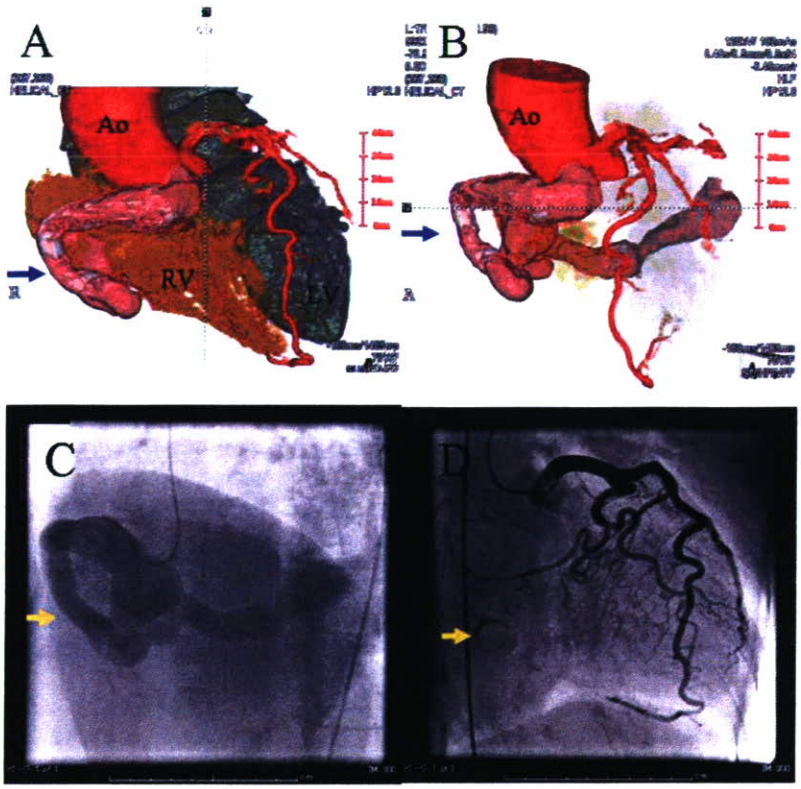

Fig. 2. MDCT (A,B) and Coronary angiogram (C,D)
A: Right anterior oblique view. B: cranial view without chamber image. C: Right anterior oblique, cranial view. D: Right anterior oblique view. The enlarged and tortuous right coronary artery is flowing into the posterior wall of left ventricle (arrows). The left anterior descending artery and circumflex artery are visualized and appeared normal. The left anterior descending artery has a postero-descending branch and irrigates the inferior wall. The arrow in D shows calcification of the fistula.
Ao, LV and RV indicate aorta, left ventricle, right ventricle. MDCT indicates multidetector computed tomography.

hemodynamics of grade two aortic regurgitation. Tl-201 perfusion scintigram did not show any myocardial ischemia.

Surgical or transcatheter closure of the coronary fistula was not selected as she had no sign of heart failure and myocardial ischemia.

Discussion

Coronary anomalies are found in 1.3% of adult patients undergoing coronary angiogram. Eighty seven percent had anomalies of origin and distribution, and 13% had coronary artery fistula. Coronary artery fistulas are uncommon entities defined as a communication between coronary artery and a cardiac chamber or another vascular structure. Congenital fistulas appear to represent persistence of embryonic intertrabecular spaces and sinusoids. Acquired fistulas are caused by atherosclerosis, arteritis, and trauma[1]. The right coronary artery fistula is 55% of cases; the left coronary artery fistula is 35%; both coronary artery fistula is 5%. Drainage site of fistulas occurs into the right ventricle in 41% of cases, right atrium in 26%, pulmonary artery in 17%[2], coronary sinus in 7%, the left atrium in 5%, and the left ventricle only in 3%[3].

Congestive heart failure is most likely to occur in infancy or in old age. Also because myocardial perfusion of other coronary areas decreases, myocardial ischemia or hemodynamic steal phenomenon may occur.

The main indications for closure of coronary artery fistula depend on whether the patient has heart failure and myocardial ischemia. In adults, the treatment of asymptomatic patients with significant shunting is still controversial[4,5].

In this case, the patient's shunt flow streams from the aorta to left ventricle in diastolic phase; her hemodynamics appeared similar to that of grade-two aortic regurgitation. Surgical or transcatheter therapy was not considered because she had no sign of volume overload. Follow-up by checking left ventricular end-diastolic diameter and ventricular function using echocardiography should be performed. A recent report from the Mayo Clinic[6], that shows asymptomatic patients with an ejection fraction >55% and end-systolic diameter normalized to body surface area <25mm/m^2 incurred a 10-year mortality rate between 14% and 17% (not significantly different from expected), may be useful for deciding surgical intervention.

Echocardiogram is very useful to diagnose non-invasively these diseases by determining coronary conformation and coronary traveling. We can evaluate the change of coronary conformation and cardiac function with time to determine indication of operation by echocardiogram.

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Magnetic Resonance Evaluation of the Associations of Thoracic and Abdominal Aortic Plaques with the Presence and Extent of Coronary Artery Stenosis

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ABSTRACT

The association between coronary artery disease (CAD) and thoracic aortic plaques has often been reported using transesophageal echocardiography. However, studies showing the association between CAD and abdominal aortic plaques are scarce. CMR can visualize plaques in both the thoracic and abdominal aortas. Using CMR, we investigated the associations of thoracic and abdominal aortic plaques with the presence and extent of coronary artery stenosis in 146 patients undergoing coronary angiography, of whom 108 had CAD. The prevalence of thoracic and abdominal aortic plaques was higher in patients with CAD than in those without CAD (73% and 94% vs. 32% and 79%, $p < 0.025$). Stepwise increases in the prevalence and extents of both thoracic and abdominal plaques were found depending on the number of stenotic coronary vessels. Plaque extent in the thoracic aorta correlated with the numbers of >50% and >25% stenotic coronary segments (rs = 0.30 and 0.41). Plaque extent in the abdominal aorta also correlated with the numbers of >50% and >25% stenotic segments (rs = 0.40 and 0.44). Notably, the total plaque extent in the aortas correlated best with the numbers of >50% and >25% stenotic coronary segments (rs = 0.41 and 0.49, $p < 0.001$), and this factor was found to be the best predictor for the presence of CAD by the receiver-operating-characteristics curve analysis. Thus, the total plaque extent in the aortas was found to be more closely associated with the presence and extent of coronary stenosis than the thoracic or abdominal aortic plaque extent.

INTRODUCTION

The atherosclerotic process that results in coronary artery disease (CAD) is recognized to be a generalized process that may involve the entire vasculature (1, 2). The association between CAD and thoracic aortic plaques has often been reported using transesophageal echocardiography (TEE) (3–7). However, studies showing an association between CAD and abdominal aortic plaques are scarce. An autopsy study reported plaques in the abdominal aorta, but not in the thoracic aorta, to be severe in patients with cardiac catastrophe (2). Using computed tomography, Takasu el al. (8) reported both thoracic and abdominal aortic plaques to be associated with the presence of CAD.

Recently, cardiovascular magnetic resonance (CMR) has become a useful tool for non-invasively evaluating atherosclerotic plaques in both the thoracic and abdominal aortas (9–11). We (12–14) and others (15) showed good correlations regarding the aortic plaque extent between in vivo and ex vivo CMR findings and histopathology in animal models. In humans, we reported that MRI evaluations of the thoracic aorta closely correlated with TEE findings (9). Using CMR, we previously reported the associations of thoracic and abdominal aortic plaques with risk factors and CAD in 102 patients undergoing coronary angiography (10). We showed the prevalence of thoracic and abdominal aortic plaques to be high in patients with CAD and to increase as the number of stenotic coronary vessels increased. Moreover, we reported complex plaques in the abdominal aorta to be associated

