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Original article

Long-term prognosis and clinical characteristics of young adults (≤40 years old) who underwent percutaneous coronary intervention

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ABSTRACT

Background: Limited data exist regarding the long-term prognosis of percutaneous coronary intervention (PCI) in young adults. The aim of this study was to retrospectively assess the long-term clinical outcomes in young patients who underwent PCI.

Methods and results: Between 1985 and 2011, 7649 consecutive patients underwent PCI, and data from 69 young adults (age ≤40 years) and 4255 old adults (age ≥65 years) were analyzed. A Cox proportional hazards regression analysis was used to determine the independent predictors of a composite endpoint that included all-cause death and acute coronary syndrome (ACS) during the follow-up period. The mean age of the 69 young patients was 36.1 ± 4.9 years, and 96% of them were men. Approximately 30% were current smokers, and their body mass index (BMI) was 26.7 ± 5.0 kg/m^2. The prevalence of diabetes and hypertension was 33% and 48%, respectively. All patients had ≥1 conventional cardiovascular risk factor. At a median follow-up of 9.8 years, the overall death rate was 5.8%, and new-onset ACS occurred in 8.7%. Current smoking was an independent predictor of the composite endpoint (hazard ratio 4.46, confidence interval 1.08–19.1, $p = 0.04$) for young adults.

Conclusion: Current smoking and obesity (high BMI) are the important clinical characteristics in young Japanese coronary heart disease patients who undergo PCI. The long-term prognosis in young patients is acceptable, but current smoking is a significant independent predictor of death and the recurrence of ACS in young Japanese coronary heart disease patients who are obese.

Introduction

Coronary heart disease (CHD) is recognized as one of the lifestyle-related diseases [1]. Since lifestyle-related burden increases the risk of CHD events by age, CHD mainly occurs in patients over 40 years of age. On the other hand, young adults ≤40 years of age rarely suffer from CHD, and epidemiologic data show that this group accounts for only about 3% of all coronary artery disease (CAD) cases [2]. However, autopsies have shown that about 50% of young individuals have progressive coronary atherosclerosis even though they were not diagnosed with CHD [3].

Several studies suggest that young CHD patients already have multiple lifestyle-related risk factors and consequently have the potential to develop coronary atherosclerosis [4,5]. One study has shown that cigarette smoking, diabetes, and dyslipidemia are prominent risk factors for the development of early atherosclerosis in young populations [6]. Previous studies regarding differences in characteristics of CHD between younger and older patients demonstrated that smoking, obesity, and the presence of diabetes were associated with CHD in younger patients [7,8]. Despite multiple lifestyle-related risk factors, younger CHD patients have a better short-term clinical outcome compared with older CHD patients [9]. However, there are few reports investigating the long-term clinical outcome and the predictors of a poor long-term prognosis in young CHD patients.

Thus, the purpose of this study was to examine the long-term clinical outcomes and assess the predictors of a poor long-term prognosis in young patients (≤40 years old) who underwent percutaneous coronary intervention (PCI).

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Methods

Patients and data collection

Data from consecutive patients who underwent PCI at Juntendo University Hospital (Tokyo, Japan) between February 1985 and February 2011 were analyzed. The data collected on each patient included age, gender, body mass index (BMI), blood pressure (BP), total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), triglycerides, fasting blood glucose (FBG), smoking status, family history of CHD, medication use, revascularization procedure-related factors, and comorbidities. Young adults were defined as those ≤40 years of age, because that is the most commonly used cut-off point for young age in previous studies [10,11]. Hypertension was defined as a systolic BP ≥ 140 mmHg, a diastolic BP ≥ 90 mmHg or treatment with antihypertensive medications. Diabetes mellitus (DM) was defined as a fasting plasma glycemic level ≥126 mg/dl or treatment with oral hypoglycemic drugs or insulin injections. A current smoker was defined as one who smoked at the time of PCI or had quit smoking within 1 year before PCI. In all patients, indications for PCI were based on objective evidence of myocardial ischemia (positive stress test), ischemic symptoms or signs associated with significant angiographic stenosis. The hospital's internal review board approved this study. At our institution, informed consent to record patient data is obtained from all patients who undergo PCI.

