CHARACTERISTICS OF SYSTOLIC TIME INTERVALS IN PATIENTS WITH PHEOCHROMOCYTOMA

MAREOMI HAMADA, M.D., TAKETOSHI ITO, M.D., KUNIO HIWADA, M.D.
TATSUO KOKUBU, M.D.*, AKIRA GENDA, M.D.**
AND RYOYU TAKEDA, M.D.**

The effect of chronic catecholamine excess on cardiac function was assessed in 8 patients with surgically proven pheochromocytoma and the results compared with data obtained from normal controls and essential hypertensives. Major findings in systolic time intervals (STI) in patients with pheochromocytoma were a marked shortening of electromechanical systole and left ventricular ejection time (ET), but pre-ejection period (PEP) remained within normal limits. These findings were not altered by correction for heart rate. The ET/PEP ratio was very low (1.87 ± 0.31) due to the remarkable shortening of ET. The ET/PEP ratio in essential hypertensives was also low (1.77 ± 0.38), but this was mainly due to a remarkable prolongation of PEP. Low cardiac index, low stroke index and high total peripheral resistance index were preoperative characteristics in patients with pheochromocytoma, but returned to normal after operation.

These results suggest that chronic excessive production of catecholamines from pheochromocytoma has deleterious effects on the heart, and that wide differences in STI exist between patients with pheochromocytoma and those with essential hypertension.

EARLY diagnosis of pheochromocytoma is very important, because when unrecognized it is a potentially lethal condition. Much has been written about the clinical and hormonal findings in patients with pheochromocytoma and the diagnosis of the disease rests on laboratory test results. On the other hand, though it is supposed that catecholamine overproduction from pheochromocytoma markedly affects hemodynamics, only a few papers are available on the hemodynamics of this disorder!^{1,2} Even less informa-

tion is available on the noninvasive estimation of left ventricular function in this disorder.

The purpose of this investigation was firstly to elucidate the influence of chronic overproduction of catecholamines from pheochromocytoma on cardiac functions, and secondly to examine whether differences in cardiac function exist between patients with pheochromocytoma and those with essential hypertension.

METHODS

Key words:

Catecholamine overproduction
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Study subjects

We had 8 patients with surgically proven pheochromocytoma between January 1978 and December 1987 (Table I). In pa-

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The 2nd Department of Internal Medicine, Ehime University School of Medicine, Ehime, Japan

*The Department of Internal Medicine, Kinki Central Hospital (Itami), Hyogo, Japan

**The 2nd Department of Internal Medicine, Kanazawa University School of Medicine, Ishikawa, Japan

Mailing address: Mareomi Hamada, M.D., The 2nd Department of Internal Medicine, Shigenobu, Onsen-gun, Ehime 791-02, Japan

TABLE 1 PROFILES OF 8 PATIENTS WITH PHEOCHROMOCYTOMA

Patients	Age (years)	Sex	Hypertension type	Hypertension duration (years)	Ocular fundus	Urinary norepinephrine ($\mu\text{g/day}$)	Urinary epinephrine ($\mu\text{g/day}$)
1 K.A.	36	M	persistent paroxysmal	0.7	K-W 0	133— 9576	47—2743
2 Y.U.	41	M	paroxysmal	1.25	K-W 0	853— 2971	166— 944
3 T.M.	53	M	persistent	11	K-W III	613— 1330	44— 197
4 Y.S.	56	M	persistent paroxysmal	4	K-W I	792— 2060	155— 460
5 R.Y.	25	F	persistent paroxysmal	8	K-W IV	5210—35500	23— 142
6 K.M.	55	M	persistent	5	K-W III	420— 3672	82— 1066
7 T.H.	53	M	paroxysmal	3	K-W I	655— 3350	24— 112
8 N.K.	60	M	persistent paroxysmal	2	K-W I	212— 501	24— 116

Abbreviations: M=male, F=female, K-W=Keith-Wagener.

