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Evaluation of coronary blood flow reserve by ^{13}N-NH_3 positron emission computed tomography (PET) with dipyridamole in the treatment of hypertension with the ACE inhibitor (Cilazapril)

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Purpose: The purpose of this study was to evaluate the effect of treatment with an angiotensin-converting enzyme (ACE) inhibitor (Cilazapril) for early hypertensive patients in terms of coronary blood flow reserve evaluated by $^{13}NH_3$-positron emission tomography (PET).

Methods: Before and after 12 weeks of ACE inhibitor treatment, $^{13}NH_3$-PET with dipyridamole provocation test was performed, and definite myocardial perfusion and coronary flow reserve (CFR) were calculated.

Results: Compared to our normal subjects previously reported (2.61 ± 0.74), average coronary flow reserve was decreased (1.70 ± 0.64 in hypertensive patients), and improved after treatment (1.77 ± 0.52), but not significantly. Of 12 patients, five (42%) showed improved coronary flow reserve from 1.34 to 1.99 without a significant change in the resting flow. Only one patient (8%) showed deterioration after the ACE inhibitor treatment. The coronary vascular resistance (CVR) after ACE inhibitor treatment of the patients with CFR < 2.0 decreased significantly compared with those with CFR $\geqq$ 2.0 ($p < 0.03$).

Conclusions: These results indicate that hypertensive patients at the early stage show decreased coronary flow reserve despite having normal resting flow. Treatment with an ACE inhibitor (Cilazapril) for 12 weeks improved coronary flow reserve in 42% of our patients. The CVR of the patients with CFR < 2.0 showed improvement compared to those with CFR $\geqq$ 2.0.

This result indicates that an ACE inhibitor (e.g., Cilazapril) should be one of the choices for improving CFR if hypertensive patients in early stage show signs of ischemia or diastolic dysfunction, which may be one of the sequels of reserve restriction.

Key words: coronary flow reserve, angiotensin-converting enzyme inhibitor, positron emission computed tomography, hypertension, cilazapril

INTRODUCTION

HYPERTENSION is known to be associated with a reduction in the coronary blood flow reserve (CFR) with or without hypertrophy.[1,2] The reduction in the CFR may be the cause of endocardial ischemia and diastolic dysfunction.[3] Ischemia would also modify the hypertensive heart with hypertrophy. Antihypertensive treatment with a combination of metoprolor and felodipine can increase maximum coronary blood flow,[4] and the angiotensin converting enzyme (ACE) inhibitor Cilazapril was reported to prevent[5] or reverse[6] the decrease in coronary vascular reserve in spontaneous hypertensive rats (SHRs).

Nevertheless, the coronary flow at rest and CFR including the effect of ACE inhibitors in the early stage of hypertension with mild or no hypertrophy have not been

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clinically evaluated precisely.

There are reports that even early stage hypertension reduced the CFR in an experimental model[7] and increased microvascular resistance.[2] We therefore evaluated the coronary flow and CFR of hypertensive patients without visible hypertrophy by positron emission tomography (PET) with $^{13}NH_3$, a tracer that is clinically one of the best for calculating flow non-invasively.[8]

In the present study we found that 42% of the hypertensive patients studied achieved improved CFR, and decreased coronary vascular resistance (CVR) in those with CFR < 2.0 by ACE inhibition after anti-hypertensive treatments.

MATERIALS AND METHODS

Patients were selected by the following inclusion criteria. 1) The average blood pressure evaluated at least two different time points before the study was more than 160 mmHg in systolic and/or 95 mmHg in diastole, 2) Patients with stage 1 or 2 World Health Organization (WHO) hypertension criteria, 3) Patients followed up only at the outpatient department, 4) Age less than 75 years, 5) Patients without serious complications in the liver, heart or kidneys.

The exclusion criteria were as follows. 1) Patients with myocardial infarction with an onset less than 6 months, or cerebral vascular disease, 2) Severe congestive heart failure (NYHA > 2), 3) Advanced arrhythmia, 4) Severe essential hypertension, 5) Patients suffering from allergic reaction or drug allergy, and 6) Patients determined as inappropriate for the study design by the attending physician.

