Lowering mPAP as a Treatment Goal in PAH

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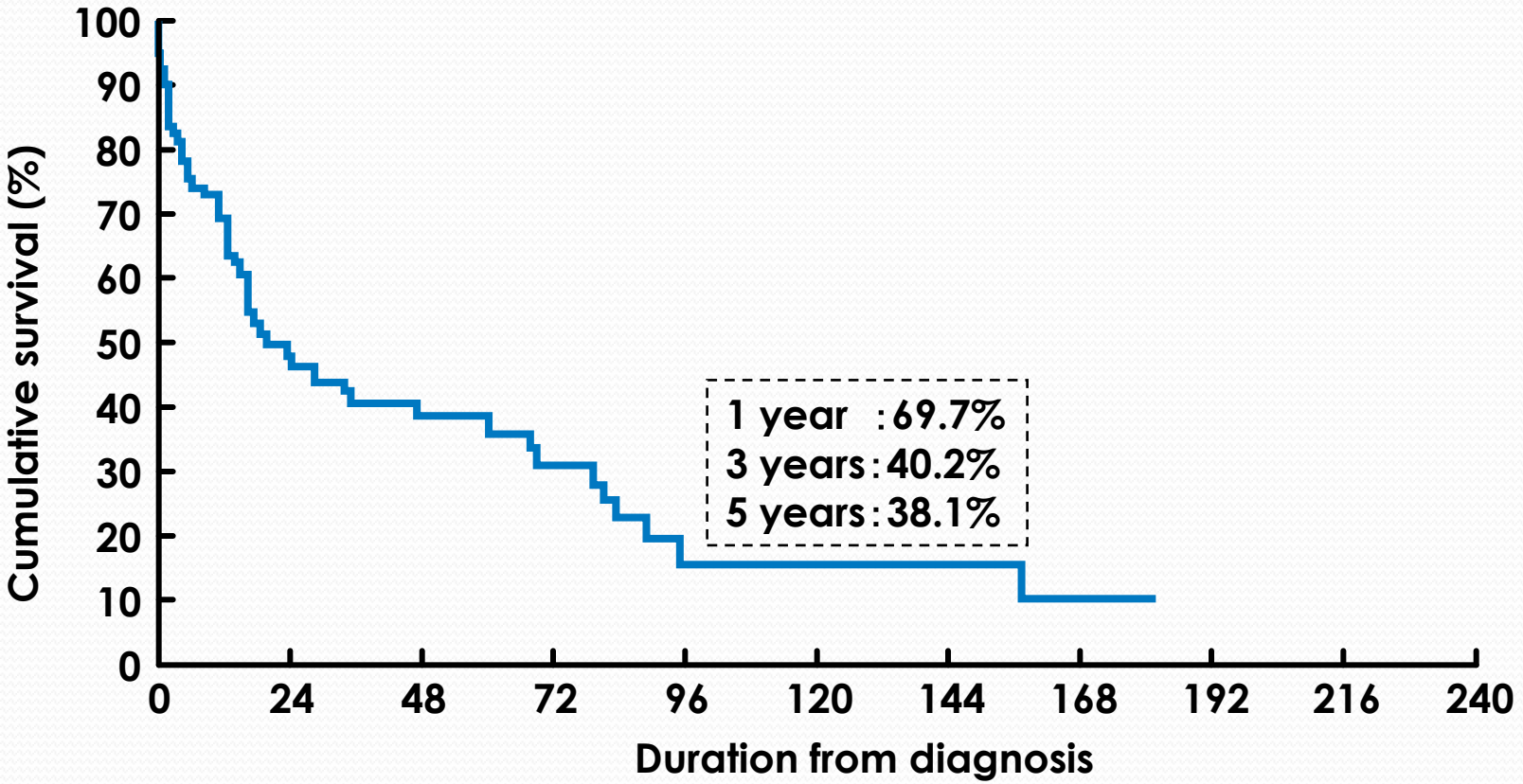
Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
Consulting Fees/Honoraria	• Actelion Pharmaceuticals, Ltd; AOP orphan Pharmaceuticals AG; Bayer, Ltd; GSK; Pfizer Japan, Inc; Nippon Shinyaku, Co, Ltd; Kaneka Medix Corporation; United therapeutics.

Survival of Japanese Patients with I/H PAH before approval of Epoprostenol

● Data from National Cardio Vascular Center



中西 宣文:“Ⅱ肺高血圧症 疫学と予後”新目でみる循環器病シリーズ16. 肺循環障害 第1版 メジカルビュー社:45, 2007[L20071217077]より改変

Survival in Patients with Primary Pulmonary Hypertension

Results from a National Prospective Registry

Gilbert E. D'Alonzo, DO; Robyn J. Barst, MD; Stephen M. Ayres, MD; Edward H. Bergofsky, MD; Bruce H. Brundage, MD; Katherine M. Detre, MD; DrPH; Alfred P. Fishman, MD; Roberta M. Goldring, MD; Berton M. Groves, MD; Janet T. Kernis, MPH; Paul S. Levy, ScD; Giuseppe G. Pietra, MD; Lynne M. Reid, MD; John T. Reeves, MD; Stuart Rich, MD; Carol E. Vreim, PhD; George W. Williams, PhD; and Margaret Wu, PhD

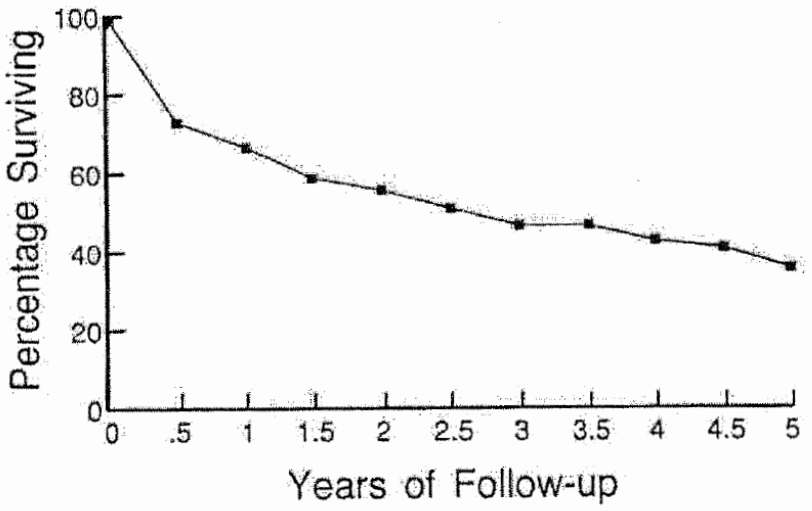


Figure 1. Estimated percentage of patients surviving over time from the baseline catheterization. Number of patients at risk are shown for 0 through 5 years. Median survival is estimated at 2.8 years. Estimated percentages of patients surviving at 1, 3, and 5 years are 68%, 48%, and 34%, respectively.

