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Significance of systolic time intervals in predicting prognosis of primary pulmonary hypertension

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Summary

To elucidate the characteristics of left ventricular (LV) function and LV shape in primary pulmonary hypertension (PPH), systolic time intervals (STIs) and two-dimensional echocardiograms in seven patients with PPH were studied and compared with those of 12 normal controls. Serial changes in STIs were also analyzed as to clinical outcomes. All patients were females and aged from 14 to 53 years. The follow-up period was 50±30 months, and five patients died of cardiac causes during the study period.

The patients with PPH had a significantly prolonged pre-ejection period (PEP) and PEP index. Left ventricular ejection time (LVET) and the LVET index in the PPH group, at the time of diagnosis, showed no statistical differences compared with those of the controls, but three patients with PPH showed a marked shortening of LVET. A significant decrease in the LVET/PEP ratio was observed in patients with PPH. Left ventricular end-diastolic dimension (EDD) and end-systolic dimension (ESD) were significantly less in patients with PPH than in the controls. No difference in percent fractional shortening of the left ventricle and the mean velocity of circumferential fiber shortening was observed. The degree of LVET shortening correlated with the decrease in EDD ($r=0.97$). During follow-up, marked shortening of the LVET index, below approximately 350 msec, was observed immediately before death or clinical deterioration.

From these results, we conclude that in PPH, (1) left ventricular function is impaired due to reduced volume of the left ventricle during diastole, reflecting a shortening of LVET and the LVET index, and (2) analysis of serial LVET indexes is useful for predicting the prognosis.

Key words

Primary pulmonary hypertension Systolic time intervals Prognosis

Introduction

Primary pulmonary hypertension (PPH) is defined as pulmonary arterial hypertension of unknown etiology[1~3]. It is widely accepted that PPH is progressive and an ultimately fatal

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illness which resists medical treatment. A definitive diagnosis of this disease requires confirmation of pulmonary arterial hypertension and the exclusion of other pathologic entities that secondarily elevate pulmonary arterial pressure. Therefore, right cardiac catheterization is necessary for making the diagnosis. However, it is hazardous to examine severely ill patients having PPH or to follow the clinical course serially using this procedure[4,5]. It is important to determine which noninvasive parameters are useful to evaluate responses to drug therapy and prognosis in patients with PPH.

In this study, we analyzed the characteristics of left ventricular (LV) function and shape by systolic time intervals (STIs) and two-dimensional echocardiography. In addition, serial changes in STIs were examined to identify parameters which might be helpful in predicting the clinical course of PPH.

Subjects and Methods

Subjects

Seven patients undergoing diagnostic cardiac catheterization and 12 normal volunteers participated in this study. All were in sinus rhythm, and they were categorized according to the following guidelines.

PPH: The profiles of this group are summarized in **Table 1**. The diagnosis of PPH was made on the basis of the diagnostic guidelines prepared by the Primary Pulmonary Hypertension Research Committee in Japan[3].

Normal controls: This group was composed of 12 normal volunteers (7 males, 5 females), whose mean age was 42±10 years. They were considered free of cardiac abnormalities by history, physical examination, electrocardiography (ECG), chest X-ray, and complete echocardiography.

Methods

STIs: STIs were measured by recording ECG, phonocardiogram, and carotid pulse tracing simultaneously at a paper speed of 100 mm/sec. MA-250 and TY-303 transducers (Fukuda Denshi Co., Ltd) were used to record the phonocardiogram and carotid pulse tracing, respectively. The following STIs were measured by the method as previously reported[6].

Q-II intervals: The interval from the Q wave on the ECG to the onset of the aortic component of the second heart sound.