Before enrollment in the study, informed written consent was obtained from each patient, and recorded in the patient's record. The study design received Ethics Committee Approval.

Study Design

1) Schedule of the study: In the observation and treatment periods, each patient's blood pressure, pulse rates, ECG, coronary flow at rest and CFR as measured by PET with dipyridamole provocation were evaluated.

In the 2 to 4 weeks of the observation period, drugs that might affect the results of this study were withdrawn. In the patients medicated with another anti-hypertensive drug, such drugs were washed out within 4 weeks.

In the treatment period, Cilazapril (1 to 2 mg/day) was prescribed for 12 weeks, and other drugs that might affect the effect of Cilazapril were forbidden. The first dose of Cilazapril was 1 mg/day (before breakfast, or around 8 a.m.), and if it was considered ineffective the dose was increased to 2 mg/day. If the 1 mg/day dose appeared to be too strong, the dose was decreased to 0.5 mg/day.

2) Regional myocardial flow: PET with the $^{13}NH_3$ tracer was performed to evaluate regional myocardial flow. The rest flow and CFR with dipyridamole provocation tests were calculated before and at the end of the treatment protocol.

3) Drugs forbidden during the study:

1. Antihypertensive drugs. No antihypertensive drugs other than Cilazapril were permitted.
2. Sleeping-draught. If a sleeping-draught had been prescribed before the study, the dose and the method of use were not changed during the study period.
3. Any other inappropriate drugs that might affect the patients were prohibited.

4) In the observation and follow-up period: Hematological and serological studies were done. X-ray and ophthalmological studies were also done during the observation period. The drug intake conditions were strictly followed and recorded. If a patient dropped out, the reason for dropping out, adverse effects of the drugs and the relation between the findings and the drugs were investigated and followed up.

5) The study period was from December 1996 to March 1998.

Positron Emission Computed Tomography

1) Radiopharmaceuticals: $^{13}NH_3$ was produced by means of an ultracompact cyclotron installed at our institution (CYPRIS model 325; Sumitomo Heavy Industries, Tokyo, Japan), by $^{16}O(p,a)^{13}N$ nuclear reaction with water irradiation, followed by a reduction of the ^{13}N compounds to ammonia with titanous hydroxide. The ^{13}N-ammonia was collected in a saline solution and passed through a 0.22 micron Millipore filter before injection. The radiochemical purity was greater than 99%.

The PET studies were done with a whole-body PET camera (PCT 3600W, Hitachi Medical Co., Tokyo, Japan). It provides 15 slices at 7 mm intervals simultaneously. The scanner has an effective resolution of 9 mm and an axial resolution of 7 mm at full-width half-maximum after reconstruction. Each subject was positioned on the PET camera with the aid of an ultrasound technique. At the beginning of the PET study, a transmission scan was obtained for 20 minutes with a germanium-68/gallium-68 external source in order to correct photon attenuation.

Approximately 370 MBq (10 mCi) of N-13 ammonia was intravenously administered over a 30-sec period, and the intravenous line was flushed with additional saline over a 30-sec interval. Serial dynamic PET scans (10 sec × 12 frames, 1 min × 8 frames) were started simultaneously with the N-13 ammonia injection. The total acquisition time after the injection of N-13 ammonia was 10 min.

Approximately 100–120 minutes after the baseline study, dipyridamole (0.56 mg/kg) was infused intravenously for 4 minutes. During dipyridamole provocation, the heart rate and blood pressure had been monitored. The

Table 1 Blood presssure and heart rate data of hypertensive patients before (Control) and after 12-week treatment with the ACE inhibitor Cilazapril