Fig.1. Comparisons of Q-II and Q-IIi in normal controls, patients with essential hypertension and pheochromocytoma.

tients with pheochromocytoma, the mean duration of hypertension from the initial discovery to admission was 4.4 ± 3.6 years. All patients except case 3 had experienced paroxysmal blood pressure elevation. For the measurement of preoperative urinary norepinephrine (UNE) and epinephrine (UE), 24-hour urine samples were collected and UNE and UE were measured as previously reported³. The UNE and UE were measured for 7 consecutive days, which included a hypertensive spell. For normal controls, 7 men and 3 women without any history of hypertension were selected from those who underwent cardiac catheterization due to chest pain of unknown etiology, and whose coronary arteriograms were normal. Twenty essential hypertensives were studied to compare their cardiac functions with those of the patients with pheochromocytoma. Most patients with essential hypertension had moderately to severely depressed cardiac function. Subjects who had coronary artery disease, valvular heart disease, left bundle branch block or other conduction disturbances were excluded from this study. All patients were in sinus rhythm throughout the study period.

Details of the examinations were explained to each person and each gave free consent.

Fig. 2. Comparisons of ET and ETi (left panel), and PEP and PEPi (right panel) in normal controls, patients with essential hypertension and pheochromocytoma.

Systolic time intervals (STI)

To investigate cardiac functions noninvasively, simultaneous recording of an electrocardiogram, a phonocardiogram and a carotid pulse tracing at a paper speed of 100 mm per sec was done using a MIC-8800 polygraph (Fukuda Denshi Co. Ltd, Tokyo, Japan). Phonocardiogram and carotid pulse tracing were recorded using a MA-250 and a TY-303 transducer (Fukuda Denshi Co. Ltd) with a time constant of 4 msec. The following STI were measured as reported previously:⁴ 1) Q-II time (electromechanical systole; the interval from the beginning of the Q wave of the electrocardiogram to the beginning of the aortic component of the second heart sound), 2) ET (left ventricular ejection time; from the onset of the upstroke to the dicrotic notch on the carotid pulse tracing. The initial upstroke and end point of ET were determined tangentially), 3) PEP (pre-ejection period=Q-II-ET), 4) ET/PEP ratio. These intervals were ex-

pressed as the mean of the measurements of 5 consecutive beats. In addition, heart rate-corrected Q-II, ET and PEP (Q-II index, ET index and PEP index) were calculated using the regression equations of Weisler et al.⁵

Hemodynamic parameters

To assess the differences between pre- and post-operative hemodynamics, cardiac index (CI), stroke index (SI), mean blood pressure (MBP) and total peripheral resistance index (TPRI) were calculated in 5 patients with pheochromocytoma. Cardiac output was measured by the dye-dilution method using a cuvette densitometer, and was determined by the method of Stewart-Hamilton. MBP and TPRI were calculated from the formula: MBP (mmHg)=diastolic pressure+1/3 pulse pressure, TPRI (dyne·sec·cm⁻⁵)=MBP×1332×60/CI.

Measurement of preoperative STI and cardiac output in patients with pheochromocytoma

Fig.3. Comparisons of ET/PEP ratio in normal controls, patients with essential hypertension and pheochromocytoma.

toma was carried out when patients were asymptomatic after the discontinuance of medication for at least one week. Postoperative measurement of cardiac output was performed 4 weeks after the removal of the tumor. The measurement of STI in normal subjects and essential hypertensives was made after discontinuance of medication for one week.

Cardiac catheterization and selective coronary cineangiography

Four of 8 patients with pheochromocytoma showed electrocardiographic changes suggesting coronary artery disease. Electrocardiographic changes in case 1 during a hypertensive spell had a strong resemblance to those of acute myocardial infarction. Cases 2 and 4 also showed marked electrocardiographic changes including T wave inversion, and case 3 exhibited marked ST-T depression. In these patients, routine cardiac catheterization and selective coronary cineangiography by the Judkins technique were performed before operation to confirm

or deny the presence of coronary artery disease. Ejection fraction (EF) and left ventricular end-diastolic pressure (LVEDP) were measured.

Statistical analysis

The values in the text and table are mean $\pm$ SD. Statistical analyses were performed by the Mann-Whitney U test for unpaired data and the Wilcoxon matched-pairs signed-ranks test for paired data. Differences with P values of <0.05 were considered significant.