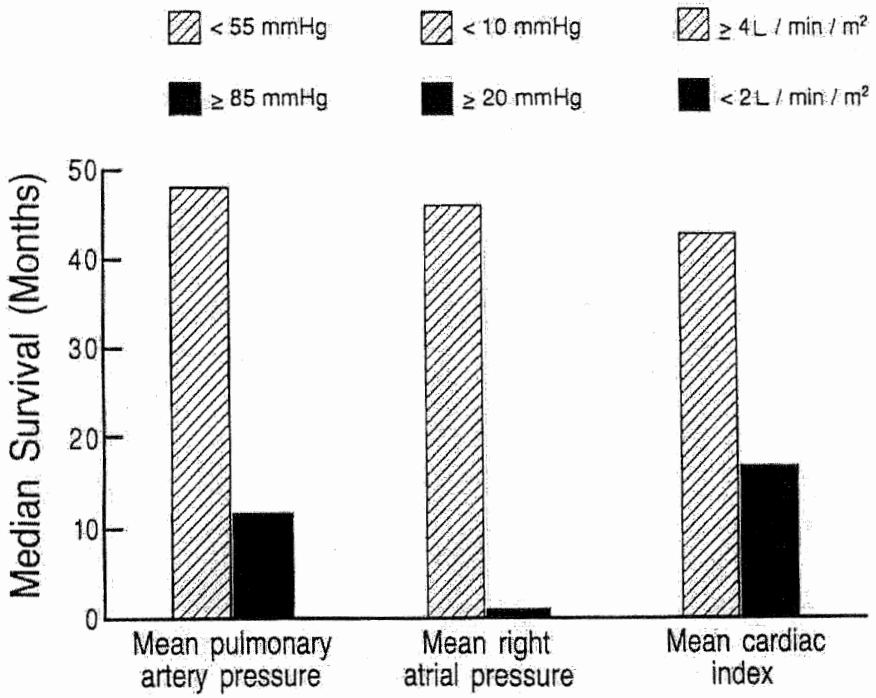
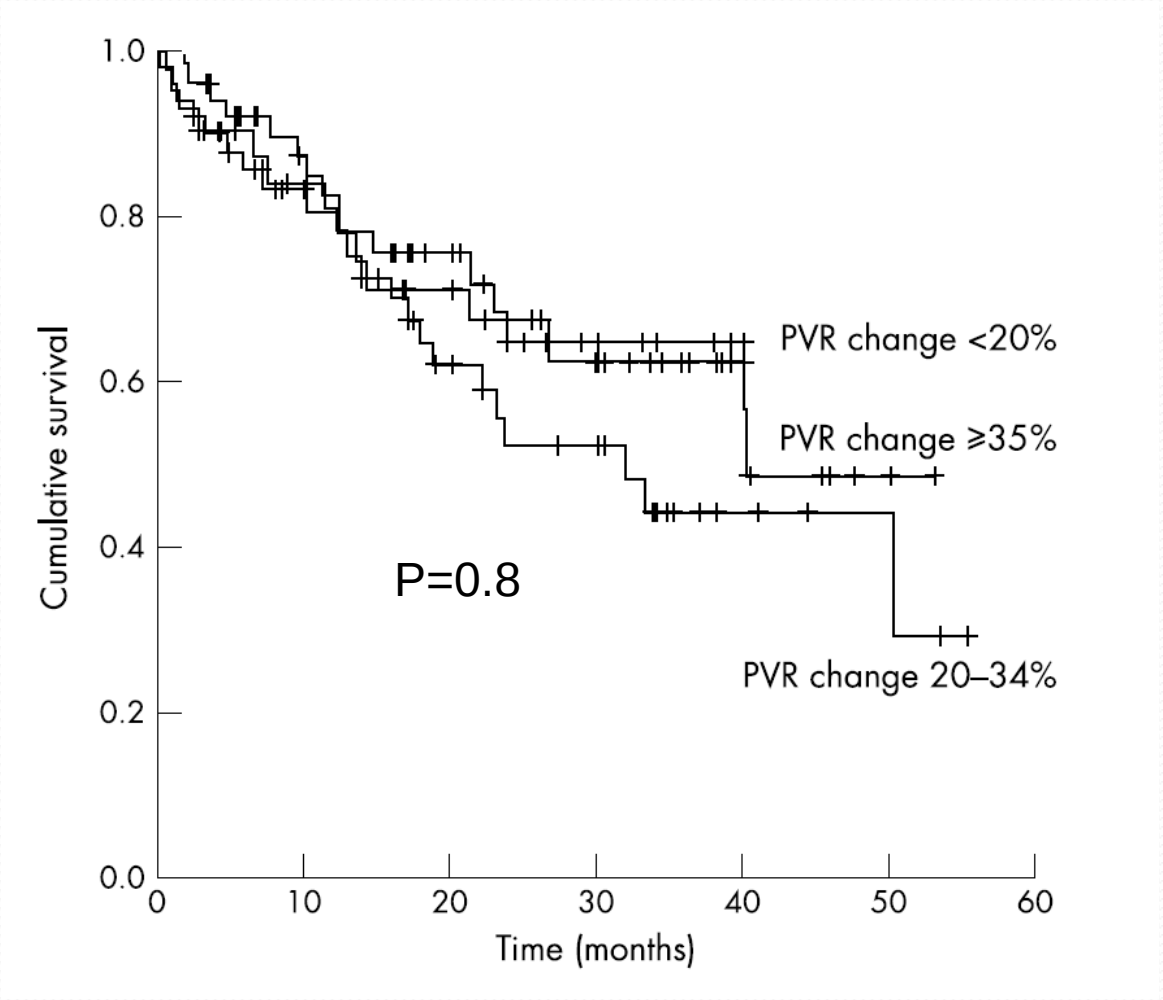
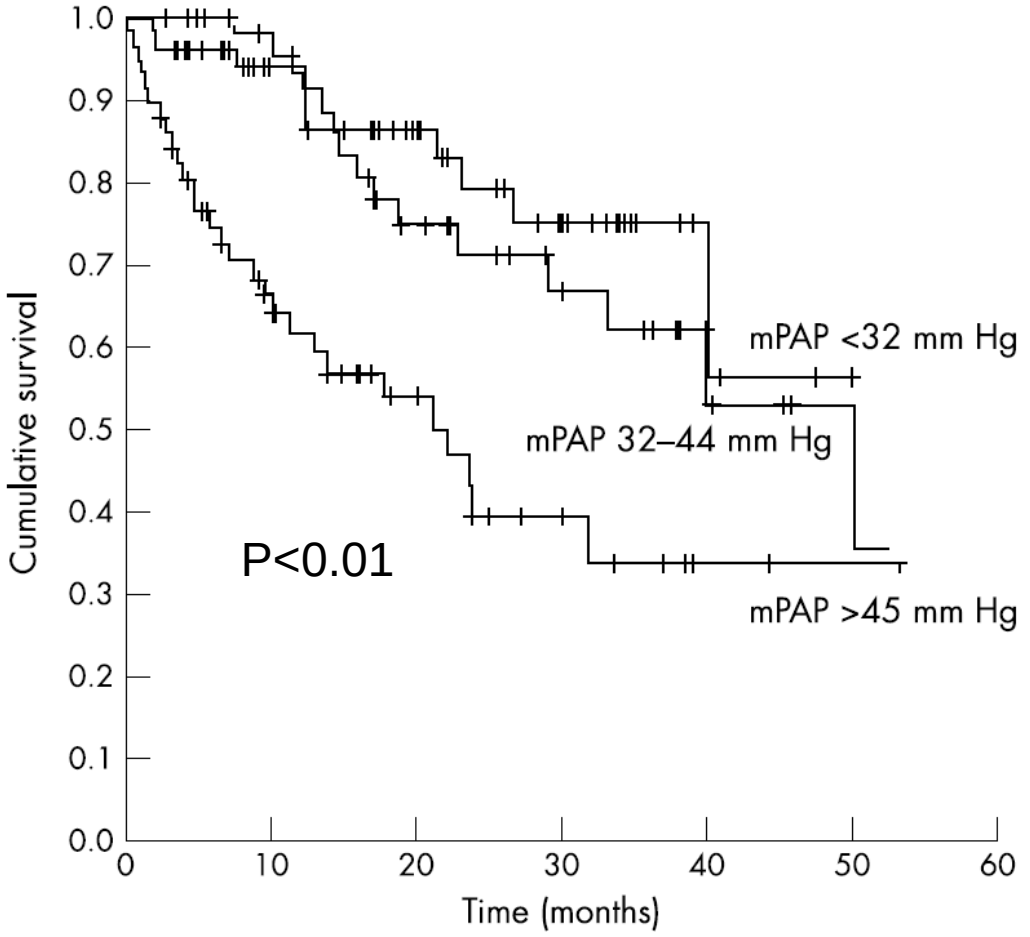


Figure 2. Median survival in months for patients with primary pulmonary hypertension compared with three hemodynamic variables.

D'Alonzo GE et al.
Ann Intern Med. 1991 Sep 1;115(5):343-9..

Survival of SScPAH patients





Mukerjee D et al.
Ann Rheum Dis 2003; 62:1088–93.

