

Heart-Carotid Pulse Wave Velocity a Useful Index of Atherosclerosis in Chinese Hypertensive Patients

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(*Medicine* 94(51):e2343)

Abstract: This study was designed to investigate the relationship between heart-carotid pulse wave velocity (hcPWV) and carotid intima-media thickness (CIMT) in hypertensive patients, and also to examine the effect of pre-ejection period (PEP) on it. Doppler ultrasound device was used to measure CIMT in left common carotid artery. Hypertensive patients were divided into normal ($n=36$, $\text{CIMT} \leq 0.8$ mm) and thickened ($n=31$, $\text{CIMT} > 0.8$ mm) group. Electrocardiogram R-wave-based carotid pulse wave velocity (rcPWV) and aortic valve-carotid pulse wave velocity (acPWV) were calculated as the ratio of the travel length to the pulse transit time with or without PEP, respectively. CIMT has significant relations with rcPWV ($r=0.611$, $P < 0.0001$) and acPWV ($r=0.384$, $P=0.033$) in thickened group. Moreover, CIMT showed stronger correlation with rcPWV than with acPWV in thickened group. Furthermore, both acPWV and rcPWV were determinant factors of CIMT in thickened group, independent of clinical confounders including age, gender, smoking behavior, systolic blood pressure, diastolic blood pressure, fasting blood glucose, total cholesterol, high-density lipoprotein cholesterol, antihypertensive medication, and plaque occurrence. However, similar results were not found in normal group. Since CIMT has been considered as an index of atherosclerosis, our results suggested that both rcPWV and acPWV could be useful indexes of atherosclerosis in thickened CIMT hypertensive patients. Additionally, if hcPWV is computed with heart-carotid pulse transit time, including PEP could improve the accuracy of atherosclerosis assessment in hypertensive patients.

Abbreviations: acPTT = aortic valve-carotid pulse transit time, acPWV = aortic valve-carotid pulse wave velocity, BMI = body mass index, CCA = common carotid artery, CIMT = carotid intima-media thickness, DBP = diastolic blood pressure, D_{hc} = the path length of the left heart-carotid segment, ECG = electrocardiogram, FBG = fasting blood glucose, hcPTT = heart-carotid pulse transit time, hcPWV = heart-carotid pulse wave velocity, HDL-C = high-density lipoprotein cholesterol, HR = heart rate, LVEF = left ventricular ejection fraction, MAP = mean arterial pressure, PEP = pre-ejection period, PWV = pulse wave velocity, rcPTT = R-wave-based carotid pulse transit time, rcPWV = electrocardiogram R-wave-based carotid pulse wave velocity, SBP = systolic blood pressure, Total-C = total cholesterol.

INTRODUCTION

Arterial stiffness has gradually shown its ability on predicting cardiovascular events in general population, diabetes, and cardiovascular patients.¹⁻⁴ Apart from invasive methods, pulse wave velocity (PWV) is regarded as the most useful and robust index of arterial stiffness, because it is not derived from pressure-volume, pressure-diameter, or pressure-strain relationship.⁵ According to the European Society of Hypertension/European Society of Cardiology, carotid-femoral PWV has been suggested as the “gold standard” of arterial stiffness and a tool for assessment of subclinical target organ damage in hypertensive patients.⁶ Brachial-ankle PWV, which is commonly used in Japan and other East Asian countries, has been proven to be related with coronary artery disease, increased blood pressure, and other cardiovascular events.⁷ However, the clinical significance of PWV of other arterial tree segments, such as heart-carotid PWV (hcPWV), has not been fully studied.

Many studies included hcPWV as one of their measurements,⁸⁻¹² but only a few studies investigated the clinical significance of hcPWV specially.¹³ Nevertheless, hcPWV still shows important clinical significance on cardiovascular system. For instance, hcPWV shows strong and significant relations with cardiovascular risk factors (age, gender, hypertension, and diabetes mellitus) in the general population.¹² Nagasaki et al¹³ determined that hcPWV has similar reliability with common carotid arterial stiffness index beta in measuring arterial stiffening of healthy Japanese people. Moreover, flow-mediated dilation and carotid intima-media thickness (CIMT), both of which are good surrogate markers of clinical atherosclerosis, were independent determinants of hcPWV in general people less than 70 years old.¹¹ Additionally, significant difference was found in hcPWV between healthy controls and young patients who have undergone arterial switch operation at rest, while similar results were not found in brachial-ankle PWV, heart-femoral PWV, and femoral-ankle PWV.⁸ Therefore, it is worthy to further study the clinical significance of hcPWV on cardiovascular system.