LVET (left ventricular ejection time): LVET was measured from the onset of the upstroke to

Table 1. Clinical course and hemodynamic data of 7 patients with primary pulmonary hypertension

Case no.	Sex	Age (years)	CI (L/min/m²)	SI (ml/beat/m²)	Pressure (mm Hg) PA syst	PA dias	PA mean	PCW mean	Ao syst	Ao dias	Prognosis (months)
1	F	21	2.08	29	108	48	68	10	108	78	63, alive
2	F	28	2.52	35	100	40	60	8	112	70	64, alive
3	F	51	2.23	31	100	30	53	10	106	68	104, dead
4	F	29	2.97	41	102	45	64	7	100	74	75, dead
5	F	27	2.08	26	110	50	70	9	130	80	24, dead
6	F	53	1.43	20	95	56	69	10	138	80	39, dead
7	F	14	1.21	17	85	55	65	10	86	60	9, dead
Mean		32	2.07	28	100	46	64	9	111	72	50
±SD		14	0.56	8	8	6	6	1	16	7	30

Abbreviations: CI=cardiac index; SI=stroke volume index; PA=pulmonary artery; PCW=pulmonary capillary wedge; Ao=aorta; syst=systole; dias=diastole; SD=standard deviation.

the dicrotic notch on the carotid pulse tracing.

PEP (pre-ejection period): PEP was calculated by subtracting LVET from Q-II interval.

LVET/PEP ratio: The ratio of left ven tricular ejection time to the pre-ejection period.

These intervals were expressed as the mean of the measurements of five consecutive heart beats. Q-II interval, LVET, and PEP were corrected for heart rate by the regression equation of Weissler et al[7]. Rate-corrected Q-II interval, LVET and PEP were expressed as the Q-II index (Q-IIi), the LVET index (LVETi), and the PEP index (PEPi).

Echocardiography: Two-dimensional (2-D) echocardiograms were obtained using one of two commercially-available instruments: an SSH-11A 2-D echocardiograph with a 2.5 MHz transducer (Toshiba Co., Ltd) or an SSD-810 2-D echocardiograph with a 2.5 MHz transducer (Aloka Co., Ltd). Left ventricular internal dimension was ascertained in the standard parasternal short-axis view at the level of the mitral valve-chordae tendineae transition. End-diastolic (EDD) and end-systolic (ESD) dimensions were measured in appropriate stop frame images depicting end-diastole and end-systole using a method previously reported[8]. End-diastole was defined as the peak of the R wave on a simultaneously-derived ECG. End-systole was defined as the frame in which the smallest internal dimension was measured. The following parameters were derived from EDD and ESD. (1) Percent fractional shortening of the left ventricle: percent FS=(EDD−ESD)/EDD×100. (2) Mean velocity of circumferential fiber shortening: mean Vcf=(EDD−ESD)/EDD/LVET.

Cardiac catheterization: Written consent was obtained from all patients. All patients underwent right-sided cardiac catheterization with conventional pressure measurements, by a balloon floatation catheter (Swan-Ganz). Cardiac output was measured in triplicate by the thermodilution method. Stroke volume index (SI) was calculated as the cardiac output/heart rate/body surface area.

Table 2. Comparison of systolic time intervals in patients with primary pulmonary hypertension (PPH) **and normal controls** (C)

Case no.	HR (beats / min)	Q-II (msec)	Q-IIi (msec)	LVET (msec)	LVETi (msec)	PEP (msec)	PEPi (msec)	LVET / PEP
1	54	394	502	275	361	119	141	2.31
2	65	415	545	290	394	125	151	2.32
3	58	404	520	280	373	124	147	2.26
4	57	395	509	270	361	125	148	2.16
5	85	372	540	226	360	146	180	1.55
6	98	336	532	235	392	120	159	1.96
7	90	378	558	230	374	148	184	1.55
Mean	72	385	529	258	374	130	159	2.02
± SD	17	24	19	25	13	11	16	0.32
C: Mean	67	398	534	280	392	115	142	2.44
± SD	9	25	19	22	14	9	10	0.24
p	NS	NS	NS	NS	NS	0.02	0.05	0.02

Abbreviations: HR=heart rate; Q-II and Q-IIi=Q-II time and index; LVET and LVETi=left ventricular ejection time and index; PEP and PEPi=pre-ejection period and index; p=probability; SD=standard deviation; NS=not significant.

The first measurement of the STIs and 2-D echocardiographic studies was performed within one week before cardiac catheterization.

Statistical analysis: Dispersion from the mean is reported as ±standard deviation (SD) of the mean. The data of the two groups were compared using the Mann-Whitney U test.