The follow-up period ended on October 31, 2011. Survival data and data on incident acute coronary syndrome (ACS) were collected by serial contact with the patients or their families, and were assessed from the medical records of patients who had died or of those who were followed up at our hospital. Information about the circumstances and date of death were obtained from the families of patients who died at home, and details of the events or the cause of death was supplied by other hospitals or clinics where the patients had been admitted. All data were collected by blinded investigators. ACS was identified if patients had ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), or unstable angina (UAP). STEMI was determined based on symptoms of ischemia with ST-segment elevation on the electrocardiogram and increased serum levels of cardiac enzymes [troponin, creatine kinase (CK-MB, CK ≥2-fold increase] [12,13]. NSTEMI was determined based on symptoms of ischemia without ST-segment elevation on the electrocardiogram and increased serum levels of cardiac enzymes [14]. UAP was determined based on the symptoms of ischemia at rest or with a crescendo pattern of symptoms or new-onset symptoms associated with transient ischemic ST-segment shifts and normal serum levels of cardiac enzymes [14].

Statistical analysis

The results are expressed as the mean ± SD for continuous variables and as a percentage for categorical variables. To determine factors associated with the composite endpoint of all-cause death and ACS, univariate Cox regression analysis was performed. Variables which had a significant or borderline significant association ($p < 0.10$) with the composite endpoint were included in multivariate Cox regression analysis along with age and gender as independent variables for both young and old adult groups. In young adults, BMI was added as a covariate because it was an important feature of young patients. Survival curves were drawn using the Kaplan–Meier method and the log-rank test was used to compare two survival curves. A p-value <0.05 was considered significant, unless otherwise indicated. All data were analyzed using JMP10.0 MDSU statistical software (SAS Institute, Cary, NC, USA).

Results

Characteristics of patients

Among 7649 patients who underwent PCI, 69 patients (1.3%) who were below 40 years and 4225 patients (55.2%) who were above 65 years were identified as young adults and old adults, respectively. The baseline characteristics of these patients are shown in Tables 1 and 2. Young patients were predominantly men and the mean age was 36 years. Thirty percent of them were current smokers, and the mean BMI was 26.7 ± 5.0 kg/m^2. All patients had ≥1 conventional cardiovascular risk factor, and 75% of them had single vessel disease.

Univariate and multivariate analysis for the composite endpoint

Outcome data were fully documented during the follow-up period (median 9.8 years, interquartile range: 3.9–18.8 years).

In young adults, during the follow-up period, 4 (5.8%) patients died (2 sudden death, 1 STEMI, 1 sepsis), and 6 (8.7%) suffered from ACS (3 STEMI, 1 NSTEMI, 2 UAP). In univariate analysis, current

Table 1
Baseline characteristics.

	Young adults (age ≦40, n = 69)	Old adults (age ≧65, n = 4225)	p-Value
Age	36.1 ± 4.9	73.1 ± 5.7	<0.0001
Male, n (%)	66 (95.7)	3210 (75.7)	<0.0001
Smoking, n (%)			<0.0001
Current smoker	21 (30.5)	671 (15.8)	
Former smoker	31 (44.9)	1925 (45.5)	
Never smoker	17 (24.6)	1629 (38.7)	
HT, n (%)	33 (47.8)	3104 (73.2)	0.003
DM, n (%)	23 (33.3)	1958 (46.2)	0.32
BMI	26.7 ± 5.0	23.5 ± 3.3	<0.0001
LDL-C (mg/dl)	127.9 ± 52.7	110.4 ± 31.9	0.02
HDL-C (mg/dl)	41.8 ± 20.8	42.6 ± 12.9	0.81
TG (mg/dl)	174.1 ± 89.7	120.3 ± 63.8	<0.0001
eGFR (ml/min/1.73 m^2)	90.1 ± 21.6	61.4 ± 22.1	<0.0001
EF (%)	59.1 ± 11.2	61.3 ± 13.7	0.41
ACS, n (%)			0.34
STEMI	12 (17.4)	666 (15.7)	
NSTEMI	2 (2.9)	55 (1.3)	
UAP	8 (11.6)	514 (12.8)	
Family history of CHD, n (%)	27 (40.9)	1136 (26.7)	0.03
Vessel disease, n (%)			<0.0001
1VD	51 (75)	1648 (38.7)	
2VD	13 (18)	1364 (32.1)	
3VD	5 (7)	1243 (29.2)	

