ORIGINAL RESEARCH

Catecholamine Support at the Initiation of Epoprostenol Therapy in Pulmonary Arterial Hypertension

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Abstract

Rationale: Epoprostenol is a first-line therapy for patients with pulmonary arterial hypertension (PAH) in World Health Organization functional class IV who often have low cardiac output and hypotension. However, initiation of epoprostenol can cause hemodynamic collapse in these vulnerable patients. Inotropic agent support may prevent the hemodynamic instability caused by initiation of epoprostenol; however, a protocol for supportive therapy has not been established.

Objectives: To assess the reliability and prognostic effects of dobutamine and dopamine support at the initiation of epoprostenol therapy in patients with PAH.

Methods: We initiated epoprostenol therapy in 71 patients with PAH. Hemodynamics at the initiation of epoprostenol were measured by right heart catheterization. We initiated dobutamine when a patient's mixed venous oxygen saturation was less than 60% or cardiac index was less than 2.0 L/min/m^2 or when right ventricular failure was clinically suspected. We initiated dopamine when a patient's systolic blood pressure was less than 90 mm Hg or urine volume was less than 20 ml/h.

Measurements and Main Results: At the initiation of epoprostenol, dobutamine and/or dopamine were required to support 46 patients according to protocol. Eight patients died during the hospitalization and one patient received a living-donor lobar lung transplant after the initiation of epoprostenol therapy. Neither inotropic agent was an independent risk factor for short-term mortality (dobutamine: hazard ratio, 1.63; 95% confidence interval, 0.33–8.11; dopamine: hazard ratio, 0.22; 95% confidence interval, 0.03–1.70). Sixty-two patients were discharged for home infusion of epoprostenol. Transplant-free survival rates at 5 years were 80.0% for patients who did not require inotropic support at the start of epoprostenol and 76.6% for patients with who did require dopamine and/or dobutamine support (P = 0.45).

Conclusions: Temporary use of dobutamine and dopamine appears to be safe for hemodynamic support at the initiation of epoprostenol therapy for selected patients with PAH with low cardiac output and hypotension. The protocol presented here requires validation at other centers.

Keywords: dobutamine; dopamine; right ventricle; heart failure

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Pulmonary arterial hypertension (PAH) is a life-threatening disease characterized by constriction and remodeling of small pulmonary arteries. Continuous intravenous epoprostenol is a first-line therapy for patients with PAH in World Health Organization (WHO) functional class IV by the current treatment algorithm (1). In patients with class IV PAH, low cardiac output and hypotension caused by right heart failure are common (2). Epoprostenol is a potent systemic and pulmonary vasodilator and often affects the systemic vascular bed more than it does the pulmonary vascular bed (3, 4). Initiation of epoprostenol therapy for patients with class IV disease can cause severe systemic hypotension with hemodynamic collapse when systemic vasodilatation predominates and cardiac output fails to increase proportionately. However, hemodynamics, exercise capacity, and survival of patients treated with epoprostenol over a long period have improved (5–7). Thus, it is

important to initiate epoprostenol therapy without precipitating hemodynamic instability to the extent possible. Inotropic agents are commonly used for this purpose; however, a protocol for the use of inotropic agents at the initiation of epoprostenol therapy has not been established.

We have used dobutamine and/or dopamine as first-line inotropic agents at the initiation of epoprostenol therapy in patients with PAH if inotropic agent support was required. In the present study, we investigated the safety and usefulness of our protocol for use of dobutamine and dopamine at the initiation of epoprostenol therapy by examining whether the use of dobutamine and dopamine aggravates hemodynamic parameters in patients with PAH. We also evaluated the prognosis of patients with PAH who require dobutamine and/or dopamine support at the initiation of epoprostenol therapy.

Methods

Patients

We treated 116 patients with PAH in National Hospital Organization Okayama Medical Center and Okayama University Hospital between May 1999 and March 2011. Among those 116 patients, we started intravenous epoprostenol therapy in 71 patients who were classified as WHO class IV at admission to our institution or had inadequate hemodynamic and exercise tolerance capacity improvement in response to treatment with PAH-specific drugs (prostacyclin analog, endothelin receptor antagonists, and phosphodiesterase 5 inhibitors) at follow-up. We did not start intravenous epoprostenol therapy in 45 patients because their hemodynamics and exercise tolerance capacity were significantly improved by monotherapy or combination therapy with PAH-specific drugs at follow-up right heart catheterization (treatment duration: 3.2 ± 2.6 yr) (*see* Tables E1 and E2 in the online supplement).

Pulmonary hypertension was defined as a mean pulmonary artery pressure (PAP) greater than or equal to 25 mm Hg and pulmonary arterial wedge pressure less than or equal to 15 mm Hg at rest. We started epoprostenol therapy at a low dose under right heart catheter monitoring and increased the dosage daily during hospitalization (8). Written informed consent was given by all patients, and this study was approved by the institutional review board.

Protocol for Use of Dobutamine and Dopamine

In the initial two patients in whom we initiated epoprostenol therapy alone, sudden hypotension and drop of cardiac index (CI) occurred during initiation of epoprostenol therapy (*see* case report, Figures E1 and E2). To guard against future occurrences of this hemodynamic instability at the initiation of epoprostenol therapy, we developed a protocol for use of dobutamine and dopamine at the initiation of epoprostenol therapy.

Our protocol calls for initiation of dobutamine infusion at a low dose (3 μg/kg/min) under the following conditions: (*1*) the value of mixed venous oxygen saturation (Sv_{O_2}) was under 60% or CI was less than 2.0 L/min/m^2 with monitoring by a right heart balloon-directed catheter (Edwards Lifesciences, Irvine, CA) performed immediately before the start of epoprostenol therapy, or (*2*) right ventricular (RV) failure was present clinically before placement of the right heart catheter. Clinical RV failure was defined as leg edema and jugular venous distention, heart enlargement in a chest radiograph (cardiothoracic ratio > 50%), and a high level of brain natriuretic peptide (>100 pg/ml). If the value of Sv_{O_2} did not increase over 60% or CI did not increase over 2.0 L/min/m^2 or if RV failure was not improved, the dose of dobutamine was titrated up.

We began dopamine infusion at a low dose (3 μg/kg/min) under the following conditions: (*1*) systolic blood pressure (BP) was less than 90 mm Hg before the start of epoprostenol therapy, or (*2*) urine volume was less than 20 ml/h before the start of epoprostenol therapy. If systolic BP could not be kept over 90 mm Hg, the dose of dopamine was titrated up.

Additional Therapies after Use of Dobutamine and Dopamine

We added noradrenaline when systolic BP could not be maintained over 90 mm Hg

Table 1. Clinical characteristics at the initiation of epoprostenol therapy

	All	None	DOB	DOA	DOB+DOA
Patients, n (%)	71	25	24	8	14
Male	18 (25.4)	7 (28.0)	6 (25.0)	2 (25.0)	3 (21.4)
Female	53 (74.6)	18 (72.0)	18 (75.0)	6 (75.0)	11 (78.6)
Age, yr	33 ± 13	31 ± 13	31 ± 10	39 ± 16	35 ± 14
WHO FC, n (%)					
III	23 (32.4)	21 (84.0)	1 (4.2)*	1 (12.5)*	0 (0)*
IV	48 (67.6)	4 (16.0)	23 (95.8)*	7 (87.5)*	14 (100)*
Diagnosis, n (%)					
Idiopathic PAH	48 (67.6)	16 (64.0)	19 (79.2)	6 (75.0)	7 (50.0)
Associated PAH					
Connective tissue disease	11 (15.5)	4 (16.0)	3 (12.5)	1 (12.5)	3 (21.4)
Congenital heart disease	11 (15.5)	4 (16.0)	2 (8.3)	1 (12.5)	4 (28.6)
Portal hypertension	1 (1.4)	1 (4.0)	0 (0)	0 (0)	0 (0)
Oral specific PAH drug use, n (%)					
None	16 (22.5)	6 (24.0)	6 (25.0)	1 (12.5)	3 (21.4)
PGI_2 analog	43 (60.6)	12 (48.0)	13 (54.2)	6 (75.0)	10 (71.4)
ERAs	29 (40.8)	12 (56.0)	9 (37.5)	1 (12.5)	7 (50.0)
PDE5 inhibitors	17 (23.9)	16 (64.0)	7 (29.2)*	6 (75.0)	2 (14.3)*†
DOB dose, γ	—	—	3.1 ± 1.1	—	4.9 ± 2.7
DOA dose, γ	—	—	—	3.6 ± 1.4	3.8 ± 1.8
DOB duration, d	—	—	34 ± 62	—	22 ± 18
DOA duration, d	—	—	—	22 ± 7	20 ± 7
Hospitalization, d	42 ± 29	35 ± 22	45 ± 32	48 ± 31	44 ± 30

Definition of abbreviations: DOA = dopamine; DOB = dobutamine; ERAs = endothelin receptor antagonists; PAH = pulmonary arterial hypertension; PDE = phosphodiesterase; PGI_2 = prostaglandin I_2; WHO FC = World Health Organization functional class.
Data presented as mean ± SD unless otherwise noted. Hospitalization indicates duration from epoprostenol initiation to discharge.
*$P < 0.05$ vs. none.
†$P < 0.05$ vs. DOA.

despite titration of the dose of dopamine to 5 μg/kg/min or when sudden cardiogenic shock (systolic BP < 90 mm Hg) occurred. When the clinical course further deteriorated, we initiated mechanical ventilation or percutaneous cardiopulmonary bypass if appropriate.