Patients No.		Age	Control			Treatment		
			BP (mmHg)	HR (bpm)	DP	BP (mmHg)	HR (bpm)	DP
1	M.K.	62	178/80	65	11.6	150/65	72	10.8
2	H.N.	72	178/101	94	16.7	120/56	75	9.0
3	H.T.	78	190/100	90	17.1	136/82	80	10.9
4	H.T.	73	169/90	89	15	136/65	71	9.7
5	H.W.	63	163/91	65	10.6	150/90	57	8.6
6	H.K.	84	170/90	70	11.9	150/85	65	9.8
7	K.K.	61	164/87	60	9.8	116/70	66	7.7
8	S.T.	60	182/90	82	14.9	145/70	80	11.6
9	H.Y.	62	176/92	93	16.4	139/81	83	11.5
10	M.T.	63	165/90	78	12.9	150/70	70	10.5
11	F.U.	62	175/100	85	14.9	140/85	82	11.5
12	K.W.	67	170/90	77	13.1	142/91	73	10.4
mean ± S.D.		67 ± 8	173 ± 8/92 ± 6	79 ± 11	13.7 ± 2.4	139 ± 11*/76 ± 11*	73 ± 8	10.1 ± 1.3*

BP = blood pressure, HR = heart rate, Control = before treatment, Treatment = after treatment, DP = double products ($\cdot 10^3$·mmHg·bpm). *: $p < 0.01$ compared with control

second injection of N-13 ammonia was started at 4 min after the end of the dipyridamole infusion and the heart rate and blood pressure were stable. The dynamic PET image acquisition followed the same protocol as that used in the baseline study. The follow-up study after medication also followed this protocol. In cases of an adverse effect of dipyridamole, Neophillin was used to suppress the side effect and symptoms.

N-13 ammonia static images were reconstructed from the last 8 frames (between 2 and 10 minutes postinjection).

Data Analysis

Three regions of interest (4 mm-wide) were drawn on the left ventricular myocardium of the mid-horizontal static images (septal, apical and lateral). Partial volume effects are corrected with a constant recovery coefficient of 0.78 assuming that the myocardium is uniform and its thickness is 1 cm. Small square regions of interest (ROIs) with an area of about 50 mm were assigned to the left ventricular cavity. These ROIs were copied onto the serially-acquired transaxial dynamic image frames. In order to reduce the noise of the blood-pool activities, two ROIs were drawn on the cavity of the mid-ventricular imaging planes and were averaged. To calculate the true input function, Ca(t), the fraction of N-13 metabolites was subtracted on the basis of the previous report.[9]

1) To evaluate data: To evaluate data, two ideologies were applied and the patients were classified. One was classification by improvement in CFR (> 20%), and the patients were divided into three groups: improvement, no change and deterioration. The another was by CFR = 2, and the patients were divided into two groups: CFR≧2 and CFR < 2.[10–16]

2) Calculation of myocardial blood flow (MBF): The estimation of regional myocardial blood flow (MBF) by a Patlak plot analysis. The two-compartment mathematical model[16] was used for quantifying MBF by N-13 ammonia dynamic PET. In accord with this model, we used the modified microsphere method reported by Tadamura et al.,[17] a very simple and reliable approach for quantifying MBF with $^{13}NH_3$ PET, which is comparable to a Patlak graphical analysis. It also provides a CFR assessment as accurate as that obtained with a Patlak graphical analysis.[18]

3) Estimation of coronary flow reserve (CFR): The CFR was defined as the ratio of MBF during hyperemia to MBF at the baseline. The CFR of each region at the three ROIs was calculated separately, and these 3 values for CFR were averaged to show the mean CFR of the patient.

4) Calculation of coronary vascular resistance (CVR): During dipyridamole provocation test, the blood pressure was monitored. The mean blood pressure was calculated. The CVR was calculated with the mean blood pressure, when N-13 ammonia was injected in dipyridamole provocation, divided by the MBF.

Statistical Analysis:

Student's t-test was applied to compare the same conditions. Two-way ANOVA repeated measure, followed by Scheffe's F test was used for multiple comparisons among groups and to compared data obtained in the same patients under different conditions. One-way ANOVA was used to compare the rate of change between with that after treatment. A p value less than 0.05 was thought to be significant. Data were expressed as the mean ± SD.

