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Clinical Significance of Inter-Arm Pressure Difference and Ankle-Brachial Pressure Index in Patients With Suspected Coronary Artery Disease

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Abstract

Background. Although measuring blood pressure at the bilateral brachia is common in medical practice, its clinical significance in patients with suspected coronary artery disease (CAD) has not been fully clarified.

Methods. To define the significance of inter-arm systolic blood pressure difference in patients with suspected CAD, and to assess the relationship between inter-arm pressure difference and CAD, simultaneous brachial and ankle blood pressure measurements and stress myocardial single-photon emission computed tomography (SPECT) were performed in 386 consecutive patients with suspected CAD, excluding those with previous myocardial infarction or coronary revascularization.

Results. Subclavian artery stenosis, defined as $\geq$ 15 mmHg inter-arm systolic blood pressure difference, was found in 27 patients (7%). Age (65 ± 12 vs 65 ± 11 years), male sex (21/27 vs 244/359), prevalence of hypertension (63% vs 56%), hypercholesterolemia (63% vs 62%), diabetes mellitus (33% vs 38%), cigarette smoking (44% vs 41%) and family history of CAD (15% vs 12%) were similar between patients with subclavian artery stenosis and those without. The incidence of decreased ankle-brachial pressure index (ABI) was higher (37% vs 12%, $p = 0.001$), and percentage ischemic myocardium as assessed by SPECT was greater (9.0 ± 8.5% vs 5.6 ± 6.6%, $p < 0.05$) in patients with subclavian artery stenosis than in those without. Furthermore, significant correlations were observed between inter-arm pressure difference and percentage ischemic myocardium ($r = 0.13$; $p = 0.01$), and ABI ($r = -0.26$, $p < 0.0001$). Among 386 patients, 283 underwent coronary angiography, and 63% of those who had inter-arm blood pressure difference had CAD. Furthermore, 83% of those CAD patients had multi-vessel CAD, which is regarded as a high-risk subset for subsequent cardiac events.

Conclusions. Inter-arm pressure difference is often found in patients with suspected CAD, and is associated with significant CAD and peripheral artery disease. Thus, inter-arm pressure difference may be regarded as a simple marker for coronary and peripheral artery diseases.

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Key Words

■ **Blood pressure (inter-arm blood pressure difference)**
■ **Coronary artery disease (subclavian artery disease)**
■ **Radionuclide imaging (myocardial perfusion imaging)**

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INTRODUCTION

The development of simultaneous brachial and ankle blood pressure measurements enable us to evaluate not only ankle-brachial pressure index (ABI) but also inter-arm systolic blood pressure difference at the same time.[1,2] Although an ABI of < 0.9 is regarded as an index of peripheral artery disease, one of the most common diseases related to atherosclerosis, and widely applied in clinical practice, less accepted is inter-arm pressure difference despite its diagnostic accuracy for subclavian artery stenosis.[3] Among diseases related to atherosclerosis, diagnosis and therapeutic management of coronary artery disease (CAD) is very important in clinical practice because of its prevalence and mortality.[4] Although measuring blood pressure at the bilateral brachia is common in medical practice in the outpatient clinic without requiring any expensive diagnostic modalities except for a sphygmomanometer, its diagnostic utility for CAD is largely unknown. Therefore, the objectives of this study were to define the prevalence of significant inter-arm pressure difference in patients with suspected CAD, and to assess the relationship between inter-arm systolic blood pressure difference and CAD as assessed by myocardial perfusion imaging.

SUBJECTS AND METHODS

Study patients

We retrospectively evaluated 386 consecutive patients with suspected CAD, who underwent both simultaneous brachial and ankle blood pressure measurements and myocardial perfusion imaging. Clinical grounds for suspected or unknown CAD were based on clinical symptoms, coronary risk profiles, electrocardiographic findings, or past medical history. The patient were aged 65 ± 11 years; 265 were men and 121 women. No patient with previous myocardial infarction, unstable angina, or history of coronary revascularization was included. Among the 386 patients, 253 patients underwent coronary angiography because of clinical symptoms, electrocardiographic abnormalities or scintigraphic findings. Written informed consents were obtained from these patients.