Hemodynamics

We evaluated hemodynamics at the start of epoprostenol therapy by right heart catheterization in all patients. We measured heart rate, BP, PAP, right atrial pressure (RAP), CI, Sv_{O_2}, and pulmonary vascular resistance. CI was measured by the Fick method. In addition, heart rate, BP, PAP, RAP, CI, Sv_{O_2}, and pulmonary vascular resistance were monitored by a right heart catheter after the initiation of epoprostenol therapy.

Statistical Analysis

All statistical analyses were performed with SPSS software version 11.0 (SPSS Inc., Chicago, IL). All data are expressed as mean values ± SD. Categorical variables at the initiation of epoprostenol therapy were compared by the Chi-square test. Continuous variables at the initiation of epoprostenol therapy and at the start of dobutamine plus/or dopamine infusion were compared by one-way analysis of variance with Tukey *post hoc* test.

In the dobutamine plus dopamine group, systolic BP at the start of dobutamine plus/or dopamine administration was a value at the dopamine administration, and CI and Sv_{O_2} at the start of dobutamine plus/or dopamine administration was a value at the dobutamine administration.

Continuous variables in two groups (survivors or nonsurvivors) were compared by the unpaired *t* test, and categorical variables were compared by the Chi-square test. Kaplan-Meier analysis was used to estimate survival status, and the log-rank test was used for survival distribution comparison in patients discharged for home infusion of epoprostenol. Patients were censored if they died or underwent lung transplantation. Cox proportional hazards analysis was performed to evaluate the factors associated with short- and long-term survival. Values of *P* less than 0.05 were considered significant.

Table 2. Hemodynamic parameters

	All	None	DOB	DOA	DOB+DOA
At the initiation of epoprostenol therapy					
HR, /min	82 ± 20	78 ± 15	83 ± 20	71 ± 17	91 ± 25
sBP, mm Hg	111 ± 16	112 ± 19	112 ± 15	108 ± 16	108 ± 13
sPAP, mm Hg	103 ± 24	103 ± 26	105 ± 24	98 ± 22	103 ± 23
dPAP, mm Hg	45 ± 18	45 ± 18	49 ± 21	34 ± 15	43 ± 16
mPAP, mm Hg	65 ± 18	66 ± 20	65 ± 15	57 ± 16	66 ± 20
RAP, mm Hg	7.9 ± 4.2	7.5 ± 4.0	9.0 ± 3.8	4.8 ± 4.2	8.6 ± 4.8
CI, L/min/m^2	2.5 ± 0.9	2.5 ± 0.8	2.4 ± 0.7	2.2 ± 0.6	2.7 ± 1.4
Sv_{O_2}, %	65.5 ± 10.1	69.6 ± 8.5	64.3 ± 8.8	63.4 ± 8.2	61.8 ± 13.6
PVR. Wood units	18.9 ± 7.9	18.9 ± 8.7	18.2 ± 5.8	20.3 ± 9.7	19.6 ± 9.2
At the start of DOB plus/or DOA administration					
sBP, mm Hg	92 ± 9.1	—	108 ± 13.6	90 ± 11	89 ± 11*
CI, L/min/m^2	1.6 ± 0.4	—	1.7 ± 0.4	2.2 ± 0.3	1.4 ± 0.4†
Sv_{O_2}	56.7 ± 9.1	—	57.0 ± 10.0	66.4 ± 6.5	53.8 ± 9.2

Definition of abbreviations: CI = cardiac index; DOA = dopamine; DOB = dobutamine; dPAP = diastolic pulmonary artery pressure; HR = heart rate; mPAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; sBP = systolic blood pressure; sPAP = systolic pulmonary artery pressure; Sv_{O_2} = mixed venous oxygen saturation.
Data presented as mean ± SD. In the DOB plus DOA group, sBP at the start of DOB plus/or DOA administration was a value at the DOA administration, and CI and Sv_{O_2} at the start of DOB plus/or DOA was a value at the DOB administration.
*$P < 0.05$ vs. DOB
†$P < 0.05$ vs. DOA.

Results

Clinical Characteristics of the Patients

Clinical characteristics of the patients at the initiation of epoprostenol therapy are shown in Table 1. The patients were predominantly women, had idiopathic disease, and were in WHO functional class IV. A prostacyclin analog, endothelin receptor antagonists, and phosphodiesterase 5 inhibitors were used alone or in combination at the initiation of epoprostenol therapy. Sixteen patients received no treatment with oral PAH-specific drugs at the initiation of epoprostenol therapy.

Neither dobutamine nor dopamine was administered to 25 of the 71 patients at the initiation of epoprostenol therapy.

Table 3. Hemodynamic parameters at a Swan-Ganz catheter removal

	All	None	DOB	DOA	DOB+DOA
Patients, n	62	24	22	6	10
HR, /min	77 ± 15	70 ± 13	85 ± 14*	71 ± 16	80 ± 10
sBP, mm Hg	106 ± 13	104 ± 11	107 ± 15	100 ± 12	110 ± 10
sPAP, mm Hg	89 ± 20	83 ± 21	91 ± 19	95 ± 22	95 ± 17
dPAP, mm Hg	37 ± 12	36 ± 13	40 ± 13	32 ± 12	36 ± 9
mPAP, mm Hg	56 ± 14	53 ± 14	59 ± 15	55 ± 12	59 ± 12
RAP, mm Hg	5.3 ± 3.1	4.9 ± 2.2	5.8 ± 3.8	4.3 ± 3.3	5.9 ± 3.2
CI, L/min/m^2	2.4 ± 0.7	2.7 ± 0.5	2.1 ± 0.5	2.6 ± 1.0	2.4 ± 0.6
Sv_{O_2}, %	70 ± 8.2	73 ± 7.7	68.6 ± 8.3	71.4 ± 4.6	65.6 ± 8.7
PVR, Wood units	16.9 ± 7.9	14.2 ± 7.4	18.7 ± 7.4	16.6 ± 9.1	18.9 ± 8.9
PGI_2 dosage	4.4 ± 1.8	5.1 ± 1.9	3.8 ± 1.7	4.3 ± 1.5	4.0 ± 1.2
SG duration	7.7 ± 1.8	7.1 ± 1.7	8.2 ± 1.8	7.8 ± 1.9	8.1 ± 2.2

Definition of abbreviations: CI = cardiac index; DOA = dopamine; DOB = dobutamine; dPAP = diastolic pulmonary artery pressure; HR = heart rate; mPAP = mean pulmonary artery pressure; PGI_2 = prostaglandin I_2; PVR = pulmonary vascular resistance; RAP = right atrial pressure; sBP = systolic blood pressure; SG = Swan-Ganz catheterization; sPAP = systolic pulmonary artery pressure; Sv_{O_2} = mixed venous oxygen saturation.
Data presented as mean ± SD. PGI_2 dosage denotes dosage at Swan-Ganz catheter removal.
*$P < 0.05$ vs. none.

Dobutamine alone was administered to 24 patients, dopamine alone was administered to 8 patients, and dobutamine plus dopamine was administered to 14 patients. Dopamine was administered because of oliguria to two patients in the dopamine group and three patients in the dobutamine plus dopamine group. Dobutamine was administered to 7 patients in the dobutamine group and 10 patients in the dobutamine plus dopamine group before the placement of a right heart catheter. All of those patients had leg edema and jugular venous distention, heart enlargement in a chest radiograph (cardiothoracic ratio: 61 ± 5%), and a high level of brain natriuretic peptide (807 ± 463 pg/ml).

The ratio of patients with WHO class IV to WHO class III disease was higher in the dobutamine plus/or dopamine group than in the nondobutamine, nondopamine group. The frequency of use of phosphodiesterase 5 inhibitors was significantly lower in the dobutamine group. Significant differences in sex, age, diagnosis, use of PAH-specific drugs except for phosphodiesterase 5 inhibitors, durations of administration and doses of dobutamine and dopamine, and hospitalization were not found between the groups.

Hemodynamic Parameters at the Initiation of Epoprostenol Therapy

Hemodynamic parameters at the initiation of epoprostenol therapy and at the start of dobutamine plus/or dopamine administration are shown in Table 2. Systolic BPs at the start of dopamine administration were 90 ± 11 mm Hg in the dopamine group and 89 ± 11 mm Hg in the dobutamine plus dopamine group. Except for patients in whom dopamine was administered because of oliguria, systolic BPs at the start of dopamine administration were 85 ± 9.8 mm Hg in the dopamine group and 84 ± 6.1 mm Hg in the dobutamine plus dopamine group. CI and Sv_{O_2} at the start of dobutamine administration were 1.7 ± 0.4 L/min/m^2 and 57.0 ± 10% in the dobutamine group and 1.4 ± 0.4 L/min/m^2 and 53.8 ± 9.2% in the dobutamine plus dopamine group, respectively.