RESULTS

Of 13 hypertensive patients enrolled in the study, 12 completed it. One patient dropped out because of failure

Table 2 Coronary blood flow, coronary flow reserve and coronary vascular resistance in hypertensive patients before (Control) and after 12-week treatment with the ACE inhibitor Cilazapril

	Patients No.		Control				Treatment			
			Rest	DIP	CFR	CVR	Rest	DIP	CFR	CVR
A	1	M.K.	1.24	1.16	0.93	97.2	1.37	2.52	1.19	37.1
	2	H.N.	0.64	1.16	1.77	108.8	0.72	1.63	2.29	47.4
	3	H.T.	1.05	2.07	1.99	62.8	0.79	2.07	2.80	48.3
	4	H.T.	0.91	1.14	1.19	101.8	0.75	1.61	2.19	55.2
	5	H.W.	0.55	0.41	0.75	283.3	0.53	0.58	1.09	190.0
B	6	H.K.	11.45	2.02	1.39	57.7	1.30	1.49	1.15	71.4
	7	K.K.	1.45	2.50	1.72	45.1	1.14	1.75	1.63	48.7
	8	S.T.	1.30	1.63	1.25	74.2	0.93	1.17	1.26	81.3
	9	H.Y.	0.53	0.89	1.68	135.6	0.63	1.09	1.72	91.9
C	10	M.T.	1.19	2.88	2.48	39.9	1.15	2.32	2.02	41.6
	11	F.U.	0.79	1.91	2.53	65.3	0.42	0.42	1.88	148.0
	12	K.W.	0.93	2.10	2.71	55.6	0.61	0.61	1.29	140.8
mean ± S.D.			1.00 ± 0.33	1.66 ± 0.72	1.70 ± 0.64	97.0 ± 66.2	0.86 ± 0.31	1.43 ± 0.64	1.77 ± 0.52	86.5 ± 50.0

Rest = rest flow (ml/min/gram), DIP = flow after dipyridamole provocation test (ml/min/gram), CFR = coronary flow reserve, CVR = coronary vascular resistance (mmHg·ml·min·gram), group A = flow reserve improved more than 20% of control, group B = flow reserve showed no change, group C = flow reserve detetiorated less than 20% of control

Table 3 Blood presssure and heart rate data of hypertensive patients before (Control) and after treatment with the ACE inhibitor in the improvement of CFR

Group	Age	Control			Treatment		
		BP (mmHg)	HR (bpm)	DP	BP (mmHg)	HR (bpm)	DP
A (n = 5)	70 ± 7	176 ± 10/92 ± 9	81 ± 14	14.2 ± 3.0	138 ± 12*/72 ± 14*	71 ± 9	9.8 ± 1.0
B (n = 4)	67 ± 12	173 ± 8 /90 ± 2	76 ± 14	13.3 ± 2.9	138 ± 15*/77 ± 8	74 ± 9	10.1 ± 1.9
C (n = 3)	64 ± 3	170 ± 5 /93 ± 6	80 ± 4	13.6 ± 1.1	144 ± 5* /82 ± 11	75 ± 6	10.8 ± 6.1
mean ± S.D.	67 ± 8	173 ± 8 /92 ± 6	79 ± 11	13.7 ± 2.4	139 ± 11*/76 ± 11*	73 ± 8	10.1 ± 1.3*

BP = blood pressure, HR = heart rate, Control = before treatment, Treatment = after treatment, DP = double products ($\cdot 10^3$·mmHg·bpm). *: $p < 0.01$ compared with control

to take the Cilazapril, as the protocol required. No adverse effect was observed in these 12 patients with drug treatment. The data for the normal control were those obtained and reported before in the study of flow with the same method.[17]

Patients' background

The 12 patients' blood pressure, heart rate and double products before (control) and after the Cilazapril treatment are shown in Table 1. The male to female ratio was 5/7. The patients' average age was 67 ± 8 years. Blood pressure before treatment was 173 ± 8 mmHg (163–190) systolic and 92 ± 6 mmHg (80–100) diastolic. Four patients had a history of hyperlipidemia, 3 of diabetes mellitus, and 3 were smokers. The average total cholesterol after treatment was similar to that of the control (control : after = 218 ± 20 : 220 ± 19, NS). The coronary arteriography (CAG) findings were all normal except for the patient (#7) who refused to do the catheterization because of no ischemic signs or symptoms. The Echo cardiographic data showed septal thickness values of 10.0 ± 1.2 mm, and posterior wall thickness of 10.1 ± 1.1 mm; both values showed slight hypertrophy according to the criteria of our institute (5 patients had wall thickness > 10 mm).