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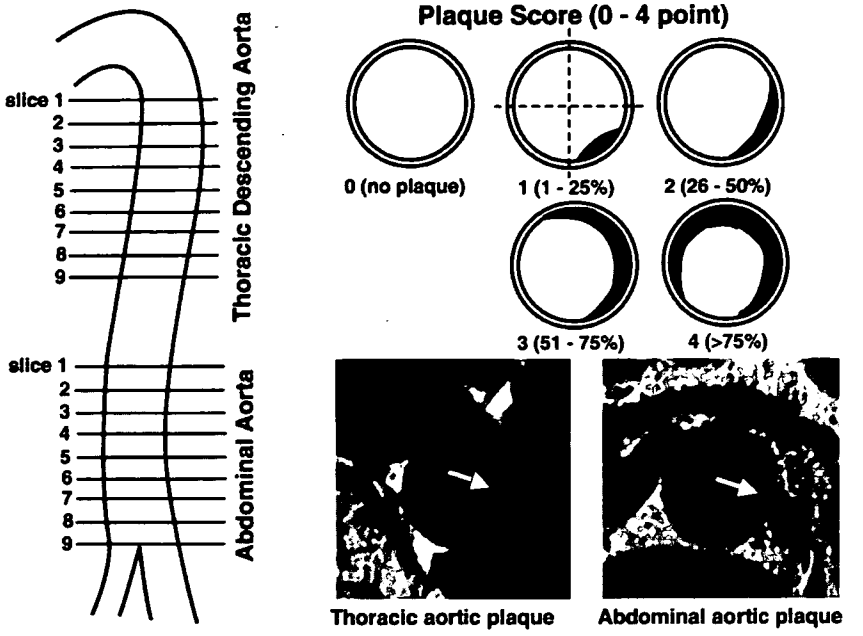

Figure 1. MRI slices of the aortas and plaque scores. In each patient, 9 slices of thoracic aorta and 9 slices of abdominal aorta were obtained at 12 mm intervals, which each covered about 10 cm portions of thoracic aorta below the arch and of abdominal aorta above the bifurcation. In each slice, the plaque extent was scored from 0 to 4 points by the percentage of the luminal surface involved by plaque. Arrows indicate aortic plaques.

with myocardial infarction (MI) and complex coronary lesions (16). However, the association between aortic plaques and the extent of coronary artery stenosis has not been fully elucidated yet. The present study was done to elucidate the associations of thoracic and abdominal aortic plaques with the extent of angiographic coronary stenosis (the number of >50% stenotic vessels, the number of >50% stenotic segments, and the number of >25% stenotic segments) and to elucidate the predictive values of thoracic and abdominal aortic plaques for CAD in 146 patients undergoing coronary angiography.

MATERIALS AND METHODS

Patient population

The study patients consisted of 146 patients (male, 76%; mean age, 64 ± 9 yrs; range 40 to 80 yrs) undergoing coronary angiography for suspected or known CAD at National Defense Medical College Hospital, who were the same patients in our recent study (16). Patients with a history of cardiac surgery, aortic disease, or valvular or congenital heart disease were excluded. Of the 146 patients, 108 (74%) had CAD (>50% stenosis) on coronary angiograms, of whom 26 had a history of percutaneous coronary intervention (PCI) and 44 had MI. The diagnosis of acute and old MI was given to 25 and 19 patients, respectively. Our study was approved by institutional ethics committee. After written informed consent was obtained, CMR of the aortas was performed at Iruma Heart Hospital within 2 weeks of angiography. However, of the 25 patients with acute MI, 13 had CMR in 1 to 3 months after the onset of MI, and 12 did it in 4 to 8 months because of stent implantation. Of the 146 patients, 85 (58%) had hypertension (blood pressures ≥140/90 mm Hg or on drugs), of

Table 1. Clinical characteristics in patients with and without CAD

	CAD(-) (n = 38)	(+)*vs*(−)	CAD(+) (n = 108)
Age (yrs)	63 ± 9	*NS*	64 ± 9
Gender (male)	24 (63%)	*NS*	87 (81%)
Hypertension	21 (55%)	*NS*	64 (59%)
Systolic blood pressure (mmHg)	126 ± 16	*<0.05*	133 ± 20
Hyperlipidemia	15 (39%)	*NS*	64 (59%)
Total cholesterol (mg/dl)	206 ± 29	*NS*	205 ± 35
HDL-cholesterol (mg/dl)	57 ± 13	*<0.005*	50 ± 13
Diabetes mellitus	7 (18%)	*NS*	29 (27%)
Smoking	14 (37%)	*NS*	53 (49%)
Thoracic aorta			
Plaque (+)	12 (32%)	*<0.001*	79 (73%)
Plaque slice number	0.0	*<0.005*	1.5
Abdominal aorta			
Plaque (+)	30 (79%)	*<0.025*	102 (94%)
Plaque slice number	2.0	*<0.001*	4.0

Data are presented as the mean value ±SD or the number (%) of patients, except for plaque slice numbers that are presented as the median value.

Table 2. Factors associated with the presence of CAD (Multiple logistic regression analysis of the 146 study patients)

Variables	Odds ratio	(95% CI)	P value
Hyperlipidemia	2.7	(1.1–6.7)	*<0.05*
HDL-cholesterol	0.9	(0.8–0.9)	*<0.05*
Thoracic aortic plaques	5.2	(2.0–13.5)	*<0.002*

The dependent variables were the presence of CAD.
The factors analyzed included age, gender, hypertension, hyperlipidemia, HDL-cholesterol, diabetes, smoking, thoracic aortic plaque, and abdominal aortic plaque.

whom 68 were on antihypertensive drugs, and 79 (54%) had hyperlipidemia (total cholesterol level >240 mg/dL or on drugs), of whom 57 were taking a statin. Diabetes mellitus (fasting glucose level ≥126 mg/dL or on treatment) was present in 36 (25%) patients, and 67 (46%) were smokers (≥10 packs-year). Fasting blood samples were taken on the day of angiography. Serum lipid levels were measured by standard laboratory methods.

Coronary angiography

Coronary angiograms were recorded using the Judkins technique and a cineangiogram system (Toshiba, Tokyo, Japan). Coronary arteries were divided into 27 segments defined by Coronary Artery Surgery Study (CASS) classification (17). The degree of stenosis in each segment was evaluated according to 5 grades (≤25%, 26–50%, 51–75%, 76–90%, >90% stenosis). In patients with a history of PCI, the degree of stenosis in the segment where PCI had been performed was defined as the degree of stenosis before PCI. All angiograms were evaluated by Y.M., who was blinded to the CMR data. The intra-observer agreement for the assessment of the grade of stenosis was evaluated in 20 patients (540 segments), and it was found to be 98% of segments. CAD was defined as at least one coronary artery having >50% luminar diameter stenosis on angiograms. The extent of coronary artery stenosis was represented as the number of >50% stenotic vessels, the number of >50% stenotic segments, and the number of >25% stenotic segments.

CMR of the aorta

Aortic CMR was performed on Signa 1.5T Cvi scanner with a phased-array body coil (GE Medical Systems, Mount Prospect, IL). Transverse proton density-weighted (PDW) and T2-weighted (T2W) images of the thoracic descending and abdominal aortas were obtained using an ECG-gated, double-inversion-recovery fast spin-echo sequence. The imaging parameters were TR = 2 RR intervals, TE = 10 ms (PDW) and 60 ms (T2W), 20 cm FOV, 4 mm slice thickness, 8 mm inter-slice gap, 256 × 256 acquisition matrix, and 32 echo-train. As in our previous studies (10, 16, 18), 9 slices of the thoracic aorta and 9 slices of the abdominal aorta were obtained at 12 mm intervals, which each covered about 10 cm portion of the thoracic aorta below the arch and 10 cm portion of the abdominal aorta above the bifurcation of the common iliac artery (Fig. 1). For each patient, we assessed the presence and extents of plaque in 9 slices of the thoracic aorta and 9 slices of the abdominal aorta. As in our previous study (10), plaque was defined as a clearly identified luminal protrusion with focal wall thickening, and the plaque extent in each slice was scored from 0 to 4 points based on the percentage of the luminal surface involved by plaque: 0 (no plaque), 1 (1–25%), 2 (26–50%), 3 (51–75%), and 4 (>75%) point. The plaque extents in the thoracic and abdominal aortas were represented as the number of slices with plaque (plaque slice number) and the sum of scores of 9 slices (plaque extent score). The plaque extents were evaluated by two observers, and

Table 3. Associations between the number of >50% stenotic coronary vessels and the extents of plaques in thoracic and abdominal aortas

	CAD(-) (n = 38)	1-VD (n = 47)	2-VD (n = 39)	3-VD (n = 22)	P value
Age (yrs)	63± 9	62± 9	66± 7	66± 8	*NS*
Gender (male)	24 (63%)	37 (79%)	33 (85%)	17 (77%)	*NS*
Thoracic aorta					
Plaque (+)	12 (32%)	32 (68%)	28 (72%)	19 (86%)	<0.001
Plaque slice number	0.0	1.0	1.0	2.0	<0.005
Plaque extent score	0.0	2.0	2.0	2.5	<0.005
Abdominal aorta					
Plaque (+)	30 (79%)	43 (91%)	37 (95%)	22 (100%)	<0.05
Plaque slice number	2.0	4.0	4.0	4.5	<0.001
Plaque extent score	3.5	8.0	8.0	7.5	<0.001
Thoracic and abdominal aortas					
Plaque (+)	30 (79%)	44 (94%)	37 (95%)	22 (100%)	<0.025
Total plaque slice number	3.0	6.0	6.0	7.0	<0.001
Total plaque extent score	4.0	9.0	10.0	12.0	<0.001

Data are presented as the mean value ±SD or the number (%) of patients, except for plaque slice number and plaque extent score that are presented as the median value.
Total plaque slice number was defined as a total of plaque slice numbers in the thoracic and abdominal aortas, and total plaque extent score was defined as a total of plaque extent scores in the aortas. *1-VD*, 1-vessel disease; *2-VD*, 2-vessel disease; *3-VD*, 3-vessel disease.