Results

1. Hemodynamic data (Table 1)

All patients with PPH were characterized by severe pulmonary hypertension. The mean pulmonary capillary wedge pressure was within normal limits. The SI was 28±8 ml/beat/m^2 and the cardiac index was 2.07±0.56 L/min/m^2, which were significantly less than normal.

2. Systolic time intervals (Table 2)

The heart rate, Q-II and Q-IIi of the two groups did not differ significantly. Three patients (Cases 5, 6, and 7) had markedly shortened LVET, although the PPH group as a whole showed no statistical difference in LVET or LVETi compared to those of the controls. PEP and PEPi were significantly prolonged in PPH. The LVET/PEP ratio in PPH was significantly smaller than that of the controls.

3. Echocardiographic data (Table 3)

Both EDD and ESD were significantly smaller in PPH than in the controls. There was no significant difference in percent FS or mean Vcf between the two groups.

Table 3. Comparison of results of echocardiography in patients with primary pulmonary hypertension (PPH) and normal controls (C)

	EDD (mm)	ESD (mm)	percent FS (%)	mean Vcf (circ./sec)
C	48.5±3.0	31.5±4.0	36.2±5.3	1.30±0.21
PPH	26.1±6.7	15.4±4.6	41.0±8.4	1.60±0.45
p	0.01	0.01	NS	NS

Abbreviations: EDD = end-diastolic dimension; ESD = end-systolic dimension; percent FS = percent farctional shortening of the left ventricle; mean Vcf = mean velocity of circumferential fiber shortening; p = probability; NS = not significant.

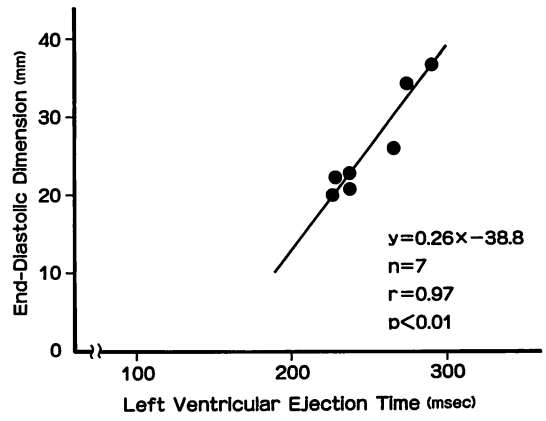

Fig. 1. Left ventricular ejection time (LVET) plotted against end-diastolic dimension (EDD) for patients with primary pulmonary hypertension.

LVET correlates closely with EDD (r=0.97).

4. Relationship between LVET and EDD

LVET correlated closely with EDD (r=0.97) (**Fig. 1**).

5. Prognosis in PPH (Table 1, Fig. 2)

Patients with PPH were followed from the day of cardiac catheterization until the time of their death or until the end of the study in August 1987. The mean follow-up period was 50±30 months. During this period, five patients died of cardiac causes. LVETi correlated well with survival in patients with PPH, and LVETi of 350 msec was the critical cut-off for determining the eventual outcome (**Fig. 2**).

Discussion

Our results showed that marked shortening of LVET and the LVET index, which reflected low stroke volume, was present in patients with PPH, and that the magnitude of the LVET index was a good indicator of its prognosis. Rich et al[9] reported that a lower stroke volume index had a strong prognostic value in patients with PPH. Recently, Kanemoto[10] reported that a reduced cardiac index was associated with poor survival. The results of these two reports

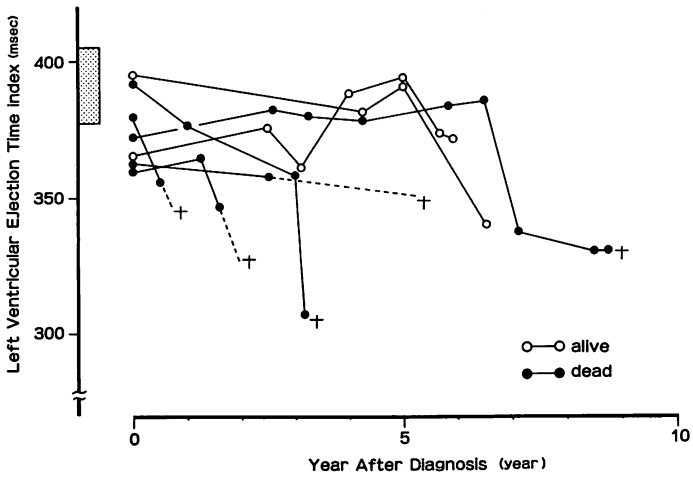

Fig. 2. Serial changes in the left ventricular ejection time index (LVETi) **in patients with primary pulmonary hypertension.**