HT, hypertension; DM, diabetes mellitus; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; eGFR, estimated glomerular filtration rate; EF, ejection fraction; ACS, acute coronary syndrome; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; UAP, unstable angina; CHD, coronary heart disease; VD, vessel disease.

Table 2
Use of medications (young adults) at discharge.

	n = 69
Aspirin, n (%)	64 (92.9)
Antiplatelet drug, n (%)	47 (68.1)
ACE-I/ARB, n (%)	23 (34.8)
β-Blocker, n (%)	21 (31.8)
Calcium channel blocker, n (%)	31 (46.9)
Statin, n (%)	30 (45.5)
OHA, n (%)	6 (8.7)
Insulin, n (%)	3 (4.3)

ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; OHA, oral hypoglycemic agent.

smoking was identified as the only significant predictor of the composite endpoint (all-cause death and ACS) (Table 3). Survival curves of patients with and without current smoking are shown in Fig. 1. Multivariate Cox proportional hazards regression analysis revealed that current smoking was a significant independent predictor of the composite endpoint (HR 4.46, 95% CI 1.08–19.1, $p = 0.04$) (Table 3).

In older adults, univariate analysis revealed age, EF, use of statin, HDL-C, TG, and CKD were significant or borderline factors ($p < 0.10$) for the composite endpoint. Multivariate Cox proportional hazards regression analysis adjusted for these factors revealed that age and use of statins and EF were significant independent predictors of the composite endpoint (HR 1.05, 95% CI 1.03–1.07, $p < 0.0001$; HR 0.65, 95% CI 0.54–0.78, $p < 0.0001$; HR 0.98, 95% CI 0.97–0.99, $p < 0.0001$, respectively).

Discussion

The important new finding of this study is that current smoking was a determinant of poor prognosis in young CHD patients (≤40 years old) who underwent PCI and young patients represented 1.3% of all who underwent PCI in our institution over a 26-year period. Previous reports indicated that the development of CHD in young adults is rare ranging from 1 to 10% [2,15–18]. In agreement with previous reports, the features of background in young patients of our study were higher prevalence of smokers and obesity, and three-quarters of patients had single-vessel disease. The prevalence of diabetes and hypertension was 33% and 48%, respectively. All patients had >1 conventional cardiovascular risk factors. The risk factors associated with atherosclerosis in young patients are similar to those in older patients, and nearly all young patients had at least one conventional cardiovascular risk factor [19]. Furthermore, although older patients had higher rates of diabetes and hypertension, younger patients showed higher rates of smoking and obesity [20].

Table 3
Cox proportional hazards model for the predictors of the composite endpoint.

	Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p
Age	1.02	0.92–1.17	0.78	1.01	0.89–1.21	0.95
Gender (F/M)	1.34	0.07–7.04	0.79	3.91	0.20–26.1	0.29
BMI	1.06	0.95–1.16	0.29	1.04	0.93–1.15	0.47
HT	1.87	0.59–6.37	0.28		–	
DM	1.68	0.49–5.27	0.38		–	
Metabolic syndrome	1.51	0.41–5.47	0.52		–	
LDL-C	0.99	0.98–1.01	0.37		–	
HDL-C	0.99	0.96–1.02	0.97		–	
TG	1.01	0.99–1.02	0.71		–	
Current smoker	3.79	1.05–13.1	0.04	4.46	1.08–19.1	0.04
Family history of CHD	1.24	0.38–4.64	0.72		–	
CKD	1.72	0.10–13.3	0.66		–	
OMI	2.02	0.40–9.17	0.37		–	
EF	0.99	0.93–1.06	0.72		–	

HR, hazard ratio; CI, confidence interval; BMI, body mass index; HT, hypertension; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; CHD, coronary heart disease; CKD, chronic kidney disease; OMI, old myocardial infarction; EF, ejection fraction.

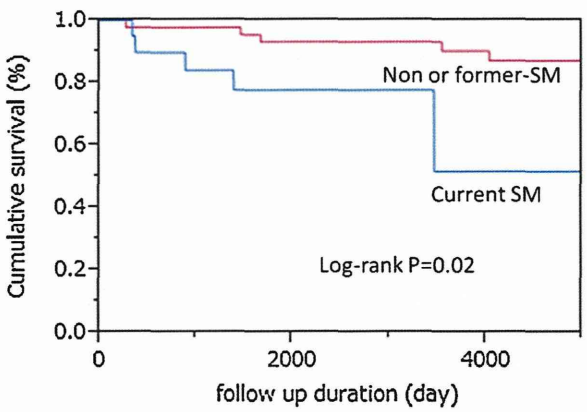

Fig. 1. Kaplan–Meier curve for the composite endpoint of all-cause death or acute coronary syndrome. Current smokers had a significantly worse outcome compared with non- or former smokers (log-rank test; $p = 0.02$). SM, smoker.

There are only a few previous reports that evaluated long-term outcomes of young patients following PCI. Rallidis and colleagues found that smoking was the most powerful predictor for recurrence of cardiac events in young AMI patients (age ≦35 years) [21]. Cole and colleagues found that DM, active smoking, and left ventricular systolic dysfunction were predictors of increased mortality in young patients (≤40 years) with CHD [11]. In their study, the number of subjects was large (843 patients ≤40 years with CHD) and the subjects were followed for 15 years. However, the baseline data were collected from 1975 to 1985 and revascularization was performed in only 60% (27% underwent PCI and 34% underwent coronary artery bypass surgery). Therefore, these results might have been different from current results, which were derived from current medical and revascularization practice of CHD treatment. More recently, Meliga and colleagues found that active smoking and a left ventricular ejection fraction <50% were independent predictors of major adverse cardiac and cerebrovascular events in young patients (≤40 years) who underwent PCI [22]. The subjects in their study were similar to those in our study in terms of patient characteristics. Although a greater number of patients (214 patients ≤40 years) underwent PCI in their study, the follow-up duration was much shorter (median 757 days) compared with the present study. Furthermore, there are no previous studies of PCI in young patients in a Japanese population. Thus, our study is the first to evaluate the long-term outcomes of PCI in young Japanese patients.

In general, patients with CHD usually have one or more traditional risk factors (e.g. hypertension, DM, dyslipidemia, obesity, smoking, family history of CHD). This is true even in young CHD patients and these patients often have multiple traditional CHD risk factors. It was reported that young CHD patients were likely to be smokers, men, obese and to have a positive family history of CHD [10]. However, young patients are more likely to have less extensive coronary atherosclerotic lesion (i.e. single-vessel disease) and less complex CAD than elderly patients [5]. Indeed, in the present study, 75% of patients had single-vessel disease. Azegami and colleagues compared the clinical characteristics of young (≤40 years) and old (≥50 years) Japanese CHD patients who were diagnosed with CHD between 1992 and 2002 [8]. In their study, young CHD patients were more likely to be men, obese, smokers, and to have hyperlipidemia. Similarly, patients in our study were obese (BMI 26.7 ± 5.0) and likely to be smokers.