CI and Sv_{O_2} at the start of dobutamine administration in the dobutamine plus dopamine group were lowest among all groups ($P < 0.05$). Although RAP tended to be high in the dobutamine group compared with that in the dopamine group ($P = 0.06$), all hemodynamic parameters at the start of epoprostenol therapy were not significantly different between the four groups. The duration of right heart catheter deployment after the initiation of epoprostenol therapy was 7.7 ± 1.8 days in patients with successful introduction of epoprostenol therapy (n = 62). At the time of right heart catheter removal, heart rate in the dobutamine group was significantly higher than that in the nondobutamine and dopamine group. Other hemodynamic

Table 4. Demographic and clinical characteristics of the patients according to survival during hospitalization

	Survivors (*n* = 62)	Nonsurvivors (*n* = 9)
At the initiation of epoprostenol therapy		
Male	15 (24.2)	3 (33.3)
Female	47 (75.8)	6 (66.7)
Age, yr	32 ± 12	40 ± 16
WHO FC, n (%)		
III	23 (37.1)	0 (0)*
IV	39 (62.9)	9 (100)*
Diagnosis, n (%)		
Idiopathic PAH	42 (67.7)	6 (66.7)
Associated PAH		
Connective tissue disease	10 (16.1)	1 (11.1)
Congenital heart disease	9 (14.5)	2 (22.2)
Portal hypertension	1 (1.6)	0 (0)
Oral specific PAH drug use, n (%)		
None	14 (22.6)	2 (33.3)
PGI_2 analog	38 (61.3)	5 (66.7)
ERAs	26 (41.9)	3 (33.3)
PDE5 inhibitors	16 (25.8)	1 (11.1)
Catecholamine use, n (%)		
None	24 (38.7)	1 (11.1)
DOB	22 (35.5)	2 (22.2)
DOA	6 (9.7)	2 (22.2)
DOB+DOA	10 (16.1)	4 (44.4)
Hemodynamic parameters		
HR, /min	80 ± 19	90 ± 24
sBP, mm Hg	111 ± 16	106 ± 13
sPAP, mm Hg	103 ± 24	102 ± 27
dPAP, mm Hg	44 ± 17	49 ± 26
mPAP, mm Hg	65 ± 18	63 ± 16
RAP, mm Hg	7.7 ± 4.3	9.1 ± 3.6
CI, L/min/m^2	2.5 ± 0.7	2.3 ± 1.8
Sv_{O_2}, %	67.3 ± 7.9	53.9 ± 15.2†
PVR, Wood units	18.3 ± 7.4	23.4 ± 10.4
During hospitalization		
NA, n (%)	2 (3.2)	8 (88.9)†
MS, n (%)	0 (0)	7 (77.8)†
DOB		
Duration, d	29 ± 53	30 ± 14
Initiation dose, γ	3.2 ± 1.5	3.5 ± 1.9
Max dose, γ	4.7 ± 2.0	9.2 ± 3.8†
DOA		
Duration, d	17 ± 16	29 ± 24
Initiation dose, γ	3.5 ± 2.1	3.8 ± 1.6
Max dose, γ	4.5 ± 2.2	12.5 ± 4.9*

Definition of abbreviations: CI = cardiac index; DOA = dopamine; DOB = dobutamine; dPAP = diastolic pulmonary artery pressure; ERAs = endothelin receptor antagonists; HR = heart rate; mPAP = mean pulmonary artery pressure; MS = mechanical supports (percutaneous cardiopulmonary bypass and intubation); NA = noradrenaline; PAH = pulmonary arterial hypertension; PDE = phosphodiesterase; PGI_2 = prostaglandin I_2; PVR = pulmonary vascular resistance; RAP = right atrial pressure; sBP = systolic blood pressure; sPAP = systolic pulmonary artery pressure; Sv_{O_2} = mixed venous oxygen saturation; WHO FC = World Health Organization functional class.
Data presented as mean ± SD unless otherwise noted.
*$P < 0.05$.
†$P < 0.01$.

parameters were not significantly different between the four groups (Table 3).

Survival during Hospitalization

Sixty-two patients were discharged for home infusion of epoprostenol (Table 4). Eight patients died and one patient received living-donor lobar lung transplantation after the initiation of epoprostenol therapy during hospitalization. All of the nonsurvivors had WHO functional class IV disease. Sv_{O_2} was significantly lower in nonsurvivors than in survivors (53.9 ± 15.2% vs. 67.3 ± 7.9%, $P < 0.05$).

Maximal doses of dobutamine and dopamine, frequency of use of norepinephrine, and frequency of use of mechanical supports during hospitalization were significantly higher in nonsurvivors than in survivors. The use of norepinephrine in survivors was due to sudden cardiac shock during epoprostenol therapy. In Cox proportional hazards analysis, the use of dopamine and low Sv_{O_2} at the initiation of epoprostenol therapy and the need for treatment with norepinephrine and mechanical supports during hospitalization were significantly associated with poor short-term survival in univariate analysis. In multivariate analysis, the need for treatment with norepinephrine and mechanical supports were identified as independent factors of poor short-term survival (Table 5).

Long-term Survival in Patients Shifted to Home Infusion of Epoprostenol

Fifty-one patients were alive at the end of the follow-up period (average follow-up duration: 4.1 ± 3.1 yr). Eight patients died and three patients received lung transplantation during the observation period. Overall survival rates at 1, 3, 5 and 10 years were 93.2, 88.9, 77.2, and 72.9%, respectively (Figure 1A). Survival rates at 1, 3, and 5 years were 100, 100, and 80.0%, respectively, for patients without the need for dobutamine and dopamine support at the initiation of epoprostenol therapy, as compared with 90.6, 85.1, and 76.6% for patients with the need for dobutamine plus/or dopamine support ($P = 0.45$ by log-rank test) (Figure 1B).

Table 6 shows the characteristics of survivors and nonsurvivors. PAH associated with connective tissue disease was more frequent in nonsurvivors than in survivors (36.4 vs. 11.8%, $P < 0.05$). No significant differences were found between the two groups in other characteristics. In Cox proportional hazards analysis, there was no independent determinant of long-term mortality in patients with home infusion of epoprostenol (Table 7).

Discussion

This is the first study in which the use of dobutamine and dopamine at the initiation of epoprostenol therapy in patients with PAH was analyzed. Our protocol called for initiation of dobutamine therapy when a patient's Sv_{O_2} or CI was critically low or when patients manifested clinical RV failure before or at the initiation of epoprostenol therapy. We used dopamine when patients manifested hypotension or oliguria before or at the initiation of epoprostenol therapy. None of the hemodynamic parameters at the start of epoprostenol therapy were significantly different between the groups. The need for treatment with norepinephrine and/or mechanical supports during hospitalization was associated with poor short-term survival, although the use of dobutamine and dopamine at the initiation of epoprostenol therapy was not a risk factor for short-term mortality. There was no significant difference in long-term survival between patients who needed dobutamine plus/or dopamine support and that of patients who did not need dobutamine or dopamine support at the initiation of epoprostenol therapy.

Table 5. Cox analysis related to short-term survival

Variables	Univariate		Multivariate	
	Hazard Ratio (95% Confidence Interval)	*P* Value	Hazard Ratio (95% Confidence Interval)	*P* Value
Sex, male vs. female	1.025 (0.212–4.953)	0.98		
Diagnosis, IPAH vs. non-IPAH	0.986 (0.246–3.947)	0.98		
Oral specific PAH drug use, no vs. yes	1.091 (0.226–5.265)	0.91		
DOB, no vs. yes	1.788 (0.444–7.198)	0.41		
DOA, no vs. yes	4.269 (1.065–17.11)	0.04	0.234 (0.031–1.755)	0.158
NA, no vs. yes	66.44 (8.193–538.7)	<0.001	26.74 (1.839–388.8)	0.016
MS, no vs. yes	47.06 (9.627–230.0)	<0.001	9.915 (1.108–88.69)	0.040
Age	1.032 (0.989–1.077)	0.15		
HR	1.023 (0.992–1.056)	0.15		
sBP	0.969 (0.917–1.024)	0.26		
sPAP	0.999 (0.971–1.028)	0.95		
dPAP	1.017 (0.981–1.054)	0.36		
mPAP	0.997 (0.958–1.037)	0.88		
RAP	1.079 (0.923–1.261)	0.34		
CI	0.719 (0.290–1.781)	0.48		
Sv_{O_2}	0.895 (0.844–0.948)	<0.001	0.931 (0.874–0.991)	0.025
PVR	1.001 (1.000–1.002)	0.14		

Definition of abbreviations: CI = cardiac index; DOA = dopamine; DOB = dobutamine; dPAP = diastolic pulmonary artery pressure; HR = heart rate; IPAH = idiopathic pulmonary arterial hypertension; mPAP = mean pulmonary artery pressure; MS = mechanical supports (percutaneous cardiopulmonary bypass and intubation); NA = noradrenaline; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; RAP = right atrial pressure; sBP = systolic blood pressure; sPAP = systolic pulmonary artery pressure; Sv_{O_2} = mixed venous oxygen saturation.