Assessment of coronary risk factors

Risk factors included in the assessment were hypertension, hypercholesterolemia, diabetes mellitus, cigarette smoking, and family history of coronary artery disease. Hypertension was defined as a history of systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure ≥ 90 mmHg or documented hypertension on at least two occasions in outpatient clinics. Hypercholesterolemia was defined as fasting serum total cholesterol of ≥ 220 mg/d*l*.[5] Diabetes mellitus was diagnosed using the criteria proposed by the Japanese Diabetic Society.[6]

Measurements of blood pressure and ankle-brachial pressure indexes

Blood pressure was measured at the bilateral brachia and ankles using a volume-plethymographic apparatus (FORM/ABI, Colin Co. Ltd.) while the patient was in the supine position after resting in the same position for at least 5 min, as described previously.[7,8] In brief, this instrument simultaneously records the brachial-ankle pulse wave velocity and the brachial and ankle blood pressures on the left and right sides, as well as records electrocardiogram and heart sounds. The electrocardiographic electrodes were placed on both wrists, and cuffs were wrapped around both brachia and ankles. Inter-arm systolic blood pressure difference was calculated, and the value ≥ 15 mmHg was defined to be significant. The ABI was defined as the lowest value for both sides, and the value < 0.9 in either leg was considered to indicate the presence of peripheral artery disease.[9] All recordings were performed while the patients were taking their regular medication, but not receiving intravenous drugs at the time of the study.

Stress myocardial perfusion imaging

Using ^{99m}Tc-sestamibi (110 patients) or ^{201}Tl (276 patients), stress/rest myocardial single-photon emission computed tomography (SPECT) was performed. The stress protocol was either exercise (157 patients) or adenosine triphosphate disodium loading (229 patients).[10,11] After the stress, data was acquired with a 2 or 3-detector gamma camera (Prism 2000XP or Prism 3000XP, Picker) for 180- or 360-degree arcs. For both radioisotopes, a low-energy high-resolution parallel multi-hole collimator was used. SPECT images were reconstructed from the data by a data processor (Odyssey VP, Picker) combined with a Butterworth filter (order 8; cutoff frequency 0.25 for ^{99m}Tc-sestamibi and 0.2 for ^{201}Tl) and a ramp filter.

Scintigraphic findings were visually defined as positive if reversible and/or fixed perfusion abnor-

mality was observed. Each SPECT image was divided into 20 segments according to the reported method.[12] The myocardial uptake of ^{99m}Tc-sestamibi or ^{201}Tl was visually evaluated by two experienced cardiologists, unaware of all clinical data, using a 5-grade scale: 0 (normal), 1 (slight reduction of uptake), 2 (moderate reduction of uptake), 3 (severe reduction of uptake) or 4 (absence of radioactive uptake). The score totals for all segments during exercise and at rest were designated as the summed stress scores (SSS) and the summed rest scores (SRS), respectively. The SSS minus the SRS was defined as the summed difference score (SDS).[12] In addition, these indices were converted to percentage of the total myocardium (% myocardium) involved with stress, ischemic, or fixed defects by dividing the summed scores by 80, the maximum potential score (4×20), and multiplying it by 100.[13] Stress-induced myocardial ischemia was considered present if percentage ischemic myocardium of $\geq 5\%$ was observed.[13] Each reconstructed short-axis gated SPECT image was processed by the quantitative gated SPECT program,[14] to calculate the left ventricular end-diastolic volume, left ventricular end-systolic volume and left ventricular ejection fraction.

Coronary angiography

Based on clinical symptoms and scintigraphic findings, multi-direction coronary angiography was performed by Judkins' method in 283 of 386 patients. The degree of coronary artery stenosis was measured using a caliper according to the American Heart Association criteria.[15] Significant stenosis was deemed as present when $>50\%$ actual diameter narrowing was noted. Significant CAD was defined if a significant stenosis was present in one of the three major coronary arteries.