The adjusted hazard ratio for mortality according to mPAP

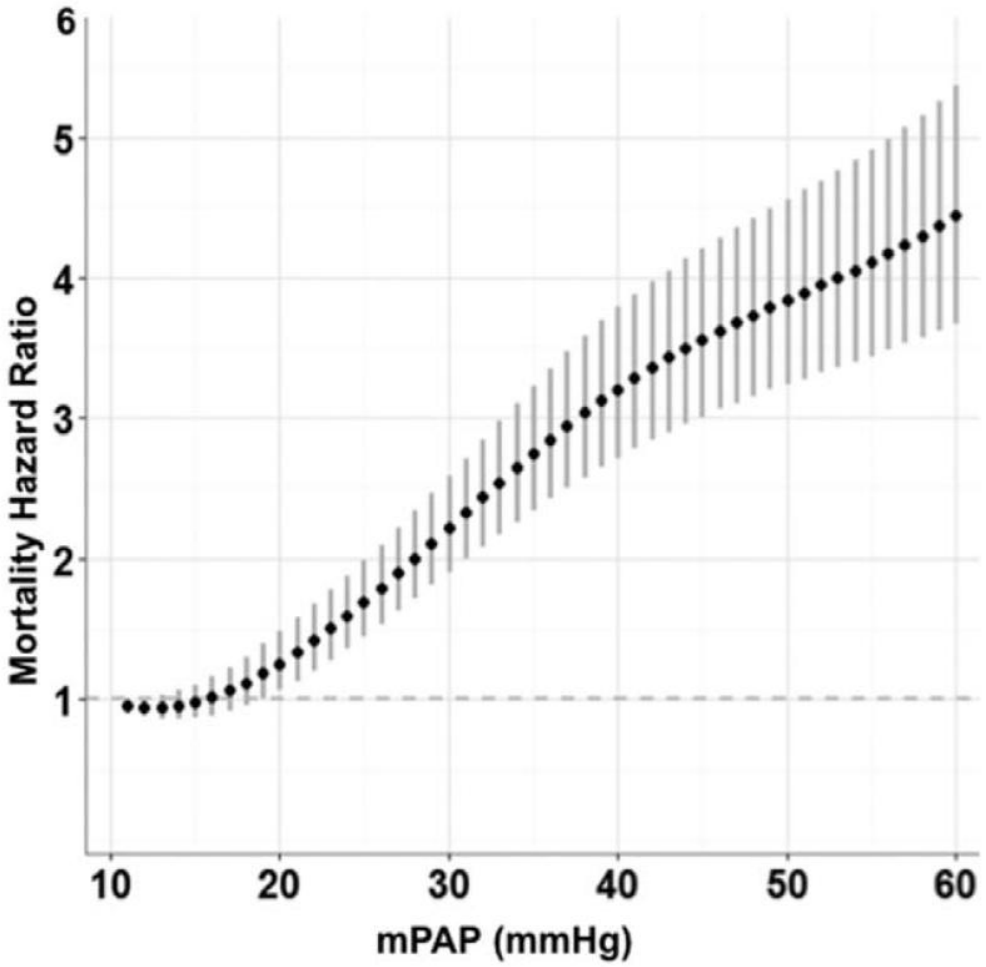
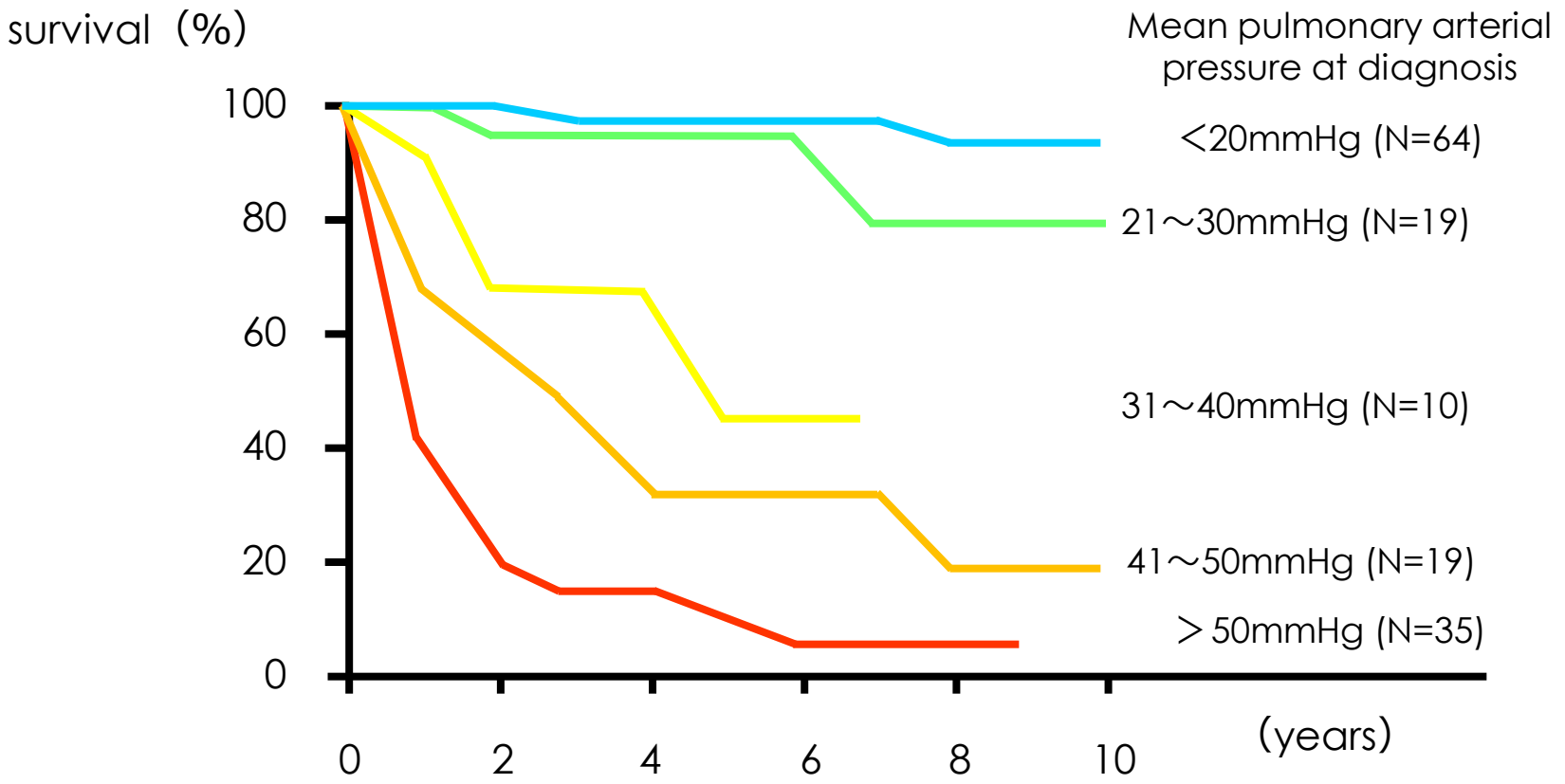


Table 1. Clinical Characteristics of Patients Stratified by Referent, Borderline PH, and PH Status

Clinical Variable	mPAP (mm Hg) ≤18 (n=4 207)	19–24 (n=5 030)	≥25 (n=12 490)	*P* Value
Age (y)	64.3 [59.6–73.0]	65.2 [60.3–73.5]	64.9 [60.2–73.4]	<0.0001
Sex (males)	96.5 (4 059)	96.6 (4 861)	96.6 (12 071)	0.8730
Body mass index categorized				<0.0001
Normal (18.5–24.9 kg/m^2)	26.2 (1 103)	18.0 (906)	17.1 (2 138)	
Underweight (<18.5 kg/m^2)	1.4 (57)	1.1 (53)	1.0 (125)	
Overweight (25–29.9 kg/m^2)	38.7 (1 628)	33.6 (1 692)	28.8 (3 603)	
Obese (≥30 kg/m^2)	33.7 (1 419)	47.3 (2 379)	53.0 (6 624)	
Systemic hypertension	82.3 (3 462)	86.0 (4 327)	89.8 (11 221)	<0.0001
Left heart failure	4.8 (201)	6.6 (333)	15.5 (1 939)	<0.0001
Congestive heart failure	34.1 (1 434)	42.7 (2 146)	67.9 (8 478)	<0.0001
Diabetes	33.4 (1 405)	40.6 (2 043)	52.6 (6 568)	<0.0001

Maron BA et al.
Circulation 2016;133:1240–8.

