Heart and Vessels (2019) 34:1325–1331
https://doi.org/10.1007/s00380-019-01362-9

ORIGINAL ARTICLE

Investigation of arterial–cardiac–pulmonary interaction

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Received: 24 November 2018 / Accepted: 15 February 2019 / Published online: 28 March 2019

Abstract
Pulmonary function and arterial stiffness correlate significantly, attributing to the chronic inflammation of atherosclerosis. However, through the pulmonary or systemic circulation, pulmonary and vascular functions associate hemodynamically with cardiac morphology and function. In the present study, we investigated arterial–cardiac–pulmonary interaction by examining how the pulmonary and vascular functions correlate with the heart. This study investigated 55 consecutive subjects not suffering from pulmonary, vascular and cardiac disease who underwent health screening test at our medical center. First, the presence of atherosclerotic disease (hypertension, dyslipidemia and diabetes) and smoking status of the patients were determined. Next, pulmonary function test, vascular function test including cardio-ankle vascular index, and echocardiography were performed. Then, we examined the correlation among the pulmonary, vascular and the heart. Our results revealed many correlations among these three factors. Especially left atrial dimension (LAD) and *E*/*A* ratio (*E*/*A*) were important cardiac factors associated with both pulmonary and vascular functions independently. Conventionally, inflammatory responses are known to involve in the correlation between pulmonary and vascular functions. Our study demonstrated that cardiac function and morphology were also involved in this correlation, signifying that LAD and *E*/*A* plays important roles in the arterial–cardiac–pulmonary interaction.

Keywords Atherosclerosis · Pulmonary age · CAVI · LAD · *E*/*A*

Introduction

Recently, association between pulmonary function and atherosclerosis has been gaining attention [1, 2]. The relationship between arterial stiffness and pulmonary functions was reported using pulse wave velocity (PWV) [3], but PWV was depending on the blood pressure at measuring time. Cardio-ankle vascular index (CAVI) was a new arterial stiffness index independently of the blood pressure at measuring time and was thought to be reflecting proper arterial stiffness [4]. Then, CAVI was adopted as index of arterial stiffness reflecting vascular function in this work.

Using CAVI, a significant and positive correlation between decreased pulmonary function and arterial stiffness has been reported in patients with chronic obstructive pulmonary disease (COPD) [5]. Chronic inflammation has been indicated as the mechanism relating to both pulmonary dysfunction and atherosclerosis [6, 7]. However, the pulmonary and vascular functions are hemodynamically related to cardiac morphology and function. In the present study, we investigated arterial–cardiac–pulmonary interaction by examining how the pulmonary and vascular functions correlate with the heart.

Methods

Study population

We investigated 55 consecutive subjects not suffering from pulmonary, vascular and cardiac disease, who underwent pulmonary function test, vascular function test and echocardiography at our center between September 1, 2016 and August 31, 2017. First, the subjects' characteristics, including sex, age, presence of atherosclerotic disease (hypertension, dyslipidemia and diabetes) and smoking status, were

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determined. Subsequently, pulmonary function test, vascular function test and echocardiography were performed. This study was approved by the ethics committee of Saitama Medical University Hospital and informed consent was obtained from all subjects.

Pulmonary function test

Pulmonary function tests were performed using a spirometer (Spiroshift SP-7710 COPD; Fukuda Denshi, Tokyo, Japan) to measure VC, %VC, FEV1.0L, FEV1.0%, and %FEV1.0. Pulmonary age was calculated based on the sex, age, height and FEV1.0L of each subject using the equation proposed by the Japanese Respiratory Society [8].

Vascular function test

Cardio-ankle vascular index was recorded using a vascular screening system (Vasera VS-1500N; Fukuda Denshi, Tokyo, Japan) with the patient resting in a supine position [9]. Pre-ejection period (PEP), ejection time (ET), and augmentation index (AIx) were determined from the pulse wave, phonocardiogram and electrocardiogram obtained during measurement of CAVI. Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (mBP) and pulse pressure (PP) were determined from the resting recumbent blood pressure.