The patients' blood pressure was significantly decreased after the 12-week Cilazapril treatment ($p < 0.01$). The post-medication pressure was 139 ± 11 mmHg (116–150) systolic, and 76 ± 11 mmHg (57–83) diastolic. No complications or side effects of the treatment except a slight cough in one patient were observed. No serological abnormality was detected in any of the patients studied. The coronary blood flow, CFR and CVR before and after treatment are summarized in Table 2.

The dipyridamole provocation before and after treatment

No complication after dipyridamole infusion was observed, and the patients' blood pressure was effectively

Table 4 Coronary blood flow, coronary flow reserve and coronary vascular resistance in hypertensive patients before (Control) and after treatment with ACE inhibitor in the improvement of CFR

Group	Control				Treatment			
	Rest	DIP	CFR	CVR	Rest	DIP	CFR	CVR
A (n = 5)	0.88 ± 0.28	1.19 ± 0.59	1.34 ± 0.54*	130.8 ± 87.1	0.83 ± 0.32	1.68 ± 0.72	1.99 ± 0.57#	75.6 ± 64.3
B (n = 4)	1.18 ± 0.44	1.76 ± 0.68	1.51 ± 0.23**	78.1 ± 40.1	1.00 ± 0.29	1.38 ± 0.31	1.42 ± 0.26	73.3 ± 18.4
C (n = 3)	0.97 ± 0.20	2.30 ± 0.51	2.37 ± 0.10	53.6 ± 12.8	0.73 ± 0.38	1.26 ± 0.92	1.64 ± 0.38##	110.2 ± 59.5
mean ± S.D.	1.00 ± 0.33	1.66 ± 0.72	1.70 ± 0.64	97.0 ± 66.2	0.86 ± 0.31	1.43 ± 0.64	1.77 ± 0.52	86.5 ± 50.0

Rest = rest flow (ml/min/gram), DIP = flow after dipyridamole provocation test (ml/min/gram), CFR = coronary flow reserve, CVR = coronary vascular resistance (mmHg·ml·min·gram). group A = flow reserve improved more than 20% of control, group B = flow reserve showed no change, group C = flow reserve deteriorated less than 20% of control. *: $p < 0.01$ compared with group C, **: $p < 0.03$ compared with group C, #: $p < 0.03$ compared with control, ##: $p < 0.05$ compared with control

Table 5 Blood presssure and heart rate data of hypertensive patients before (Control) and after treatment with the ACE inhibitor in CFR ≥ 2.0 and in CFR < 2.0

Group	Age	Control			Treatment		
		BP (mmHg)	HR (bpm)	DP	BP (mmHg)	HR (bpm)	DP
CFR < 2.0 (n = 9)	68 ± 9	174 ± 9/91 ± 6	79 ± 14	13.8 ± 2.8	138 ± 13*/74 ± 11*	72 ± 8	9.9 ± 1.3*
CFR ≥ 2.0 (n = 3)	64 ± 3	170 ± 5/93 ± 6	80 ± 4	13.6 ± 1.1	144 ± 5* /82 ± 11	75 ± 6	10.8 ± 6.1
mean ± S.D.	67 ± 8	173 ± 8/92 ± 6	79 ± 11	13.7 ± 2.4	139 ± 11*/76 ± 11*	73 ± 8	10.1 ± 1.3*

BP = blood pressure, HR = heart rate, Control = before treatment, Treatment = after treatment, DP = double products ($\cdot 10^3$·mmHg·bpm), CFR: coronary flow reserve. *: $p < 0.01$ compared with control

decreased by the infusion. The systolic blood pressure values at the end of the dipyridamole infusion were 141 ± 16.0 mmHg and 128 ± 20.0 mmHg before and after the treatment, respectively (non-significant, NS). The diastolic pressure values were 70 ± 5 mmHg and 65 ± 8 mmHg before and after treatment, respectively (NS).