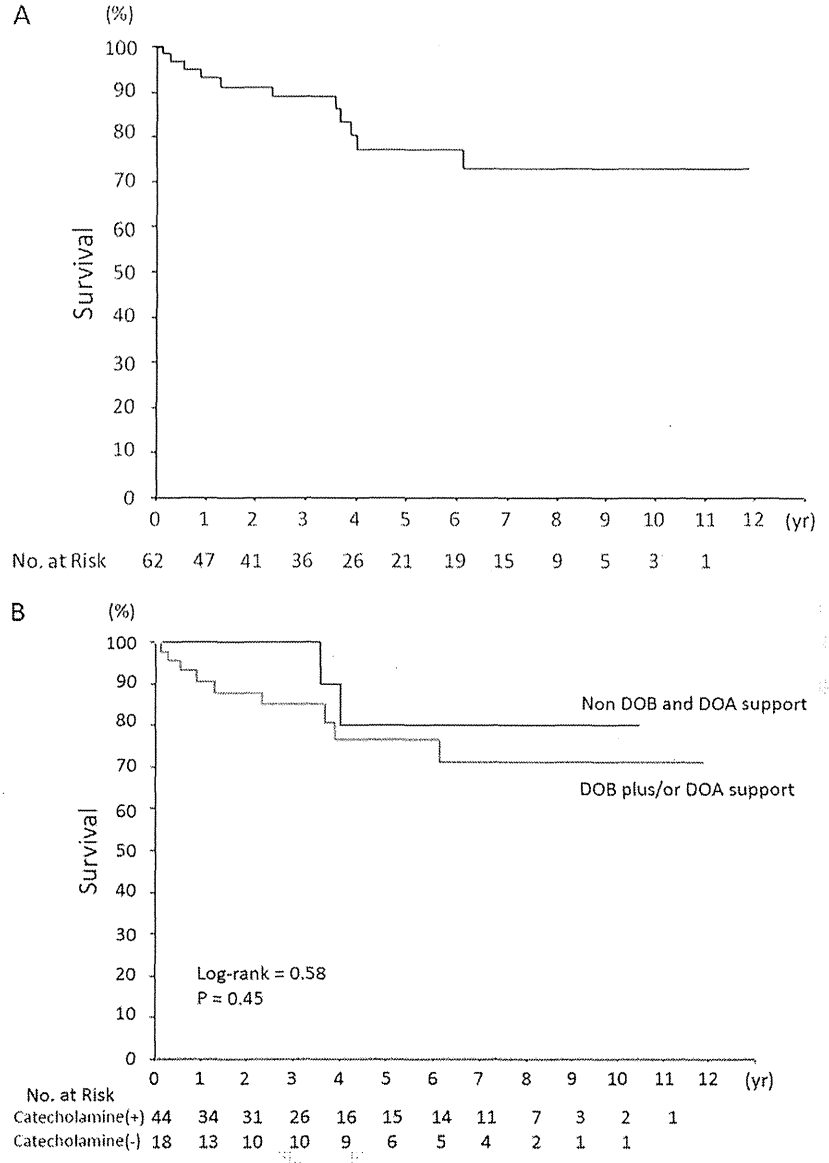

Figure 1. Long-term survival. (*A*) Survival in all patients discharged for home infusion of epoprostenol. (*B*) Survival in patients discharged for home infusion of epoprostenol according to dobutamine and dopamine support. DOA = dopamine; DOB = dobutamine.

Little is known about the hemodynamic effects of administering inotropic agents at the initiation of epoprostenol therapy for severe PAH. In patients with cardiomyopathic heart failure, dobutamine increases cardiac output by increasing stroke volume and decreases pulmonary vascular resistance without altering heart rate or BP at clinical doses up to 5 μg/kg/min (9). Others have used noradrenaline (10), milrinone (11), vasopressin (12), and levosimendan (13) for hemodynamic support of patients with PAH and RV failure. However, dobutamine in particular is expected to improve RV failure without increasing PAP in patients with PAH. Dobutamine did not contribute to worsening of pulmonary hypertension in a hypoxic pulmonary hypertension dog model (14). These effects support the use of dobutamine in patients with PAH with RV failure (10, 15). Therefore, we started to use low-dose dobutamine in patients with low cardiac output and clinically apparent RV failure for support at the initiation of epoprostenol therapy.

We selected dopamine for support at the initiation of epoprostenol therapy in patients with hypotension and oliguria. Dopamine increases cardiac output, heart rate, BP, and systemic vascular resistance dose dependently. Doses of dopamine up to 25 μg/kg/min had no effect on PAP in a hypoxic pulmonary hypertension dog model (14). However, a higher dose of dopamine was shown to be an independent predictor of high mortality rate in patients with PAH with RV failure (16). Furthermore, tachycardia caused by dopamine might deteriorate RV failure. Clinicians might be hesitant to use dopamine in severely ill patients with PAH. In the present study, the use of dopamine did not elevate PAP or increase heart rate at the initiation of epoprostenol therapy.

We decided to begin to administer a low dose (3 μg/kg/min) of dopamine, because low-dose dopamine could maintain normotension, leading to an increase in urine output (17). The doses of dopamine in our study were low (3.6 ± 1.4 γ in the dopamine group and 3.8 ± 1.8 γ in the dobutamine plus dopamine group) at the initiation of epoprostenol therapy. Campo and colleagues reported that low systolic BP was the main prognostic factor for in-hospital mortality in patients with PAH admitted for RV failure. Maintenance of normotension by temporary low-dose dopamine support is recommended for the initiation of epoprostenol therapy in patients with PAH with hypotension.

Thirteen percent of the patients included in our study died or received living-donor lobar lung transplantation during hospitalization for epoprostenol therapy. A few studies have shown short-term prognosis in patients with decompensated RV failure during the course of pulmonary hypertension (2, 10, 16). Sztrymf and colleagues reported that progressive increase of dobutamine was associated with poor survival in the intensive care unit (10). Kurzyna and colleagues reported that higher dopamine dose was an independent factor of in-hospital death (16).

In the present study, dobutamine and dopamine support at the initiation of

Table 6. Demographic and clinical characteristics according to long-term survival in patients discharged for home infusion of epoprostenol

	Survivors (*n* = 51)	Nonsurvivors (*n* = 11)
At the initiation of epoprostenol therapy		
Male	11 (21.6)	4 (36.4)
Female	40 (78.4)	7 (63.6)
Age, yr	32 ± 11	32 ± 15
WHO FC, n (%)		
III	21 (41.2)	2 (18.2)
IV	30 (58.8)	9 (81.8)
Diagnosis, n (%)		
Idiopathic PAH	36 (70.6)	6 (54.5)
Associated PAH		
Connective tissue disease	6 (11.8)	4 (36.4)*
Congenital heart disease	8 (15.7)	1 (9.1)
Portal hypertension	1 (2.0)	0 (0)
Oral specific PAH drug use, n (%)		
None	12 (23.5)	2 (18.2)
PGI_2 analog	29 (56.9)	9 (81.8)
ERAs	22 (43.1)	4 (36.4)
PDE5 inhibitors	14 (27.5)	2 (18.2)
Catecholamine use, n (%)		
None	22 (43.1)	2 (18.2)
DOB	18 (35.3)	4 (36.4)
DOA	5 (9.8)	1 (9.1)
DOB+DOA	6 (11.8)	4 (36.4)
Hemodynamic parameters		
HR, /min	79 ± 19	88 ± 17
sBP, mm Hg	112 ± 16	109 ± 19
sPAP, mm Hg	104 ± 24	100 ± 25
dPAP, mm Hg	44 ± 18	43 ± 14
mPAP, mm Hg	65 ± 18	63 ± 17
RAP, mm Hg	7.7 ± 4.1	8.1 ± 5.3
CI, L/min/m^2	2.5 ± 0.7	2.4 ± 0.7
Sv_{O_2}, %	67.6 ± 8.4	65.7 ± 5.1
PVR, Wood units	18.4 ± 7.2	18.1 ± 8.3
During hospitalization		
NA, n (%)	1 (2.0)	1 (9.1)
MS, n (%)	0 (0)	0 (0)
DOB		
Duration, d	18 ± 13	86 ± 87
Initiation dose, γ	3.3 ± 2.1	2.7 ± 0.5
Max dose, γ	4.5 ± 2.9	4.7 ± 1.3
DOA		
Duration, d	18 ± 6	14 ± 5
Initiation dose, γ	4.0 ± 2.4	2.5 ± 0.5
Max dose, γ	4.9 ± 2.4	3.7 ± 1.6

Data presented as mean ± SD unless otherwise noted.
For definition of abbreviations, *see* Table 4.
*$P < 0.05$.

epoprostenol therapy was not an independent risk factor for short-term mortality. Dobutamine and dopamine have known adverse effects, including predisposition to arrhythmias and cutaneous ischemia. However, none of the patients in the present study developed a hemodynamically significant arrhythmia or cutaneous ischemia in response to inotropic therapy. Dobutamine and dopamine support at the initiation of epoprostenol therapy was also not an independent risk factor associated with long-term survival in patients with home infusion of epoprostenol.

In our study, nonsurvivors during hospitalization had low cardiac output that required progressive increases in dobutamine and dopamine doses and treatment with norepinephrine and mechanical supports. These patients were severely decompensated at baseline. It is important to initiate epoprostenol therapy before deterioration of the patient's clinical condition, because initiation of epoprostenol therapy is difficult in severely ill patients.

In the present study, we started epoprostenol therapy with dobutamine when a patient's Sv_{O_2} or CI was critically low or when patients manifested clinical RV failure, and we started epoprostenol therapy with dopamine when patients manifested hypotension or oliguria. Our protocol of dobutamine and dopamine support may be a reasonable approach to minimize hemodynamic compromise at the initiation of epoprostenol therapy in severely ill patients with PAH.

Limitations

There are several limitations to this study. Patients were not randomized to inotropic support with epoprostenol or received epoprostenol alone. Our study could not show the necessity of catecholamine support in these patients. Further studies are needed to confirm the efficacy and necessity of catecholamine support. However, no significant difference was found in duration of hospitalization or mean PAP at the initiation of epoprostenol therapy between the four groups, and catecholamine support was not an independent risk factor associated with short- and long-term survival. Our study implied that catecholamine support by our protocol was safe and at least not harmful.

The study was performed only in two hospitals, and the patient population was relatively small. However, we performed right heart catheterization at the start of epoprostenol therapy in all patients and could evaluate hemodynamics in detail. These data from right heart catheterization clarified the protocol and prognostic effects for dobutamine and dopamine support at the start of epoprostenol therapy. Regardless of whether dobutamine and/or dopamine were used or not at the start of epoprostenol therapy, the patients in the present study had a better prognosis. We previously reported that high-dose epoprostenol therapy caused marked hemodynamic improvements (8, 18) and that a closed-hub system prevented catheter-related infections in patients with PAH (19).