Statistical analysis

Results were expressed as means $\pm$ SD, except for percentage ischemic myocardium, which was expressed as mean $\pm$ standard error. Student's *t*-test was used to compare the means of the continuous variables, and contingency tables were analyzed using the chi-square test. A p value of <0.05 was regarded as denoting a statistically significant difference. Multivariate analysis with logistic regression analysis was used to identify the independent predictors for myocardial ischemia. The computations were performed using the SPSS-PC + computer program (Version 11.0; SPSS).

Table 1 Clinical characteristics of 386 patients with and without subclavian artery stenosis

	Subclavian artery stenosis		
	(+) (n=27)	(−) (n=359)	p value
Age (yr, mean±SD)	65±12	65±11	NS
Male	21 (78)	244 (68)	NS
Hypertension	17 (63)	202 (56)	NS
Hypercholesterolemia	17 (63)	224 (62)	NS
Diabetes mellitus	9 (33)	137 (38)	NS
Smoking	12 (44)	147 (41)	NS
Family history of CAD	4 (15)	44 (12)	NS
Peripheral artery disease	10 (37)	43 (12)	0.001

( ): %.
Subclavian artery stenosis: ≥15 mmHg inter-arm pressure difference.
CAD = coronary artery disease.

RESULTS

Clinical risk factors and blood pressure differences

Mean inter-arm pressure difference in all of the patients was 5.6 ± 7.2 mmHg. Inter-arm pressure difference of ≥ 10 mmHg was observed in 59 patients (15%). Systolic blood pressure was higher at the right brachium in 31 patients, and at the left in the remaining 28. Subclavian artery stenosis defined as inter-arm pressure difference ≥ 15 mmHg[16] was found in 27 patients (7%); systolic blood pressure was higher at the right in 13 and at the left in the remaining 14 patients. Various clinical characteristics examined in the patients with and without subclavian artery stenosis are shown in **Table 1**. No statistically significant difference was seen except in the patients with peripheral artery disease ($p = 0.001$). In the patients with and without peripheral artery disease (**Table 2**), the statistically significant clinical characteristics were age ($p = 0.019$) and diabetes mellitus ($p = 0.001$). Ten patients fulfilled both inter-arm pressure difference ≥ 15 mmHg and ABI < 0.9. Multiple coronary risk factors were found in 63% of the patients with only subclavian artery stenosis, and in 80% of the patients with both subclavian artery stenosis and peripheral artery disease. A significant inverse correlation was observed between ABI and inter-arm pressure difference ($r = -0.26$, $p < 0.0001$;

Table 2 Clinical characteristics of 386 patients with and without peripheral artery disease

	PAD(+) (n=53)	PAD(−) (n=333)	p value
Age (yr, mean±SD)	68±12	65±11	0.019
Male	36(68)	229(69)	NS
Hypertension	32(60)	187(56)	NS
Hypercholesterolemia	36(68)	205(62)	NS
Diabetes mellitus	31(59)	115(35)	0.001
Smoking	23(43)	136(41)	NS
Family history of CAD	5(9)	43(13)	NS

( ): %.
PAD=peripheral artery disease. Other abbreviation as in Table 1.

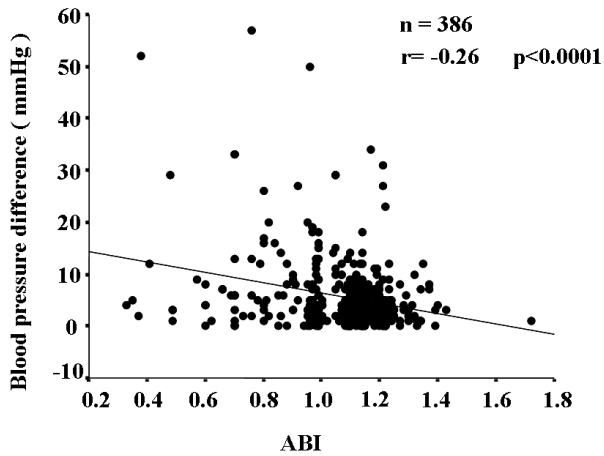

Fig. 1 Trend analysis for the correlation of inter-arm blood pressure differences and ankle-brachial pressure index
ABI = ankle-brachial pressure index