Classification by improvement in CFR

Table 3 showed the comparisons of blood pressure, heart rate and double products. The coronary blood flow, CFR and CVR before and after treatment are summarized in Table 4. The mean CFR values were 1.70 ± 0.64 in the 1st (control), and 1.77 ± 0.52 in the 2nd (after treatment) flow study with PET (NS). The 12 patients were divided into 3 groups according to the amount of CFR change. Since a 20% variation was thought to be within the physiological range of CFR or a normal regional variation in our patient population (data not shown), we used a > 20% change in CFR as the criterion for the decision on patients. Thus, 5 patients showed improved CFR (group A), 4 patients showed no change (group B) and 3 patients showed deteriorated CFR (group C) after treatment (Table 4). Nevertheless, when we consider the normal range[17] of CFR as 2.61 ± 0.74, the data for the deteriorated patients were completely within this normal range, and the results of the follow-up data for 2 of the 3 were also within the normal range, so that true deterioration was obtained only in patient #12 (shown in Table 2).

Mean dipyridamole-induced flow calculations in the improved patients (group A) were 1.19 ± 0.59 and 1.68 ± 0.72 in the 1st (control) and 2nd (after treatment), respectively. The mean rest flow calculations in this group were 0.88 ± 0.28 ml/min/gram in the first and 0.83 ± 0.32 ml/min/gram in the second, showing no significant difference, so that the improvement in CFR observed in this group was purely that of a dipyridamole-induced CFR improvement (1.34 ± 0.54 and 1.99 ± 0.57 before and after treatment, $p < 0.03$, respectively). The double products at the end of the dipyridamole infusion also showed no significant difference (8,013 and 8,329 before and after treatment, respectively).

Patient #12, who showed signs of worsening of CFR, also had deterioration in both the rest and dipyridamole-induced flow (Table 2).

Thus, of the 12 patients, 5 patients (5/12 = 42%) had improved CFR, 4 patients (33%) had no change, and 2 patients had normal variation despite reduced CFR, and 1 patient deteriorated (8%) after ACE inhibitor treatment (Tables 2 and 4).

Classification by CFR = 2

Tables 5 and 6 show the vital parameters in CFR≧2 and

Table 6 Coronary blood flow, coronary flow reserve and coronary vascular resistance in hypertensive patients before (Control) and after treatment with ACE inhibitor in CFR ≥ 2.0 and CFR < 2.0

Group	Control				Treatment			
	Rest	DIP	CFR	CVR	Rest	DIP	CFR	CVR
CFR < 2.0 (n = 9)	1.01 ± 0.37	1.44 ± 0.66	1.42 ± 0.41	107.4 ± 71.8	0.90 ± 0.30	1.55 ± 0.57	1.74 ± 0.53	74.6 ± 46.8
CFR ≥ 2.0 (n = 3)	0.97 ± 0.20	2.30 ± 0.51	2.37 ± 0.10*	53.6 ± 12.8	0.73 ± 0.38	1.26 ± 0.92	1.64 ± 0.38	110.2 ± 59.5
mean ± S.D.	1.00 ± 0.33	1.66 ± 0.72	1.70 ± 0.64	97.0 ± 66.2	0.86 ± 0.31	1.43 ± 0.64	1.77 ± 0.52	86.5 ± 50.0

Rest = rest flow (ml/min/gram), DIP = flow after dipyridamole provocation test (ml/min/gram), CFR = coronary flow reserve, CVR = coronary vascular resistance (mmHg·ml·min·gram). *: $p < 0.01$ compared with CFR < 2.0

CFR < 2 patients, before (control) and after treatment.