RESULTS

UNE and UE

As shown in table I, even UNE and UE values relating to days without a hypertensive spell were significantly higher than the upper limits obtained in normal subjects (normal values: UNE 8.5–54.1 μ g/day, UE <8.4 μ g/day).

STI in patients with pheochromocytoma

Marked shortenings of Q-II, Q-II index, ET and ET index were common characteristics of preoperative STI (Figs. 1 and 2). On the other hand, no differences in PEP or PEP index between patients with pheochromocytoma and normal subjects were noted (Fig. 2). As a result, the preoperative ET/PEP ratio in patients with pheochromocytoma was significantly lower than that in normal subjects (Fig. 3, Table II).

As shown in Fig. 4, both ET/PEP ratio (left panel) and ET index (middle panel) showed improvement in all patients and returned to normal except in case 3 between 2 and 12 weeks after operation. PEP index (right) showed no significant changes between pre- and post-operative values.

Hemodynamic measurements

Table III shows the differences between pre- and post-operative hemodynamic measurements. Heart rate and MBP returned to normal after operation. The preoperative CI and SI were significantly lower than those in normal subjects and, conversely, TPRI was higher. Postoperative CI, SI and TPRI were normal.

TABLE II COMPARISON OF SYSTOLIC TIME INTERVALS IN NORMAL CONTROLS, PATIENTS WITH ESSENTIAL HYPERTENSION AND PHEOCHROMOCYTOMA

	Age (years)	MBP (mmHg)	HR (beats/min)	Q-II (msec)	Q-IIi (msec)	ET (msec)	ETi (msec)	PEP (msec)	PEPi (msec)	ET/PEP
Normal control (group I: n=10)	Mean	92	64	409	543	293	398	116	141	2.52
	± SD	3	7	16	11	14	9	4	3	0.12
Essential hypertension (group II: n=20)	Mean	125	64	418	552	265	378	153	178	1.77
	± SD	13	9	20	13	30	18	18	20	0.38
Pheochromocytoma	1	118	98	268	474	180	347	88	127	2.05
	2	84	86	322	503	202	348	120	154	1.68
	3	146	77	337	499	186	317	151	182	1.23
	4	137	82	326	498	208	347	118	151	1.76
	5	140	86	362	543	240	378	122	156	1.96
	6	97	67	355	496	240	354	115	142	2.09
	7	108	63	349	475	235	336	114	139	2.06
	8	118	64	364	498	249	358	115	141	2.17
	Mean	119	78	335	499	218	349	118	149	1.87
	± SD	22	12	31	20	27	17	17	16	0.31
I vs II	NS	0.01	NS	NS	NS	0.02	0.01	0.01	0.01	0.01
I vs III	NS	0.01	0.01	0.01	0.01	0.01	0.01	NS	NS	0.01
II vs III	NS	NS	0.02	0.01	0.01	0.01	0.01	0.01	0.05	NS

Abbreviations: MBP=mean blood pressure, HR=heart rate, Q-II=electromechanical systole, Q-IIi=Q-II index, ET=left ventricular ejection time, PEP=pre-ejection period.

Fig. 4. Changes of ET/PEP ratio, ET index and PEP index between pre-and post-operation in 7 patients with pheochromocytoma.

Cardiac catheterization and selective coronary cineangiography

Both right and left coronary arteries were normal in all patients who underwent the selective coronary angiography (patients 1, 2, 3 and 4). EF was also normal, except in case 3. LVEDP was considerably elevated in 3 out of 4 patients.

Comparison of STI between patients with pheochromocytoma and essential hypertension

Fig. 5 shows the relationships between ET, PEP and the ET/PEP ratio in patients with pheochromocytoma (open circles) and essential hypertension (open squares). Hemodynamic changes in essential hypertensives initially appear as the prolongation of PEP with unchanged ET (from section A to B), and subsequently further prolongation of PEP and the shortening of ET occur (from B to C). In contrast, STI in pheochromocytoma were characterized by the marked shortening of ET with unchanged PEP (mainly on section D). This observation in STI was applicable even to cases 6, 7 and 8 whose heart rates were the same as those of normal controls and essential hypertensives. Owing to these differences in STI between patients with pheochromocytoma and essential hypertensives, the 2 groups could easily be differentiated from each other.