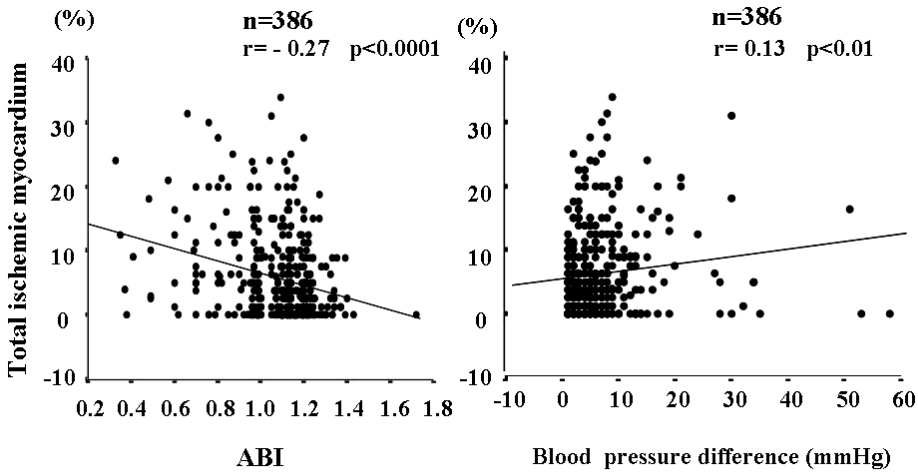

Fig. 2 Relationship between the magnitude of stress-induced myocardial ischemia (percentage ischemic myocardium) and ankle-brachial pressure index (*left*), and percentage ischemic myocardial and inter-arm pressure difference (*right*)
Abbreviation as in Fig. 1.

Fig. 1).

Scintigraphic findings

Visual analysis of stress myocardial SPECT revealed positive findings in 245 patients (63%) and negative findings in 141 patients (37%). Stress-induced myocardial ischemia, as semi-quantitatively defined as percentage ischemic myocardium of $\geq$5%, was found in 177 patients (46%), and no significant myocardial ischemia in the remaining 209 patients (54%). In all 386 patients, percentage ischemic myocardium was 4.9±0.4%, and percentage fixed myocardium was 4.5±0.4%. Quantitative gated SPECT was performed in 339 patients (88%) with a mean left ventricular ejection fraction of 54%, whereas the analysis could not be performed in the remaining 47 patients (12%) due to cardiac arrhythmias such as atrial fibrillation.

Relationship of inter-arm pressure difference with scintigraphic findings

A weak but significant inverse correlation was observed between ABI and percentage ischemic myocardium ($r=-0.27$, $p<0.0001$; **Fig. 2-left**). A weak but significant correlation was also