Differences between them in blood pressure, heart rate and double products were not significant (Table 5), but, in CFR < 2 group, the systolic blood pressure, diastolic blood pressure, and double products were significantly decreased after treatment compared with those before (all parameter: $p < 0.01$, respectively). In CFR≧2 group, only the systolic blood pressure changed significantly ($p < 0.01$).

The MBP values for CFR≧2 and CFR < 2 at rest before and after treatment, showed no significant change (Table 6), and the dipyridamole-induced MBP and CFR values after treatment had not changed either.

Nevertheless, the CVR in CFR≧2 group decreased significantly compared with that in CFR < 2, in spite of no significant decrease in double products (ΔCVR: CFR≧2 vs. CFR < 2: 34.8 ± 51.3 vs. −32.8 ± 34.8 (mmHg × ml × min × g), respectively; $p < 0.03$).

DISCUSSION

In this study, 42% of the hypertensive patients treated with an ACE inhibitor had improved CFR. The rest flow of the improved patients was not remarkably changed, but their dipyridamole-induced CFR values might reveal significant improvement. Although several patients showed physiological variations before and after treatment within the normal range, or our patient population was quite small, the blood pressure in most patients showed a good response to the ACE inhibitor treatment in spite of the poor CFR at the baseline. Furthermore, the 12-week ACE inhibitor treatment selectively improved the dipyridamole-induced CFR in our patients without definite hypertrophy or ischemic heart disease. Only one patient showed deterioration in CFR after ACE inhibitor treatment. In addition, CVR was decreased with dipyridamole in patients of CFR < 2.0.

Hypertensive patients usually have reduced CFR as a consequence of the following[19,20]: 1) an increase in resting coronary flow secondary to an increase in cardiac workload, 2) structural and functional change in the coronary micro-circulation (microvascular disease), and 3) an increase in extravascular components of coronary resistance.

It is usually difficult to estimate the extravascular pressure in the clinical setting, but, considering that diastolic relaxation is related to ventricular wall thickness,[21] and diastolic dysfunction is related to subendocardial reduced CFR in the hypertrophied heart exposed to stress,[22] the almost normal wall thickness observed in our patients indicates functional deterioration of the coronary vessels. Although there are physiological variations in the resting and dipyridamole-induced coronary flows, we did not consider that the increased resting flow is due to increased demand in our patients, because of the decrease in double products after treatment.

The reports of endothelial dysfunction in hypertensive patients even without hypertrophied muscle,[2,23] and the improvement in this dysfunction with ACE inhibitor treatment,[6] support our consideration that the improvement in CFR was due to dipyridamole-induced vasodilatation as one of the endothelial functions.

An impairment of CFR may depend on the duration of hypertension, degree of hypertension and treatment with drugs used in the past, so that it may be difficult to obtain uniform responses to drugs such as ACE inhibitors. Nevertheless, our results strongly suggest that the decreased CFR in hypertensive patients tends to normalize with such treatment, although 33% of our patients showed no response.

Parodi et al. reported CFR of hypertensive patients measured by NH_3-PET and reported good response to enalapril with more than 6 months' follow-up.[19] Motz et al. reported that it needed approximately 12 months for improvement in CFR.[24] Furthermore, Parodi et al. reported that 6 months is not enough to improve CFR with enalapril.[25] Our treatment interval was only 12 weeks, and 33% of our patients were resistant to treatment, They may not have had a long enough follow-up to show a good response.