Table 4. Correlations between the numbers of stenotic coronary segments and the extents of plaques in thoracic and abdominal aortas

	Number of >50% stenotic coronary segment		Number of >25% stenotic coronary segment	
	rs*	*p value*	rs*	*p* value
Thoracic aorta				
Plaque slice number	0.31	<0.002	0.41	<0.002
Plaque extent score	0.30	<0.001	0.41	<0.001
Abdominal aorta				
Plaque slice number	0.39	<0.001	0.43	<0.001
Plaque extent score	0.40	<0.001	0.44	<0.001
Thoracic and abdominal aortas				
Total plaque slice number	0.40	<0.001	0.49	<0.001
Total plaque extent score	0.41	<0.001	0.49	<0.001

*By Spearman's rank correlation test.

any discrepancy was resolved by consensus. The intra-observer and inter-observer agreement for the assessment of plaque extents was 98% and 92% of slices, respectively (10).

Statistics

Differences between 2 groups were evaluated by the unpaired t-test for parametric variables, by Mann-Whitney's U-test for nonparametric variables and by the chi-square test for categorical variables. Differences among 3 or more groups were evaluated by ANOVA with Scheffe's test for parametric variables, by Kruskal-Wallis rank test for nonparametric variables, and by the chi-square test for categorical variables. Correlations between the extents of aortic plaques and that of coronary stenosis were evaluated by Spearman's rank correlation test. A multiple logistic regression analysis was used to elucidate the associations between aortic plaques and CAD. The diagnostic abilities of aortic plaques for CAD were evaluated by the receiver-operating-characteristics (ROC) curve analysis, and the areas under ROC curves (AUC) were compared. A p value of <0.05 was considered statistically significant. The results are presented as the mean value ± SD or the median value.

RESULTS

Of the 146 patients, 108 had CAD (>50% stenosis). Compared with 38 patients without CAD, 108 with CAD had higher blood pressures and lower HDL-cholesterol levels (Table 1). Plaques were more prevalent in the abdominal aorta than in the thoracic aorta ($p < 0.001$). Patients with CAD more often had plaques in the thoracic (73% vs. 32%) and abdominal (94% vs. 79%) aortas than those without CAD ($p < 0.025$). The plaque slice numbers in the thoracic and abdominal aortas were also greater in patients with CAD than in those without CAD (median 1.5 and 4.0 vs. 0.0 and 2.0, $p < 0.005$) (Table 1).

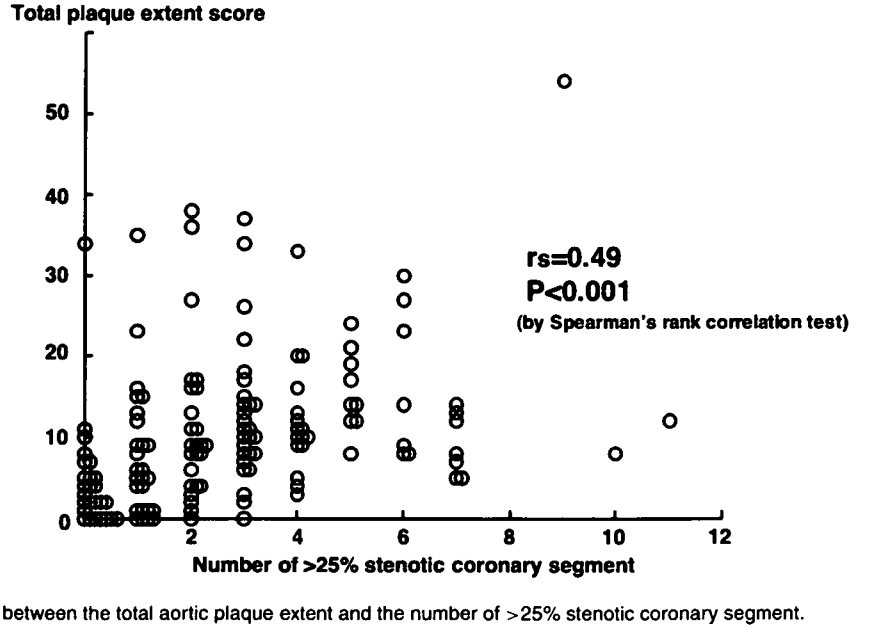

Figure 2. Correlation between the total aortic plaque extent and the number of >25% stenotic coronary segment.

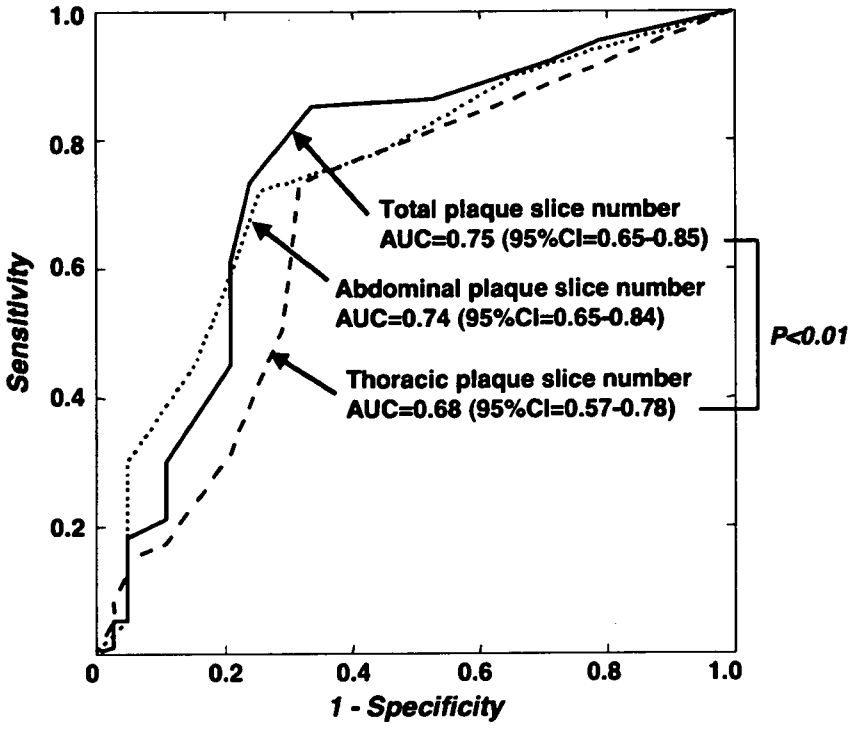

Figure 3. ROC curves of thoracic plaque slice number, abdominal plaque slice number, and total plaque slice number for the prediction of CAD. The AUC for total plaque slice number was found to be largest ($p < 0.01$).

To identify any independent association between aortic plaques and CAD, clinical variables (age, gender, hypertension, hyperlipidemia, HDL-cholesterol, diabetes, and smoking) and aortic plaques were entered into a multivariate logistic regression model. In multivariate analysis, thoracic aortic plaques were an independent factor associated with the presence of CAD (odds ratio = 5.2; 95%CI = 2.0–13.5; $p < 0.001$), while abdominal aortic plaques were not (Table 2).

Of the 108 patients with CAD, 47 had 1-vessel, 39 had 2-vessel, and 22 had 3-vessel disease. As shown in Table 3, stepwise increases in the prevalence and extents of thoracic and abdominal aortic plaques were found depending on the number of >50% stenotic coronary vessels. The plaque slice number and plaque extent score in the thoracic aorta correlated with the numbers of >50% stenotic coronary segments (rs = 0.31 and rs = 0.30) and >25% stenotic segments (rs = 0.41 and rs = 0.41) (Table 4). The plaque slice number and plaque extent score in the abdominal aorta also correlated with the numbers of >50% stenotic segments (rs = 0.39 and rs = 0.40) and >25% stenotic segments (rs = 0.43 and rs = 0.44). Notably, the total plaque slice number (a total of plaque slice numbers in the thoracic and abdominal aortas) and the total plaque extent score (a total of plaque extent scores in the aortas) were found to correlate best with the numbers of >50% stenotic segments (rs = 0.40 and rs = 0.41) and >25% stenotic segments (rs = 0.49 and rs = 0.49) (Fig. 2). The ability of aortic plaques to predict CAD was assessed by the ROC curve analysis (Fig. 3). The AUC for the total plaque slice number was thus found to be largest ($p < 0.01$). Sensitivity, specificity, and positive and negative predictive values of aortic plaques for CAD are shown in Table 5.