Echocardiography

Echocardiography was performed using the Aplio500 System (Canon medical systems, Tochigi, Japan). Using M-mode, we measured dimension of the ascending aorta (AoD), left atrial (LA) dimension (LAD), left ventricular (LV) septal thickness (IVSd), LV end-diastolic dimension (LVEDd), LV end-systolic dimension (LVEDs), LV posterior wall dimension (PWd), right ventricular (RV) pressure (RVP), stroke volume (SV), ejection fraction (EF) and fractional shortening (%FS). The LV mass index (LVMI) and relative wall thickness (RWT) were calculated using the following formula according to the American Society of Echocardiography convention [10].

$$\mathrm{LVM\ (g)} = 0.8 \times \{1.04 \times [([\mathrm{LVEDd} + \mathrm{IVSd} + \mathrm{PWd}] \times 3 - \mathrm{LVEDd} \times 3)]\} + 0.6,$$

$$\mathrm{LVMI}\left(\mathrm{g/m^2}\right) = \mathrm{LVM/BSA},$$

$$\mathrm{RWT} = 2 \times \mathrm{PWd/LVEDd},$$

where $\mathrm{BSA(m^2)}$ is the body surface area.

Next, the parameters of LV diastolic function were measured by recording the transmitral flow velocity using conventional Doppler echocardiography [11, 12]. The transmitral flow velocity was recorded from the apical transducer position, with the sample volume situated between the mitral leaflet tips. The peak early transmitral flow velocity (*E* velocity) and the peak late transmitral flow velocity (*A* velocity) were recorded, and the *E*/*A* ratio (*E*/*A*) was calculated. The deceleration time of the *E* velocity (DcT) and the Tei index (Tei) [13] were also measured.

Statistical analysis

Linear regression analysis was performed to evaluate the association between pulmonary and vascular parameters, between pulmonary and cardiac parameters, and between vascular and cardiac parameters. Stepwise multiple regression analysis was performed to identify the independent determinants of each parameter. Values of $p < 0.05$ were considered statistical significant. Data were expressed as mean ± standard deviation (SD). Statistical analysis was performed using the SPSS ver. 24 software package (SPSS, Chicago, IL, USA).

Results

Characteristics of 55 subjects are shown in Table 1, composed of 32 males and 23 females, and mean age was 66.1 ± 10.0 years old. 17 patients suffered from hypertension, 11 dyslipidemia and 5 diabetes. Current smoker was 7.

Correlation between pulmonary and vascular function

As shown in Table 2, pulmonary age correlated with CAVI and PP on linear regression analysis, and CAVI was an independent predictor in stepwise multiple regression analysis. Likewise, VC and FEV1.0L correlated with AIx. FEV1.0% correlated with CAVI.

Correlation between pulmonary function and the heart

Pulmonary age correlated significantly with LAD and RVP, and LAD was an independent predictor according to the multivariate analysis (Table 3). VC correlated significantly with systolic function (i.e., SV, EF, and %FS) and *E*/*A*, and *E*/*A* was an independent predictor. FEV1.0L correlated significantly with systolic function (i.e., EF and %FS) and *E*/*A*,

Table 1 Patients' characteristics

Number (male/female)	55 (32/23)
Age (years)	66.1 ± 10.0
Hypertension [*n* (%)]	17 (31)
Dyslipidemia [*n* (%)]	11 (20)
Diabetes [*n* (%)]	5 (10)
Current smoker [*n* (%)]	7 (13)
Pulmonary parameters	
VC (L)	3.5 ± 0.9
%VC (%)	108.2 ± 13.0
FEV1.0L (L)	2.7 ± 0.7
FEV1.0% (%)	77.5 ± 6.5
%FEV (%)	106.0 ± 16.2
Pulmonary age (years)	59.9 ± 19.5
Arterial parameters	
CAVI	8.3 ± 1.2
PEP (ms)	89.8 ± 13.7
ET (ms)	309.9 ± 27.4
AIx	0.99 ± 0.21
SBP (mmHg)	127.0 ± 13.2
DBP (mmHg)	80.0 ± 8.3
mBP (mmHg)	111.3 ± 10.8
PP (mmHg)	47.0 ± 10.2
Cardiac parameters	
AoD (mm)	32.0 ± 3.2
LAD (mm)	36.6 ± 4.4
RVP (mmHg)	20.5 ± 8.2
SV (ml)	74.4 ± 19.1
EF (%)	75.2 ± 6.1
%FS	44.1 ± 5.7
LVMI (g/m^2)	96.4 ± 27.1
RWT	0.43 ± 0.11
E/*A*	1.0 ± 0.3
DcT (ms)	239.9 ± 34.2
TEI	0.33 ± 0.18

and EF and *E*/*A* as independent predictors. FEV1.0% correlated significantly with LAD.