The presence of multiple coronary risk factors in young CHD patients may play important roles in the secondary prevention of CHD. In the present study, current smoking was the only independent predictor of long-term outcome. There were three other studies in which the predictors of morbidity and mortality in young patients with CHD were assessed [11,21,22]. Although the independent predictors of outcomes appear to vary across studies, including ours, these differences are probably due to differences in the characteristics of the study populations. However, smoking was a consistent predictor of major adverse events in all studies.

Smoking may increase the risk of incident adverse events through the activation of the inflammatory cascade and endothelial dysfunction [23–25]. Zieske and colleagues found smoking was strongly associated with presence of advanced atherosclerosis [26]. Furthermore, Burke and colleagues demonstrated that smoking is associated with coronary thrombosis in both young men [27] and

women [28]. The results of these studies and ours show the impact of smoking on clinical outcomes in young CHD patients, and emphasize the importance of smoking cessation in young adults [29], even in those without other CHD risk factors.

Our study is subject to some limitations. First, the number of subjects was limited and PCI was performed at a single center. Second, the present study was observational in nature. Although we adjusted our Cox proportional hazards model for known confounding variables, other unknown confounders might have affected the outcome.

Conclusions

In conclusion, current smoking and obesity (high BMI) are the important clinical characteristics in young Japanese CHD patients who undergo PCI. Although the long-term prognosis of young Japanese CHD patients is acceptable, current smoking is a significant independent predictor of death and the recurrence of ACS in young Japanese CHD patients who are obese.

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Letter to the Editor

Estimation of nocturnal cardiac output by automated analysis of circulation time derived from polysomnography

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To the Editors;

Two-thirds of heart failure (HF) patients are reportedly accompanied by comorbid sleep disordered breathing (SDB) [1]. Pulmonary congestion, low cardiac output and enhanced ventilatory response to carbon dioxide in HF have been observed to cause Cheyne–Stokes respiration [2,3]. Aside from the above, fluid accumulation and nocturnal rostral fluid shift may also predispose to obstructive sleep apnea in this particular group [4]. A community-based cohort study has shown that comorbid obstructive sleep apnea is associated with an increase in the risk of death in patients with HF [5]. Several existing non-randomized studies have suggested that treatment with continuous positive airway pressure improved the prognosis of such patients [5,6].

With the spread of awareness of these mutual relationships between SDB and HF, sleep study has become one of the most fundamental examinations in current HF management [7] and a large number of polysomnography studies are carried out on HF patients every year for this very reason. Among the data obtained in polysomnography study, the lag time from the start of re-breathing to the rising point of pulse oximetric saturation (SpO_2) during periodic breathing was reported to significantly correlate to the parameters of cardiac function [8,9]. Namely, the lag time from the lungs to the fingertips (lung-to-finger circulation time (LFCT), Fig. 1) is expected to lengthen in patients with lower cardiac output, and this relationship has a strong possibility of being used as an indicator of cardiac function in the subjects.

However, past studies conducted through the use of polysomnography have been far from satisfactory from the standpoint of daily clinical use. First, researchers had to manually and repeatedly measure numerous LFCTs from the long readout of a whole night of recorded polysomnography. Second, the precise causal association between cardiac output and LFCT was undetermined, even though LFCT is theoretically expected to correlate to the reciprocal value of cardiac output. Hence, we set out to develop a novel algorithm that could automatically and continuously detect LFCT from polysomnography data in an attempt to better clarify the relationship between LFCT and cardiac output.

The outlines of the algorithm detecting LFCT are illustrated in Fig. 1. The algorithm begins by fully rectifying the respiratory airflow signal, which then has a low-pass filter applied to it. Thereby, the resultant shape of the converted rectified airflow wave becomes more similar to that of the fingertip SpO_2 waveform. LFCT is then determined by a cross correlation analysis between the modified air-flow signal and the SpO_2 signal. This calculation can be automatically repeated every 2 min through to the end of the data collection period. Once the series of LFCT readouts are obtained, the algorithm automatically removes unreliable values and outliers.