Reported Survival of the Patients with CTEPH



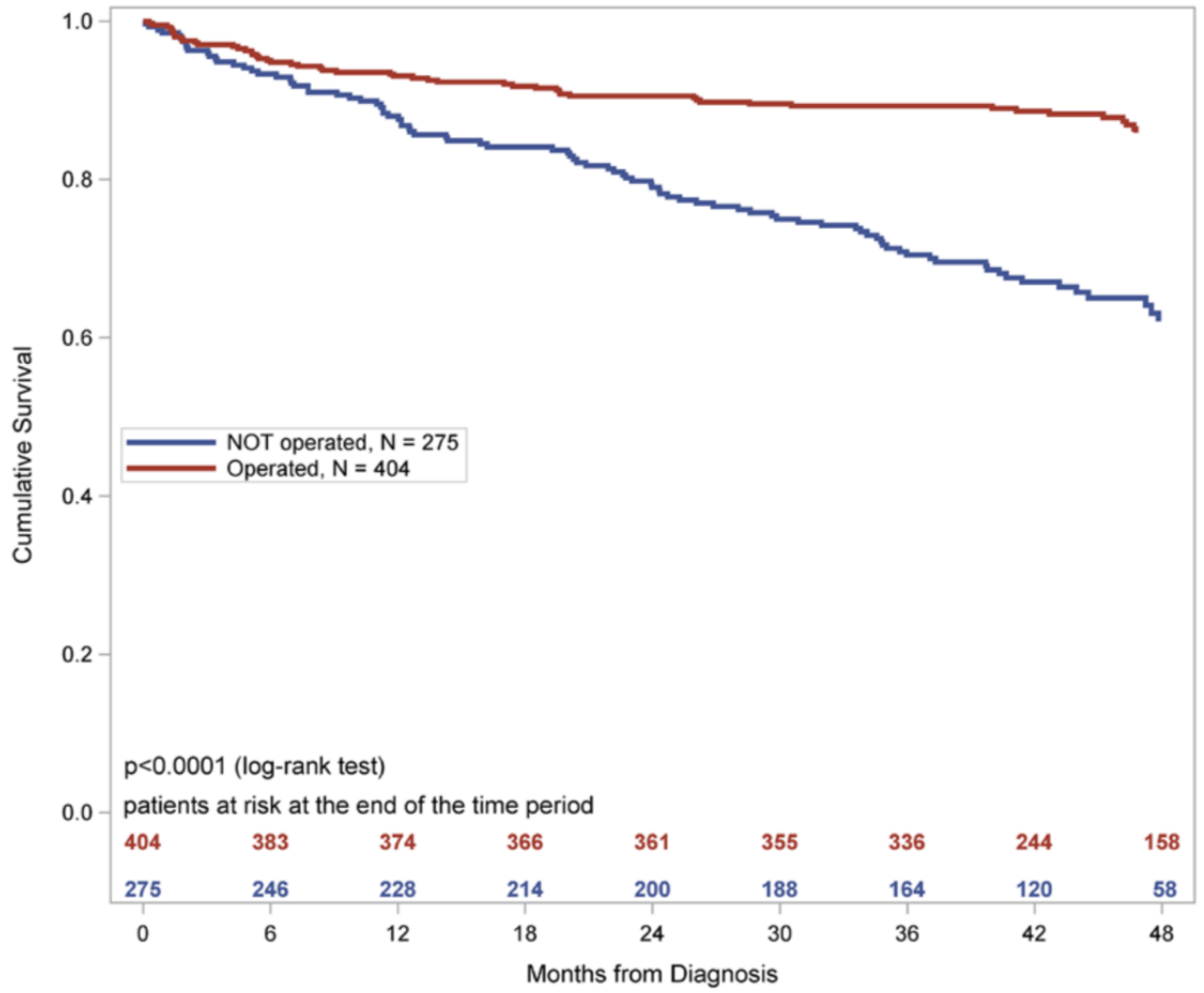
Riedel et al, Chest 1982: 81: 151-8
Lewczuk et al, Chest 2001; 119: 818-23

Background

- Pulmonary hypertension has been defined by abnormally high PA pressure.
- High PA pressure would increase the mortality of PAH patients.

Survival of the Patients with CTEPH treated by PEA

3-year Survival:
Operated = 89%
Not Operated = 70%



Delcroix M, et al. *Circulation* 2016

Mid term survival after BPA

308 patients treated in Japanese 7 centers between 2004 – 2013

	Before BPA (n=308)	After BPA (n=249)	At Follow-Up (n=196)	*P* Value
WHO FC (median)	3	2*	2*	<0.001
6MWD, m	318.1±122.1	401.3±104.8*	429.7±108.5*	<0.001
BNP, pg/mL	239.5±334.2	43.3±76.4*	38.7±71.2*	<0.001
HR, bpm	74.9±13.6	70.8±11.9*	67.3±11.0*	<0.001
mPAP, mm Hg	43.2±11.0	24.3±6.4*	22.5±5.4*	<0.001
RAP, mm Hg	6.5±4.1	3.2±2.4*	4.7±3.0*	<0.001
PAWP, mm Hg	8.6±3.3	7.3±3.1*	8.3±3.3	<0.001
CI, $L \cdot min^{-1} \cdot m^{-2}$	2.6±0.8	2.9±0.7*	2.8±0.6†	<0.001
SvO_2, %	66.3±9.1	71.5±8.0*	68.8±6.4*	<0.001
PVR, $dyne \cdot sec \cdot cm^{-5}$	853.7±450.7	359.5±222.6*	288.1±194.5*	<0.001
SaO_2, %	93.3±4.5	96.1±4.4*	94.0±5.2	<0.001

Values are expressed as mean±SD unless otherwise specified. *P* value in the right column indicates the *P* value among 3 data points. 6MWD indicates 6-minute walk distance; BNP, B-type natriuretic peptide; BPA, balloon pulmonary angioplasty; CI, cardiac index; HR, heart rate; mPAP, mean pulmonary artery pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SaO_2, arterial oxygen saturation; SvO_2, mixed venous oxygen saturation; and WHO FC, World Health Organization functional class.