DISCUSSION

The association between CAD and thoracic aortic plaques has often been reported using TEE (3–7). Thoracic plaques have been shown to be more strongly associated with CAD than carotid or femoral artery plaques detected by ultrasonography (7) and to be associated with cardiovascular events (6, 19). Although an autopsy study reported plaques in the abdominal aorta, but not in the thoracic aorta, to be severe in patients with cardiac catastrophe (2), studies showing the association between CAD and abdominal aortic plaques are scarce, and little attention has so far been paid to abdominal plaques. Using CMR, we investigated plaques in the thoracic and abdominal aortas in 146 patients undergoing coronary angiography. The prevalence and extents of plaques in both the thoracic and abdominal aortas were greater in patients with CAD than in those without CAD, and the extents of both thoracic and abdominal plaques correlated with the extent of coronary stenosis. Notably, the total plaque extent in the aortas appeared to correlate better with the

Table 5. Sensitivity, specificity, and positive and negative predictive values of aortic plaques for predicting the presence of CAD

	N = 146 Patients	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Thoracic plaque slice number					
>1 slices	(n = 91)	73%	68%	87%	47%
>2	(n = 65)	50%	71%	83%	33%
>3	(n = 42)	31%	79%	81%	29%
Abdominal plaque slice number					
>1 slices	(n = 132)	94%	21%	77%	57%
>2	(n = 122)	90%	34%	80%	54%
>3	(n = 101)	78%	55%	83%	47%
>4	(n = 88)	72%	74%	89%	48%
Total plaque slice number					
>1 slices	(n = 133)	95%	21%	77%	62%
>2	(n = 126)	92%	29%	79%	55%
>3	(n = 113)	86%	47%	82%	55%
>4	(n = 105)	85%	66%	88%	61%
>5	(n = 88)	73%	76%	90%	50%

extent of coronary stenosis than the plaque extents in either the thoracic or abdominal aortas. The total aortic plaque extent was the best predictor for the presence of CAD.

We previously reported that plaques in the thoracic and abdominal aortas were characteristically associated with hyperlipidemia and smoking, respectively (10). Tribouilloy et al. (20) reported an association between LDL-cholesterol levels and thoracic plaques by TEE, whereas Giral et al. (21) showed no association between LDL-cholesterol and abdominal plaques by ultrasound. An autopsy study reported patients with hyperlipidemia to have severe plaques in the thoracic aorta (1). In contrast, autopsy studies reported smoking to be more closely associated with plaques in the abdominal aorta than in the thoracic aorta (22, 23). Giral et al. (21) showed smoking to be associated with abdominal plaques by ultrasound. The thoracic and abdominal aortas may thus have different susceptibilities to atherosclerotic risk factors. The abdominal aorta tapers geometrically and has higher pressure waves reflecting off of the iliac and other arteries, resulting in a higher pulsatile stress in the abdominal aorta than in the thoracic aorta (24). The abdominal aorta is also stiffer with less elastin and more collagen (24). Vasa vasorum is common in thoracic aorta but rare in abdominal aorta, suggesting that the oxygen and nourishment of the abdominal aorta comes mainly by diffusion from the aortic lumen (25). These may be the reasons for different susceptibilities to risk factors between the aortas. In our study, thoracic aortic plaques were an independent factor for CAD, while abdominal aortic plaques were not. Takasu et al. (8) also reported thoracic plaques to be more closely associated with CAD than abdominal plaques by computed tomography. The presence of thoracic plaques may thus be a better marker of CAD than abdominal plaques. However, our study showed total aortic plaque extent to be most closely associated with the extent of coronary artery stenosis and to be the best predictor for CAD. Because patients have various risk factors and because the thoracic and abdominal aortas may have different susceptibilities to risk factors, it appears to be preferable to evaluate atherosclerosis in both the aortas than in either the thoracic or abdominal aortas. MRI is a useful tool for evaluating atherosclerosis in multiple vascular beds in the same exam session, thereby determining the degree of systemic atherosclerotic involvement and predicting the degree of coronary atherosclerosis more accurately.

Our study has several limitations. First, CMR was used to evaluate aortic atherosclerosis, but angiography was used to evaluate coronary atherosclerosis. Angiography cannot visualize plaques, and it only shows lumen characteristics. Although intravascular ultrasound (IVUS) can visualize coronary plaques, IVUS was not used in our study. Second, in the thoracic aorta, we did not evaluate the arch or ascending aorta to reduce the examination time. Because plaques were reported to be more prevalent in the thoracic descending aorta (45%) than in the arch (31%) or the ascending aorta (8%) (6) and because plaques in the descending aorta were reported to be a stronger factor for CAD than those in the arch or ascending aorta (4), we only assessed the descending aorta. Third, since aortic images were obtained at 12 mm interval, we evaluated these images not blinded to the adjacent slices. This may have caused some bias and have confounded the results. Finally, our study was in Japanese patients undergoing angiography, who are generally considered to be a highly selected population at high-risk for CAD. Our results may not be applicable to the general or other ethnic populations.

In summary, the prevalence of plaques in both thoracic and abdominal aortas was high in patients with CAD. Although only thoracic aortic plaques were an independent factor for CAD, the extents of plaques in both the thoracic and abdominal aortas correlated with the extent of coronary artery stenosis. As a result, the total plaque extent in the aortas was found to be most closely associated with the extent of coronary stenosis, and this factor was considered to be the best predictor for CAD.

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Effect of hemoglobin vesicle, a cellular-type artificial oxygen carrier, on middle cerebral artery occlusion- and arachidonic acid-induced stroke models in rats

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Abstract

Hemoglobin vesicle (HbV), which is also called liposome-encapsulated hemoglobin, functions as a hemoglobin-based oxygen carrier and is expected to be utilized in emergency situations including hemorrhagic shock and several kinds of ischemic diseases. In the present study, we evaluated the efficacy of HbV for improving stroke-related symptoms induced by middle cerebral artery (MCA) occlusion/reperfusion and an intra-internal carotid arterial injection of arachidonic acid (AA) in rats. When HbV (10 mL/kg, i.v.) was administered to rats immediately after the MCA occlusion, it reduced the cerebral infarct volumes of the cortex and total of the cortex plus sub-cortex significantly as compared with saline as a vehicle. In AA-induced stroke model, HbV (10 mL/kg, i.v.) improved the motor dysfunction score and inhibited the increase in cerebral water content suggesting it could suppress cerebral edema. These results strongly suggest that HbV would provide a novel beneficial option for the treatment of stroke, especially acute ischemic stroke.

Keywords: Hemoglobin vesicle; Oxygen carrier; Red blood cell substitute; Artificial; Liposome; Stroke

Hemoglobin vesicle (HbV) is a cellular-type hemoglobin-based oxygen carrier encapsulated by liposome. Since HbV has been already demonstrated to deliver oxygen to organs in the same manner as normal red blood cells (RBCs), it is expected to play an important role as RBC substitute (artificial RBC). Its long stability at room temperature and compatibility to all blood types make it specifically attractive for use in emergency situations. Main characteristics of the HbV that we employed in the present study are as follows [21,13,22]: median particle diameter, 262–269 nm; Hb concentration, 10.0–10.6 g/dL; p50, 23–25 Torr; lipid concentration, 6.9–7.2 g/dL; lipid components, 1, 2-dipalmitoyl-*sn*-glycero-3-phosphatidylecholine (DPPC)/cholesterol/1,5-*O*-dihexadecyl-*N*-succinyl-L-glutamine (DHSG)/1, 2-distearoyl-*sn*-glycero-3-phosphatidylethanolamine-*N*-polyethylene glycol 5000 (PEG5000-DSPE). The biological activity of HbV has been previously studied in several kinds of animal models. For instance, Izumi et al. demonstrated in a rat exchange-transfusion model that HbV has an oxygen transporting capability almost equivalent to rat RBCs and can be considered as a potential artificial oxygen carrier [12]. As another potential advantage, HbV has been projected to improve ischemia-related symptoms since it can penetrate into ischemic areas through incompletely occluded arteries, arterioles and/or collateral vessels because the particle size is much smaller than that of normal RBC. In fact, HbV improved oxygenation in acutely ischemic hamster flap tissue [8] and augmented oxygen delivery trough transiently occluded arterioles in a hamster window model [17]. However, the effects of HbV in stroke and myocardial infarction models, which are typical ischemic

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models, have not been fully investigated. In the present study, we evaluated the effect of HbV on stroke episodes using a transient middle cerebral artery (MCA) occlusion model and an arachidonic acid (AA)-induced stroke model in rats.