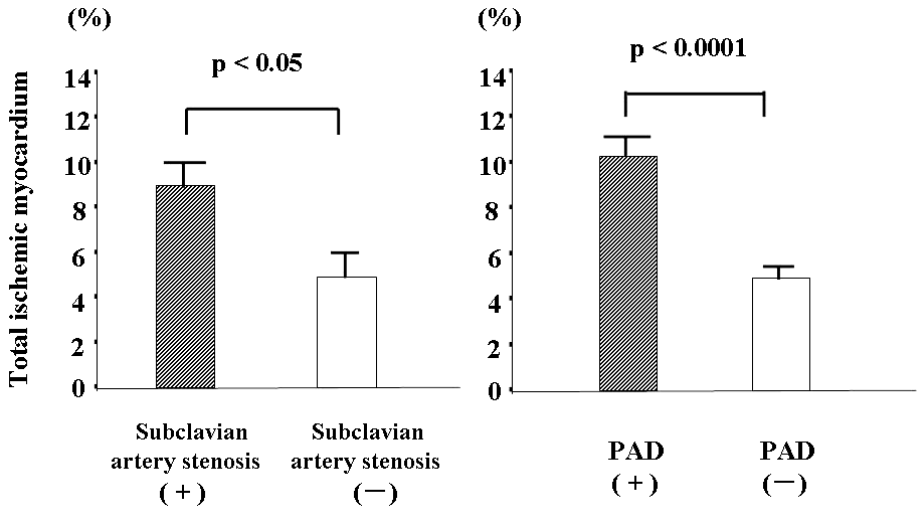

Fig. 3 Comparison of the magnitude of stress-induced myocardial ischemia (percentage ischemic myocardium) between patients with and without subclavian artery stenosis (*left*), and between patients with and without peripheral artery disease (*right*)
Abbreviation as in Table 2.

observed between inter-arm pressure difference and percentage ischemic myocardium ($r = 0.13$, $p < 0.01$; **Fig. 2−right**). Patients with subclavian artery stenosis had greater percentage ischemic myocardium than those without ($9.0 \pm 1.6\%$ vs $5.6 \pm 0.4\%$, $p < 0.05$; **Fig. 3−left**). Percentage ischemic myocardium was greater in patients with peripheral artery disease than in those without ($10.2 \pm 1.2\%$ vs $5.1 \pm 0.3\%$, $p < 0.0001$; **Fig. 3−right**). In 10 patients who had both inter-arm pressure difference ≥ 15 mmHg and ABI < 0.9, percentage ischemic myocardium was $9.7 \pm 2.6\%$.

Coronary angiographic findings

Based on clinical symptoms, electrocardiographic and scintigraphic findings, coronary angiography was performed in 283 of 386 patients (73%). Among 283 patients who underwent coronary angiography, 1-vessel CAD was found in 60 patients, 2-vessel CAD in 57, 3-vessel CAD in 48; and insignificant lesions in the remaining 118. Among 27 patients with subclavian artery stenosis, 19 patients underwent coronary angiography; 1-vessel CAD was found in 2 patients, 2-vessel CAD in 7, 3-vessel CAD in 3; and insignificant lesions in the remaining 7. Among 10 patients with both inter-arm blood pressure ≥ 15 mmHg and ABI < 0.9, 8 patients underwent coronary angiography, 1-vessel CAD was found in 1 patient, 2-vessel CAD in 2, 3-vessel CAD in 3; and insignificant lesion in the remaining 2.

Table 3 Clinical characteristics of 386 patients with and without myocardial ischemia as assessed by myocardial scintigraphy

	Myocardial ischemia (+) ($n=177$)	Myocardial ischemia (−) ($n=209$)	p value
Male	30 (74)	135 (65)	NS
Hypertension	113 (64)	106 (51)	0.01
Hypercholesterolemia	123 (70)	118 (57)	0.009
Diabetes mellitus	79 (45)	67 (32)	0.01
Smoking	83 (47)	76 (36)	0.04
Family history of CAD	24 (14)	24 (12)	NS
Peripheral artery disease	38 (22)	15 (7)	<0.0001
Subclavian artery stenosis	18 (10)	9 (4)	0.03

( ): %.
Subclavian artery stenosis: ≥15 mmHg inter-arm pressure difference.
Abbreviation as in Table 1.

Detection of myocardial ischemia and CAD with inter-arm pressure difference

The prevalence of classical coronary risk factors, inter-arm pressure difference and peripheral artery disease in the presence or absence of stress-induced myocardial ischemia documented by myocardial SPECT is shown in **Table 3**. In all of the 386 patients, inter-arm pressure difference ≥ 15 mmHg

detected myocardial ischemia with a sensitivity of 11%, specificity of 96% and a positive predictive value of 67%. Among 283 patients who underwent coronary angiography, inter-arm pressure difference detected a significant CAD with a sensitivity of 7%, specificity of 94% and a positive predictive value of 63%. In addition, an ABI of < 0.9 showed a sensitivity of 17%, specificity of 92% and a positive predictive value of 76% in the detection of CAD.

