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Coronary Atherosclerosis Reduction Project (CARP)Investigators*.

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Cardiovascular Intervention

Beneficial Effects of Valsartan on Target Lesion Revascularization After Percutaneous Coronary Interventions With Bare-Metal Stents

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Background: Angiotensin II receptor blockers (ARB) have been shown to reduce cardiovascular events in patients at risk. The effect of valsartan on outcomes after percutaneous coronary interventions (PCI) with bare-metal stents (BMS) was investigated.

Methods and Results: The prospective, randomized study included 191 patients at 5 participating institutions, who were randomly assigned to either a 40–80 mg valsartan add-on or non-ARB treatment. The primary endpoint was a composite of all-cause death, non-fatal myocardial infarction, and target lesion revascularization (TLR) at 18 months. Enrollment was stopped when the use of drug-eluting stents has been expanded in Japan. No significant differences existed between the groups in terms of primary endpoint (18.9% vs. 24.8%; hazard ratio [HR], 0.84; 95% confidence interval [CI], 0.61–1.14; P=0.26). In the valsartan group, as compared with the non-ARB group, the secondary endpoint of TLR was significantly reduced at a median follow-up 4.4 years; the rate of TLR was from 27.8% to 14.5% (HR, 0.69; 95%CI, 0.49–0.96; P=0.024).

Conclusions: Valsartan treatment was not superior to non-ARB treatment in reducing the primary endpoint after PCI at 18 months. The pre-specified secondary endpoint of TLR was lower in the valsartan group, but this needs to be proved statistically with an adequate study sampling. (*Circ J* 2011; **75:** 1641–1648)

Key Words: Percutaneous coronary intervention; Restenosis; Revascularization; Stents

The growing use of coronary stents has improved the results of percutaneous coronary intervention (PCI) over the last decade.[1] However, in-stent restenosis continues to limit the long-term success of this procedure.[2] Drug-eluting stents (DES) coated with strong antiproliferative agents such as sirolimus or paclitaxel have dramatically reduced the need for repeat revascularization procedures due to reduction in restenosis rates after PCI.[3–6]

Notwithstanding this tremendous progression in antirestenotic therapies, with the use of DES, target lesion revascularization (TLR) remains necessary in approximately 12% of patients at 2 years after PCI.[7] Moreover, there is increasing concern about the safety of DES, in light of reports that they are associated with a slightly increased rate of late stent thrombosis and possibly increased rates of myocardial infarction (MI) and death after PCI.[8] Although the efficacy of DES lies in reducing restenosis-related TLR, lesions at low risk of restenosis might still be considered suitable for bare-metal stents (BMS) in the contemporary DES era.[9]

Previous studies have shown the benefits of angiotensin converting enzyme (ACE) inhibitors in patients with coronary artery disease.[10,11] In contrast, the effects of angiotensin II receptor blockers (ARBs) with coronary artery disease remain to be determined. While 2 open-label studies suggested beneficial effects of ARBs on neointimal proliferation at 6 months,[12,13] a smaller randomized open-label study did not show a reduction in neointimal proliferation for ARB-related patients after coronary stent implantation at 6 months.[14]

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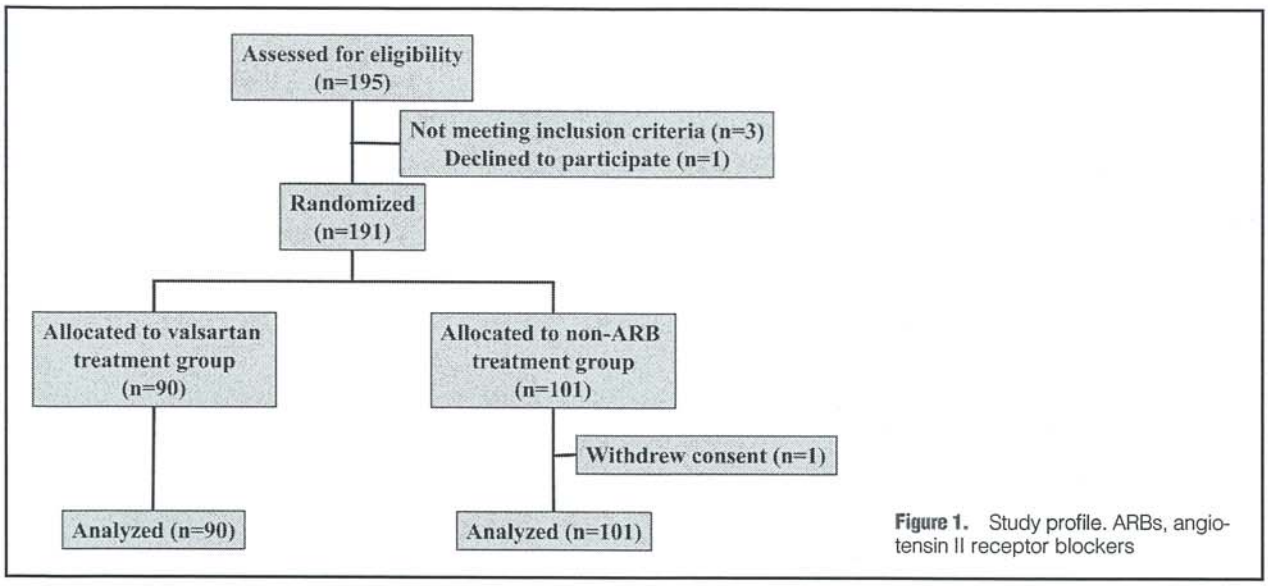

Figure 1. Study profile. ARBs, angiotensin II receptor blockers

The purpose of the present study was to investigate the effects of valsartan on long-term outcomes after PCI with BMS in coronary artery disease patients.

Methods

Patient Population

This study was a prospective randomized, open, and non-placebo-controlled trial performed at 5 participating institutions. It was approved by the ethics committee at each participating institution, and all patients gave written informed consent.

Patients were eligible for the study if they were 30–80 years old and had received a coronary stent implantation. Clinical exclusion criteria included a left ventricular ejection fraction of less than 30%, a serum creatinine concentration >2.0 mg/dl, pregnancy, hemorrhagic diatheses, contraindication or allergy to aspirin, ticlopidine, or stainless steel, a history of anaphylaxis in response to iodinated contrast medium, and treatment with an ARB 4 weeks or less before randomization. Angiographic eligibility criteria were the presence of at least 1 target lesion in a native coronary artery with a reference vessel diameter (RVD) between 2.5 and 4.0 mm suitable for stent implantation. There were no limitations on the number of treated lesions and vessels, or lesion length. Angiographic exclusion criteria included: a left main lesion, ostial lesion, severe calcification of the target lesion, or use of atherectomy before stenting.