Table 7. Cox analysis related to long-term survival in patients discharged for home infusion of epoprostenol

Variables	Univariate	
	Hazard Ratio (95% Confidence Interval)	*P* Value
Sex, male vs. female	0.524 (0.153–1.794)	0.30
Diagnosis, IPAH vs. non-IPAH	2.189 (0.666–7.199)	0.20
Oral specific PAH drug use, no vs. yes	1.759 (0.378–8.173)	0.47
DOB, no vs. yes	1.207 (0.352–4.143)	0.77
DOA, no vs. yes	0.655 (0.083–5.154)	0.69
NA, no vs. yes	3.254 (0.406–26.083)	0.27
Age	1.010 (0.959–1.064)	0.72
HR	1.013 (0.983–1.044)	0.40
sBP	0.990 (0.949–1.034)	0.66
sPAP	0.987 (0.958–1.017)	0.38
dPAP	0.987 (0.945–1.032)	0.58
mPAP	0.986 (0.947–1.025)	0.47
RAP	1.024 (0.896–1.169)	0.73
CI	0.935 (0.378–2.314)	0.89
Sv_{O_2}	0.977 (0.910–1.049)	0.53
PVR	1.000 (0.998–1.001)	0.45

Definition of abbreviations: CI = cardiac index; DOA = dopamine; DOB = dobutamine; dPAP = diastolic pulmonary artery pressure; HR = heart rate; IPAH = idiopathic pulmonary arterial hypertension; mPAP = mean pulmonary artery pressure; NA = noradrenaline; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; RAP = right atrial pressure; sBP = systolic blood pressure; sPAP = systolic pulmonary artery pressure; Sv_{O_2} = mixed venous oxygen saturation.

We treated all patients with high-dose epoprostenol by using a closed-hub system in the present study. Therefore, there is believed to be no bias due to differences in treatment with respect to prognosis.

Our criterion of clinical RV failure might be subjective for diagnosis of RV failure, because we did not examine RAP at the time of diagnosis of clinical RV failure. RAP measured at the initiation of epoprostenol therapy (10 ± 4 mm Hg) tended to be higher in patients with clinically diagnosed RV failure, which supports the accuracy of our criteria for diagnosis of clinical RV failure.

Conclusions

Dobutamine and dopamine support at the initiation of epoprostenol therapy by our protocol allowed initiation of epoprostenol therapy without exacerbation of pulmonary hypertension, and it was not an independent risk factor associated with short- or long-term mortality. Temporary use of dobutamine and dopamine appears to be safe for hemodynamic support at the initiation of epoprostenol therapy in patients with PAH with low cardiac output and hypotension. Testing of this protocol is called for at other institutions to validate or further refine the approach presented here. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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» One Point Advice

手術前後の抗凝固薬の使い方

1 本当に中断すべきか？[1~4]

待機的手術時の中断に関してはワルファリンとNOACに差異はない．中断による塞栓症のリスクと手術による出血のリスクを参考に，塞栓症より出血のリスクが上回る場合に中断する．

中断すべき手術を**表1**に示す．出血リスクが低い手術に関しては，中断せず継続してよい．ただし，NOACは濃度ピーク時の手術を回避するため内服12時間以降に行うべきである．出血低リスク手術と出血高リスク手術は中断を要する．

消化器内視鏡診療に関しては2012年にガイドラインが改訂された．通常の消化器内視鏡検査，内視鏡的粘膜生検および出血低危険度の消化管内視鏡では，抗凝固薬の中断を要さなくなったことが大きな改訂点である．

2 いつ中止すべきか？[1~7]

半減期の違いから，中止時期はワルファリンとNOACで大きく異なる．ワルファリンは基本的に手術3~5日前に中止する．NOACは半減期が約12時間前後であるが，各薬剤の腎排泄率に違いがあるため，腎機能と手術の出血リスクを考慮して休薬期間を設けることが勧められている．NOACの薬剤中止時期を**表2**に示す．なお，中止が必要な消化管内視鏡診療は，**表2**の出血低リスク手術として対応を行う．

表1　待機的手術における出血のリスク分類

出血リスク
抗凝固の中止が不必要な手術
歯科領域
1～3本の抜歯
歯周の手術
膿瘍の切開
インプラント手術
眼科領域
白内障・緑内障手術
内視鏡検査
表皮手術(膿瘍切開や小さな皮膚切除術)
出血低リスク手術
内視鏡的生検
前立腺・膀胱の生検
血管造影検査
ペースメーカ・ICD手術
出血高リスク手術
脊椎麻酔，硬膜外麻酔，脊髄穿刺
胸部手術
腹部手術
整形外科手術
肝生検
経尿道的前立腺切除術
腎生検

(文献1，4より引用改変)

3 ヘパリン置換は必要か？[1~4, 8]

ワルファリンは体薬期間が長く，再開後も有効血中濃度に達するのに時間を要するため，手術前後のヘパリン置換を要する．ワルファリン中止後すぐにヘパリンを開始し，PT-INR値1.5以下を確認してから手術を行う．

休薬が5日以内なら塞栓症のリスクは低いとされており[8]，半減期の短いNOACは基本的に手術前後のヘパリン置換を必要としない．腎機能低下などで長時間の休薬が必要な場合は，ヘパリン置換を考慮すべきであろう．また，塞栓症のリスクが高ければヘパリン置換をしてもよいが，エビデンスはない．ただ，中止を要する消化管内視鏡診療に関してはガイドラインでヘパリン置換が推奨されており，最終の内服から12時間後にヘパリンを開始する．

ヘパリン置換(1~2.5万単位/日)は，APTTを正常対照値の1.5~2.5倍に延長するよう調節する．術前4~6時間にヘパリンを中止するか，術直前に硫酸プロタミンで中和し，APTTが正常化してから手術を行う．

表2 待機的手術の薬剤中止推奨時間

	ダビガトラン(プラザキサ)		リバーロキサバン(イグザレルト)		アピキサバン(エリキュース)	
手術の出血リスク	低リスク	高リスク	低リスク	高リスク	低リスク	高リスク
Ccr≧80 mL/min	≧24時間	≧48時間	≧24時間	≧48時間	≧24時間	≧48時間
Ccr 50～80 mL/min	≧36時間	≧72時間	≧24時間	≧48時間	≧24時間	≧48時間
Ccr 30～50 mL/min	≧48時間	≧96時間	≧24時間	≧48時間	≧24時間	≧48時間
Ccr 15～30 mL/min	適応外	適応外	≧36時間	≧48時間	≧36時間	≧48時間
Ccr＜15 mL/min	適応外	適応外	適応外	適応外	適応外	適応外

(文献1より引用改変)

いつ再開すべきか？[1, 4]

塞栓症予防のため，止血が確認できれば可及的速やかに再開する．ワルファリンはヘパリン開始後に移行させる．NOACは止血確認6～8時間後に維持量で再開してよい．NOACは出血低リスク手術では術後24時間が再開の目安であり，高リスク手術では症例毎に検討を要する．一般に塞栓症のリスクが出血のリスクを上回る術後48～72時間以内に維持量で再開することが勧められる．減量での再開は安全性・有効性ともにデータがない．

救急手術にはどう対応すべきか？[1, 2, 6]

ワルファリンは出血性合併症時に準じた対処を行う．内服中止およびビタミンK投与である．急ぐ場合は，新鮮凍結血漿や乾燥ヒト血液凝固第Ⅸ因子複合体製剤を投与する．

NOACは拮抗薬がないため，効果が切れるのを待つしかない．少なくとも内服12時間後，できれば24時間後に手術を行う．待てないときは出血リスクを覚悟して行う．

NOACに対して考慮可能な対処法を後述する．新鮮凍結血漿投与や血小板輸血，凝固因子製剤(プロトロンビン複合体製剤，活性型プロトロンビン複合体製剤，遺伝子組み換え第Ⅶ因子製剤)の投与を考慮できる．内服2時間以内なら胃洗浄や活性炭吸着も考慮してよい．輸液利尿による腎排泄維持も重要となる．また，ダビガトランは透析で除去できるが，リバーロキサバンとアピキサバンは蛋白結合率が高く透析で除去できない．

まとめ

周術期における抗凝固療法の管理で重要なことは，塞栓症と出血合併症の発症リスクを常に意識することと，抗凝固薬の種類や患者背景に応じた対応である．出血リスクを軽減させるために，抗凝固薬使用が不十分となることは慎むべきであり，塞栓症を予防するという最も重要なコンセプトを忘れてはならない．なお，NOACに関しては十分なエビデンスがないため，記載内容は現時点で妥当と思われるものであることを付記する．

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>>> One Point Advice

なぜ新規抗凝固薬では出血性合併症が少ないか

はじめに

抗凝固療法を施行する際，頭蓋内出血は最も重篤な合併症である．従来のワルファリンでは抗血栓作用を得るために出血性副作用が出現するといったジレンマが問題であった．しかし，新規経口抗凝固薬novel oral anticoagulants(NOACs)を用いた大規模臨床試験[1~3]の結果，ワルファリンと比較していずれのNOACにおいても頭蓋内出血の発生が有意に減少した．

NOACsでワルファリンに比べ頭蓋内出血の頻度が圧倒的に少ない理由として主に下記の4つの薬理学的特徴の関与が推察されている．

1 凝固第Ⅶ因子の関与

フィブリン血栓の形成に重要な血液凝固機序は外因系(組織因子系)と内因系経路がある(**図1**)．血管損傷時には傷害組織の細胞膜に存在する凝固惹起因子である組織因子tissue factor(TF)に血中の第Ⅶ因子が結合し，TF/Ⅶa因子複合体が形成されることで外因系凝固カスケードが開始される．この凝固反応は血小板膜上でのXa因子の生成，さらにXa因子，Va因子複合体によるトロンビン生成，フィブリン形成がなされ，止血作用が発揮される．ワルファリンはこの初期段階の第Ⅶ因子を阻害するためTF/Ⅶ因子複合体形成を阻害し出血を助長する．一方で，NOACsはトロンビンもしくはXaを直接阻害し血漿中の第Ⅶ因子活性を低下させないため，組織因子が豊富な脳組織では凝固開始機序に影響を及ぼさないことが脳出血の少ない理由と考えられている[4~6]．