Coronary endothelial dysfunction was found to be associated with deteriorated myocardial perfusion as detected by the tracer ^{99m}Tc-sestamibi[26]; in that study, the investigators revealed the importance of epicardial and

microvascular endothelium in regulating myocardial perfusion with the use of acetylcholine. NH_3-PET is clinically very useful and feasible for calculating definite myocardial flow. Our calculation method is also authorized with a use of a tracer, and flow measurement can be routinely applied to detect endothelial dysfunction and to observe the effects of treatments.[8,17]

Endothelial dysfunction is characterized by the complication of abnormal vasodilatation and vasoconstriction, especially by abnormal pharmacological vasodilatation in this study. Cilazapril and Captopril, two chemically different ACE inhibitors, markedly increased endothelium-dependent relaxation in response to acetylcholine and decreased endothelium-dependent contraction in response to serotonin.[26] In addition, it was speculated that the improved endothelial function observed in SHR is due to an increase in the release or the action of endothelium-derived relaxing factor (EDRF).[27] Enhanced endothelial production of EDRF[28] is related to a bradykinin mechanism, whereas the prevention of smooth muscle cell migration and proliferation, anti-atherosclerotic defects, and the reduction in the incidence of plaque rupture, are possibly related to the combined effects of ACE inhibitors in reducing bradykinin degradation as well as limiting the production of angiotensin II, which is a potent vasoconstrictor. Therefore, endothelial dysfunction is characterized by either the complication of structural alteration or to reduction in a chemical mediator's response.

It would require several months until the effect of ACE inhibitor is clinically visible in patients. Indeed, our treatment interval was only 12 weeks, and we did not consider the follow-up interval long enough to show a good effect in improved endothelial function, but, our results suggested that it might be almost enough to improve the response of dipyridamole-induced CVR.

Dipyridamole has an inhibiting effect on phosphodiesterase V, which catabolizes cGMP to 5′-GMP. If either the EDRF or nitric oxide (NO) production were enough, dipyridamole would effectively dilate smooth muscle by increasing the cGMP level, so that dipyridamole will effectively increase the CFR when endothelial function or EDRF (NO) production is sufficient. In addition, the CVR in CFR < 2 decreased significantly compared with that in CFR $\geqq$ 2 ($p < 0.03$) in this study. These data indicate that the dipyridamole-induced vasodilatation improved after the ACE inhibitor treatment despite normal flow at rest in the present study. Furthermore, the vascular size where dipyridamole induces vasodilatation is reported to be < 100 μm, and it never be epicardial vessels.[15] The blood pressure at rest just before the PET studies showed a difference between the control and after treatment, but the difference did not reach statistical significance. Strauer et al.[29] showed an increase in coronary flow in hypertensive patients compared to normal controls, by using an Argon tracer. In addition, Krams and coworkers reported that the coronary resistance reserve was linearly related to normalized arteriolar lumen in hypertrophic cardiomyopathy.[20] The increased perfusion pressure in their hypertensive patients showed decreased CFR with dipyridamole. The perfusion pressure after dipyridamole may modify the CFR, but our present data do not support this idea, because our rest flow values were comparable and the peak dipyridamole-induced dilation did not induce a significant change in BP.

Hypertrophy decreases CFR.[20,22] Our patient group showed a trivial hypertrophy in the control condition on the echo examination. Although we did not evaluate the decrease in wall thickness after 12 weeks of treatment, it is unlikely that an improvement in hypertrophy increased the CFR in such a short treatment, so that our results strongly suggest that the PET study revealed that dipyridamole-induced CFR improved due to ACE inhibitor.

Study limitations

Although several clinical limitations remain, the ideal study for evaluating ACE inhibitor might be a comparison of patients treated with and without ACE inhibitor. It is ethically difficult to discriminate between them, because we recognize that ACE inhibitor plays a role in improving cardiovascular disease.

The number of patients in this study was quite small, but the results after ACE inhibitor treatment were encouraging. The short duration (3 months) of follow-up is another critical point, because the optimal period for obtaining enough endothelial improvement has yet to be determined.

Furthermore, these results did not determine if the effect of CFR is due to the effect of general ACE inhibitor or a specific effect of Cilazapril.

CONCLUSIONS

Our results indicate that short-term treatment with ACE inhibitor (Cilazapril) improves dipyridamole-induced vasodilatation as one of the endothelial functions, and is followed by improvement of CFR in hypertensive patients.

It is also suggested that ACE inhibitor treatment is a reasonable attempt to obtain good CFR in hypertensive patients even at the stage in which there is no definite hypertrophy.

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