As LFCT is expected to be shorter in smaller subjects in terms of height if they have similar cardiac output, we adopted the use of the measured cardiac index (CI), which is standardized by body surface area, for the values that were to be compared to those of the LFCT. Once again applying this algorithm, we performed following study to determine the relationship between LFCT and CI in 31 consecutive stable HF patients, who were admitted to our cardiovascular department due to various underlying cardiac diseases that required a right-sided standard cardiac catheterization: ischemic heart disease (n = 14), valvular heart disease (n = 6), cardiomyopathy (n = 4) and others (n = 7) (Table 1). The study protocol was approved by the institutional ethics committee, and conducted in strict accordance with the Helsinki Declaration. Cardiac output was measured principally by the standard technique (Fick's method) during the right-sided catheterization.

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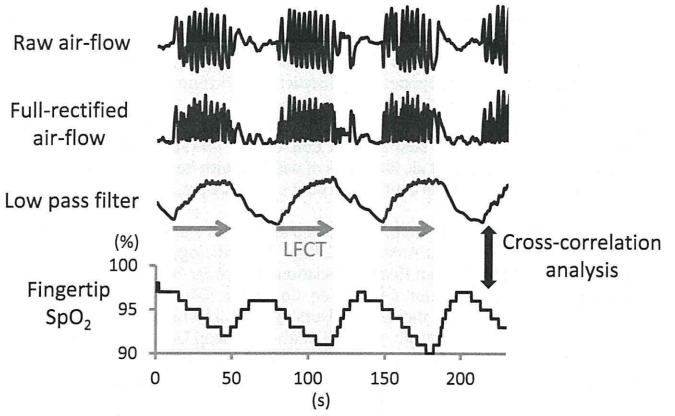

Fig. 1. Outlines of the algorithm automatically detecting lung-to-finger circulation time (LFCT). Respiratory airflow and SpO_2 in a patient with Cheyne–Stokes respiration are shown. LFCT is defined as the lag time from the start of re-breathing to the rising point of SpO_2. First, the algorithm full-rectified airflow and applying a 1st order low-pass filter onto that without phase delay to attain a similar waveform to that of fingertip SpO_2. After preparing respiratory signal, the algorithm determined LFCT using a cross correlation analysis between respiratory signal and SpO_2. LFCT: lung to fingertip circulation time.

Table 1
Patient characteristics.

Age	66.7 ± 10.1	(y)
Male	61	(%)
Ischemic heart disease	45	(%)
3% ODI	19.1 ± 13.4	(/h)
LV ejection fraction	49.4 ± 15.3	(%)
BNP[a]	288 ± 303	(pg/ml)
PAW pressure	9.5 ± 5.2	(mm Hg)
Cardiac index	2.52 ± 0.51	(L/min/m^2)

[a] Data of 3 patients were not available. ODI: oxygen desaturation index, LV: left ventricle, BNP: brain natriuretic peptide, PAW pressure: pulmonary artery wedge pressure.

Portable polysomnography (SAS-2100 Nihon-Kohden Corp, Japan) was performed within 3 days of the catheterization.

After we confirmed that the algorithm had detected appropriate LFCT values compared with manually measured LFCT (RMSE of auto-detection vs. manual detection: 2.3 ± 1.9 s) in a representative patient, we averaged all the overnight LFCTs to yield one mean value for each patient, and then compared them to the respective individual's CI. As shown in Fig. 2, the overnight mean LFCT values significantly correlated to the measured CI ($R^2 = 0.44$, $p < 0.001$). We approximated the relationship to the hyperbolic function (Fig. 2, left), and calculated an estimated CI from each obtained LFCT. The RMSE of the estimated CI vs. the actual measured CI was limited to 0.33 ± 0.23 L/min/m^2, which we believe would be acceptable for clinical use. The nocturnal trend of LFCT and CI was clearly observed, as well as apnea/hypopnea events – as shown in Fig. 2, right – by overlaying this analysis on the polysomnographic data.