2 NOACsの可逆性かつ特異的な阻害作用

ワルファリンはビタミンK依存性の凝固因子である第Ⅱ，Ⅶ，Ⅸ，Ⅹ因子と複数の凝固因子の生成を不可逆的に阻害し抗凝固作用を発揮する．NOACsはトロンビンもしくはXa因子のいずれかを可逆的に阻害している．そのため，軽微な頭蓋内出血時の局所出血ではNOACsによる可逆的な結合阻害を凌駕するほどの大量なトロンビン生成が生じ，それに引き続きフィブリン血栓が形成されることで局所止血がなされる．これにより，NOACs使用時にはワルファリン使用時より軽微な出血で済み，無症候性となる可能性が大きいものと思われる．また，Xa阻害薬はトロンビンによる血小板活性や細胞増殖作用を阻害しないことも止血や創傷治癒に影響を与えないことも要因であるかもしれないと考えられている[5]．

3 NOACsの広い治療域および安全域

ワルファリンは至適治療域が狭く，その代謝における遺伝的個人差，食物摂取や種々薬剤との相互作用などの変動が大きく，抗凝固作用が増強することがある．NOACsは抗血栓作用を示す有効域と出血を起こさない安全域の幅が広く，モニタリングを必ずしも必要としない特徴がある．この広い治療域が頭蓋内出血の頻度低下に寄与している可能性がある．なお，NOACsの血中濃度はダビガトランではAPTT値[7,8]と，リバーロキサバンではPT値と相関する[9]ため，それらはNOACs使用時の出血性合併症予防の指標になりうると考えられている．

4 NOACsの短い半減期

ワルファリンは半減期が3～5日と長く抗凝固作用は1日を通じてほぼ一定であるのに対して，

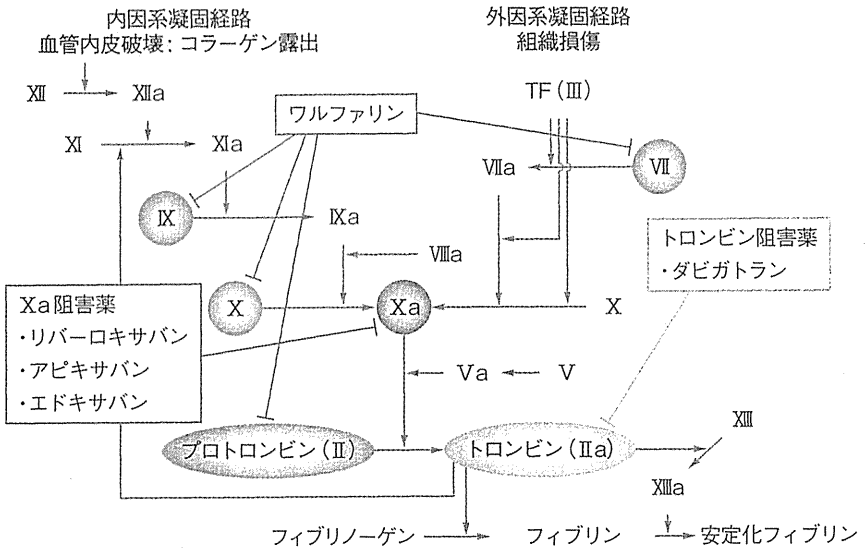

図1 凝固カスケード
血管が損傷すると，傷害組織の細胞膜に存在する組織因子 tissue factor（TF）に血中の第VII因子が結合し，外因系凝固経路が惹起される．ワルファリンはII，IX，VII，Xの生成を不可逆的に阻害する．Xa阻害薬はアンチトロンビン（AT）と結合している遊離Xaだけでなく，ATと結合していないXaも阻害する．トロンビン阻害薬はトロンビン活性を可逆的に阻害する．

NOACsは半減期が短く，血中薬物濃度にピークとトラフを有する．NOACsではピーク時では出血リスクは上昇する可能性はあるがトラフ時には出血時の生理的止血機構を阻害しにくいことも出血イベント抑制に寄与しているものと考えられる．

また，一般的に頭蓋内での微小血管障害は通常でも常時生じていると考えられており，BAT試験のサブ解析では抗凝固療法中の頭蓋内出血発現については血圧が大きく影響することが知られている[10]．しかし，RELY，ROCKET-AF，ARISTOTLEのいずれの大規模臨床試験においても血圧に関連する背景因子においてNOACsとワルファリン群における有意差はみられなかった．このことから，NOACsの頭蓋内出血頻度低下の要因として血圧が関与していた可能性は低いものと考えられる[1~3, 9]．

最後に，現在の日本でもNOACsによる頭蓋内出血の出現頻度の減少を受けガイドラインの見直しが進んでいる．それに伴い，$CHADS_2$スコアがより低い患者や出血リスクの高い高齢者も抗凝固療法を受ける機会が増えていくものと予測される．このような幅広い患者がNOACsの使用でより安全に抗凝固療法を受けられることが期待される．

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A 抗凝固療法は必須—では具体的にどうする？

8 高齢者・腎不全患者における抗凝固薬をどうするか

はじめに

心房細動患者において，高齢であることは脳梗塞のリスクを高めるだけでなく，出血イベントに関連する重要な因子であることが報告されている．また腎不全を伴った患者は，独立した脳梗塞の危険因子ではないが，出血イベントに密接に関連することが報告されている．したがってこうした患者への抗凝固療法については投与薬剤の種類や投与量について大変慎重にならねばならない．

ここでは，現時点で示されているデータと問題点について述べる．

1 高齢者における抗凝固療法

高齢化社会を迎えて，わが国の心房細動は激増している．年齢はそれ自体が心房細動の発生数増加の因子になるばかりでなく，脳梗塞自体の発生率自体も上昇させる重要な因子であり，高齢者に対する抗凝固療法はわが国で今後大変重要な課題となっているといっても過言ではない．現在，京都府伏見区で開業医を中心とした前向き登録研究(Fushimi Registry)が行われているが[2]，それらの患者背景をみてみると，平均年齢は74.2±11.0歳とこれまで基幹病院を中心にわが国で行われてきたJ Rhythm試験[3]やJ Rhythm Registry試験[4]よりも高齢者が多く，実臨床では，やはり高齢者に対する抗凝固療法のあり方が重要になってきていることがわかる．

年齢は，心原性脳梗塞の危険因子の1つであり，$CHADS_2$スコアでは75歳以上が危険因子として用いられているが，最近の報告では，年齢の因子は，他の因子(心不全，糖尿病，高血圧)よりも脳梗塞発生に重要な因子であることが報告され[5]，ヨーロッパのガイドラインでは新たにCHA_2DS_2-VAScスコアという新たな脳梗塞のリスク評価が

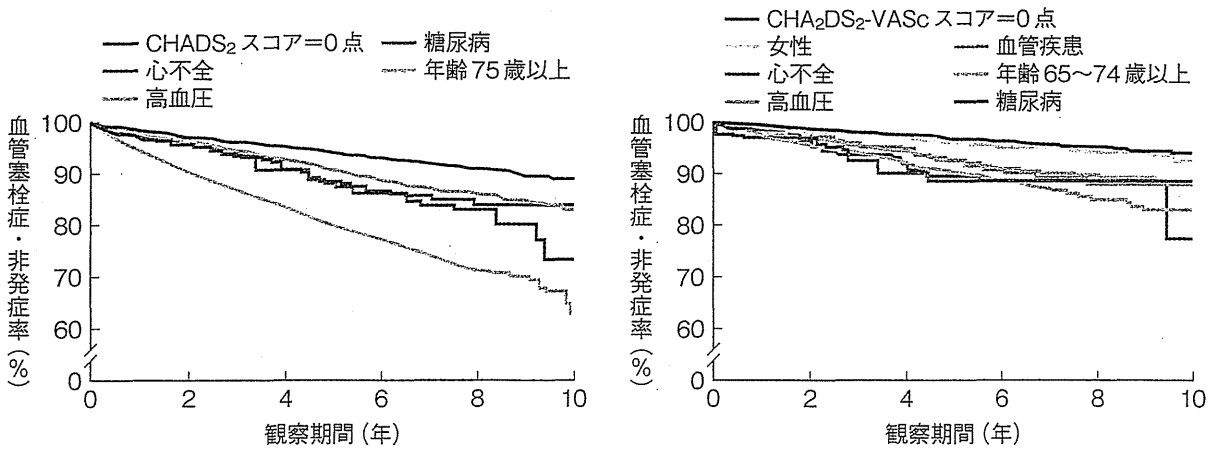

図1 $CHADS_2$スコアとCHA_2DS_2-VAScスコアの各因子と血栓塞栓症の発症
左：$CHADS_2$スコアの年齢75歳以上が，他の因子よりもイベントが多い．
右：年齢を65〜74歳にすると，他の因子と同程度のイベント発生となる．
(文献5より引用改変)