Patients were randomly assigned to receive either valsartan (valsartan add-on group) or conventional treatment by non-ARB antihypertensives (non-ARB group). Patients in the valsartan add-on group were prescribed 40–80 mg/day starting the next morning following PCI and continuing for at least 3 years. Figure 1 shows that 1 patient (0.52%) withdrew consent after eligibility.

Randomization was undertaken using the minimization method controlling for the following 2 factors: acute MI and participating institution.

Evaluation of Renal Function

The glomerular filtration rate was calculated for each patient according to the simplified Modification of Diet in Renal Disease equation for Japanese,[15] using the value of serum creatinine closest to the time of, but before, the index PCI. Patients were then stratified in 2 groups using the cut-off value 60 $ml \cdot min^{-1} \cdot 1.73 m^{-2}$ below which chronic kidney disease (moderate to severe renal impairment) is defined according to the latest National Kidney Foundation practice guidelines.[16]

Patient Follow up

Clinical follow up was scheduled for all patients at 6 months, 12 months, 18 months, 24 months, and then yearly for a total of 4 years after the procedure by office visit or direct telephone call to the patients. A follow-up angiography with quantitative coronary angiography (QCA) was systematically performed at 180±30 days. The decision to perform further TLR after the 6-month angiographic follow up was left to the investigators' discretion.

PCI

Lesions were treated with the use of standard interventional techniques, and stenting without predilatation was allowed. After the stent had been implanted, further dilatation was performed as necessary to ensure that there was less than 20% residual stenosis, with a Thrombolysis In Myocardial Infarction grade III flow rate. Postprocedural dual antiplatelet therapy consisted of 81–250 mg/day aspirin, indefinitely, and 200 mg/day ticlopidine, for at least 4 weeks.

Coronary Lesion Analysis

Lesions were classified according to the modified American Heart Association/American College of Cardiology (AHA/ACC) classification.[17] Lesions were measured on angiograms by experienced cardiologists. Lesion length, RVD, minimal lumen diameter (MLD), and percent diameter stenosis were measured in the Cardiovascular Measurement System (CMS, MEDIS, Leiden, The Netherlands).[18]

Clinical Outcomes

The primary endpoint was a composite of death from any cause, non-fatal acute MI, or TLR at 18 months. Secondary endpoints included the individual rates of death from any cause, non-fatal acute MI, TLR, stroke (hospitalization and

diagnosed by CT and/or MRI), heart failure (hospitalization, clinical symptoms, clinical signs, and the need for treatment with intravenous diuretics, vasodilators, or inotropic drugs), and the need for non-TLR at a long-term clinical follow up (median 4.4 years; interquartile range, 3.9–5.0). Elective angiographic control at 6 months was specified as a secondary endpoint.

Binary restenosis was considered as the occurrence of stenosis of >50% diameter in the stented lesions. Late lumen loss was defined as MLD at follow up minus post-procedural MLD measured by QCA. TLR was defined as a repeat intervention (PCI or coronary artery bypass graft) to treat a luminal stenosis within the stent or in the 5-mm distal or proximal segments adjacent to the stent. Non-TLR was defined as clinically driven revascularization of the lesions other than the target lesion. The diagnosis of MI during follow up was established whenever a Q-wave in at least 2 contiguous leads appeared on the electrocardiogram, or there was an elevation in serum creatine kinase-MB fraction levels >3 times the upper limit of the normal range.

Statistical Analysis

On the basis of the study in Japan, we had hypothesized that Japanese patients with coronary artery disease might have approximately 30% of composite cardiovascular events (death, non-fatal MI and TLR) in 18 months follow up after PCI with BMS. We estimated the number of enrolled patients as 240 (120 in each group) to validate the hypothesis under the assumption that the valsartan add-on group achieves a 40% risk reduction compared with the non-ARB group and gives 80% statistical power for detecting a clinical significance with a 2-tailed 5% statistical significant level. All analyses were based on the intention-to-treat principle. For continuous variables, data are presented as mean±SD and were compared by the Student's t-test. For categorical numbers, data are shown as number and percentage, and were compared by the chi-square test. An event rate was estimated by the Kaplan-Meier approach. A Cox proportional hazard model was used to assess the risk of adverse events at long term clinical follow up after the index PCI. Multivariate analysis were performed to identify independent predictors of TLR, using clinical and angiographic variables of age, gender, diabetes status, concomitant antihypertensive treatment (use of valsartan, use of ACE inhibitors, and use of calcium-channel blockers), small vessel size (≤2.75 mm), and long lesion (>20 mm). A probability of <0.05 was considered significant. All statistical analyses were performed using the JMP for Windows, version 5.1 (SAS Institute, Cary, NC, USA).

Table 1. Baseline Clinical Characteristics

	Valsartan (n=90)	Non-ARB (n=101)	P value
Age (years)	64±10	65±9	0.31
Male gender	71 (79)	79 (78)	0.91
Hypertension	63 (70)	75 (74)	0.51
Dyslipidemia	63 (70)	72 (71)	0.85
Diabetes mellitus	36 (40)	46 (46)	0.44
Current smoker	45 (50)	51 (50)	0.95
Body mass index	24±2.8	24±2.6	0.31
SBP (mmHg)	134±17	133±19	0.96
DBP (mmHg)	76±12	74±13	0.43
Triple vessel disease	15 (17)	14 (14)	0.60
Prior MI	9 (10)	9 (9)	0.80
Prior PCI	15 (17)	15 (15)	0.73
Prior CABG	4 (4)	2 (2)	0.33
LVEF (%)	61±11	62±11	0.51
Acute MI	36 (40)	36 (36)	0.54
Q wave MI	17 (19)	15 (15)	0.46
CKD	23 (26)	34 (34)	0.22

Values are number of patients (%) or mean±SD.
ARB, angiotensin II receptor blockers; SBP, systolic blood pressure; DBP, diastolic blood pressure; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; CKD, chronic kidney disease.

Results

Baseline Characteristics

From August 2002 through December 2004, a total of 191 patients were randomized in this study. In December 2004, the enrollment was stopped because the use of DES had been expanded in Japan. Table 1 shows the baseline clinical char-

Table 2. Medical Treatment

	Valsartan (n=90)	Non-ARB (n=101)	P value
Medical treatment before randomization			
Statins (%)	27 (30)	30 (30)	0.96
ACE inhibitors (%)	11 (12)	12 (12)	0.94
β-adrenergic blockers (%)	9 (10)	7 (7)	0.45
Calcium-channel blockers (%)	39 (43)	46 (46)	0.76
Nitrates (%)	27 (30)	30 (30)	0.96
Nicorandil (%)	12 (13)	20 (20)	0.23
Medical treatment at discharge			
Statins (%)	54 (60)	58 (57)	0.72
ACE inhibitors (%)	12 (13)	39 (39)	<0.001
β-adrenergic blockers (%)	14 (16)	16 (16)	0.96
Calcium-channel blockers (%)	30 (33)	53 (52)	0.008
Nitrates (%)	30 (33)	33 (33)	0.26
Nicorandil (%)	26 (29)	31 (31)	0.79

Values are number of patients (%) or mean±SD.
ARB, angiotensin II receptor blockers; ACE, angiotensin-converting enzyme.