Editor: Yutang Wang.

Received: July 19, 2015; revised: November 27, 2015; accepted: November 30, 2015.

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This work was supported in part by the Key Lab for Health Informatics of Chinese Academy of Sciences, the science technology and innovation committee of Shenzhen for research projects (Grant CXZZ20140909004122087), Shenzhen innovation funding (JCYJ 20140901003939025, JCYJ20140414170821323, JCYJ20140414170821311), and Guangdong Image-guided Therapy Innovation Team (2011S013).

The authors have no conflicts of interest to disclose.

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ISSN: 0025-7974

DOI: 10.1097/MD.0000000000002343

One popular method to compute PWV is dividing pulse wave propagation distance by the transit time measured between the feet of 2 waveforms.¹⁴ However, the foot point of waveform is easily contaminated by motion artifacts and noises, thus the R-wave of the electrocardiogram (ECG) is commonly used as the starting point because it corresponds approximately to the opening of the aortic valve.¹⁵ Although R-wave is easily identifiable, it introduces an extra pre-ejection period (PEP) in transit time. So far, the effect of PEP on the clinical significance of hcPWV has not been studied.

In the present study, we investigated the relationship between hcPWV and CIMT in hypertensive patients. Moreover, we also explored that if hcPWV was calculated as the ratio of travel length to pulse transit time, whether including PEP would affect the correlation between hcPWV and CIMT. Because the thickening and the stiffening of the arterial vessel can lead to the increase of PWV, we hypothesized that CIMT was significantly correlated with hcPWV in thickened CIMT hypertensive patients. Additionally, since CIMT is a general marker of atherosclerosis, this study could add the information that whether hcPWV could be a useful index of atherosclerosis in hypertensive patients.

PATIENTS AND METHODS

Patients

In the present study, hypertension was defined as systolic and/or diastolic blood pressure (SBP and/or DBP) measurements continuously higher than 140 mmHg and/or 90 mmHg, respectively. Total of 85 hypertensive patients were included in this study. The exclusion criteria were: people whose body mass index (BMI) ≥ 30 kg/m² were excluded; people who have unnormal heart rate (HR) (HR < 60 bpm or HR > 100 bpm) or unnormal left ventricular ejection fraction (LVEF) (LVEF < 50%) were excluded; people who have heart diseases, chronic kidney disease, or cancer were excluded in this study. SBP, DBP, and HR were measured 3 times, at 3 minutes interval, from the right upper arm using Oscar 2 device (SunTech Medical, Morrisville, NC) after at least a 5-min rest. The average of three measurements was used in the analysis. Pulse pressure was calculated as SBP–DBP, and the mean arterial pressure was calculated as $23 \times \text{DBP} + 13 \times \text{SBP}$. LVEF was measured with Doppler ultrasound device (iU22, Philips Ultrasound, Bothell, WA). Fasting blood glucose (FBG), total cholesterol (Total-C), and high-density lipoprotein cholesterol (HDL-C) were measured by Hitachi 7600 auto biochemistry instrument (Hitachi Company, Tokyo, Japan). BMI was calculated as weight in kilograms divided by height in meters squared. Age, gender, smoking behavior, and antihypertensive medication were obtained using a questionnaire. Moreover, all participants were required to perform vascular ultrasound examination. Additionally, anything that can increase blood pressure was forbidden for all patients on the day of the experiment. The protocol of this study was approved by Clinical Ethics Committee of the Second Peoples' Hospital of Shenzhen, China. The written informed consent was obtained from each patient before the experiment.

Carotid Artery Ultrasound Examination

It has been well proved that Doppler ultrasound is a reliable and reproducible method for measuring PWV.^{16–18} Therefore, we obtained CIMT and hcPWV measurements with

the same ultrasound Doppler system (iU22, Philips Ultrasound, Bothell, WA).

