pressure in isolated microvessels. Recently, several investigators, using different techniques, have reported that myocardial perfusion and coronary blood flow reserve remained impaired after "successful" coronary recanalization.[48,49] The limited impact of revascularization procedures on prognosis and the persistence of angina in a large number of patients after removal of coronary obstructions indirectly support the concept of additional factors contributing to the pathogenesis of coronary syndromes. In the Randomised Intervention Treatment of Angina (RITA)-2 trial, after a median 7 years of follow-up, death or myocardial infarc-

tion occurred in 14.5% of patients who had undergone revascularization by percutaneous transluminal coronary angioplasty (PTCA) and in 12.3% of medically treated patients. Furthermore, the prevalence of angina remained increased in both groups, with 70% and 83%, respectively, of patients treated medically or with PTCA receiving at least one antianginal drug at 5 years.[50] According to these findings, patients with epicardial coronary artery stenosis may also have microvascular obstruction, which could not be detected by coronary angiography. Fearon et al. have stated that microvascular resistance is not influenced by epicardial coronary artery stenosis severity. Myocardial ischemia will persist even after angioplasty for a significant epicardial coronary lesion.[51] These reasosns might explain why most of the CPX parameters in our study did not have dramatic changes after PCI. In our study, at least 50% of patients after PCI still had ST depressions in TET ECG, although all of them had improvement with fewer ST depressions. It may be due to the effect of the microvascular factor or the residual stenosis in the smaller size vessels (< 2 mm). However, we couldn't completely exclude the possibility of early restenosis.

In summary, this pilot study, in the utility of CPX, uncovered a novel contribution, showing that there are significantly lower levels of CPOmax and cardiac reserve in men with stable significant epicardial coronary stenosis before PCI in comparison to those with microvascular disease presenting as syndrome X. There appears to be tendency toward improvement of cardiac reserve after PCI, although with an insignificant statistical result. Nevertheless, other parameters of CPX don't show obvious significant changes. Whether PCI is able to improve CPX remained unclear after this study, a larger-scale trial is needed to further elucidate this issue.

Limitations

Limitations include at least (1) no sample size estimation in this study, and a small sample size may obviously cause type 2 error; (2) no follow-up thallium 201 myocardial scan to demonstrate the effectiveness of PCI. Hence, if there was indeed no improvement in cardiopulmonary exercise testing following PCI, we cannot exclude the possibility that the lack of physiological benefit was due to suboptimal PCI rather than simply PCI not working.

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