Table 3. Angiographic and Procedural Characteristics

Lesions	Valsartan (n=111)	Non-ARB (n=127)	P value
Type B2 or C lesion*	68 (61)	67 (53)	0.19
Treated vessel			
Right coronary artery	42 (38)	49 (39)	0.83
Left anterior descending artery	40 (36)	49 (39)	
Left circumflex artery	29 (26)	29 (22)	
Restenotic lesion	4 (4)	2 (2)	0.32
Chronic total occlusion	5 (5)	3 (2)	0.36
Calcified lesion	14 (13)	18 (14)	0.72
Eccentric lesion	57 (51)	70 (55)	0.56
Diffuse lesion	17 (15)	19 (15)	0.94
Stents/patient	1.1±0.2	1.1±0.3	0.66
Stent diameter (mm)	3.2±0.4	3.2±0.5	0.95
Small-size stent use (≤2.75 mm)	26 (23)	29 (23)	0.91
Thin-strut stent use (≤0.10 mm)	89 (80)	93 (73)	0.21
Total stent length/lesion (mm)	19±8	19±8	0.77
Maximal balloon pressure (atm)	14±3	14±4	0.63
Bifurcation with kissing balloon technique	5 (5)	5 (4)	0.83
Direct stenting	19 (17)	14 (11)	0.18

Values are number of patients (%) or mean±SD. *American College of Cardiology/American Heart Association lesion classification.
ARB, angiotensin II receptor blockers.

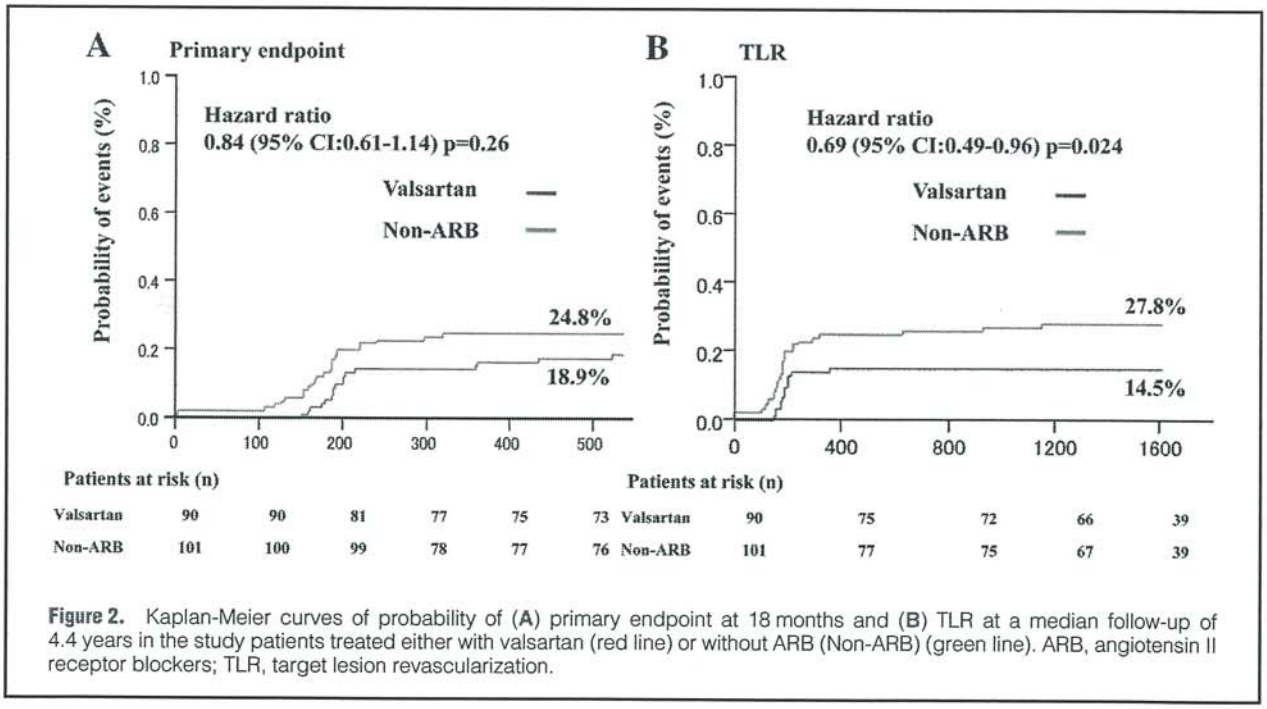

Figure 2. Kaplan-Meier curves of probability of (**A**) primary endpoint at 18 months and (**B**) TLR at a median follow-up of 4.4 years in the study patients treated either with valsartan (red line) or without ARB (Non-ARB) (green line). ARB, angiotensin II receptor blockers; TLR, target lesion revascularization.

acteristics for all the patients who were assigned to treatment. The 2 groups were similar with respect to all variables examined; all patients were Japanese, with a mean age of 64 years, a mean body mass index of 24 kg/m^2, and a mean systolic and diastolic blood pressure of 134/75 mmHg. About two-thirds were male. Clinical presentation at index PCI included 72 cases of acute MI (36 cases in the valsartan add-on group and 36 cases in the non-ARB group, P=0.54). As shown in **Table 2**, medical treatment before randomization was similar for the 2 groups; 30% of patients were receiving statins, 12% ACE inhibitors, 7–10% β-adrenergic blockers, and 43–46% calcium-channel blockers. However, at discharge, approximately 60% of the patients were treated with statins in both groups (60% vs. 57%, P=0.72) and there was more use of ACE inhibitors (13% vs. 39%, P<0.001) and calcium-channel blockers (33% vs. 52%, P=0.008) in the non-ARB group than in the valsartan add-on group. At follow up, the mean systolic and diastolic blood pressure levels were 128±16/74±9.8 mmHg in the valsartan add-on group and 130±13/73±9.4 mmHg in the non-ARB group. Blood pressure

Table 4. **Angiographic Results**

	Valsartan (n=90)	Non-ARB (n=101)	P value
Lesion, n	111	127	
Lesion length (mm)	12.6±6.7	12.4±7.1	0.80
Reference vessel diameter (mm)	2.77±0.67	2.81±0.67	0.60
Pre-procedural MLD (mm)	0.54±0.46	0.59±0.46	0.36
Post-procedural MLD (mm)	2.91±0.56	2.99±0.67	0.26
Complete revascularization (%)	65 (72)	69 (68)	0.56
Angiographic follow-up (per lesion)	98 (88)	117 (92)	0.32
Follow-up MLD (mm)	1.98±0.85	1.80±0.90	0.13
Late lumen loss (mm)	0.95±0.76	1.20±0.92	0.037
Binary restenosis	22 (22)	30 (26)	0.59

Values are number of patients (%) or mean±SD.
ARB, angiotensin II receptor blockers; MLD, minimal lumen diameter.