CIMT was measured by an experienced high-level clinician with a 7.5 MHz linear array probe. Each participant was examined in supine position and the head slightly turned away from the examined side. Previous studies showed that left common CIMT was significantly thicker than the right side both in general population and untreated hypertensive patients; moreover, the left common CIMT thickened 10 years earlier than the right common CIMT,^{19,20} which suggested that left common CIMT is more vulnerable and more sensitive to atherosclerosis than the right side. Therefore, left common CIMT was used in our study. The CIMT was measured on the far wall of left common carotid artery (CCA) at a distance of 1.0–2.0 cm to the carotid bifurcation from 3 angles: lateral, anterior, and posterior. If a plaque presented at the measuring point, an appropriate adjacent site was chosen. The average of the measurements from the 3 angles was used as the value of CIMT. Furthermore, plaque occurrence was screened in the common, internal, and external carotid arteries, and was scored as present or absent.

In this study, hcPWV was calculated as the ratio of the travel distance to heart-carotid pulse transit time (hcPTT). The path length of the left heart-carotid (D_{hc}) segment was estimated based on the height using the formula $D_{hc} = 0.2437 \times \text{height} - 18.999$. To determine whether including PEP in hcPTT will affect the correlation between hcPWV and CIMT, ECG R-wave-based carotid pulse transit time (rcPTT) and aortic valve-carotid pulse transit time (acPTT) were used to represent the hcPTT with or without PEP, respectively. The rcPTT and PEP were measured as the time difference between the R peak of ECG and the foot of the systolic upstroke in the Doppler spectral envelope at left carotid artery bifurcation and at aortic valve (Fig. 1), respectively. The acPTT was calculated by $\text{acPTT} = \text{rcPTT} - \text{PEP}$. Therefore, the ECG

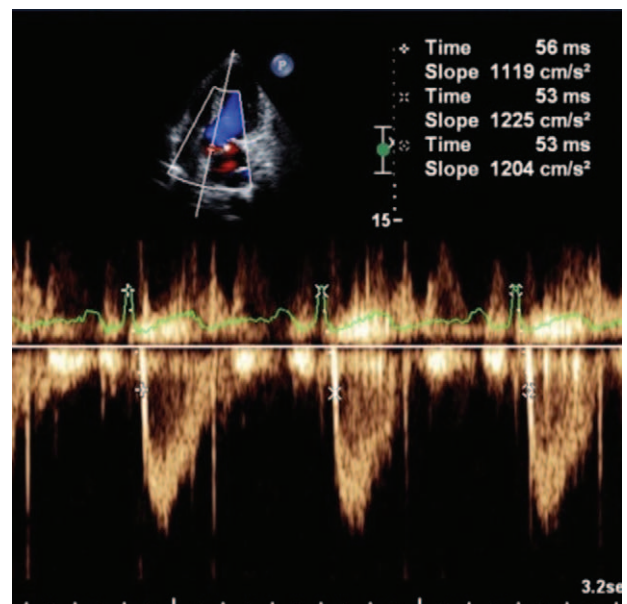


FIGURE 1. PEP in aortic valve was measured with ECG synchronized ultrasound Doppler system in three consecutive cardiac cycles for hypertensive patients. ECG = electrocardiogram, PEP = pre-ejection period.

R-wave-based carotid PWV (rcPWV) and aortic valve-carotid PWV (acPWV) were calculated as follow:

$$rcPWV = \frac{D_{hc}}{rcPTT}$$

$$acPWV = \frac{D_{hc}}{acPTT}$$

All the measurements were measured under the best resting conditions to avoid the effect of HR and were averaged over 3 consecutive cycles.

Statistical Analysis

Data are expressed as mean ± standard deviation unless specified. Clinical characteristics of different groups were compared with Student’s *t*-test. Univariable regression analysis was first performed to assess the relationships of CIMT with rcPWV, PEP, and acPWV in hypertensive groups. Multivariate stepwise regression analysis were used to examine the independence of observed associations after adjustment for clinical confounders including age, gender, smoking behavior, SBP, DBP, FBG, Total-C, HDL-C, antihypertensive medication, and plaque occurrence. All of the statistical analyses were performed using SPSS software package (SPSS Inc., Chicago IL).