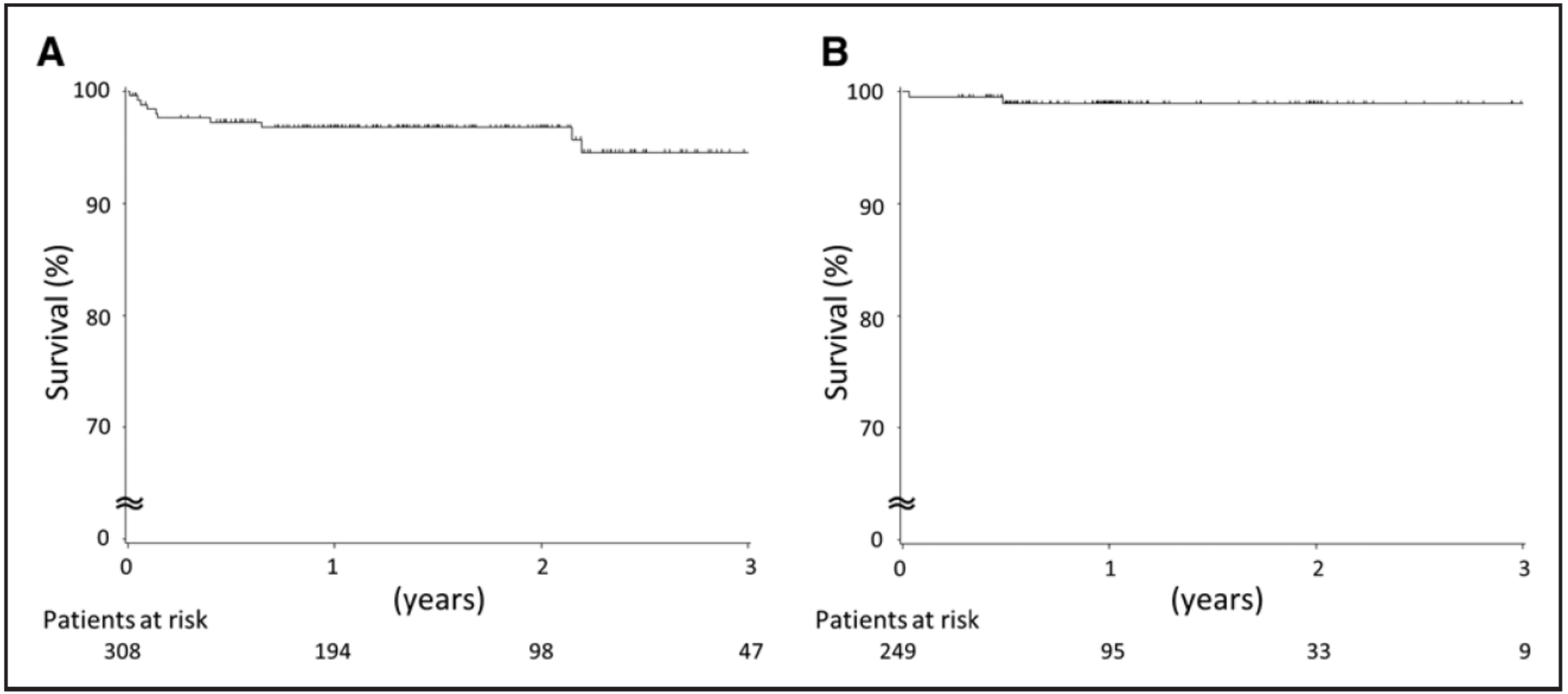
*$P<0.001$ and †$P<0.01$ versus before BPA in post hoc analysis.

Ogawa A, et al. Circ Cardiovasc Qual Outcomes. 2017 Nov;10(11). pii: e004029. doi: 10.1161/CIRCOUTCOMES.117.004029.

Mid term survival after BPA

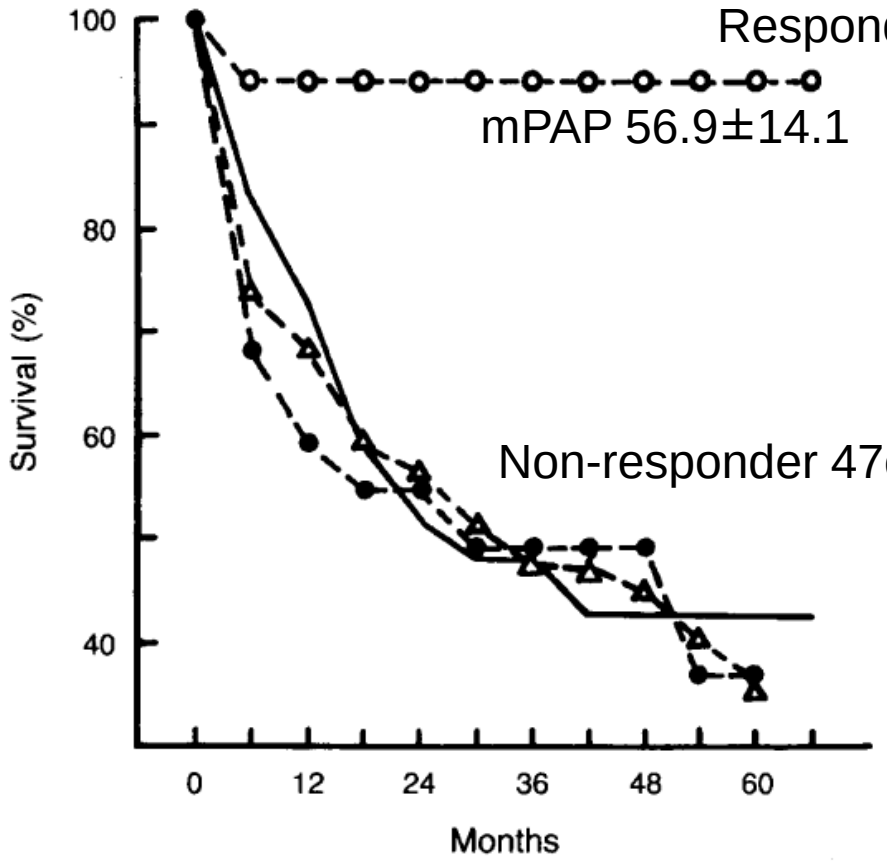
308 patients treated in Japanese 7 centers between 2004 – 2013

From the initial BPA ***From the final BPA***



Ogawa A, et al. Circ Cardiovasc Qual Outcomes. 2017 Nov;10(11). pii: e004029. doi: 10.1161/CIRCOUTCOMES.117.004029.

Effect of High Dose CCBs on Survival of the Patients with PPH



Rich S et al. N Engl J Med 1992; 327: 76-81.

Background

- Pulmonary hypertension has been defined by abnormally high PA pressure.
- High PA pressure would increase the mortality of PAH patients.
- Lowering mPAP in some PH patients could show the improvement of survival irrespective of the type of treatments.

Changes of mean PAP by each monotherapy

Drug	Amount	Pts.No.	Duration	6MWD	mPAP
Beraprost[1]	360μg/day	44	12w	+33.4m	-2.8mmHg
Bosentan[2]	250mg/day	16	12w	+70m	-1.6mmHg
Ambrisentan[3]	10mg/day	29	12w	+36.1m	-5.2mmHg
Macitentan[4]	10mg/day	49	24w	+12.5m	-5.3mmHg
Sildenafil[5]	60mg/day	65	12w	+45.0m	-2.1mmHg
Tadalafil[6]	40mg/day	79	16w	+33.0m	-4.3mmHg
Riociguat[7]	7.5mg/day	241	12w	+35m	-4mmHg
Selexipag[8]	1600μg/day	33	16w	+14m	-3.1mmHg
Treprostinil[9]	<22.5ng/kg/min	134	12w	+10m	-2.3mmHg
Epoprostenol[10]	9.2±0.8ng/kg/min	41	12w	+47m	-4.8mmHg

(1) Kunieda T et al: Int Heart J. 50:513-29, 2009 (2) Channick RN et al: Lancet. 358: 1119-23, 2001
(3) Galié N et al: J Am Coll Cardiol. 46: 529-35, 2005 (4) Pulido T et al. : N Engl J Med. 369: 809\18, 2013
(5) Galiè N et al: N Engl J Med. 353: 2148-57, 2005 (6) Galiè N et al: Circulation. 119: 2894-903, 2009
(7) Ghofrani HA et al. N Engl J Med. 369:330-40, 2013 (8) Tanabe N et al: Circ J. 81: 1360-1367, 2017
(9) Simoneau G et al: Am J Crit Care Med. 165: 800-4, 2002 (10) Barst RJ et al: N Engl J Med. 334: 296-301, 1996