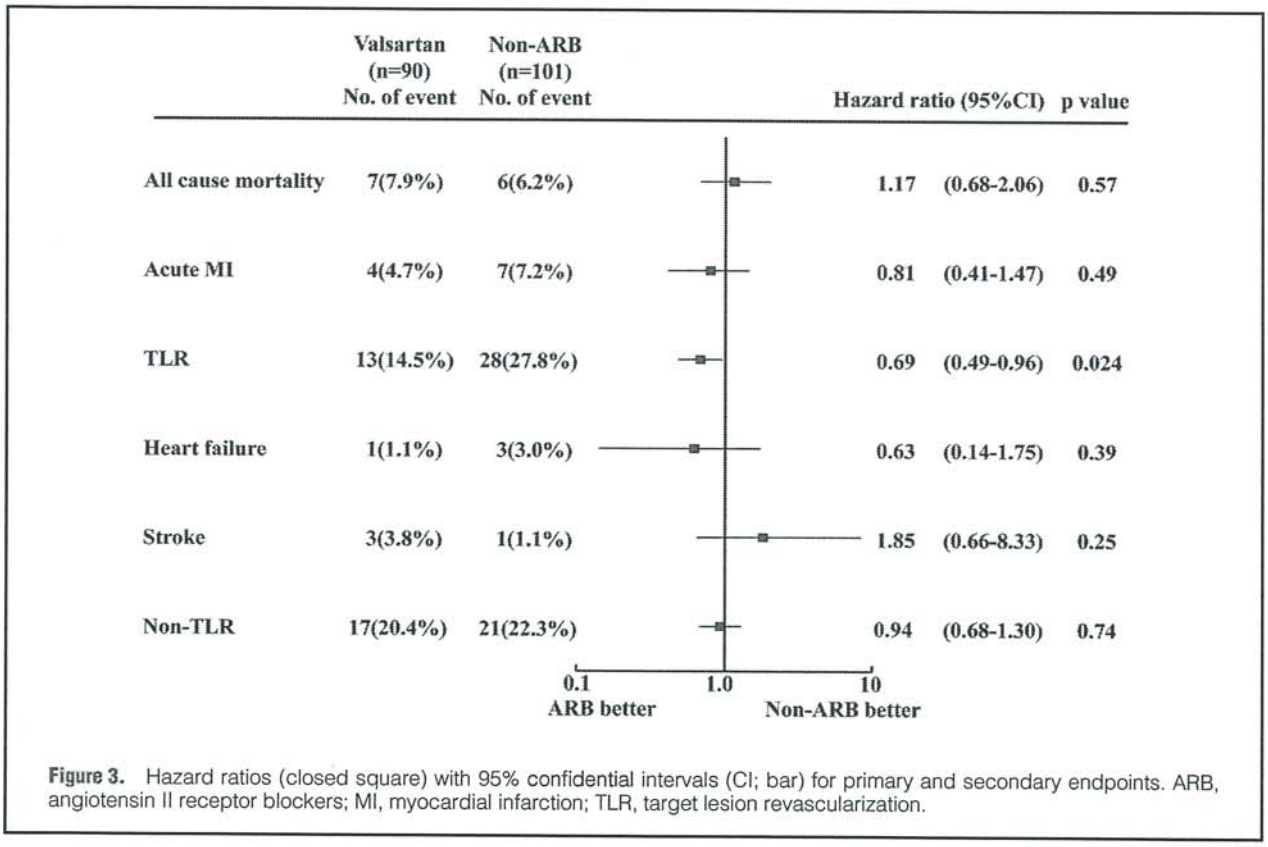

Figure 3. Hazard ratios (closed square) with 95% confidential intervals (CI; bar) for primary and secondary endpoints. ARB, angiotensin II receptor blockers; MI, myocardial infarction; TLR, target lesion revascularization.

levels were not significantly different between the groups during follow up (systolic blood pressure, P=0.23; diastolic blood pressure, P=0.38)

The angiographic and procedural characteristics are shown in Table 3. The lesions in the 2 groups were treated similarly with the use of conventional techniques. The choice of BMS was at the discretion of the operator; however, the distribution of commercially available stents in the 2 groups was similar. The valsartan add-on group consisted of 111 lesions and the non-ARB group consisted of 127 lesions.

Primary Endpoint

At 18 months, the incidence of the primary endpoint was 18.9% in the valsartan add-on group and 24.8% in the non-ARB group. The reduction of primary outcome did not achieve statistical significance (hazard ratio [HR], 0.84; 95% confidence interval [CI], 0.61–1.14; P=0.26; Figure 2A).

Secondary Endpoints

Angiographic data at 6 months were available for 79 of the 90 patients (88%) in the valsartan add-on group and 91 of the 101 patients (90%) in the non-ARB group. The mean RVD of the target vessel and the mean length of the lesion at baseline were similar in the 2 groups. The mean MLDs of the stented segment before and after the procedure were similar between the 2 groups. At 6 months, the mean in-stent late luminal loss was significantly smaller (0.95±0.76mm vs. 1.20±0.92mm; P=0.037) in the valsartan add-on group than in the non-ARB group (Table 4). However, the binary restenosis rate was not significantly different between the 2 groups

Table 5. Multivariate Predictors of TLR at a Long-Term Follow-up

	HR	95%CI	P value
Age	0.98	0.46–0.94	0.32
Female gender	0.80	0.95–1.02	0.29
Diabetes mellitus	1.18	0.86–1.62	0.32
Use of valsartan	0.67	0.46–0.94	0.020
Use of ACE inhibitors	0.81	0.55–1.16	0.25
Use of calcium-channel blockers	0.96	0.69–1.33	0.80
Small vessel size (≤2.75 mm)	1.47	1.02–2.06	0.038
Long lesion (>20 mm)	1.76	1.29–2.45	<0.001

TLR, target lesion revascularization; HR, hazard ratio; CI, confidence interval; ACE, angiotensin-converting enzyme.