DISCUSSION

Common findings in preoperative STI of 8 patients with pheochromocytoma were a marked shortening of Q-II and ET, and a low ET/PEP ratio with no change in PEP. The STI corrected for heart rate also showed the same tendency. Significantly decreased CI and SI and a significantly increased TPRI were also common preoperative hemodynamic characteristics. These preoperative data returned to normal within 2 to 12 weeks after operation. Abnormalities in electrocardiographic measurements observed before operation also returned to normal. Time to normalization of STI showed no significant difference among patients with pheochromocytoma, except in case 3 who had marked left ventricular hypertrophy. However, Lam et al⁶ and Imperato-McGinley et al⁷ reported a young patient with pheochromocytoma having a markedly depressed left ventricular function, whose cardiac size and function returned to normal 6 months after surgery in the former patient and 18 months after in the latter patient. In a patient with severely depressed cardiac function, time to normalization of cardiac changes may depend upon the severity of left ventricular dysfunction.

It has been widely acknowledged that an abbreviated Q-II is related to a rise in adrenergic activity⁸⁻¹⁰. Therefore, it is quite reasonable that marked shortening of Q-II

TABLE III HEMODYNAMIC CHANGES BETWEEN PRE- AND POST-OPERATION IN PATIENTS WITH PHEOCHROMOCYTOMA

	HR (beats/min)		MBP (mmHg)		CI (l/min/m ²)		SI (ml/beat/m ²)		TPRI (dyne·sec·cm ⁻⁵ ·m ⁻²)		LVEDP (mmHg)		EF (%)
	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post	
<i>Pheochromocytoma</i>													
1 K.A.	100	74	115	93	2.6	3.2	26	43	3540	2330	26		66
2 Y.U.	61	68	80	90	2.3	3.6	38	53	2780	2000	8		76
3 T.M.	72	61	149	96	2.6	3.3	36	54	4530	2330	21		49
4 Y.S.	82	74	137	110	3.2	3.7	39	50	3422	2378	18		70
5 R.Y.	103	64	137	97	3.3	3.4	32	53	3318	2280	—		—
Mean	84	68	124	97	2.8	3.4*	34	51*	3518	2264*	18		65
± SD	18	6	27	8	0.4	0.2	5	5	636	151	8		12
<i>Normal controls</i>													
Mean	63		93			3.6		58		2045	8		72
± SD	8		6			0.5		9		249	4		9
<i>Pheochromocytoma vs Normal controls</i>	0.01	NS	0.01	NS	0.01	NS	0.01	NS	0.01	NS	0.01	NS	NS

Abbreviations: HR=heart rate, MBP=mean blood pressure, CI=cardiac index, SI=stroke index, TPRI=total peripheral resistance index, LVEDP=left ventricular end-diastolic pressure, EF=ejection fraction. *p<0.01 (pre vs post).

Fig.5. Relationships among ET, PEP and ET/PEP ratio in patients with pheochromocytoma (open circles) and essential hypertension (open squares). The shaded area on x and y axes represents the mean $\pm$ 1 SD of each parameter obtained from normal controls. Horizontal and longitudinal dashed lines on the figure represent the lower limit of ET and higher limit of PEP in normal controls, respectively. Number of the shoulder of open circle represents the case 6, 7 and 8.

and Q-II index was observed in patients with pheochromocytoma. However, the ET and PEP data from patients with pheochromocytoma were quite different from those obtained following acute infusion of epinephrine into normal controls^{8,11} Epinephrine or norepinephrine infusion induces PEP shortening and a dose-dependent increase in the ET/PEP ratio while leaving the ET index unchanged. These findings indicate that the effect of acute administration of catecholamines on the heart was very different from the effect of chronic catecholamine excess resulting from pheochromocytoma.