All animal study protocols were confirmed to be in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals and approved by the institutional animal care and use committee of Oxygenix Co. Ltd.

In the study of MCA occlusion/reperfusion [4,27], 63 male Wistar rats (Japan SLC, Shizuoka, Japan) weighing 209–245 g (9 weeks of age) were included. Under halothane anesthesia (2–3%, 0.5–1 L/min), rats underwent transient focal cerebral ischemia using an intraluminal suture. Body temperature was controlled at 37 ± 1 °C with a body temperature controller (Neuroscience, Tokyo, Japan). The right carotid artery bifurcation was exposed, and the common external and internal carotid arteries were mildly ligated transiently. The external carotid artery was incised at the 2-mm distal from the junction of internal carotid artery and a 4–0 monofilament suture (18 mm in length) coated beforehand by silicon was inserted via this incision and advanced through the internal carotid artery to the origin of the MCA. The suture was left in place for 1 h and then pulled out about 10 mm to allow reperfusion. HbV (10 mL/kg) or saline was intravenously administered immediately after the MCA occlusion at an injection speed of 2 mL/min. Twenty-three hours after the reperfusion, the neurological symptom score was determined by the following criteria: 0, no symptoms; 1, adduction of left forelimb; 2, adduction of left forelimb and decrease in response to transversal stimulus; 3, adduction of left forelimb, decrease in response to transversal stimulus, and circling movement; 4, unable to walk (abasia). Immediately after the evaluation of neurological symptoms, rats were sacrificed to excise their brains, which were then sliced into 7 sections (2-mm thick) and stained with 2% 2,3,5-triphenyltetrazolium chloride (TTC, Wako Pure Chemical Ind. Ltd., Tokyo, Japan) at 37 °C for 30 min with shaking, then immersed in 10% formaldehyde neutral buffer solution (Wako Pure Chemical Ind. Ltd.) for preservation. Photograph of each section was taken with a digital camera (Fujifilm, Tokyo, Japan) and the infarct area was measured with a personal computer (iBook, Apple) and software (Adobe Photoshop® ver. 5.5 and NIH image ver. 1.62). Infarct volume was calculated from the data of infarct area according to the following formula: infarct volume $= A + G + 2 \times (B + C + D + E + F)$, where A–G refer to the areas of 7 sections. The infarct volume was

Table 1
Criteria of motor dysfunction score

1. Rolling test

Score	Symptom
0	Rat does not fall down and run away without resistance and/or turn its face to opposite direction in response to pushing right and left flanks.
1	Rat makes resistance or move to left side in response to pushing right flank.
2	Rat does not fall down in response to pushing left flank and do roll in a clockwise direction in response to pushing right flank.
3	Rat falls down stretching hind limbs out sideways but not forelimbs in response to pushing left flank.
4	Rat falls down stretching four limbs out sideways in response to pushing left flank and rise in 4 s.
5	Rat falls down stretching four limbs out sideways in response to pushing left flank and rise in 5–29 s.
6	Rat falls down stretching four limbs out sideways in response to pushing left flank and cannot rise for 30 s or longer.
7	Rat falls down rightward without stimulus and can not rise for 30 s or longer.

2. Posture test (when neck of rat was picked up)

Part	Score	Symptom
Head	0	Rat does not lean its head to the right or left and keep its eyes horizontally.
	1	Rat leans its head to the right but keep its eyes horizontally.
	2	Rat leans its head to the right and turns slightly its right eyes downward.
	3	Rat leans its head to the right and turns markedly its right eyes downward.
Right forelimb	0	Rat does not put down its right forelimb.
	1	Rat slightly puts down its right forelimb.
	2	Rat puts down its right forelimb but does not place it on the abdomen.
	3	Rat remarkably put down its right forelimb and place it on the abdomen.
Right hind limb	0	Rat does not put down its right hind limb.
	1	Rat slightly puts down its right hind limb.
	2	Rat remarkably put down its right hind limb but keeps its adduction slightly.
	3	Rat remains down the tip of its right hind limb just underneath.

3. Hemiplegia test

Score	Symptom
0	Rat makes a strong resistance and pulls back its right hind limb immediately when it is lifted with a pen.
1	Rat makes a slight resistance and pulls back its right hind limb slowly when it is lifted with a pen.
2	Rat remains its right hind limb stretched without resistance when the limb is stretched backward.

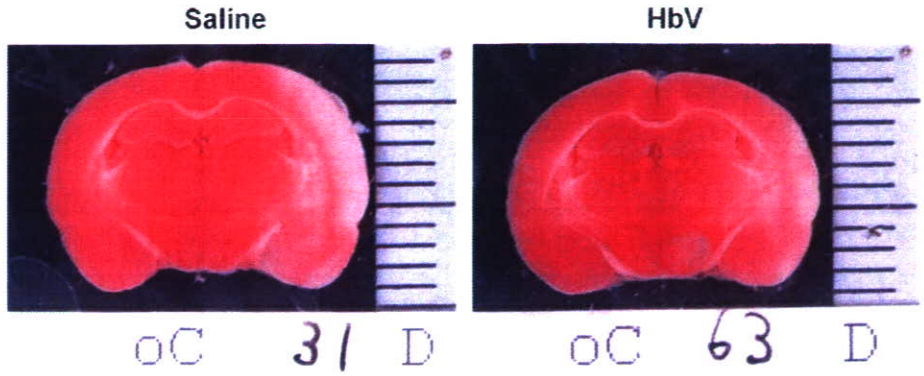

Fig. 1. Representative photographs of TTC-stained cerebral sections taken from MCA-occlusion/reperfusion-induced stroke rats. Left and right panels are photographs of saline- and HbV-treated rats, respectively. The individual rats shown here approximate mean values for the infarct volume in each group (infarct volumes of left and right panels were 194.1 and 119.0 mm^3, respectively; the mean values of saline- and HbV-treated groups were 174.8 and 114.1 mm^3, respectively).

determined separately in the cortex, sub-cortex, and the total of cortex plus sub-cortex.

For the experiment of AA-induced stroke model [23], 42 male Wistar rats (Japan SLC) weighing 223–248 g (9 weeks of age) were used. Under halothane anesthesia, rats underwent the cervical median incision. A polyethylene cannula was inserted into the left external carotid artery and advanced through it to the origin of the internal carotid artery. AA (2 mg/kg, Sigma–Aldrich, Japan) was injected trough the cannula at an injection speed of 0.4 mL/min. HbV (10 mL/kg) or saline was intravenously administered immediately after the injection of AA. Survival of rats was confirmed 3 h after the AA injection, and surviving rats were subjected to a motor dysfunction test in accordance with the criteria shown in Table 1 (maximal total score: 18). The score of a deceased rat was counted to be 19. Then, each rat was sacrificed by decapitation to obtain the whole brain. Cerebellum, medulla oblongata, ponticulus, and bulbus olfactorius were removed from the whole brain, and the remaining organ (cerebrum) was divided into right and left hemispheres along the corpus callosum. After both the hemispheres were measured for wet weight (W), they were dried in an oven heated at 80 °C for 3 days or longer and weighed again to obtain the dry weight (D). The cerebral water content was calculated as follows: cerebral water content (%) = $(W - D)/W \times 100$.

Data are indicated as the mean ± standard error. Statistical significance was determined with Excel 2003 or 2004 (Microsoft), SAS System (ver.8.2, SAS Institute, Tokyo, Japan), and EXSAS (ver.7.14, Scientist, Tokyo, Japan). Differences in the neurological symptom and the motor dysfunction score were tested by the Aspin–Welch t-test. Differences in infarct size and cerebral water content were tested by the F-test followed by either the Student's t-test or the Aspin–Welch t-test, when the variances of both groups were similar or dissimilar, respectively. Difference in survival rates was analyzed by the Chi-square test. These differences were regarded as statistically significant when p-values were less than 0.05.