Correlation between vascular function and the heart

Cardio-ankle vascular index correlated significantly with AoD, LAD, LVMI, RVP and *E*/*A*, and LAD and *E*/*A* as independent predictors according to the multivariate analysis (Table 4). PEP correlated with RVP, ET correlated with SV. SBP correlated significantly with AoD, LVMI and *E*/*A*, and LVMI and *E*/*A* as independent predictors. mBP correlated with the AoD, LVMI and *E*/*A*, with *E*/*A* as an independent predictor. PP correlated with LVMI and *E*/*A*, and LVMI as an independent predictor.

LAD and *E*/*A*

In the present study, the crucial role of LAD and *E*/*A* in arterial–cardiac–pulmonary interaction was revealed. We examined the associations of LAD and *E*/*A* with other cardiac parameters (Table 5). LAD correlated significantly with LVMI, RVP and SV. LVMI and RVP were independent predictors for LAD. *E*/*A* correlated significantly with RWT.

Discussion

Pulmonary function correlates with vascular function through atherosclerosis, and factors of inflammatory response like high-sensitivity C-reactive protein (hs-CRP) have been reported to be the common factors [8, 14, 15]. Pulmonary function is associated with atherosclerosis [1, 2, 16, 17], and COPD itself is a risk factor for cardiovascular lesions [18, 19]. Vascular function is also associated with atherosclerosis and is a risk factor for atherosclerotic diseases. Our study revealed correlation of pulmonary function with CAVI, PP and AIx. AIx is also related with atherosclerosis [20].

Table 2 Linear regression and stepwise multiple regression analysis of pulmonary and arterial parameters

	Pulmonary age				VC		%VC		FEV1.0L		FEV1.0%		%FEV	
	Univariate		Multivariate		Univariate		Univariate		Univariate		Univariate		Univariate	
	r	*p*	*β*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
CAVI	0.514	< 0.001	0.472	< 0.001	−0.171	ns	−0.203	ns	−0.253	ns	−0.292	0.031	−0.235	ns
PEP	−0.105	ns			0.052	ns	0.084	ns	0.027	ns	−0.062	ns	0.047	ns
ET	0.046	ns			0.040	ns	0.049	ns	−0.034	ns	−0.263	ns	−0.062	ns
AIx	0.051	ns			−0.306	0.023	0.033	ns	−0.324	0.016	−0.204	ns	0.017	ns
SBP	0.253	ns			−0.062	ns	−0.187	ns	−0.072	ns	−0.080	ns	−0.168	ns
DBP	0.049	ns			0.179	ns	−0.072	ns	0.173	ns	0.066	ns	−0.123	ns
mBP	0.220	ns			−0.009	ns	−0.171	ns	−0.019	ns	−0.050	ns	−0.168	ns
PP	0.288	0.033	0.115	0.370	−0.224	ns	−0.181	ns	−0.233	ns	−0.162	ns	−0.117	ns

Table 3 Linear and stepwise multiple regression analysis of pulmonary and cardiac parameters

	Pulmonary age				VC				%VC	FEV1.0L				FEV1.0%		%FEV	
	Univariate		Multivariate		Univariate		Multivariate		Univariate	Univariate		Multivariate		Univariate		Univariate	
	r	*p*	*β*	*p*	*r*	*p*	*β*	*p*	*r*	*p*	*r*	*p*	*β*	*p*	*r*	*p*	*r*	*p*
AoD	0.034	ns			0.246	ns			0.108	ns	0.258	ns			0.120	ns	0.112	ns
LAD	0.408	0.002	0.471	< 0.001	−0.010	ns			−0.102	ns	−0.103	ns			−0.295	0.029	−0.215	ns
RWT	0.049	ns			−0.134	ns			−0.031	ns	−0.126	ns			−0.058	ns	−0.025	ns
LVMI	0.189	ns			0.006	ns			−0.084	ns	−0.010	ns			−0.076	ns	−0.084	ns
RVP	0.288	0.033	0.162	0.189	−0.026	ns			−0.041	ns	−0.067	ns			−0.132	ns	−0.075	ns
SV	−0.053	ns			0.283	0.036	0.124	0.376	0.199	ns	0.234	ns			−0.040	ns	0.097	ns
EF	0.178	ns			−0.355	0.008	−0.719	0.243	−0.187	ns	−0.340	0.011	−1.197	0.035	−0.085	ns	−0.092	ns
%FS	0.141	ns			−0.316	0.019	0.433	0.478	−0.158	ns	−0.288	0.033	0.918	0.102	−0.029	ns	−0.046	ns
E/A	−0.257	ns			0.385	0.004	0.318	0.015	0.157	ns	0.328	0.014	0.294	0.021	−0.058	ns	−0.031	ns
DcT	0.192	ns			−0.180	ns			−0.224	ns	−0.148	ns			−0.008	ns	−0.125	ns
TEI	0.059	ns			0.062	ns			0.163	ns	0.005	ns			−0.129	ns	0.090	ns