The first possible explanation for the marked shortening of ET, a marked low value of ET/PEP ratio, low CI and SI, and high TPRI in patients with pheochromocytoma derives from the increased peripheral vasoconstriction associated with alpha-adrenergic stimulation. A typical example is shown in a study by Messerli et al¹² where the cardiac output of a patient showed a significant decrease only during high secretion of norepinephrine from a small tumor.

However, even normotensive patients with pheochromocytoma as in case 2 and 6 can show the same hemodynamic findings as hypertensive patients with pheochromocytoma. This may mean that the sustained effect of catecholamine excess in pheochromocytoma raises peripheral resistance with or without elevating arterial pressure.

The second possible mechanism of depressed cardiac function derives from myocardial damage by excess beta-adrenergic stimulation, so-called catecholamine myocarditis^{9,13,14} Horak and Opie¹⁵ described an isolated working rat heart model, where a concentration of 10^{-7} M epinephrine could produce an increase of myocardial cyclic AMP and induce marked cardiac enzyme release concomitant with the decrease in cardiac output. However, more recent studies suggest that the cardiomyopathy is mediated mainly by the α -adrenergic receptor system. Lee and Spontenberg¹⁶ produced cardiomyopathy in rabbits with an intravenous infusion of norepinephrine and reported that histologic damage of the heart was attenuated by pretreatment with the α_1 -receptor blocker prazosin. Bravo et al¹⁷ found that the total plasma catecholamine level in 5 of 23 patients with pheochromocytoma was over 10^{-7} M and in 15 patients was over 10^{-8} M even under basal conditions. These observations strongly suggest that the hearts of most patients with pheochromocytoma are constantly at risk because of the excess of catecholamines, irrespective of arterial pressure. Thus, it is reasonable that during a hypertensive spell the elevation of cardiac enzymes associated with catecholamine excess can occur as in case 1.

The coexistence of coronary artery disease in patients with pheochromocytoma has been reported¹⁸⁻²¹ Van Vliet et al²² reported that in a patient with suspected myocardial infarction before autopsy, there was myocarditis, but no evidence of infarction. Cheng and Bashour²³ demonstrated angiographically that the electrocardiographic changes indicative of myocardial infarction in a patients with pheochromocytoma were not due to the obstruction of coronary arteries. In our study, 4 out of 8 patients showed the electrocardiographic changes associated with coronary artery disease, but their coronary arteries

showed no significant stenosis. Therefore, it is likely in most patients with pheochromocytoma that the electrocardiographic change suggesting severe myocardial damage or ischemia is due to the influence of catecholamine excess from pheochromocytoma. However, as Radtke mentioned²⁴ clinical evidence alone is sometimes not sufficient to diagnose with certainty whether the electrocardiographic changes are due to myocardial injury caused by catecholamine excess or to coronary artery obstruction. Therefore, coronary angiography is necessary to decide whether such a patient with pheochromocytoma has coronary artery disease or not.

The third important factor is a significant reduction in the total blood volume in pheochromocytoma²⁵⁻²⁸. It is postulated that in this condition a decrease of SI and a shortening of ET, related to a decrease of venous return, are produced.

The myocardial adaptations to pheochromocytoma include a mixture of alterations directly induced by circulating catecholamines and secondary to peripheral vascular responses. These alterations in hemodynamics or their occurrence in serious arrhythmias seem to be related to the concentrations of the circulating catecholamines and the relative proportions of epinephrine and norepinephrine.

The present work reveals for the first time the clinical significance of STI for the differentiation of patients with pheochromocytoma from essential hypertensives. STI are very sensitive for the estimation of global left ventricular function in a variety of disease states^{4,29,30}. In addition, STI is the only hemodynamic parameter which provides an index of adrenergic tone. The observed differences in STI between patients with pheochromocytoma and those with essential hypertension in this study enabled differentiation of the two groups. The diagnosis of pheochromocytoma should be confirmed biochemically. However, from the point of view that STI measurements are very easy to perform, are available to every patient, and have immediate results, they can be used as one of screening procedures for the detection of pheochromocytoma.

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