Outcomes in Children With IPAH

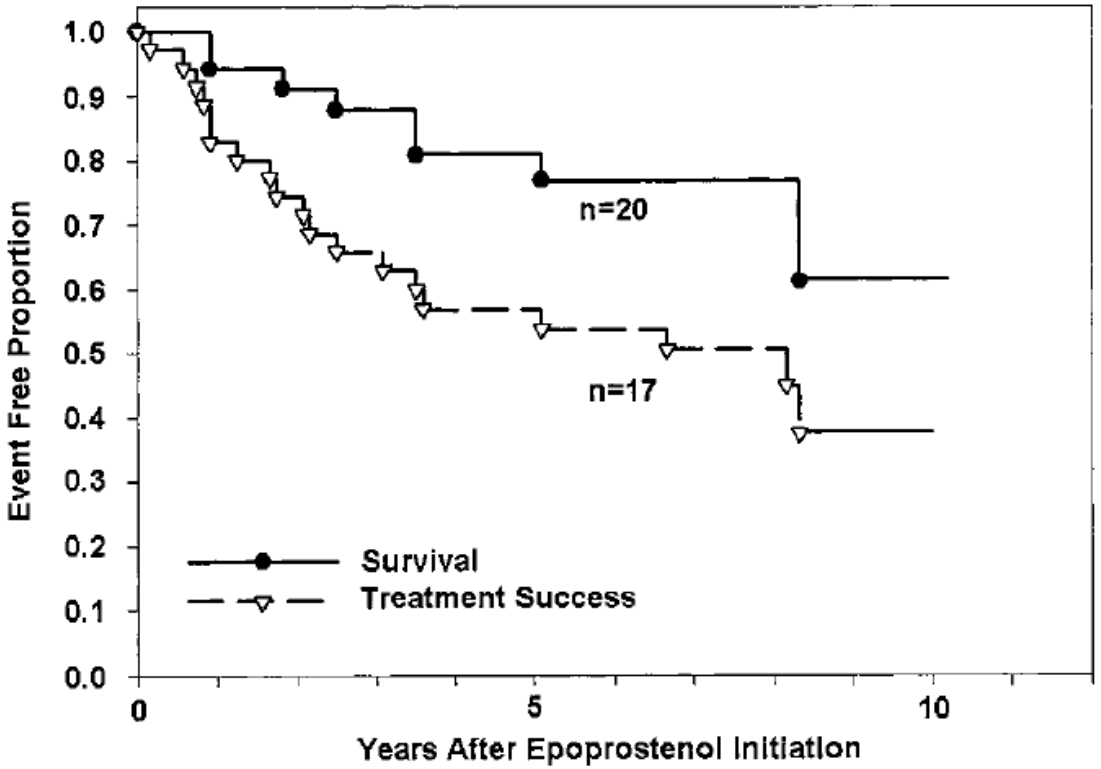


Figure 2. Kaplan-Meier curves for survival and treatment success in all patients who received epoprostenol (n=35). Survival rates at 1, 3, 5, and 10 years were 94%, 88%, 81%, and 61%, respectively; treatment success rates at 1, 3, 5, and 10 years were 83%, 66%, 57%, and 37%, respectively.

TABLE 6. Hemodynamic Effects of Long-Term Epoprostenol in Children Treated With Epoprostenol

	At Start of Epoprostenol	Last Follow-Up*	Mean Change (95% CI)
PAPm, mm Hg	76±22	57±26	−19 (−27 to −11)†
RAPm, mm Hg	5±3	6±4	1.0 (−0.6 to 2.7)
CI, $L \cdot min^{-1} \cdot m^{-2}$	3.1±1.1	4.5±1.8	1.5 (0.8 to 2.1)†
PVR, $U \cdot m^2$	26±13	12±9	−14 (−19 to −9)†
$S\bar{v}O_2$, %	64±8	72±7	7 (3 to 12)†

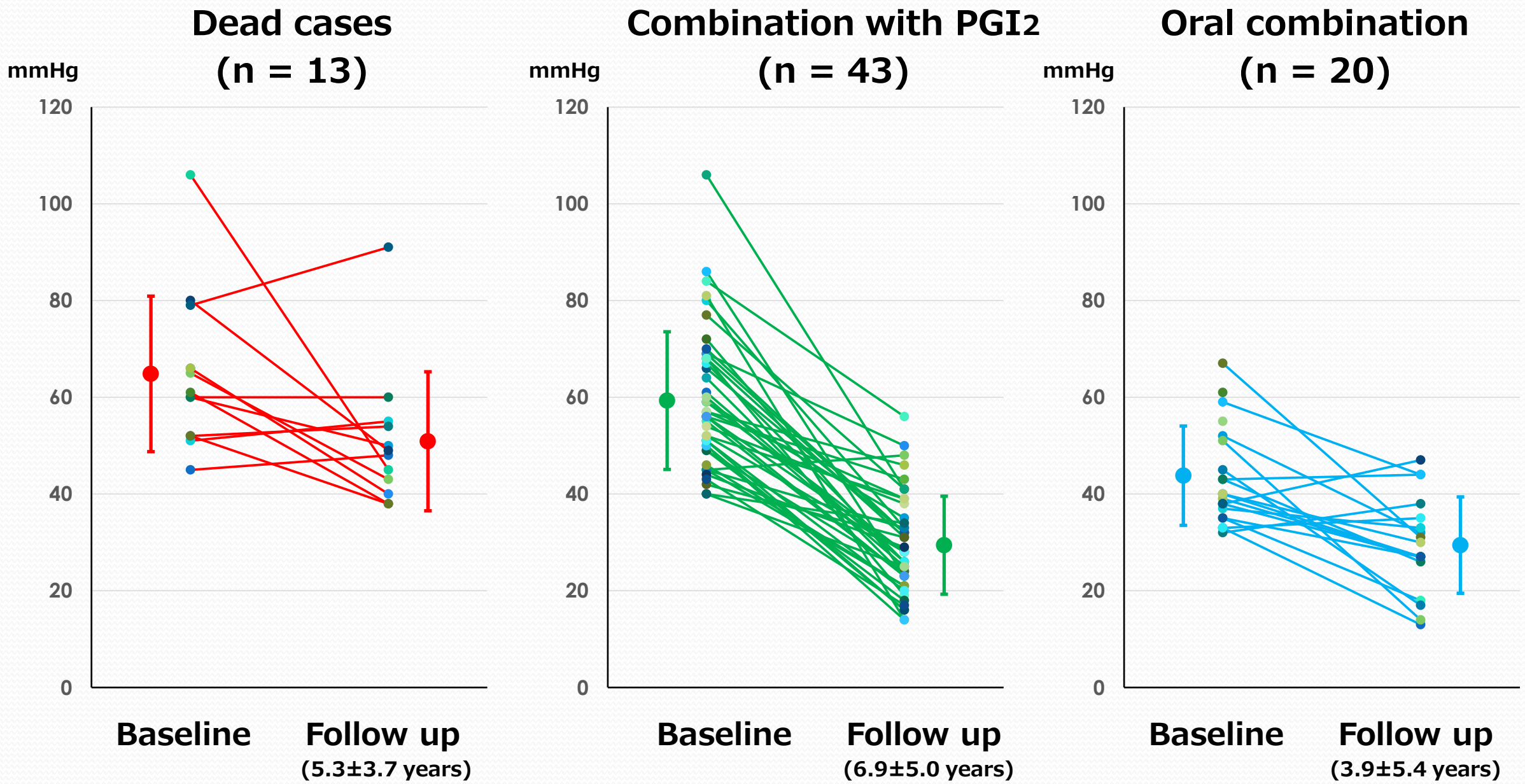
Abbreviations as in Table 1. n=31.

*Time from start of epoprostenol to last cardiac catheterization was 53±28 months (range, 9 to 102 months).

†$P<0.05$.