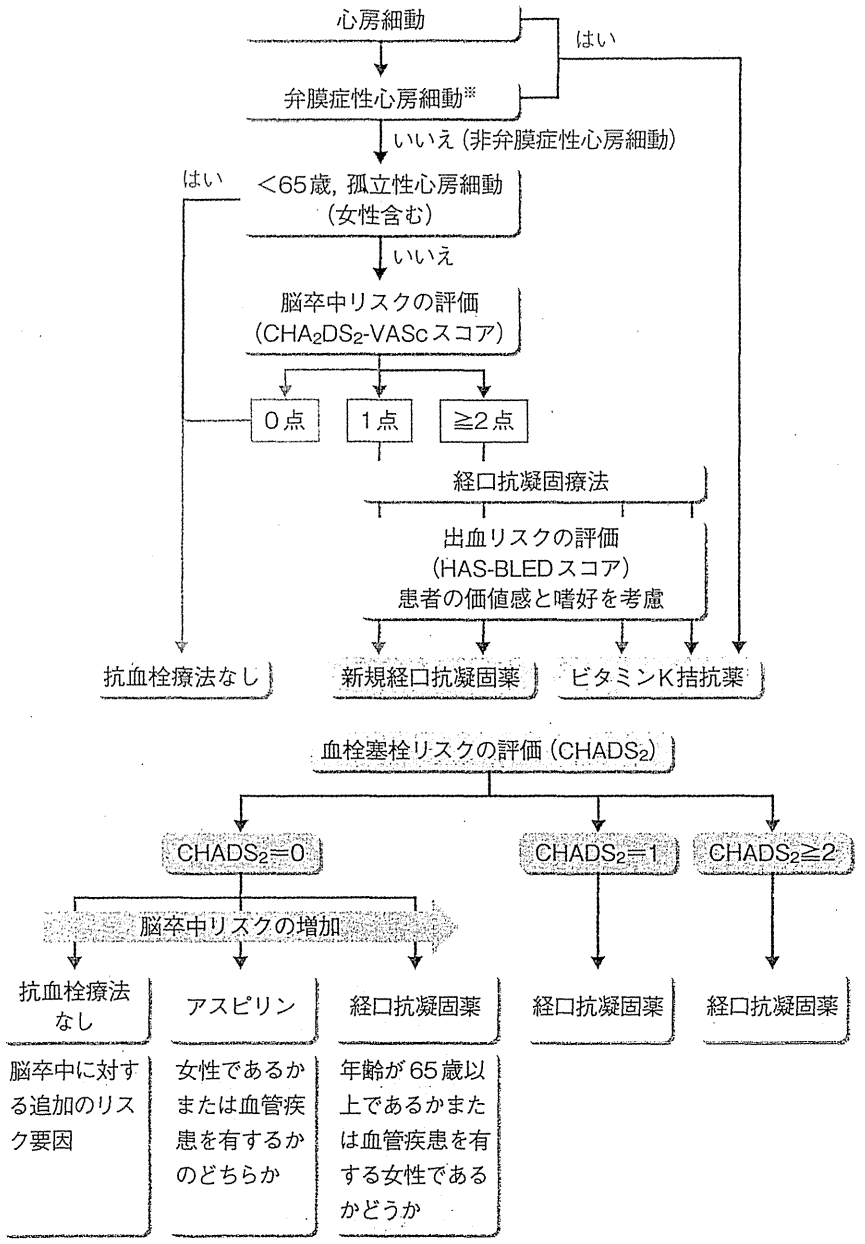

図2　欧米における脳卒中リスク評価抗凝固薬の選択
上：ヨーロッパ心臓病学会ガイドラインのFocus update 2012では，CHA_2DS_2-VAScスコアが使用されている（文献6より引用改変）．
下：カナダのガイドラインでは$CHADS_2$スコアを用いてスコアが0でも年齢が65歳以上，あるいは女性，血管病を合併している場合，OAC（経口抗凝固薬）が考慮されることが示されている．（文献7より引用改変）

提唱され，65歳へ年齢を引き下げること，75歳以上にはより大きな重みを持たせることが提案されている[6]（図1，2）．また，カナダのガイドラインでは，$CHADS_2$スコアに準じて抗凝固療法を行うが，年齢に関しては65歳を用いるというリスク評価が提唱されている（図2）[7]．こうした世界的なリスク評価の変化がわが国も当てはまるかどうか検証が必要であるが，海外データの影響を受け，実際は，より低年齢から抗凝固療法を行う風潮になってきていることは事実であろう．

一方，年齢は抗凝固療法を行う際の出血イベントを増加させる因子としても重要である．従来用いられてきたワルファリンでは，出血に注意する患者として65歳以上ということが示されている．海外で用いられている出血のリスクスコアであるHAS-BLED（詳細は別項に譲る）でも65歳が1つの出血因子として示されている．さらに，高齢者では，合併症として高血圧罹患率の増加，心不全の増加など，$CHADS_2$スコアを増大させる因子を同時に多数保有しているだけでなく，①消化管機能の低下，胃・腸管吸収面積の減少，胃酸分泌の低下，②肝血流量の低下，肝代謝酵素活性の低

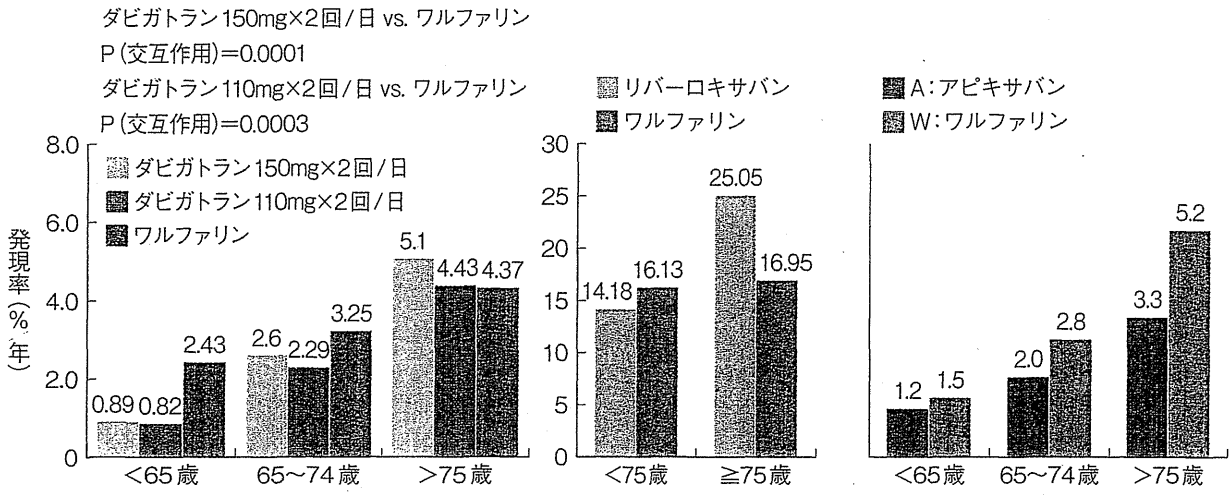

図3　年齢と出血リスク

高齢になるに従い，いずれの薬物でも出血リスクが増大していることがわかる．
(文献8～10より引用改変)

下，③腎機能．腎血流量の低下，糸球体濾過率の低下，④全身の状態．総水分量の低下，血漿アルブミン(蛋白)の減少など，薬剤の吸収代謝に影響して，抗凝固療法を行ううえで，大変出血をしやすい状況にあることがわかる．したがって，高齢者では，脳梗塞リスクと脳出血リスクの両者を併せ持っているため大変安全域が狭く，抗凝固療法をためらうが，抗凝固療法がきわめて重要であるという，一見相反する治療を医療側に求められる集団ということになる．そうしたことを受けて，従来のわが国の心房細動に対する抗凝固療法については70歳以上で目標PT-INR値を1.6～2.6にすることが推奨されてきた．現在，J Rhythm Registry試験で，この至適範囲についての調査が進行中であり，わが国独自のエビデンスとなることが期待される．

近年，新規抗凝固薬novel oral anticoagulant (NOAC)で行われた大規模試験のサブ解析の結果を図にまとめた(**図3**)[8～10]．ワルファリン，NOACいずれも高齢になれば，出血リスクは増大していることがわかる．アピキサバンは，ワルファリンに比べやや出血が少ないが，若年者と比べるとやはり出血イベントは増大しており注意が必要であることには変わりはない．ただし，ARISTOTLEの結果からNOACの中ではアピキサバンが最も使用しやすい可能性はある．NOACの欠点として，血中のモニタリングができないことが挙げられる．したがって，筆者は現時点では，75歳以上の高齢者では，低用量のワルファリンでPT-INRを1.6～2.0付近でコントロールするか，アピキサバンを慎重に使用することが安全にかつ有効に使用できるのではないかと考えている．

年齢に関しては，もう1つ85歳以上の超高齢者に対する抗凝固療法も重要である．先に述べたように，年齢は脳梗塞リスクを増大させるが，80歳以上では10％以上に達するという報告もあり年齢が上がるほうが，抗凝固療法はさらに重要になる．しかしNOACを使用した大規模試験では，これらの超高齢者に対するデータは乏しく，安全性や有効性についてのデータは現在欠如している．したがってワルファリンを使用することが望まれるが，認知症，転倒リスク，高血圧性脳出血の増大，内服コンプライアンスの問題など，高齢者特有の問題を抱えていることも事実である．今後，これらの超高齢者への対応についてわが国の指針が出てくることが重要であろう．