(22% vs. 26%; P=0.59).

There were no significant differences between the valsartan and the non-ARB groups in terms of all-cause death (7.9 vs. 6.2%), acute MI (4.7 vs. 7.2%), heart failure (1.1 vs. 3.0%), stroke (3.8 vs. 1.1%), non-TLR (20.4 vs. 22.3%) (**Figure 3**). No patients died from a cardiac cause in either group. However, at a median follow up at 4.4 years, TLR was performed in 14.5% in the valsartan add-on group and 27.8% of the patients in the non-ARB group (HR, 0.69; 95%CI, 0.49–0.96; P=0.024) (**Figure 2B**). Using a multivariate analysis after adjusting for confounders, valsartan add-on treatment (HR, 0.67; 95%CI, 0.46–0.94; P=0.020), small vessel size (HR, 1.47; 95%CI, 1.02–2.06; P=0.038), and long lesion (HR, 1.76; 95%CI, 1.29–2.45; P<0.001) were found to be the independent predictors of TLR after PCI with BMS (**Table 5**).

Among the patients who were randomly assigned to the valsartan add-on group, 86% were still taking valsartan at the end of the study. There were side effects that resulted in discontinuation (hypotension, 2%; renal dysfunction, 1%) in the valsartan add-on group. In addition, 2 patients (2%) were switched to other ARBs. In 7 patients (7%) from the non-ARB group, ARBs were prescribed at the end of the study.

Discussion

Valsartan treatment was not superior to non-ARB treatment in reducing the primary endpoint at 18 months after PCI. In a recent major trial in Japanese patients with hypertension and/or coronary artery disease, candesartan was similar to standard non-ARB treatment in reducing rates of cardiovascular events among patients with angiographically documented coronary artery disease.[19] However, in the JIKEI-Heart Study, which included hypertensive patients with coronary artery disease and/or heart failure, valsartan add-on treatment significantly inhibited the incidence of cardiovascular mortality and morbidity.[20] At the time of this study, which was designed with a target of 120 patients in each group, the incidence of composite cardiovascular events was expected to be 30% in the non-ARB group. Because the study patients did not reach the target, and the incidence of the primary endpoint was lower than expected, the statistical power was considered insufficient for verification of the efficacy of valsartan. In addition, no patients died of a cardiac cause in either group at a long-term follow up (>4 years); this implies a selection for a very low-risk clinical population. Moreover, because the patients in the non-ARB group had received more ACE inhibitors and calcium-channel blockers than those in the valsartan group, these drugs seemed to reduce the cardiovascular events after PCI.

This trend might be attributable to the previous studies regarding these agents.[10,21] Because various kinds and doses of agents including ACE inhibitors and calcium-channel blockers were used, the assessment of such agents might be limited in the present study.

ARB and In-Stent Restenosis

Although the rate of binary restenosis revealed no statistically significant differences between the 2 groups, late lumen loss was significantly reduced in the valsartan add-on group compared with the non-ARB group at the 6-month follow up period.

In-stent restenosis occurs mainly from excessive neointimal formation.[22] Neointimal formation after stent placement results from deep focal injury caused by the penetration of stent struts and the chronic presence of foreign body material. The amount of neointimal area is proportional to the severity of the injury inflicted on the arterial wall by the stent struts.[23] It has been reported that an ARB inhibits neointimal formation in the rat carotid injury model.[24] Patients receiving a low-dose oral administration of valsartan (80 mg/day), compared with placebo and ACE inhibitors in previous trials, showed a preventive effect on in-stent restenosis after BMS implantation.[25,26] Conflicting results have been demonstrated with the use of other ARBs such as candesartan cilexetil[27] and losartan.[28] The effect of valsartan is likely to be, at least in part, a decrease in markers of inflammation.[28]

Valsartan Dosage

Our study demonstrated that low-dose valsartan treatment (average of 60.7 mg/day) had a favorable effect on reducing TLR after coronary stenting. It has been previously shown that administration of a high-dose oral valsartan (160–320 mg/day) after implantation of BMS in type B2/C coronary artery lesions reduces angiographic in-stent restenosis, TLR, late lumen loss, and major cardiovascular event rates more effectively than a low-dose valsartan (80 mg/day).[29] However, several studies in Japanese patients have shown that a treatment with a daily dose of 80 mg valsartan has similar antihypertensive effects to that of 20 mg nifedipine[30] or 5 mg amlodipine.[31] Doses of all antihypertensive drugs, including valsartan, were based on the guidelines of the Japanese Hypertension Society.[32] In addition, our study was designed for coronary artery disease patients, including normotensive patients. The mean blood pressure at baseline was 134/75 mmHg, and therefore we considered that the dose of valsartan in the present study was adequate.

TLR

The prespecified secondary endpoint of TLR was lower in the valsartan add-on treatment group compared with the conventional non-ARB treatment at a median follow-up period of 4.4 years. Kaplan-Meier curves of probability of TLR have suggested that most of the difference in TLR was driven by surveillance angiography rather than clinical indications. Because ischemia testing was not required before follow-up angiography in this open study, revascularization decisions at angiographic follow-up might have been affected by treatment assignment. Moreover, Cutlip et al[33] reported that in multicenter trials, a follow-up angiography led to 44% more repeated interventions than studies without mandated angiography. This suggests that non-ischemia-producing lesions were treated at the time of follow-up angiography.

We identified valsartan add-on treatment, small vessel, and long lesion as independent predictors of TLR. The patients in the non-ARB group were treated with ACE inhibitors more frequently than those in the valsartan add-on group. In the large studies, ACE inhibitor therapy was shown to significantly increase the rate of in-stent restenosis after PCI with BMS.[34,35] From our data, however, it appears unlikely that ACE inhibitor therapy could offer the same results as those obtained in these studies.

After coronary stent implantation, recognized predictors of increased restenosis include diabetes mellitus, small vessel diameter and long lesion. The effect of these variables could not be analyzed because of the sample size and study design. Whether the positive effect of valsartan on TLR rate is pronounced in diabetics and patients with small vessels or long lesions must be re-evaluated with a large number of study patients.

Study Limitations

Major limitations of the present study are the small sample size in both groups as well as the lack of mechanistic insight of valsartan's effect on reducing the need for TLR. Moreover, the present study was randomized, but was neither placebo-controlled nor blinded. Therefore, larger studies are needed to further elucidate the antirestenotic effect of valsartan. If larger trials can confirm the beneficial effects on reducing the need for TLR, this treatment with an orally taken drug might be a promising tool to modulate restenosis after coronary stenting. This might also be important with respect to DES, for which the restenosis rate is significantly lower compared with BMS. However, in more complex lesions, the binary restenosis rate is approximately 15% and is as high as 31% in small vessels, despite the use of DES, as shown in the TAXUS-V study.[36] Finally, intravascular ultrasound data were not available in this study and therefore it was not possible to analyze optimal stent expansion. In addition, we could not assess the shear stress at the site of the target lesion.