In the MCA-occlusion/reperfusion-induced stroke model, neurological symptom scores (mean ± S.E.M.) of the saline- and HbV-treated groups were 2.3 ± 0.2 and 1.9 ± 0.1, respectively. The difference between the groups was not statistically significant although HbV showed a tendency to decrease the score. Fig. 1 shows representative photographs of TTC-stained cerebral sections derived from MCA-occlusion/reperfusion-induced stroke rats. The left panel (saline-treated rat) shows that about half of the area (infarct area) of the right hemisphere did not stain with TTC. On the other hand, an area that is not stained with TTC in a HbV-treated rat (right panel) reduced remarkably as compared with that of a saline-treated rat. The infarct volumes of rats corresponding to left and right panels were 194.1 and 119.0 mm^3, respectively. These rats shown in the images were selected to represent mean values for infarct volume in each group (saline-treated group, 174.8 mm^3; HbV-treated group, 114.1 mm^3) as described below. The results of quantitative analysis on the infarct volumes are summarized in Fig. 2. Infarction volumes of the cortex and the cortex plus sub-cortex in HbV-treated rats were significantly smaller than those in saline-treated rats. Infarction volumes of the sub-cortex was also decreased to 81.4% of saline-treated rats by HbV treatment although the difference was not statistically significant ($P = 0.0572$).

In response to the injection of AA into the internal carotid artery, 3 of 19 saline-treated rats (15.8%) died within 3 h (Table 2). On the other hand, all rats treated with HbV sur-

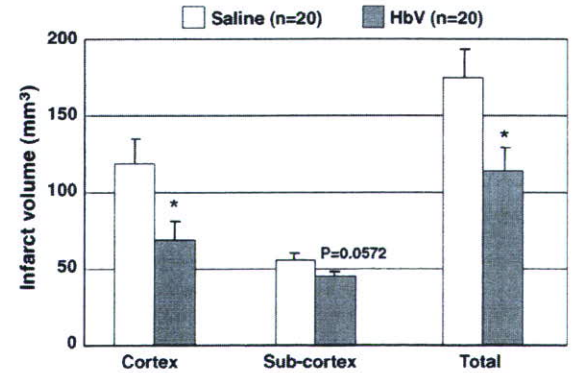

Fig. 2. Effect of HbV on MCA-occlusion/reperfusion-induced cerebral infarction in rats. Columns and bars indicate the mean and standard error of cerebral infarct volume, respectively. *$P < 0.05$, significantly different from the saline group (Student's t-test).

Table 2
Survival rate and motor dysfunction score

Test material	Survival rate	Rolling test	Posture test			Hemiplegia test	Total (mean ± S.E.)
			Head	Right forelimb	Right hind limb		
Saline	16/19 (84.2%)	4.6	2.4	2.7	1.7	1.3	12.8 ± 0.9
HbV	20/20 (100.0%)	3.5	1.8	2.6	0.9	0.7	9.4 ± 0.7[a]

[a] $P < 0.01$ vs. saline (Aspin–Welch t-test).

vived the injection of AA although the difference in survival rate between saline- and HbV-treated groups was not statistically significant. The motor dysfunction score of the HbV-treated group was significantly lower than that of the saline-treated group. As a result of AA injection, cerebral water content of left hemisphere (AA-injected side) was increased, indicating that cerebral edema was induced, and the administration of HbV significantly inhibited that increase (Fig. 3).

In the present study, HbV has been demonstrated to have protective effects on ischemic brain both in rat MCA-occlusion/reperfusion- and AA-induced models. MCA occlusion/reperfusion model has been well characterized and frequently used to evaluate drug efficacy on cerebral ischemia and infarction [24,26,2,11,1]. Treatment with HbV immediately after MCA occlusion significantly reduced infarct size (34.7% reduction), which is comparable to t-PA in the embolic model with blood clot (34% reduction) [6]. Edaravone, a radical-scavenging neuroprotectant that is in routine use for acute phase stroke in Japan, inhibited cerebral infarction by 20–25% in MCA occlusion models [16,14]. Although different experimental conditions were employed for each of these products, HbV was concluded to be effective in a model of stroke, as compared to well-known anti-stroke drugs.

AA-induced model has been used as an experimental thrombo-embolic stroke model, which is characterized by inducing platelet aggregation, endothelial damage and cerebral edema [23,9], and as a peripheral vascular disease model, e.g. gangrene in rats [25]. In addition to platelet activation and aggregation resulting in the formation of vascular occlusive blood clot, AA induces a rupture of the blood brain barrier and an increase in vascular permeability. In this model, HbV suppressed the increase in cerebral water content, a parameter representing the cerebral edema, of which inhibition was closely related to the improvement of motor dysfunction score seen in the HbV-treated group.

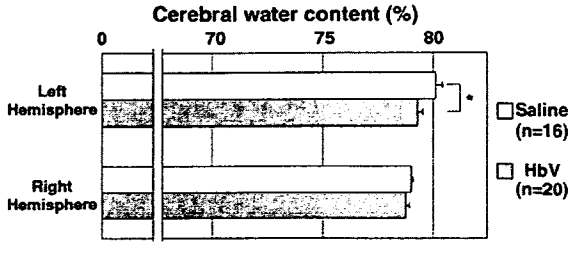

Fig. 3. Effect of HbV on AA-induced cerebral edema in rats. Columns and bars indicate the mean and standard error of cerebral water content, respectively. *$P < 0.05$ (Aspin–Welch t-test).

Thus, HbV has been found to be effective in the treatment of stroke as shown in the present experiments, but its mode of protective action has not been fully clarified. Protection of ischemic cerebral tissues by medical and drug interventions is mainly attributable to the oxygen supply to ischemic regions during ischemia, and the increased oxygen supply during ischemia seems to contribute to the inhibition of injury after reperfusion. It is possible that HbV can penetrate into ischemic areas through incompletely occluded arteries, arterioles and/or collateral vessels thanks to its small particle size, consequently deliver oxygen to the area, inhibit cerebral hypoxia, and decrease infarct size. The direct analysis of blood flow and oxygen metabolism/consumption in the ischemic brain after HbV administration remains to be investigated.

Although re-oxygenation is requisite for salvaging ischemic brain tissue, reactive oxygen and/or nitrogen species generated during reperfusion play important roles in further deterioration of ischemic brain. A nonselective nitric oxide (NO)-synthase inhibitor, L-nitro-arginine methyl ester (L-NAME) is reported to reduce cerebral infarct volume by abolishing the increase in brain NO production in a model of transient focal cerebral ischemic mice [7]. Diaspirin cross-linked hemoglobin (DCLHb) ameliorated ischemic cerebral injury in rats by binding NO, which has been implicated as neurotoxic [5]. HBOC-201, glutaraldehyde-polymerized bovine hemoglobin, reduced ischemia-reperfusion injury in canine myocardial ischemia in part by delivering more oxygen to ischemic tissue, and moreover, increased regional perfusion and blood pressure by scavenging NO [10]. These findings suggest that NO scavenging by cell-free hemoglobin is one of the possible mechanisms to mitigate ischemic injury. On the other hand, in the preclinical safety evaluation of DCLHb, myocardial lesions were observed following administration of DCLHb to certain species, and it was suggested that reduction in NO level was an important mechanistic factor for the myocardial lesions [3], indicating that the NO scavenging effect has both faces of advantage and disadvantage. Because the NO scavenging activity is an intrinsic property of hemoglobin, hemoglobin-based oxygen carriers are generally possible to capture NO, diminish NO-induced vasodilation, and cause myocardial lesions. However, it is considered that cell-free hemoglobin such as DCLHb extravasates through endothelial layer due to its small size (less than 50 nm in diameter) and trap NO, on the other hand, HbV, a first cellular-type oxygen carrier, does not extravasate owing to its moderate size (around 260 nm in diameter) [15]. In fact, HbV was generally safe in a single-dose and multiple (14 days-repeated)-dose toxicity studies as demonstrated by Sakai et al. [19,18,20], presuming that it would not induce such myocardial lesions, though more detailed

and GLP-based examinations on the safety of HbV are requisite before its clinical use.

In conclusion, HbV showed the effectiveness in two kinds of rat stroke models and was expected to provide a new therapeutic option for the treatment of stroke, especially acute ischemic stroke. To advance a clinical development of HbV as a new anti-stroke agent, further studies on a dose–response relationship, histopathological examination, and mechanism(s) of action including direct analysis of blood flow and oxygen delivery into the ischemic area would be conducted as next step.

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ORIGINAL ARTICLE

Syndrome of inappropriate secretion of antidiuretic hormone after chemotherapy with vinorelbine

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Abstract
Purpose To describe a case of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) after administration of vinorelbine (VNB) for recurrence of lung cancer.
Case A 76-year-old man underwent bronchial arterial infusion (BAI) of VNB for postoperative recurrence of lung cancer. Seven days later, hyponatremia and natriuresis developed. Based on his clinical and laboratory findings, we diagnosed him with SIADH. He improved within a couple of days with fluid restriction only.
Conclusions Administration of VNB may potentially cause SIADH. This is the second report of the SIADH caused by VNB. It is important to monitor the serum sodium level and clinical findings after chemotherapy with VNB.