RESULTS

Basic Characteristics of Researched Patients

A total of 85 hypertensive patients were recruited in this study; 11 patients were excluded because their BMI > 30 kg/m²; 7 patients were excluded because they have serious heart diseases. The other hypertensive patients were divided into 2 groups: thickened (CIMT > 0.8 mm) hypertensive group (N=31) and normal (CIMT ≤ 0.8 mm) hypertensive group (N=36). We chose 0.8 mm as the threshold of thickened CIMT according to the conclusions of previous clinical studies: thicker common carotid artery walls were no stiffer than thinner walls except for CIMT > 0.8 mm;²¹ 95.5% of individuals whose CIMT is greater than 0.8 mm have plaque in one of the bifurcations of the common carotid or common femoral arteries.²²

Table 1 shows the basic characteristics of different hypertensive groups. No significant differences were found in age, gender, BMI, HR, LVEF, SBP, DBP, mean arterial pressure, pulse pressure, Total-C, HDL-C, and antihypertensive medication between 2 groups. Moreover, thickened group presented significantly higher CIMT, FBG, the percentage of the smokers, and plaque occurrence than normal group (*P* < 0.05). Furthermore, thickened group presented obviously higher mean value in acPWV than that in normal group (*P* = 0.085). Additionally, there were no significant differences in acPTT, rcPTT, rcPWV, and PEP between the 2 groups (*P* > 0.1).

The Correlations of CIMT With acPWV, rcPWV, and PEP

We used univariable regression analysis to determine the correlations of CIMT with acPWV, PEP, and rcPWV in different hypertensive groups (Fig. 2). The results indicated that CIMT has significant relations with acPWV (*r* = 0.384, *P* = 0.033) and rcPWV (*r* = 0.611, *P* < 0.001) in thickened group. However, similar results were not found in normal group.

Multivariate Stepwise Regression of the Determinants of CIMT

We conducted multivariate stepwise regression analysis to assess the independence of observed associations between

TABLE 1. Comparison of Basic Characteristics Between Groups

Characteristics	CIMT > 0.8 mm (N = 31)	CIMT ≤ 0.8 mm (N = 36)
Male, %	67.74%	47.22%
Age, years	56.71 ± 9.87	51.94 ± 13.05
BMI, kg/m ²	24.88 ± 2.93	25.76 ± 5.31
Smoking, %	48.38%	19.44%*
SBP, mmHg	147.90 ± 11.15	145.14 ± 8.41
DBP, mmHg	92.03 ± 10.00	90.72 ± 10.55
MAP, mmHg	110.66 ± 8.08	108.86 ± 7.38
PP, mmHg	55.87 ± 13.87	54.42 ± 13.97
HR, bmp	71.97 ± 7.29	70.31 ± 9.63
LVEF, %	66.74 ± 2.72	66.01 ± 2.42
FBG, mmol/L	5.75 ± 1.09	5.25 ± 0.56*
Total-C, mmol/L	5.34 ± 1.07	5.11 ± 0.78
HDL-C, mmol/L	1.21 ± 0.27	1.23 ± 0.23
CIMT, mm	1.04 ± 0.15	0.72 ± 0.08*
rcPTT, ms	89.68 ± 16.81	92.67 ± 16.15
acPTT, ms	22.65 ± 11.92	25.61 ± 10.18
PEP, ms	67.03 ± 13.07	67.06 ± 13.15
rcPWV, m/s	2.47 ± 0.49	2.35 ± 0.47
acPWV, m/s	15.03 ± 15.11	10.23 ± 6.15 [†]
Antihypertensive medication, %	48.39%	50.00%
Plaque occurrence	54.80%	25.00%*

acPTT = aortic valve-carotid pulse transit time, acPWV = aortic valve-carotid pulse wave velocity, BMI = body mass index, CIMT = carotid intima-media thickness, DBP = diastolic blood pressure, FBG = fasting blood-glucose, HDL-C = high-density lipoprotein cholesterol, HR = heart rate, LVEF = left ventricular ejection fraction, MAP = mean arterial pressure, PEP = pre-ejection period, PP = pulse pressure, rcPTT = R-wave-based carotid pulse transit time, rcPWV = R-wave-based carotid pulse wave velocity, SBP = systolic blood pressure, Total-C = total cholesterol.

* Means there is a significant difference between the 2 groups (*P* < 0.05).

[†] Means there is a significant difference between the 2 groups (*P* < 0.09).

CIMT and acPWV, CIMT and rcPWV in researched groups (Table 2). The results showed that both acPWV and rcPWV were determinant factors of CIMT, independent of clinical confounders (age, gender, smoking behavior, SBP, DBP, FBG, Total-C, HDL-C, antihypertensive medication, and plaque occurrence) in thickened CCA hypertensive patients.