Conclusion

The valsartan treatment was not superior to the non-ARB treatment in reducing the primary endpoint at 18 months after the PCI with BMS. The pre-specified secondary endpoint of TLR was lower in the valsartan group compared with the non-ARB group. The angiographic data at 6 months supported this finding, with a significantly lower late lumen loss. Finally, the beneficial effects of valsartan on TLR need to be proven statistically with an adequate study sample.

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＜循環器科＞

①右下腹部痛を主訴とし、PCPSおよび緊急手術を要した重症急性肺血栓塞栓症の1例

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第23回 心臓性急死研究会

右下腹部痛を主訴とし，PCPSおよび緊急手術を要した重症急性肺血栓塞栓症の１例

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A case of severe acute pulmonary thormboembolism with right lower abdominal pain treated by PCPS and emergent surgery

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Key words
急性肺血栓塞栓症
下肢深部静脈血栓症
PCPS
CPR

§　抄録

症例：60歳，男性．アルコール性肝炎既往あり．２日前から出現した右下腹部痛が持続し搬入．来院時血圧70mmHg，まもなく心肺停止となった．PEAとVFが続きCPR施行．心エコーにて右心系の拡大を確認．PCPSを装着し，造影CT施行，左右肺動脈中枢側の大量血栓を認め，acute PTEと診断した．アルコール多飲あり，脱水が血栓形成に関与したと思われた．血栓量は著明であり同日転院し，緊急肺動脈血栓塞栓摘除術施行，左右肺動脈血栓を摘除し得た．全身状態は改善し，第46病日退院した．急変前には，著明な下大静脈血栓が存在した可能性が示唆され，主訴の右下腹部痛との因果関係が考えられた．右下腹部痛が初発症状の重症acute PTEであり報告する．

§　はじめに

急性肺血栓塞栓症(acute PTE)は，重症例において致命的となる疾患である．

Acute PTEの塞栓源の多くは，下肢や骨盤内の深部静脈血栓症(DVT)に由来するが，その初発症状として下肢腫脹および疼痛がしばしば見られる．このたび，われわれは，右下腹部痛の主訴にて発症し，その後，心肺停止をきたしたが，心肺蘇生法(CPR)継続および，経皮的心肺補助装置(PCPS)装着の後，外科的手術を行い回復し得た重症acute PTEを経験したため，報告する．

§　症例

患者：60歳，男性．

主訴：右下腹部痛．

既往歴：アルコール性肝炎，高血圧症．手術歴なし．

嗜好歴：飲酒日本酒３合/日，たばこ20本×40年．

現病歴：独居．アルコール多飲あるが，もともと食事摂取は少ない．2008年11月29日から右下腹部痛出現し，その後も持続していたが，自宅で我慢していた．改善なく，12月１日自力で119番通報し，救急車で当院搬入．搬入当時は，当直医１人(外科系)が対応した．

来院時身体所見：搬入時は，意識清明だったが顔面蒼白あり，全身血色不良．右下腹部痛を強く訴え，疼痛による体動も激しかった．血圧70mmHg，心拍数89bpm，SpO_2 79%(room air)，165cm，60.5kg．

当院搬入後経過(1)

17時40分 救急車にて急患室搬入，当直医の判断で，腹痛の原因精査のため，CTへ搬送した．18時 意識レベルが低下したため，CT施行できず中止．循環器医への応援を要請し再度急患室へ搬送となった．

すでにJCS300．頸動脈触知不可であり，ただちに

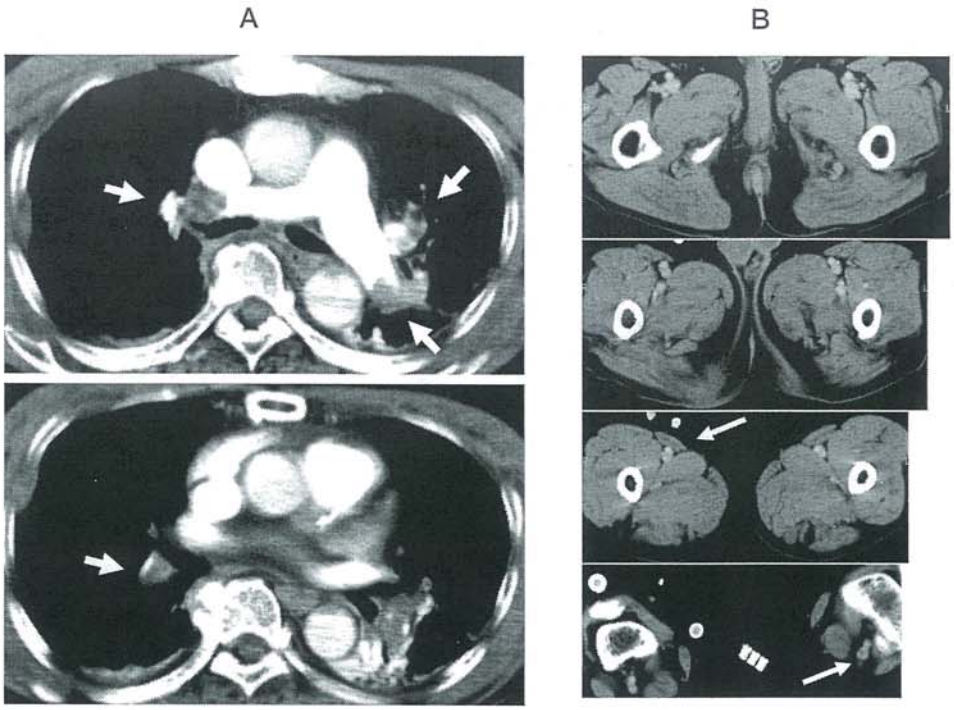

図1　胸部造影CT

A：PCPS装着直後の胸部造影CT．両側肺動脈中枢側の著明な血栓閉塞を認める（矢印）．

B：下肢造影CT．深部静脈末梢に血栓残存所見をわずかのみ認める（矢印）．

胸骨圧迫，バッグバルブマスク換気を開始した．同時に院内一斉コールにて医師応援を要請した．無脈性電気活動（PEA）を確認．気管挿管施行．その後，心室細動（VF）に移行し，電気的除細動施行．18時12分心拍再開．HR150，体動出現．血液検査施行．心エコー施行し，右室，右房の明らかな拡大を認めた．また，ドプラ法による推定肺動脈収縮期圧44mmHgを計測しacute PTEを疑った．しかし，その数分後には再度PEAとなり，CPR再開．18時28分 心拍再開したため，CT室へ搬送した．