This study showed for the first time the feasibility of this newly-developed algorithm, and introduced an easy-to-use approach for automated LFCT detection and CI estimation, by utilizing airflow and fingertip oxygen saturation data. Most importantly from this study's viewpoint, this novel technique could visually represent not only cardiac output at one specific point in the sleep period, but also its nocturnal trend without the need for any additional apparatus or specialist operator skill.

We are aware of at least a couple of variable factors that could derange CI estimation. First, the estimation may be affected by sleeping position (i.e. lateral or supine position) due to the position of elevation of the monitored fingertip relative to the heart, which would alter hydrostatic pressure. Second, contributing factors that may affect blood flow or its distribution, such as significant arterial stenosis or dialysis shunt in the monitored arm, may result in a misleading CI estimation.

This analysis can be routinely performed during or after every polysomnography, and could become a helpful tool for screening HF or evaluating the effects of treatment in the daily management of HF, though a further, larger-sized study is needed in order to validate the

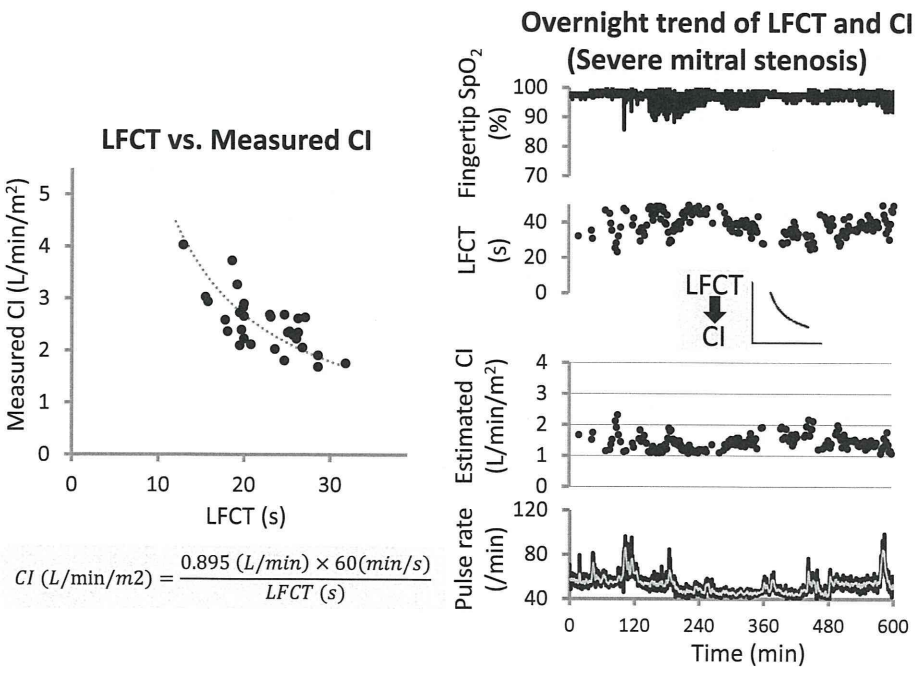

Fig. 2. Relationship between lung-to-finger circulation time (LFCT) and cardiac index. Left panel: Automatically detected LFCT was significantly correlated to cardiac index ($R^2 = 0.44$, $p < 0.001$). The relationship was approximated to the hyperbolic function. Right panel: A representative overnight chart obtained from polysomnography data and our analysis in patients with severe mitral stenosis is demonstrated. LFCT was automatically derived from polysomnography data by our algorithm. Cardiac index was estimated by the identified hyperbolic function.

accuracy of this method in a wider range of the population with various cardiac diseases.

Conflict of interest

SA received unrestricted substantial research funding from Philips Respironics and Teijin Home Healthy.

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