DISCUSSION

The contributions of this study include following aspects: this is the first study established that both rcPWV and acPWV could be useful indexes of atherosclerosis in thickened CIMT hypertensive patients; if hcPWV is computed with hcPTT, including PEP could enhance the correlation level between hcPWV and CIMT in thickened CIMT hypertensive patients. However, a large-scaled study should be conducted to confirm these conclusions in the future.

First, the basic characteristics of the patients showed that thickened group has significantly higher percentage of the smokers and level of FBG than normal CIMT group. Previous studies have shown that smoking behavior is an established causal factor for atherosclerosis; moreover, smoking behavior

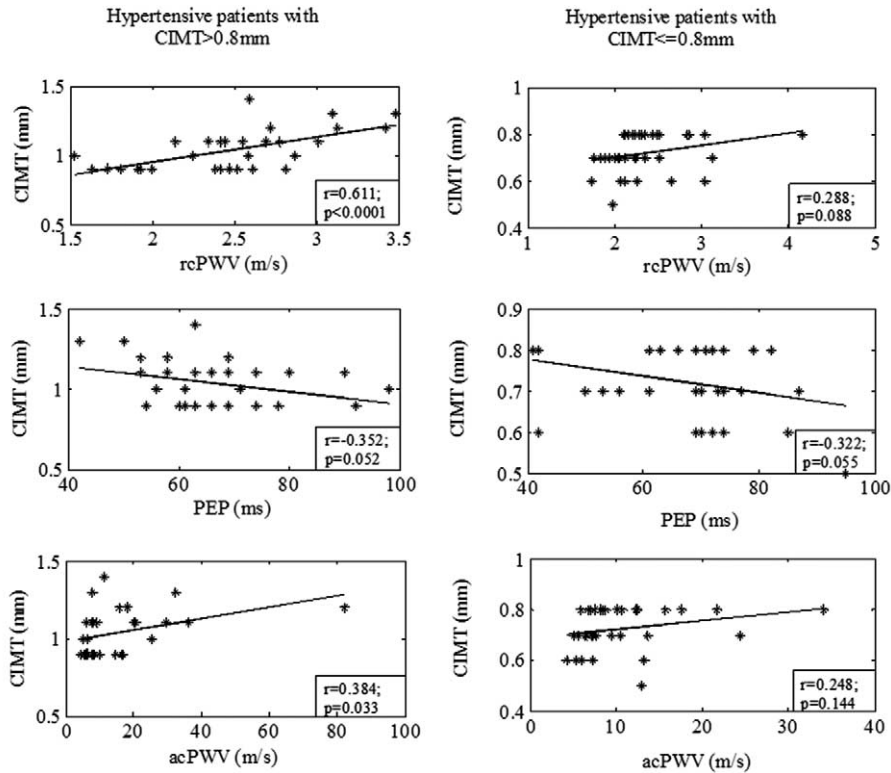


FIGURE 2. The relations of acPWV, PEP, rcPWV with CIMT in thickened CIMT hypertensive group and in normal CIMT hypertensive group. acPWV = aortic valve-carotid pulse wave velocity, CIMT = carotid intima-media thickness, PEP = pre-ejection period, rcPWV = R-wave-based carotid pulse wave velocity. $P < 0.05$: statistically significant.

and impaired fasting glucose can lead to carotid artery morphological changes.^{23,24} Therefore, the high percentage of smokers and the high level of FBG may contribute to the differences in CIMT and acPWV between thickened and normal CIMT hypertensive groups. In addition, it has been proven that the thicker CIMT has positive association with increased prevalence of plaques,²⁵ which may be because that intima-medial thickening affects endothelial function, and increasing the risk of plaque formation.