来院時血液検査

WBC 12,200/μL，Hb 15.3g/dL，Plt 7.2万/μL（前月14.9万/μL），CRP 2.24 mg/dL，Alb 3.3g/dL，GOT 56 IU/L，GPT 30 IU/L，LDH 331 IU/L，γGTP 179 IU/L，BUN 17.7mg/dL，Cre 1.69mg/dL，Na 145 mEq/L，K 5.3mEq/L．（血液ガス所見）pH 6.92，PO_2 141mmHg，PCO_2 48mmHg，BE －24.2mmol/L，Lac 19.0mmol/L．（慢性期血液データ）ATⅢ109.0 %，ループスAC 1.1（＜1.3），抗CL抗体IgG＜1 U/mL，抗CLβ2 GP1 ＜3.4U/mL，（Protein C/Sは未測定）．

上記のごとく，血小板の著明減少，著明な代謝性アシドーシスなどの所見を認めた．慢性期血液データも示すが，抗リン脂質抗体症候群関連の各指標は正常であった．

当院搬入後経過（2）

CT室で造影CT施行中に再度PEAが出現し，不十分な撮像となり終了．CPRを再開しながら血管撮影室へ搬入．19時15分　PCPS装着した（心肺停止70分後）．その後，造影CTを施行した．

造影CT所見：両側肺動脈中枢側の広範な血栓像を確認し，急性広範型肺血栓塞栓症と診断した．また，下肢については左右の浅大腿静脈および膝窩静脈にわずかな血栓像を認めたのみであった（**図1**）．

19時58分 CCUに入室した．PCPS駆動中であったが，血圧50mmHg台と低値であり，血小板数も7.5万/μLと低下．瞳孔散大はなく，自発的な強い体動がみられ脳虚血を示唆する神経サインはなかった．PCPSにより肺動脈血流はバイパスされているため，肺動脈血栓が自然溶解する可能性は低く，救命には肺動脈血栓摘除術が必要と判断し，22時40分　大学病院に搬送した．

転院後経過

12月2日午前0時50分（心肺停止6時間50分後），緊急肺動脈血栓摘除術を施行．

手術時間：6時間59分（0：50～7：49），ポンプ時間：3時間33分，心停止時間55分循環停止時間：10分．左右肺動脈より，大量の暗黒色の血栓および白色

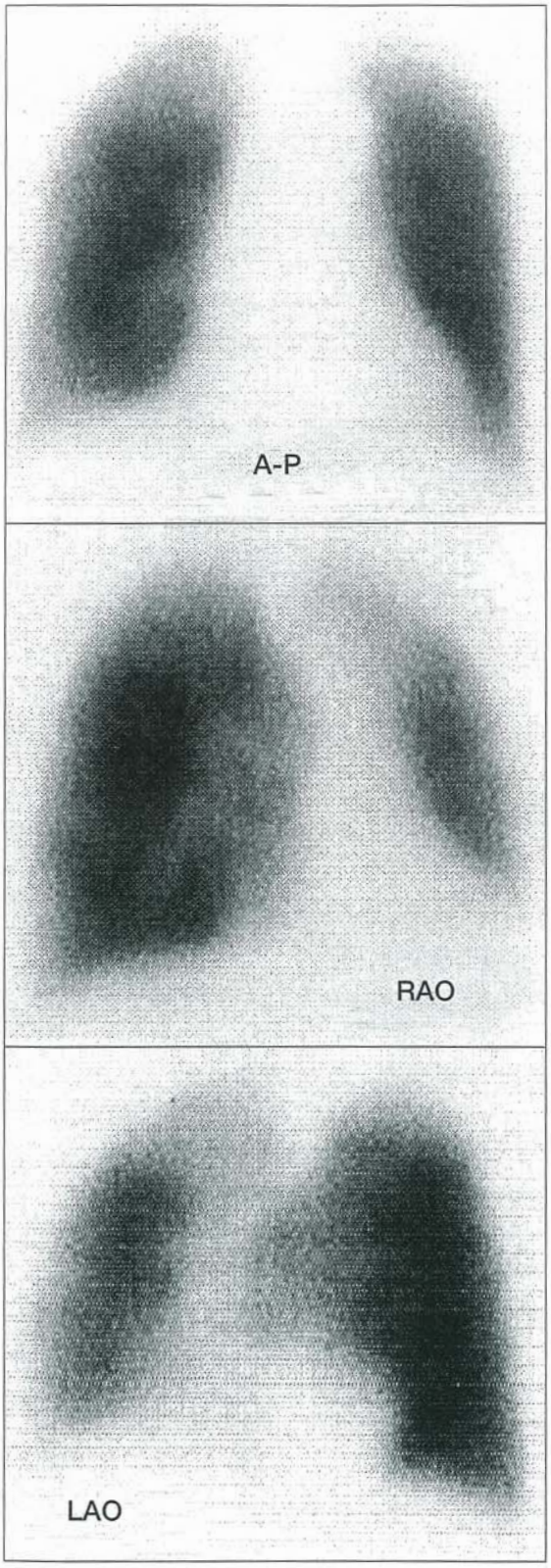

図２　術後(第38病日)の肺血流シンチグラフィ
ほとんどの領域で血流は良好である.

血栓を摘除し得た.

術後，永久IVCフィルターを挿入(Greenfield)した.

12月８日(第７病日)，抜管．第10病日，一般病棟転室．第14病日，正中創が一部離開したため，再開胸し，創部洗浄し大網充填を行った．第29病日の造影CTでは，右肺動脈下葉枝に少量の血栓の残存がみられ，両側膝窩部の深部静脈にも血栓がわずかに残存していた.

第35病日の経胸壁心エコーでは，右室肥大，右室壁運動低下あり．推定肺動脈収縮期圧40～50mmHgであり肺高血圧が残存していた．第38病日の肺血流シンチグラフィでは右肺門下部の軽度集積低下を認めたのみで，ほとんどの領域での血流は良好であった(**図２**)．第43病日の造影CTでは右肺動脈下葉枝の血栓はさらに縮小しており，深部静脈血栓は消失していた．2009年１月16日(第46病日)，神経学的後遺症なく，独歩にて大学病院退院した.

慢性期経過

その後，当院外来にて定期的にフォロー中．約１年後である2009年12月10日の経胸壁心エコーでは，右心負荷および肺高血圧所見はなかった．また同日の血清BNP値も26.1pg/mLと良好であった．2009年12月16日造影CTでは肺動脈内の血栓は，もはや認められなかった(**図３**)．2010年12月現在も再発なく経過良好にて，当院外来通院中.