Table 4 Linear and stepwise multiple regression analysis of arterial and cardiac parameters

	CAVI				PEP		ET		AIx		SBP				DBP		mBP				PP			
	Univariate		Multivariate		Univariate		Univariate		Univariate		Univariate		Multivariate		Univariate		Univariate		Multivariate		Univariate		Multivariate	
	r	*p*	*β*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*β*	*p*	*r*	*p*	*r*	*p*	*β*	*p*	*r*	*p*	*β*	*p*
AoD	0.304	0.024	0.175	0.055	0.171	ns	−0.223	ns	−0.190	ns	0.283	0.036	0.134	0.313	0.172	ns	0.274	0.043	0.133	0.323	0.224	ns		
LAD	0.492	< 0.001	0.342	0.018	−0.182	ns	0.067	ns	0.081	ns	0.212	ns			0.123	ns	0.204	ns			0.171	ns		
RWT	0.114	ns			−0.050	ns	−0.177	ns	0.154	ns	0.108	ns			0.092	ns	0.111	ns			0.062	ns		
LVMI	0.326	0.015	0.094	0.483	0.232	ns	0.197	ns	0.058	ns	0.341	0.011	0.272	0.040	0.158	ns	0.316	0.019	0.247	0.064	0.310	0.021	0.285	0.031
RVP	0.269	0.047	0.073	0.559	−0.340	0.011	−0.039	ns	−0.188	ns	−0.045	ns			−0.109	ns	−0.066	ns			0.035	ns		
SV	0.124	ns			0.218	ns	0.362	0.007	−0.149	ns	0.156	ns			0.106	ns	0.152	ns			0.117	ns		
EF	0.142	ns			−0.126	ns	−0.055	ns	0.188	ns	−0.140	ns			−0.073	ns	−0.130	ns			−0.117	ns		
%FS	0.175	ns			0.172	ns	−0.041	ns	0.196	ns	−0.102	ns			−0.024	ns	−0.087	ns			−0.108	ns		
E/A	−0.437	0.001	−0.294	0.015	0.147	ns	0.257	ns	−0.089	ns	−0.348	0.009	−0.288	0.027	−0.212	ns	−0.339	0.011	−0.281	0.033	−0.278	0.040	−0.248	0.058
DcT	0.253	ns			−0.113	ns	0.147	ns	0.180	ns	0.008	ns			−0.122	ns	−0.024	ns			0.115	ns		
TEI	−0.029	ns			0.195	ns	0.052	ns	0.104	ns	−0.035	ns			−0.167	ns	−0.073	ns			0.099	ns		

Table 5 Linear and stepwise multiple regression analysis regression analysis of LAD and *E/A* with cardiac parameters

	LAD				*E/A*	
	Univariate		Multivariate		Univariate	
	r	*p*	*β*	*p*	*r*	*p*
AoD	0.063	ns			−0.238	ns
LAD					−0.238	ns
RWT	0.198	ns			−0.291	0.031
LVMI	0.435	0.001	0.411	0.010	−0.103	ns
RVP	0.388	0.003	0.375	0.002	−0.133	ns
SV	0.345	0.010	0.023	0.880	0.252	ns
EF	0.037	ns			−0.132	ns
%FS	0.068	ns			−0.135	ns
E/A	−0.238	ns				
DcT	0.192	ns			−0.094	ns
TEI	0.085	ns			0.056	ns

On the other hand, regarding the correlation of heart with atherosclerosis, LA enlargement has been recently reported to correlate with cardiovascular lesions and mortality [21]; however, the details of this correlation have yet to be fully clarified [22]. Recently, alternation of stem cell [23] or premature aging [24] is reported as the common factors between pulmonary and vascular function. Furthermore, connection of lung and artery through heart is hemodynamically important, and cardiac morphology and function may affect this connection.

In this study, we investigated arterial–cardiac–pulmonary interaction (ACP triangle) by investigating the correlation of pulmonary and vascular function with the heart.

Correlation of pulmonary function with heart

Conventionally pulmonary function and the heart are closely related as cardiopulmonary interactions [25] or cor pulmonale [26–28].