Second, our results showed that both rcPWV and acPWV were significantly associated with CIMT in thickened CIMT hypertensive patients. Moreover, rcPWV and acPWV still independently correlated with CIMT in thickened CIMT hypertensive patients after adjusting for clinical confounders (age,

gender, smoking behavior, SBP, DBP, FBG, Total-C, HDL-C, antihypertensive medication, and plaque occurrence). However, similar results were not found in normal hypertensive group. Because CIMT and hcPWV reflect the change in carotid arterial morphology (thickening) and function (stiffening), respectively, and the structural and functional changes of carotid artery can cause the increase of hcPWV, it is reasonable that CIMT and hcPWV correlated with each other in thickened CIMT hypertensive patients. Since CIMT is a classical index of atherosclerosis, our results may indicate that both rcPWV and acPWV could be useful indexes of atherosclerosis in thickened CIMT hypertensive patients. Our results corroborated the findings of previous studies. The research of Riley et al²¹ suggested that thicker common carotid artery walls were no

TABLE 2. Multivariate Stepwise Regression Analysis of the Determinants of CIMT

Groups	Clinical Confounders + acPWV			Clinical Confounders + rcPWV		
		β	Sig.		β	Sig.
Hypertensive patients with CIMT > 0.8 mm	Age	0.009	0.000	Age	0.007	0.001
	acPWV	0.003	0.025	rcPWV	0.140	0.001
Hypertensive patients with CIMT ≤ 0.8 mm	Age	0.004	0.000	Age	0.004	0.000

Confounders include age, gender, smoking behavior, SBP, DBP, FBG, Total-C, HDL-C, antihypertensive medication, and plaque occurrence. acPWV = aortic valve-carotid pulse wave velocity, CIMT = carotid intima-media thickness, DBP = diastolic blood pressure, FBG = fasting blood glucose, HDL-C = high-density lipoprotein cholesterol, SBP = systolic blood pressure, Total-C = total cholesterol, rcPWV = R-wave-based carotid pulse wave velocity.

stiffer than thinner walls, except for CIMT > 0.8 mm. The research of Labropoulos et al²⁶ reported that the CIMT of CCA only had a positive correlation trend with pressure-strain elastic modulus at lower thickness value (CIMT < 0.88 mm, $r = 0.24$, $P = 0.08$), but this association became stronger with increasing thickness (CIMT > 0.88 mm, $r = 0.62$, $P < 0.001$). The reason why CIMT did not significantly correlate with acPWV in normal CIMT hypertensive patients may be because the complicated pathological mechanism in the early stages of atherosclerosis. Previous study showed that arterial wall will not become thicker only after the smooth muscle cells migrate into the intima.²⁷ In addition, the carotid artery stiffness might keep relative constant, when CIMT values increase moderately.²⁸

Third, to the best of our knowledge, this is the first study exploring the effect of PEP on the correlation between CIMT and hcPWV in hypertensive patients. We add the knowledge that PEP will not influence the independence of the correlations between CIMT and hcPWV in thickened CIMT hypertensive group. Moreover, CIMT showed stronger correlation with rcPWV than with acPWV in thickened CIMT hypertensive group. This may suggest that when compute hcPWV with hcPTT, PEP should not be removed if hcPWV was used to evaluate the development degree of atherosclerosis.

Several limitations should be considered in current study. First, the hypertensive patients were mainly recruited in Shenzhen, which is a southern city in China. While, although the statistically significant results were obtained in this study, more hypertensive patients of other regions of China should be included to confirm these conclusions. Second, we divide hypertensive patients into normal and thickened group according to the CIMT value; however, the value of 0.8 mm should not be considered absolutely because the variability of CIMT in different population. Third, the present study estimates the length of left heart-carotid segment based on patients' heights, which may introduce calculation errors for PWV measurements.

CONCLUSION

In this study, we demonstrated that both rcPWV and acPWV were independently associated with CIMT in thickened CIMT hypertensive patients. Since CIMT is a commonly used index of atherosclerosis, the independent correlations between rcPWV, acPWV, and CIMT might indicate that both rcPWV and acPWV could be useful indexes of atherosclerosis in thickened CIMT hypertensive patients. Moreover, CIMT showed stronger correlation with rcPWV than with acPWV in thickened CIMT hypertensive patients, which suggests that including PEP dose not influence the independence between CIMT and hcPWV, but improves the accuracy of atherosclerosis assessment.

ACKNOWLEDGMENT

The authors thank the Key Lab for Health Informatics of Chinese Academy of Sciences, the science technology and innovation committee of Shenzhen for research projects (Grant CXZZ20140909004122087), Shenzhen innovation funding (JCYJ20140901003939025, JCYJ20140414170821323, JCYJ20140414170821311), and Guangdong Image-guided Therapy Innovation Team (2011S013) for the support.

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