In detecting myocardial ischemia by multivariate analysis, 8 variables listed in **Table 3** were entered into the logistic regression analysis. This analysis showed that peripheral artery disease [odds ratio (OR) = 3.1], hypercholesterolemia (OR = 1.7) and hypertension (OR = 1.6) were the independent predictors for myocardial ischemia. After excluding peripheral artery disease, a repeated multivariate analysis demonstrated that inter-arm blood pressure difference $\geq$ 15 mmHg (OR = 2.5), hypercholesterolemia (OR = 1.7) and hypertension (OR = 1.6) were the independent predictors for stress-induced myocardial ischemia.

DISCUSSION

The present study investigated the importance of inter-arm blood pressure measurements and association with CAD, and the findings have several important implications. First, the results of this study indicated that inter-arm blood pressure measurements have a clinically important role. If both brachial blood pressures are measured on the occasion of sphygmomanometry, in accordance with the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), and an imbalance is recognized, the higher side value is recommended to be used for follow up.[17] Based on our findings, when a remarkable difference in inter-arm blood pressure is recognized, this may lead to a diagnosis of subclavian artery stenosis or peripheral artery disease. Previous studies reported that an upper extremity blood pressure difference of $\geq$ 15 mmHg identified all patients with $\geq$ 50% subclavian artery narrowing.[18] Accordingly, subclavian artery stenosis was defined as those who had inter-arm blood pressure difference of $\geq$ 15 mmHg in the present study, and was found in 7% (27/386). There was no significant relation between inter-arm blood pressure difference and age, sex and coronary risk factor. Study of the relationship between inter-arm blood pressure difference and age, and reported that although the prevalence of significant inter-arm blood pressure difference was indeed more frequent in the elderly than in younger patients, the relationship between inter-arm blood pressure difference and advancing age was not so evident as to reach statistical significance.[19] Other studies also reported no significant differences between inter-arm blood pressure difference and sex, or coronary risk factor.[20,21]

Secondly, we investigated which side had higher blood pressure. Several studies reported that in patients with significant inter-arm blood pressure difference, blood pressure in the right arm tends to be higher than that in the left arm.[22] There are several reports that this may be related to anatomical differences in right and left vascular circulation.[22] In the present study, however, when inter-arm blood pressure difference was found, the frequency was similar in the right and left sides. While most previous studies, as well as the present one, used a definition of a difference of 15 mmHg as the cutoff level to indicate a difference in inter-arm blood pressure,[16,17] our data showed that even using a cutoff of 10 mmHg there was still no difference in left or right side frequency of higher blood pressure. Therefore, we considered that it is possible that inter-arm blood pressure difference is not necessarily related only to anatomical right and left vascular circulation, but could also be linked to random presence of stenotic lesions due to atherosclerosis.

Thirdly, inter-arm blood pressure difference was strongly associated with peripheral artery disease. It is clinically useful to grasp ABI by simultaneous brachial and ankle blood pressure measurements, and an ABI value of < 0.9 is an important diagnostic index. The results of our study showed that 37% of patients who have inter-arm blood pressure difference had an ABI value of < 0.9, and this result was clearly higher than the 12% of patients who did not have an inter-arm blood pressure difference (**Table 1**). Peripheral artery disease was found to be the strongest diagnostic parameter for subclavian artery stenosis.[16]

Finally, the presence of inter-arm pressure difference $\geq$ 15 mmHg suggested myocardial ischemia and CAD with positive predictive values of 63–67%. Although we used stress myocardial SPECT to noninvasively examine the relationship between inter-arm blood pressure difference and CAD to determine percentage ischemic myocardium, the diagnostic performance of inter-arm pressure dif-

ference was similar either to detect myocardial ischemia in all of the 386 patients or to diagnose CAD in 283 patients who underwent coronary angiography. The percentage ischemic myocardium is an important index not only in predicting the extent and severity of CAD but also its outcome.[13] Our results also showed that the extent and severity of myocardial ischemia increases with higher inter-arm blood pressure difference. Among 386 patients, 283 underwent coronary angiography, and 63% of those who had inter-arm blood pressure difference had CAD. Furthermore, 83% of those CAD patients had multi-vessel CAD, which is regarded as a high-risk subset for subsequent cardiac events.