Augmentation of pulmonary artery pressure, primary or secondary to left heart failure [29] leads to the RV increased end-diastolic pressure, expansion [30, 31] and decreased output [30, 32, 33]. Recent study using color Doppler echocardiography demonstrated the so-called ventricular interdependence, in which RV pressure and diameter are associated with the filling patterns of LA [34]. Increased RV afterload leads to increased end-diastolic pressure, reduced volume (i.e., ventricular interdependence) [30, 31] and decreased preload [30, 32, 33] of LV.

Left atrial function correlates with the LV long axis systolic function [35], and both the increased pressure and enlargement of the RV restrict the dilation and contraction along the short axis of the LV, which induces dilation and over contraction along the long axis, leading to the LA enlargement. LA enlargement was accompanied by LA longitudinal strain [36]. Decreased LV compliance due to hypoxemia and hypercapnia is also reported [30].

Increased pulmonary pressure induced by pulmonary dysfunction affects the morphology and function of LV and LA through the change of RV.

Correlation of vascular function with heart

Vascular function correlates closely with the heart (ventricular–arterial coupling) [37, 38]. In this study, CAVI correlated with LAD. Increase in CAVI leads to increase in LV end-diastolic pressure [39], resulting in increased pressure and enlargement of LA.

Cardio-ankle vascular index, SBP, mBP and PP correlated with *E/A*. These factors increase arterial stiffness, causing an increase in LV end-diastolic pressure and diastolic dysfunction [39]. Hypertension patients present diastolic dysfunction regardless of LV hypertrophy [40], especially those with LA enlargement [41].

Our study showed that increased arterial stiffness or blood pressure correlates significantly with LA enlargement and *E/A* through the increased LV end-diastolic pressure.

Arterial–cardiac–pulmonary interaction (ACP triangle)

In the present study, there is a close relation in arterial–cardiac–pulmonary interaction, the so-called ACP triangle (Fig. 1), and LAD, RVP and *E/A* were key players.

As is already stated, LAD correlated closely with RV and both factors compose ACP triangle with pulmonary age and CAVI. *E/A* correlated with VC and FEV1.0L as pulmonary factor, and with CAVI, SBP, mBP and PP as vascular factor.

E/A and *E/e′* are typically used as indices of diastolic dysfunction. But the LAD, although not directly correlated

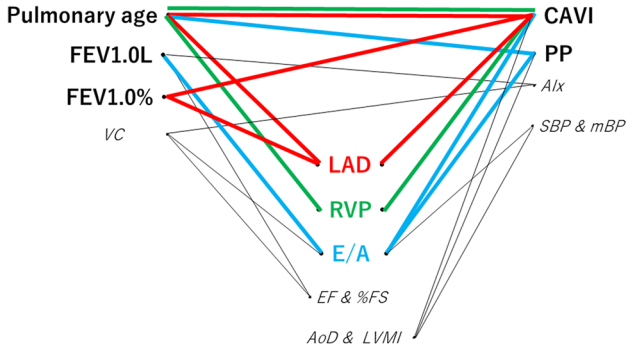

Fig. 1 Arterial–cardiac–pulmonary interaction (ACP triangle)

with these factors, is also an independent index of diastolic function [42]. Therefore, diastolic dysfunction can be accurately evaluated by taking both factors into consideration, including the conventional factors [41].

The present investigation also demonstrated association of LAD with LVMI, and *E*/*A* with RWT. Regarding LV morphology, profound associations were found between LVMI and LV enlargement, and between RWT and LV hypertrophy [43], suggesting independent association of these factors with LV diastolic dysfunction. There was no correlation between *E*/*A* and pulmonary age, resulting from important relation of blood pressure with *E*/*A*, but not with pulmonary age.

In conclusion, LAD and *E*/*A* are not directly correlated with each other, but are correlated with other cardiac parameters independently. LAD and *E*/*A* function in a complementary and compensatory manner as the markers of LV diastolic function, and play an important role in ACP triangle.

Limitations

This study did not take into consideration chronological age, which is known to be the most significant factor that influences pulmonary age, cardiac function, and vascular age. In the future, it will be necessary to investigate the age-related changes in arterial–cardiac–pulmonary interaction, including the age-related changes of each organ.

Conclusions

In addition to the conventional inflammatory responses reported, cardiac function and morphology via hemodynamics might be involved in the correlation between pulmonary and vascular functions. In particularly, LAD and *E*/*A* were independently correlated with pulmonary and vascular function, indicating that these factors play important roles in the arterial–cardiac–pulmonary interaction.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interest.

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