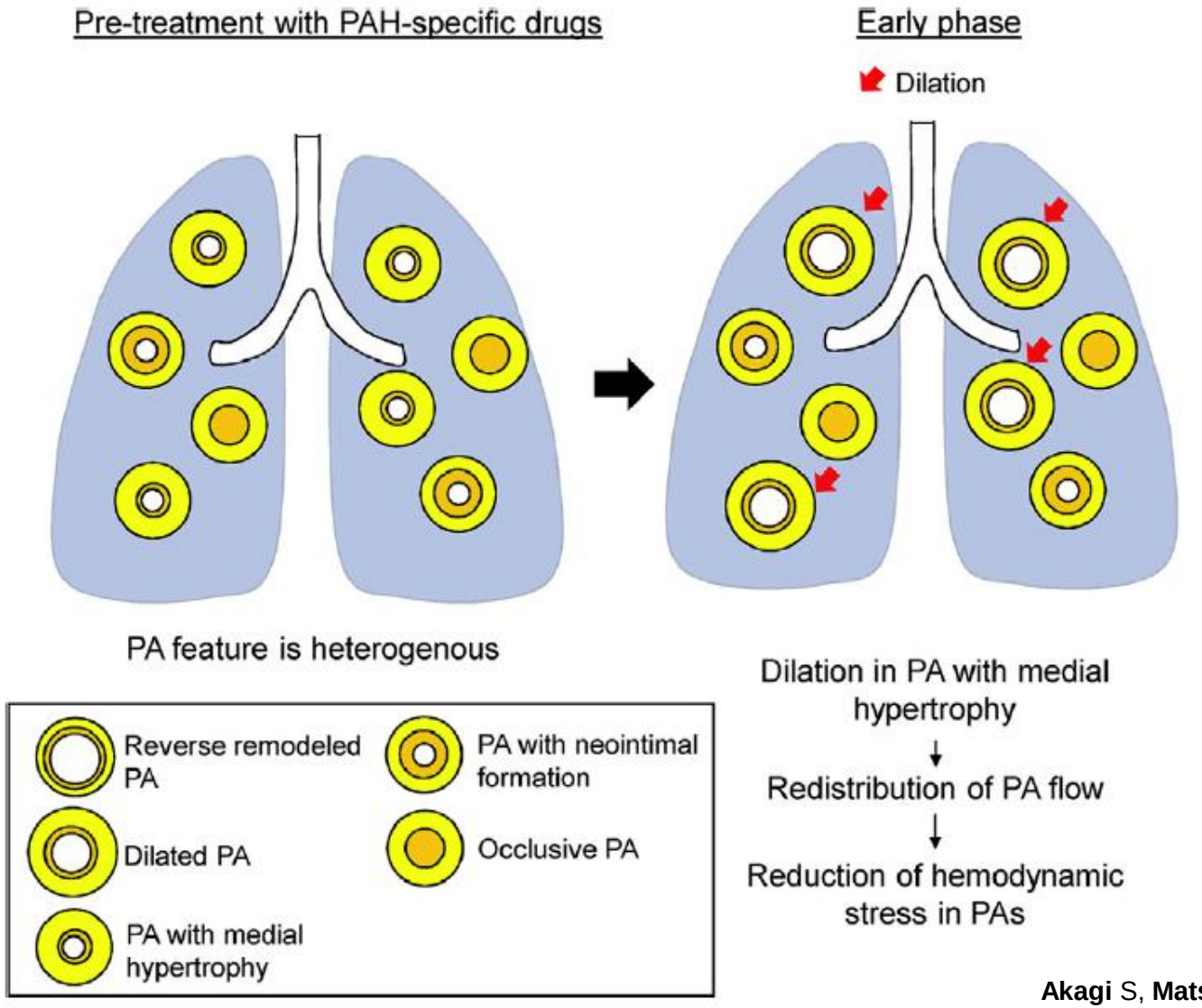
Yung D et al.
Circulation. 2004;110:660-665.

Changes of mPAP in I/H PAH patients treated at OMC



Unpublished data.

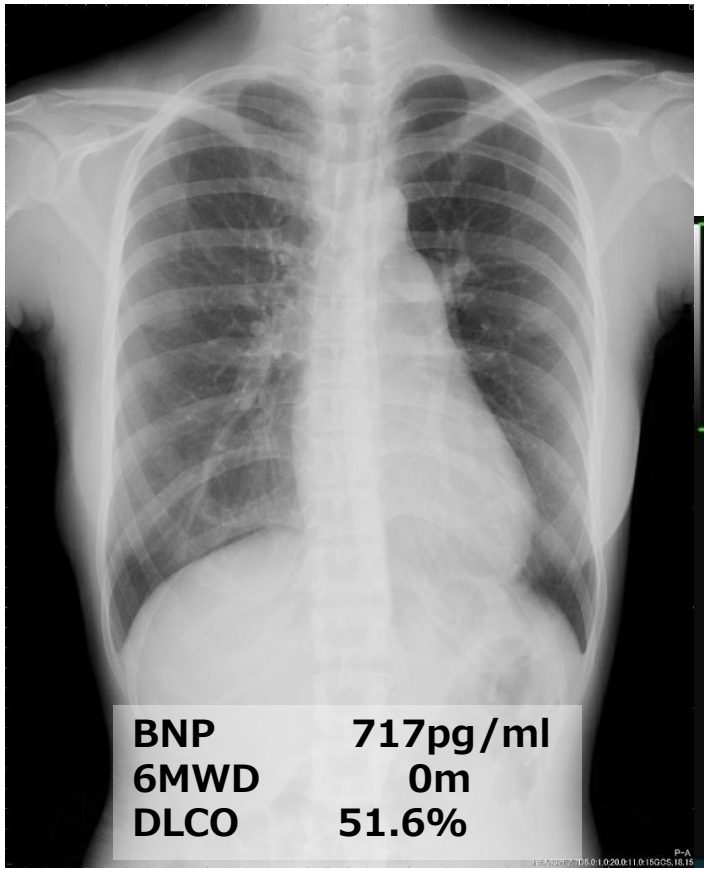
Speculated pathological change treated with PAH-specific drugs to maximally lowering PAP.

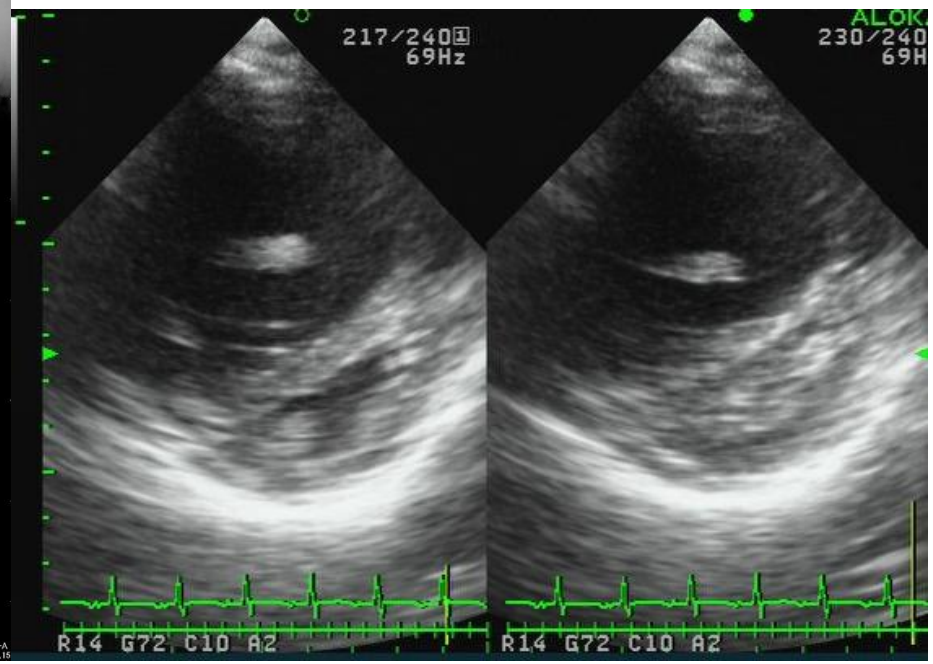


Akagi S, **Matsubara** H, Nakamura K, Ito H.
J Cardiol. 2018 Jun 10. pii: S0914-5087(18)30137-0. doi: 10.1016/j.jjcc.2018.04.014.