Study limitations

First, the patient population of the current study had increased likelihood of CAD on clinical grounds. In the general population, therefore, the reported incidence of inter-arm pressure difference of 7% may decrease. Secondly, we used stress myocardial SPECT for the standard to detect ischemic heart disease since not all the patients underwent coronary angiography. However, the fact that the diagnostic performance of inter-arm pressure difference was similar for the detection of either scintigraphic ischemia or angiographic coronary stenosis, suggested that this difference in diagnostic methods was negligible. Thirdly, inter-arm pressure difference of ≥ 15 mmHg was indeed an independent predictor for myocardial ischemia when combined with classical coronary risk factors, but not when ABI was included. Considering routine clinical practice, however, taking medical history as well as blood pressure at bilateral brachia could become an initial step to examine chronic stable patients who are at high risk for atherosclerotic diseases. To suspect CAD or peripheral artery disease at this initial stage in any outpatient clinic, not equipped with a special instrument such as a FORM/ABI, seems very important.

CONCLUSIONS

Inter-arm blood pressure difference measurements will not only contribute to the diagnosis of subclavian artery stenosis but also can indicate the presence of peripheral artery disease. Moreover, measurement of the inter-arm blood pressure difference is a simple routine clinical index that can suggest the presence of CAD.

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要　　約

冠動脈病変を疑う患者における両上腕の血圧左右差と Ankle-Brachial Pressure Index の臨床的有用性

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目　的: 両上腕の血圧測定は臨床上実用的であるが，冠動脈病変を疑う患者においての臨床的有用性は明らかではない．冠動脈病変を疑う患者における両上腕の血圧左右差と ankle-brachial pressure index（ABI）の臨床的有用性を検討した．

方　法: 冠動脈病変が疑われる患者386例を対象とし，全例に両上下肢血圧測定と負荷心筋シンチグラフィーを施行した．陳旧性心筋梗塞，不安定狭心症，すでに血行再建している患者は除外した．なお，心筋虚血は負荷心筋シンチグラフィーにより20セグメントモデルを用い，心筋虚血率を算出して評価した．

結　果: 両上腕の血圧が15 mmHg以上の患者を鎖骨下動脈狭窄と定義し，鎖骨下動脈狭窄は27例（7%）にみられた．年齢，性別，高血圧，高脂血症，糖尿病，喫煙，冠動脈病変の家族歴には鎖骨下動脈狭窄の有無に有意な差はみられなかった．ABI（37% vs 12%, $p = 0.001$）と心筋虚血率（$9.0 \pm 8.5\%$ vs $5.6 \pm 6.6\%$, $p < 0.05$）は非鎖骨下動脈狭窄群より鎖骨下動脈狭窄群で有意に高値であった．さらに，両上腕の血圧左右差と心筋虚血率（$r = 0.13$, $p < 0.01$）には，弱いが有意な相関が

みられた．両上腕の血圧左右差とABI（$r=-0.26$, $p<0.0001$）でも相関がみられた．全386例中283例に冠動脈造影が施行された．両上腕の血圧左右差を有する群では63%に有意病変がみられ，そのうちの83%は多枝病変であり，心血管事故のハイリスク群であった．

結　論：両上腕の血圧左右差はしばしば冠動脈病変が疑われる患者にみられ，有意な冠動脈病変と末梢動脈病変を持つ患者において関連がある．このように，両上腕の血圧左右差は冠動脈病変と末梢動脈病変の評価の簡便な指標として有用である．

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