Keywords Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) · Vinorelbine (VNB) · Non-small cell lung cancer · Chemotherapy

Introduction

We present a case of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in a 76-year-old man after administration of vinorelbine (VNB). He underwent bronchial arterial infusion (BAI) of VNB for postoperative recurrence of lung cancer. Seven days later, hyponatremia and natriuresis developed.

Based on his clinical and laboratory findings, we diagnosed him with SIADH. He improved within a couple of days with fluid restriction only. This is the second report of the SIADH caused by VNB therapy for lung carcinoma.

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Case report

A 76-year-old man underwent left upper lobectomy for lung adenocarcinoma (pathological staging T3N1M0, stage IIIA) and 14 months later, chest computed tomography (CT) showed bilateral pulmonary metastases. Five courses of chemotherapy with docetaxel (DOC) 100 mg and gemcitabine (GEM) 1,400 mg resulted in stable disease (SD) and he was begun on modified chemotherapy with vinorelbine (VNB 40 mg). After three courses of VNB, he was admitted to hospital, complaining of left chest pain and cough.

Chest X-ray and CT on admission showed the tumor occluding in the left main bronchus and complete atelectasis of the remaining left lower lobe (Fig. 1a, b).

Transbronchial interventions, such as tumor resection, injection of ethanol and YAG laser ablation, were performed repeatedly, after which the chest X-ray showed gradual restoration in his remaining left lobe. Irradiation (total 50 Gy) of the recurrent tumor was performed for 5 weeks and then chemotherapy with VNB 40 mg (BAI 20 mg + intravenous 20 mg) was repeated.

Seven days after administration of 40 mg VNB, he complained of anorexia, nausea and lethargy. His consciousness was clear. His physical and neurogenic examinations were almost intact. His plasma sodium concentration was 113.1 mEq/l, serum osmolality was 242 mOsm/kg lower

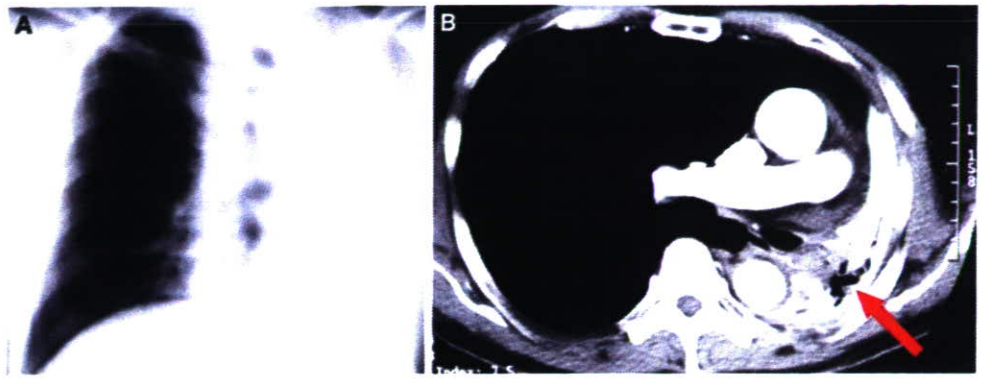

Fig. 1 **a** Chest X-ray on admission shows complete atelectasis of remaining left lobe. **b** Chest computed tomography scan shows the tumor occluding the left main bronchus (*arrow*)

than normal limit of 270 mOsm/kg and urine osmolality was 309 mOsm/kg higher than normal limit of 300 mOsm/kg. Urine sodium value was 20.2 mEq/l higher than normal limit of 20 mEq/l. His cortisol concentration value was normal. The plasma arginine vasopressin (AVP) concentration was 0.59 pg/ml, which was within normal limits, as were other parameters. Clinically, there were no symptoms related to adrenal or anterior pituitary dysfunction. The patient was euvolemic and renal function tests were within normal limits. VNB is considered to be strongly associated with SIADH, so he was diagnosed as having SIADH because his clinical features and laboratory data satisfied all standard criteria.

He was treated with water restriction, oral intake plus drip infusion into vein (DIV, total 750 ml/day). Within 2 days, his serum sodium concentration rose gradually and was restored to 130.3 mEq/l (Fig. 2). His mentation and appetite recovered in accordance with the increasing serum sodium concentration without central pontine myelinolysis. There was a possibility of developing SIADH again with a fifth cycle of VNB, so the chemotherapy agent was changed. He has been free of SIADH and has lived with lung cancer for 1 year.

Discussion

Schwartz et al. first reported SIADH in patients with lung cancer in 1957 [1]. Standard criteria include (1) hyponatremia, (2) plasma hypo-osmolality and urine hyperosmolality, (3) continuous secretion of sodium in urine, (4) normal renal function without hydration, (5) no adrenal gland dysfunction and (6) hyponatremia and hyposmotic pressure that recover with water restriction therapy without change in blood pressure [2]. The present patient fulfilled these criteria.

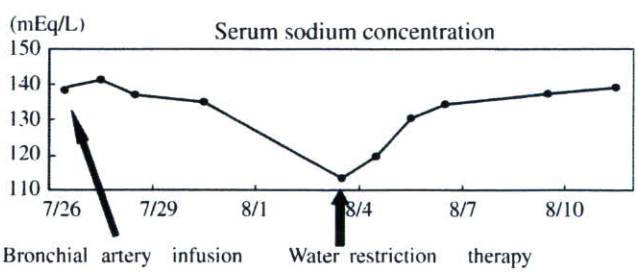

Fig. 2 Clinical course of serum sodium concentration 7 days after administration of vinorelbine. The patient complained of anorexia, nausea and lethargy and the sodium concentration was 113.1 mEq/l. He was treated with oral water restriction only and 2 days later, the serum sodium concentration was restored to 130.3 mEq/l

Various causes of SIADH have been reported, such as disorders of the cerebral nervous system, malignant tumors, diseases of the thoracic cavity, medicinal side-effects and idiopathic [3]. Approximately 75% of tumor-associated cases of SIADH are related to small-cell lung cancer (SCLC) [4]. The occurrence of SIADH with non-small-cell carcinoma (NSCLC) has been only rarely reported [5]. It has been reported that SIADH is caused by the tumor invading the vagus nerve or releasing ADH-like product. In the present study, imaging showed no evidence of invasion of the vagus nerve and we identified that the serum level of AVP was normal. We do not consider that its upregulation or secretion of ADH-like material occurred because the patient never experienced other electrolytic abnormalities and his serum sodium concentration was restored rapidly by water restriction therapy alone. There was no evidence of a relationship between progression of lung carcinoma and the onset of SIADH in this case.

Another possibility is that when the extension receptors of the left atrium detect hyperthoracic pressure and abnormal hemodynamics, they decrease the suppressor signal level and induce continuous release of ADH from the posterior lobe of the pituitary. But in the present case, bronchoscopic interventions were performed to target the local recurrence and restore his remaining left lobe. Syndrome of inappropriate secretion of antidiuretic hormone developed after 5 weeks of irradiation therapy following these interventional procedures. Even if there was a change in the respiratory circulation with release of the atelectasis, it is unlikely because of the time delay.

Enhancing release of AVP, potentiating the renal action of AVP and unknown mechanisms are reported as the main causes of SIADH by drugs [3]. Syndrome of inappropriate secretion of antidiuretic hormone associated with vinca

alkaloids, especially vincristine (VCR) and vinblastine (VBL), has been reported [6–8]. Garrett and Simpson first reported that SIADH occurred after a single treatment of VNB for breast cancer [9]. In addition, they reported that there was a slight structural difference between VNB and other vinca alkaloids, however, the precise mechanism is unclear and they may possess common neural or renal adverse effect profiles. In the present case, we firmly concluded that SIADH was induced by chemotherapy with VNB because concomitant medication was steroids only. In addition, SIADH occurred after four courses and not with earlier exposures of VNB. Although we think that repeated administration or retention of VNB may have been associated with SIADH, the precise mechanism of this SIADH was unclear.

In the report by Garrett and Simpson, SIADH from VNB did not respond to fluid restriction and patient had to be give 3% NS. But in our case, patient recovered with fluid restriction only. This difference with these two mechanisms was unclear. Furthermore, they also reported that prophylactic use of demeclocycline, which interacts with ADH at the renal collecting duct, might usefully prevent recurrence of SIADH associated with continuous treatment with VNB [9]. Stuart and Cuaso reported that SIADH was prevented by rigorous water restriction [10]. For our patients, we choose an alternative because of the high possibility of SIADH caused by VNB. If chemotherapy with VNB results in complete response or partial response, we would choose to readminister VNB with restriction of water, or use demeclocycline and monitor the sodium concentration.