Patients were followed until their deaths (†) or the end of the study period (August 1987). The dotted area indicates the normal range for LVETi. Marked shortening of the LVETi, below approximately 350 msec, is observed immediately before death or with clinical deterioration. The LVETi could not be measured immediately before death in 3 patients indicated by dashed lines.

are comparable with our data. Exact estimates of the stroke volume index or cardiac index require invasive techniques, but measurement of the LVET index can easily be done noninvasively. Therefore, STIs are of great value for estimating left ventricular function, for evaluating responses to drug therapy, and for determining the prognosis of patients with PPH.

Prolongation of the PEP and PEP index, and a marked decrease in the LVET/PEP ratio were demonstrated in patients with PPH. It has been acknowleged that the observation reflects decreased left ventricular contractility. However, it is also known that PEP is affected by preload. EDD of patients with PPH in this study was markedly decreased. Therefore, prolongation of PEP and the PEP index in patients with PPH might be due to a decrease in EDD.

In this study, left ventricular contractility, as assessed by ejection phase indexes (percent FS and mean Vcf), remained normal. This supports the hypothesis that prolongation of PEP is not due to a decrease in left ventricular contractility, but is due mainly to a decrease in preload. Shortening of LEVT also seemed to be due to a decrease in EDD, as shown by **Fig. 1.** We have already reported that this relationship was observed not only in patients with right ventricular (RV) pressure overload, such as PPH, but in patients with RV volume overload, including atrial septal defect[8].

In summary, the low cardiac index, low stroke volume index, and shortening of LVET and the LVET index were hemodynamic characteristics of PPH patients with poor prognosis. Among these hemodynamic parameters, STIs can easily be measured noninvasively. Therefore, STIs should be utilized in assessing the effects of drugs and in predicting the prognosis of patients with PPH.

要　　約

原発性肺高血圧症の予後評価における収縮期心時相分析の有用性

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原発性肺高血圧症 (PPH) の左心機能および左室形態の特徴を，収縮期心時相分析ならびに断層心エコー図検査を用いて検討した．さらに左心機能の経時的推移より，PPH の予後の評価を試みた．

対象は PPH 7 症例で，全例女性，年齢は 14 歳から 53 歳である．7 症例中 5 症例は診断より 9 ヵ月ないし 104 ヵ月で死亡した．心脈管系に異常を認めない 12 症例を正常対照群とした．

左心機能は心機図を用いた収縮期心時相 (STI) 分析で行った．すなわち，駆出時間 (LVET)，前駆出時間 (PEP)，LVET/PEP，およびその心拍数補正である LVETi，PEPi により評価した．左室形態は心エコー図を用い，拡張期左室内径 (EDD) [中隔-側壁距離]，収縮期左室内径 (ESD) で評価した．

1. PPH 3 症例では著明な LVET の短縮を認めたが，PPH 群全例では対照群と LVET，LVETi に差はなかった．PPH 群では PEP，PEPi の有意な延長，LVET/PEP の低下が認められた．

2. EDD, ESD とも PPH 群では対照群に比し，有意に小であった．

3. 平均円周短縮速度は両群間で差を認めなかった．

4. EDD と LVET は極めてよく相関した．

5. STI の経時的推移では，死亡前には著明な LVETi の短縮が認められた．

以上より，以下の事が明らかとなった．すなわち PPH 症例では右室拡大に伴う左室腔の狭小化のため，左心機能低下が出現し，また LVETi の経時的観察は，治療の効果判定，予後の評価に極めて有用である．

STI 分析は心エコー図検査と異なり，全例で施行可能であり，したがって今後，PPH 症例の左心機能評価に汎用されるべき検査法と思われる．

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