§　考察

心肺停止をきたした重症のacute PTEに対し，急変時よりCPRを継続しPCPSを装着下にて，緊急肺動脈血栓摘除術を施行したことにより救命し得た１例である.

日本での2000～2003年のacute PTEの院内死亡率は8%と比較的高い[1]．特に，心肺停止またはショックをきたした症例での死亡率は27%とかなり高率であり，また，この死亡率は近年ほとんど改善されていない[1]．別の報告では，acute PTEの約半数がショックをきたし，さらにその半数が死亡にいたっている[2]．これはacute PTEにおいてその病態上，急性循環不全の合併が多いことが，予後不良に関与していると思われる．また，ショック例における死亡例の大半は24時間以内の死亡であるため[2]，逆に，循環不全を呈した急性期を乗り切れれば，予後の改善を期待し得るといえる.

本症例においては，来院後まもなく心肺停止をきたした時点より，胸骨圧迫を主とした有効なCPRを継続することができた．心肺停止時はまだ夕方であり，院内医師の一斉招集により多くのマンパワーを確保でき

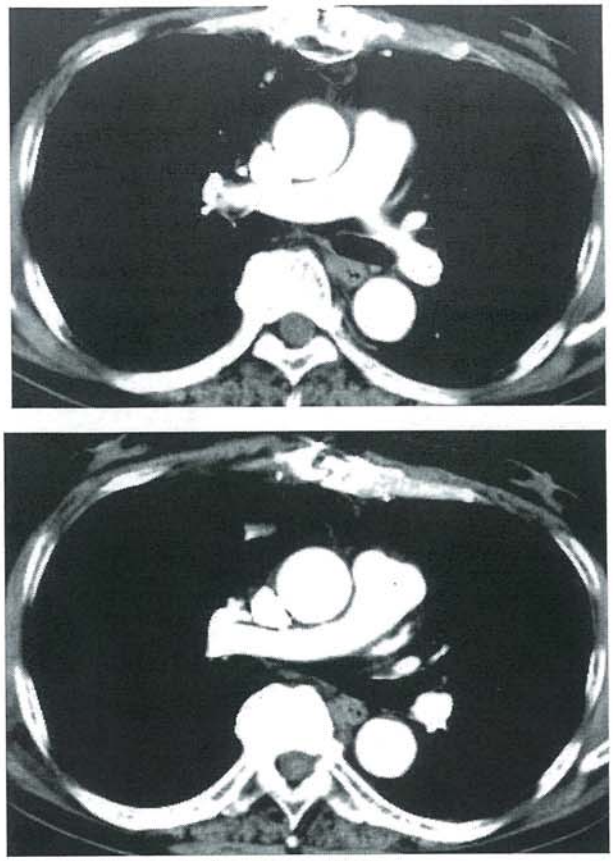

図３　慢性期(１年後)の胸部造影CT
肺動脈内血栓の残存および肺動脈拡大は認めない．

たことも幸いであった．PEAと心拍再開を繰り返し，計70分間にわたるCPRを行い，その後，PCPSを装着したものの，大量血栓の物理的な両側肺動脈閉塞により良好な循環動態までは確保し得なかった．強い体動があるなど，神経学的サインはなく脳灌流の維持は予想されたが，カテコラミン投与下にても血圧は低値であったため，内科的治療での全身状態維持は困難と判断し，緊急肺動脈血栓摘除術に踏み切った．当院では施行困難なため，手術可能な病院へPCPSを装着した状態のまま救急車にて搬送した．転院による時間消費もあり，手術開始は，心肺停止から６時間を経過していたが手術により血行動態を改善し得た．

肺動脈血栓摘除術においては除去すべき血栓が手術操作可能な部位に局在しているかどうかが重要である[3]が，本症例では，左右の主肺動脈および区域動脈など肺動脈中枢側に血栓の多くが存在し，これらを除去し得たことにより肺循環動態の改善をきたした．本症例の慢性期(１年後)の造影CTにおいては，肺動脈内の血栓残存は認めなかった．わが国における急性肺動脈血栓摘除術における死亡率は約20%である[4]が，上記のごとく，acute PTEの約50%を占めるショック例のうち，さらに内科的治療に不応性で心肺停止をきたすような重症例に対して手術を行うことを考慮すると血栓摘除術の手術成績はそれほど不良ではないと解釈し得る．重要なのは，心肺停止後，速やかに心肺蘇生術を継続的に行い，さらにPCPSなど補助循環装置装着による循環維持に移行し，acute PTEに対しての治療方針の決定を速やかに行い，しかるべき症例に対しては血栓除去術に踏み切ることであると思われる．

本症例においての初発症状は右下腹部痛であった．PCPS装着後の下肢造影CTでは，わずかな血栓の残存こそみられるも，血行動態へ影響を及ぼすほどの量の深部静脈血栓は認めなかった．Acute PTEの血栓源のほとんどは下肢DVT由来であることから，状態の急変以前には下大静脈から総腸骨静脈にかけての深部静脈中枢側に存在した大量血栓が肺動脈への塞栓を生じ，CT施行時は，すでに下肢深部静脈から遊離した後であったと推測される．下肢の疼痛および腫脹が下肢DVTの最も一般的な症状であるが，本症例においては，搬入後の状態悪化までの時間経過が急速であり，下肢腫脹がなかったかなどの十分な観察ができていないが，この中枢型DVTによる，右鼠径部から右下肢近位部付近の疼痛を，患者本人が下腹部痛と自覚的に認識したものと思われる．よって，下腹部痛と自覚するような中枢型DVTについては，重症のacute PTEを発症するリスクが示唆され，一層の注意が必要である．本症例はアルコール多飲歴があり，それによる脱水が血栓形成を助長したと推測される．なお，一般的に，深部静脈血栓症はその解剖学的特性から，左下肢のDVTが多いことが知られているが，本症例の訴えは右下腹部痛であり，右下肢に有意なDVTが存在した可能性が示唆される．右深部静脈血栓症については，先天性および後天性血液凝固異常を疑って検査を進める必要があるが，本症例においては，やや不十分な検査ながら，凝固異常は確認し得なかった．

§　結語

ショック状態に陥りながら，70分間に及ぶCPRを行った後，PCPSを装着することにより最低許容範囲の循環動態を維持し得たうえで，血栓除去術を行い，その後神経学的合併症なく，独歩退院できたacute PTEの症例を報告した．その背景には右下腹部痛を主訴とする中枢型DVTの存在が示唆された．

§　文献

1) Sakuma M, Nakamura M, Nakanishi N, et al : Inferior vena cava filter is a new additional