We consider that VNB should be regarded as very likely to cause SIADH, but as this is only the second report of SIADH associated with use of VNB alone, it is a rare occurrence.

Conclusion

It is known that lung cancer can give rise to SIADH as a paraneoplastic syndrome and there are some anticancer agents that can potentially cause SIADH. It is important to monitor the serum sodium level and clinical findings after chemotherapy for lung cancer.

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原著
論文

救急医療の現場での輸血医療の実態と人工酸素運搬体への期待*

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■要旨：わが国の186救急医療施設を対象としてアンケートを送付し，緊急輸血の実態，および人工酸素運搬体の開発に関する見解を調査した。そのうち74施設から回答が得られ，緊急輸血症例の51.5%の輸血量が1000ml以内であることが明らかになった。また人工酸素運搬体の酸素運搬機能が24時間は必要であることも明らかになり，現在開発途上にある人工赤血球で要望の77.1%に対応できることも認められた。さらに人工赤血球は検査なくただちに使用できる，血液型の取り違え，感染症などの事故がないことへの期待が大きいことが明らかになった。

■key words：人工赤血球，人工酸素運搬体，輸血代替，救急医療，安全性

はじめに

すでに前世紀初頭から人工酸素運搬体の開発は進められてきていた。しかしようやくこの数年前から臨床使用に耐え得るような人工酸素運搬体の出現をみるに至った。そして海外で2～3の臨床治験が行われた[1)~3)]。一方，わが国においてはリポソーム小胞体内にヒトヘモグロビン（Hb）を包埋した人工酸素運搬体を中心に開発が進められてきている[4)]。そしてこの製品に関しての前臨床試験はほぼ完成の域に達している。しかしこの製品の臨床使用には今後段階的に治験を施行しなければならない。したがって実際の臨床に至るまでにはなお時間を要すると思われる。またその間に製品の改良に努め，さらなる優れた製剤を作製することが期待されている。

人工酸素運搬体の臨床使用は多岐にわたると思われるが，その一つに救急医療での輸血への応用がある。すなわち搬送されてきた大量出血を伴う患者の治療，あるいは医療機関外での出血患者の治療などが該当する。この点をふまえ，今回救急医療に携わる医師を対象に人工酸素運搬体に対する意識調査をアンケート方式にて行った。すなわち，まず現在の救急医療の現場での血液製剤，とりわけ赤血球製剤の使用状況を調査し，将来もし人工酸素運搬体（人工赤血球）が臨床使用可能となったときにはどの程度の利用度があるか，どのような製品が必要とされるかなどの諸点について調査を行った。

Ⅰ　方　法

図1に示す質問事項を記載したアンケート用紙を日本救急医学会の各評議員，195名の方を対象に2005年2月に郵送した。しかし種々の理由から返送されてきたものが9通あり，186通が送付されたものと思われた。このうち，指定期限である3月末日までに回答のあったものは74通（39.8%）で，この回答についてのみ解析を行った。設問には複数回答を要求するものもあったが，あらかじめ単一回答を期待したにもかかわらず複数の回答があったものについては同意義的な項目に編入，あるいはそれぞれ該当する項目に分割する処置などを行い集計した。また設問に対して回答の記入がなかったものは無回答，0とした。そのためそれぞれの設問に対する回答総数が上記74に達しない場合が生じた。複数回答となる設問では当然回答総数が74を超えた。

Ⅱ　結　果

設問1.の輸血を必要とする症例の発生頻度は，毎日3例以上とする回答が12施設，週に3～6例

* Survey of transfusion medicine and perception of artificial oxygen carrier in acute medicine

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1. 現在先生の診療なさっている部署で輸血が必要となる症例の頻度はどれぐらいでしょうか。
   A）毎日3例以上　B）週に3から6例　C）月に3から6例　D）月3例以下
   E）ほとんどない
2. 輸血を行う症例の輸血量は症例によりさまざまと思われますが，頻度が高いのは以下のどのレンジでしょうか。
   A）400ml～1000ml　B）1000ml～2000ml　C）2000ml～3000ml　D）3000ml以上
3. 輸血を使用する際，使用を決断してから輸血が開始されるまでどの程度の時間を要していますか。
   A）5分以内　B）15分以内　D）30分以内　E）30分以上
4. 夜間に血液を使用するときに血液が使用できるまでの時間は日勤帯と比べていかがでしょうか？
   A）日勤帯とほとんど変わらない　B）日勤帯と比較すると夜間帯では時間がかかる
   C）夜間帯のほうがスムースに輸血が可能である
5. 救急の現場で，輸血を行う場合，Informed consentが必要となります。先生の施設ではICをどのようにとっていらっしゃいますか。
   A）緊急の場合は説明なしで輸血を行っている
   B）ICなしで輸血は行わない。
      i）ICは本人から取る
      ii）ICは患者家族から取る
      iii）患者あるいは家族，関係者まで含め，いずれかよりICを取る
6. 大量輸血が必要な症例で注意しておられる事項がございましたら下記から選択してください（いくつでも可）。
   A）膠質輸液も使用する
   B）凝固能をチェックしている
   C）電解質（Caも含め）をチェックしている
   D）循環系諸標をモニターする（Thermodilution catheterなど）
   E）溶血，肝機能，鉄代謝についてモニターしている（ハプトグロビン，トランスフェリンなども含め）
   F）その他（　　）
7. 輸血に伴う感染症について輸血後のモニターはどのようにされておられますか。
   A）HbV，HCV，HIVについては輸血後6から8週後に検査を行っている
   B）患者からの申し出があったときに検査を行っている
   C）他の診療科に依頼している
8. 輸血に伴う不規則抗体の発現について輸血後モニターされておられますか。
   A）している　B）していない

   ここで人工血液についてお伺いいたします。
9. 人工血液について知っていますか。
   A）医学雑誌の記事あるいは論文を読んだことがある
   B）新聞報道などで開発が進んでいることは知っている
   C）知らない

図1a　アンケート用紙

10. 人工赤血球が臨床使用できるようになれば，使用したいと思われますか。
A）使用したい　B）使用しない　C）有効性が輸血よりも優れていれば使用する

11. 人工赤血球にもっとも必要な資質は酸素運搬能と思いますがそれ以外に必要なものは何だとお考えでしょうか。
A）血液と同等の粘度を保有すること　B）循環血液量を保持する能力
C）その他（　　）

12. 人工赤血球の使用上限が規定されるとすれば，上限量がどの程度であればよいとお考えですか。次の中からお選びください。
A）100ml まで　B）250ml まで　C）500ml まで　D）1000ml 以上

13. 人工赤血球は血液型がなく，常温で保存可能となるよう設計されています。このため，輸血が必要な症例には投与を決断すれば直ちに投与が可能です。
先生が治療される輸血を必要とする患者さんの中で緊急輸血の判断を迫られる症例の頻度はどれぐらいでしょうか。
A）毎日１症例はいる　B）週に１～数症例　C）月に１～数症例
D） すべての患者で診療の初期段階は輸液で対応するので，血液が直ちに必要となる症例はない

14. 輸血治療が緊急に必要な患者で IC が取れない場合，投与可能な人工血液があれば IC が取れるまでのつなぎとして人工赤血球を使用されますか。
A）人工赤血球を使用する　B）IC が取れるまで晶質液中心の輸液で対応する
C）その他

15. 外傷による出血の症例では現場からの治療が救命に大きな役割を果たすことが明らかとなっています。救急現場での治療が可能となるとしたら，次のいずれのレベルまでが行われるべきと考えますか。
A）呼吸管理のみ（気管内挿管を含む）
B）A)+ 生食による輸液管理
C）A)+ B)+ 膠質輸液も含めた循環管理
D）A)+ B)+ C)+ 人工血液の投与も含めた循環管理

16. 人工赤血球は有効半減期が短いことが予想されています。臨床使用する際，有効半減期としてどの程度の時間が必要とお考えでしょうか。
A）２時間　B）12時間　C）24時間　D）48時間以上

17. 厚生労働省科学研究班の研究では人工赤血球は投与後脾臓や肝臓のマクロファージに補足され，代謝は細網内皮系で行われ，14日後には血液生化学，組織学的な変化を残さないことが報告されています。またその間一時的な貪食能の低下とその後の活性化が明らかとなっています。ヒトでも同様の代謝経路が予想されています。外傷患者に対して投与した場合も細網内皮系の一時的な低下とその後の活性化が予想されますが，このことは治療の上で問題となるとお考えでしょうか？
A）問題であると思われる　理由（　　）
B）問題とはならないと思う

18. 最後に人工赤血球に期待する要素について先生のお考えがございましたらお教えください。
（　　）

図１b　アンケート用紙