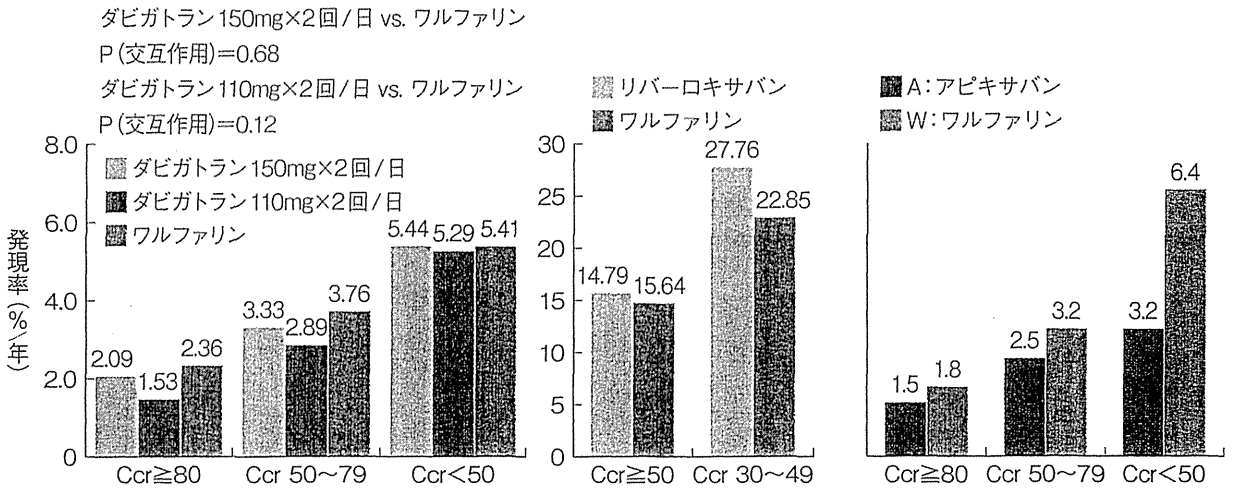

図4 腎機能と出血リスク
腎機能低下に従い，出血リスクはどの薬剤でも高くなる．
(文献9～11より引用改変)

2 腎不全例における抗凝固療法

腎不全は，それ自体は脳梗塞の危険因子にならないことが報告されているが，末期腎不全ではアシドーシスに陥っており，全身的な酸化ストレス亢進状態であること，高齢者では軽度の腎機能障害が認められることが多いこと，また腎機能障害例では，高血圧の合併が多いことなどを考えあわせると，抗凝固療法を考慮すべき病態であると考えられる．一方，出血リスクとしての腎機能障害は，HAS-BLEDでも示されているように独立した因子であることが判明している．これは，腎機能の低下が薬剤の排出を遅らせるためと考えられるが，肝代謝のワルファリンでも腎機能低下は出血の独立した因子と報告されており，血中蛋白の減少や高齢者が多く存在するなど，宿主の変化を表しているのかもしれない．NOACを使用した大規模試験のサブ解析データをまとめて示す．ダビガトランは，80％が腎排泄であるため，腎機能低下例では，ワルファリンと同等かそれ以上の出血リスクがあり，きわめて注意を要する．したがって，投与前のクレアチニンクリアランス(Ccr)測定が重要となるが，腎機能低下例(特に高齢者)では，脱水などの影響で腎機能に大きな変化が生じることがしばしば経験されるため，繰り返し腎機能を測定することが重要である．それ以外のNOACのXa阻害薬でも，腎排泄は25～33％とやや関与は少ないが，腎機能の影響を少なからず受けることが大規模試験で示されている(**図4**)[9~11]．この中ではアピキサバンが安全性の面から第一に選択される可能性があるが，先に述べたように高齢者の腎機能は，きわめて不安定であるため，Ccrが30～50未満では腎機能を繰り返して測定し，出血性副作用への配慮が重要であると考えれられる．Ccrの測定には，直接法，eGFRから求める簡易法，Cockcroft-Gault式を用いる方法の3つがある．NOACの特徴として，低体重によって出血性副作用に差が出ることが報告されており，体重と腎機能，さらに年齢が加味された，Cockcroft-Gault式をきちんと用いることが薬剤選択あるいは薬剤量の決定には重要である．**図5**に体重別，性別で分けた，eGFRから求めたCcr値とCockcroft-Gault式から算出したCcr値のシミュレーションデータを示す．体重の減少により，両者の数値に大きく乖離が生じていることがわかる．したがって真のCcrは，低体重例ではeGFRで求めたときよりもかなり低くなることを念頭に出血性副作用を未然に防ぐためにCock-

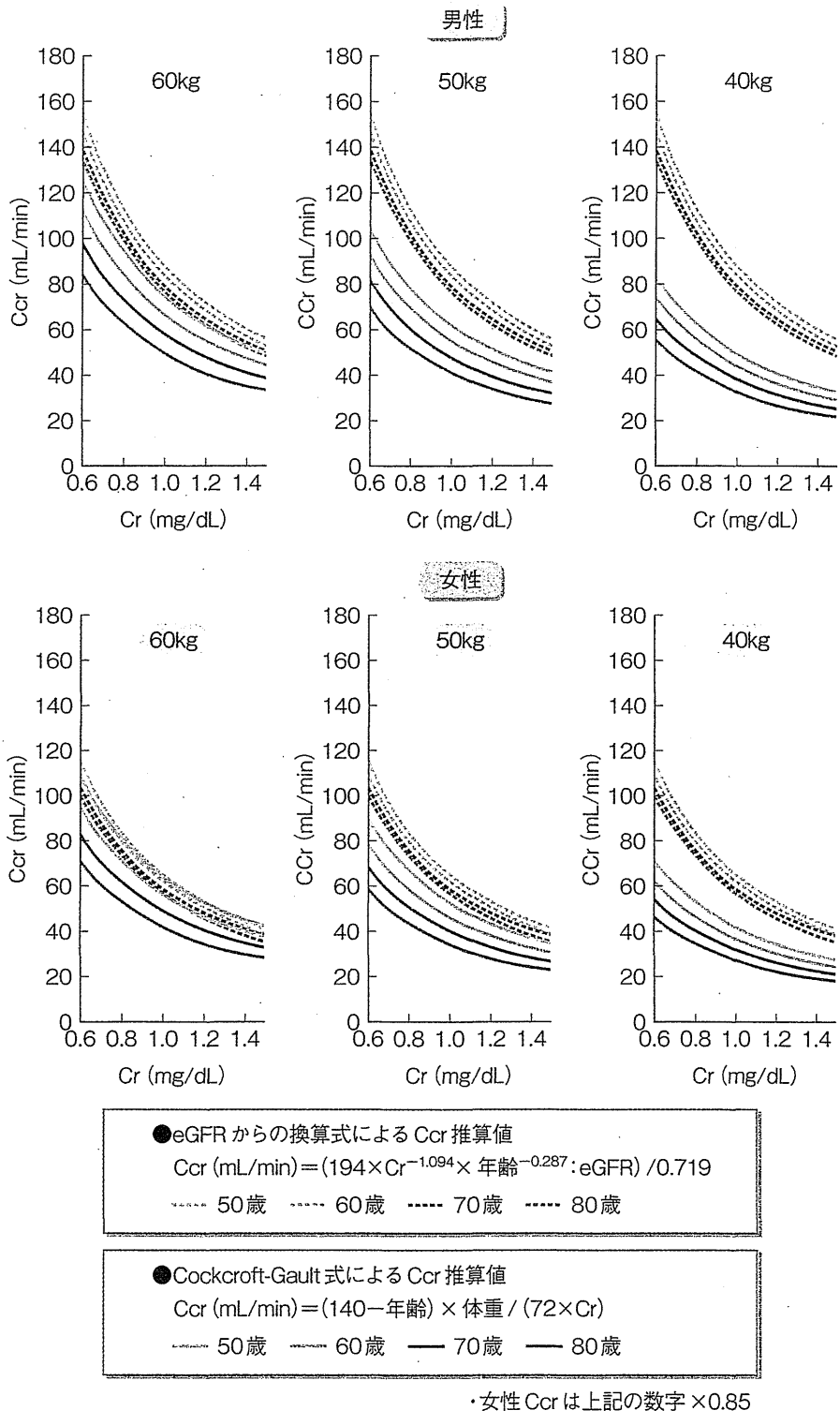

図5　計算式によるクレアチニンクリアランス(Ccr)値の違い

年齢と Cr 値をもとに算出した eGFR/0.729 で求めたものが破線，年齢，体重と Cr 値をもとに算出した Cockcroft-Gault 式で求めたものが実線．低体重になると両者の乖離が生じ，体重の因子が腎機能に大変重要であることがわかる．

croft-Gault 式を用いた腎機能の測定をしなくてはいけないことが伺える．

3　高度腎不全患者に対する治療選択

添付文書に基づけば，Ccr が 15 mL/min 未満の症例に対しては，NOAC はすべて禁忌であるた

めワルファリンの慎重投与となる．Ccrが15～30 mL/minの症例では，ダビガトランは禁忌，リバーロキサバンは適応の有無を慎重に判断して10 mg/dayが使用可能，アピキサバンは体重と年齢を加味して2.5 mg×2/day，もしくは5 mg×2/dayが使用可能となる．薬物の体内動態データ，あるいは大規模試験の結果から選択すると，腎排泄が最も少なく，出血頻度が少なかったアピキサバンがNOACの中では第一選択となるが，これらの薬物の日本人データはまだ少なく，安全性を確認するための指標もないため，筆者は血中モニタリングが可能で微調整ができるワルファリンの選択を第一として目標PT-INR＝1.6～2.0で抗凝固療法を行っている．今後，こうした腎不全患者に対するNOACの市販後調査の結果が明らかとなれば，より安全で有効な投与法が明らかとなるであろう．

◉文献

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（草野研吾）