IPAH 33y.o. female

22/Nov/2007





Aug 2007 diagnosed as IPAH, FC III
prescribed Bosentan

Oct 2007 deteriorated to FC IV
referred to OMC

On admission

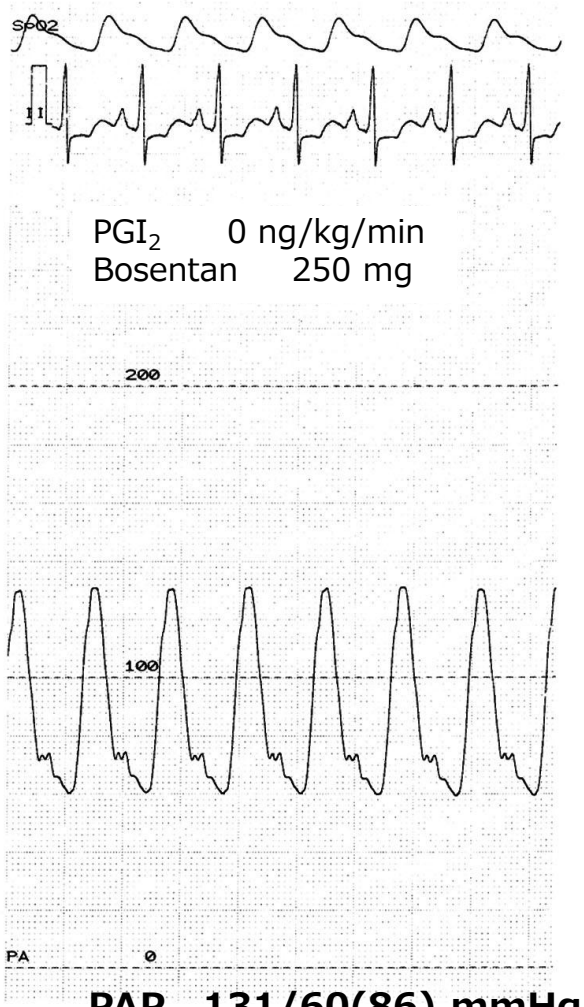
PAP 131/60(86) mmHg

CO/CI 2.9/2.1

PVR 25.2 WU

IPAH 33y.o. female

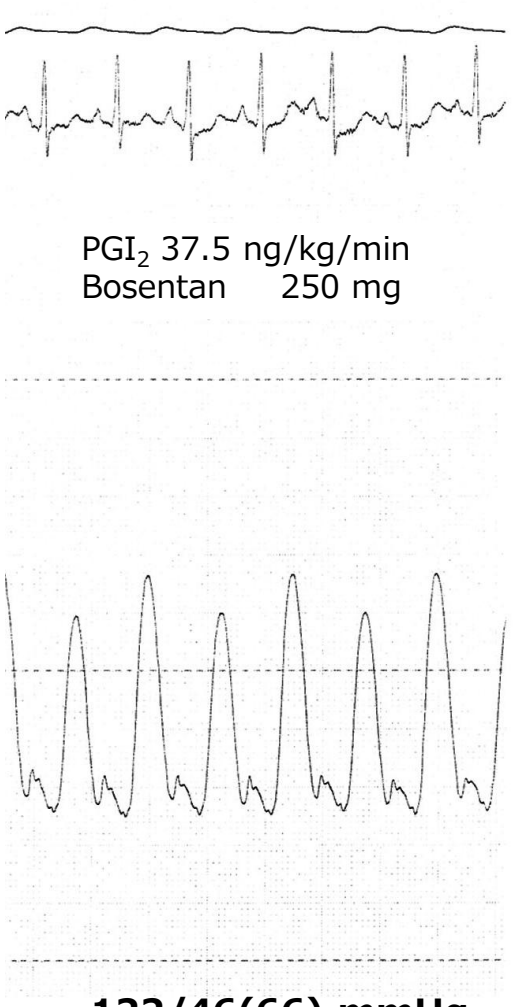
22/Nov/2007



PGI_2 0 ng/kg/min
Bosentan 250 mg

PAP 131/60(86) mmHg
CO/CI 2.9/2.1
PVR 25.2 WU

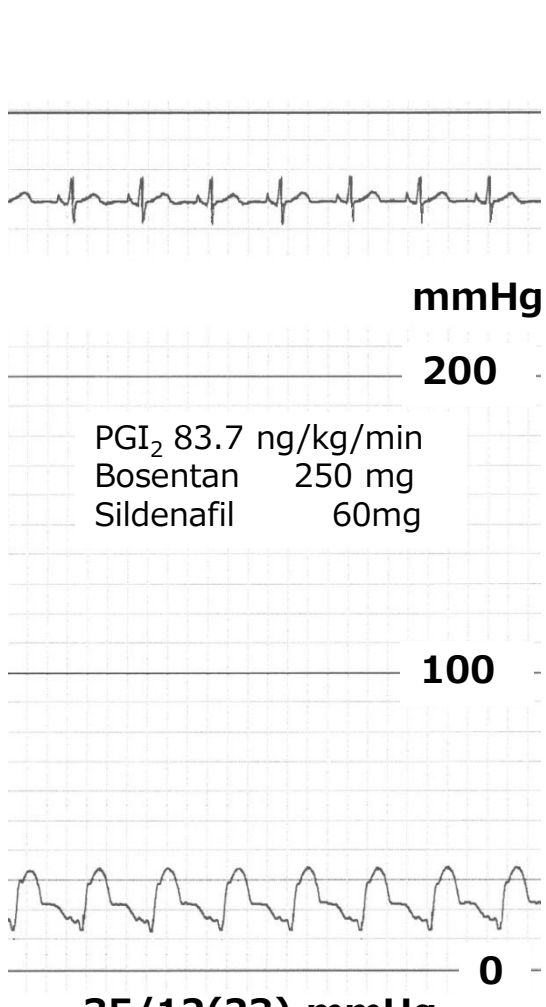
18/Jan/2008



PGI_2 37.5 ng/kg/min
Bosentan 250 mg

122/46(66) mmHg
4.4/3.2
10 WU

19/May/2011

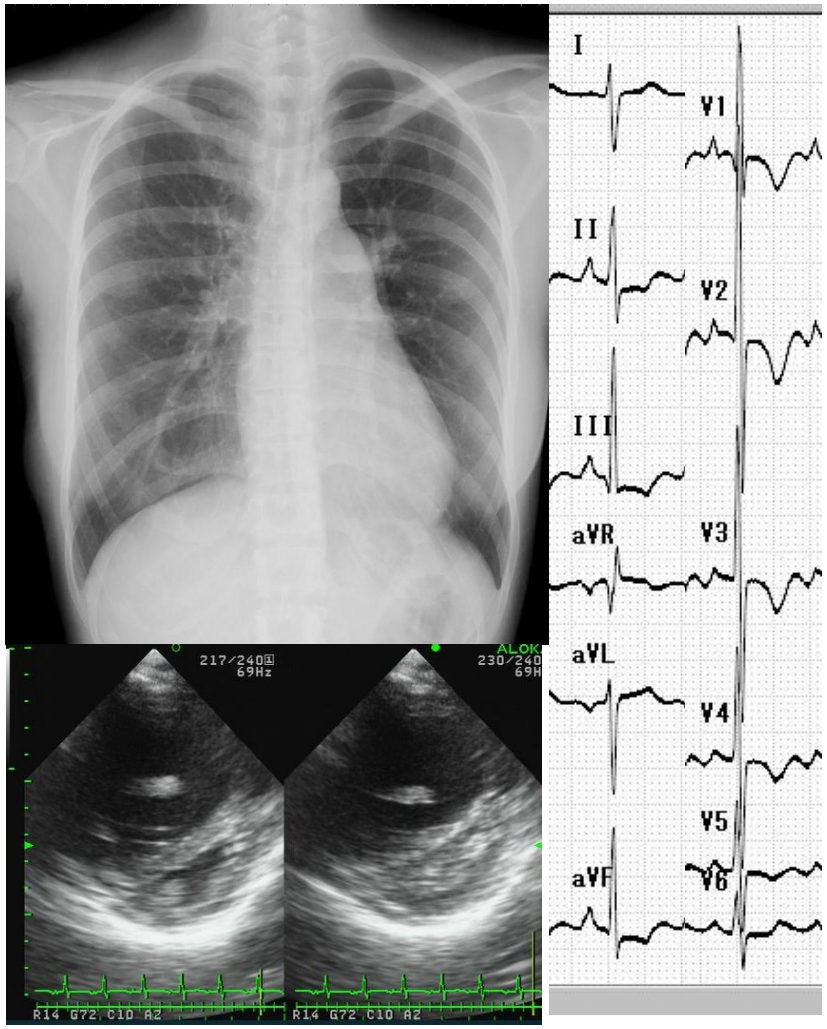


PGI_2 83.7 ng/kg/min
Bosentan 250 mg
Sildenafil 60mg

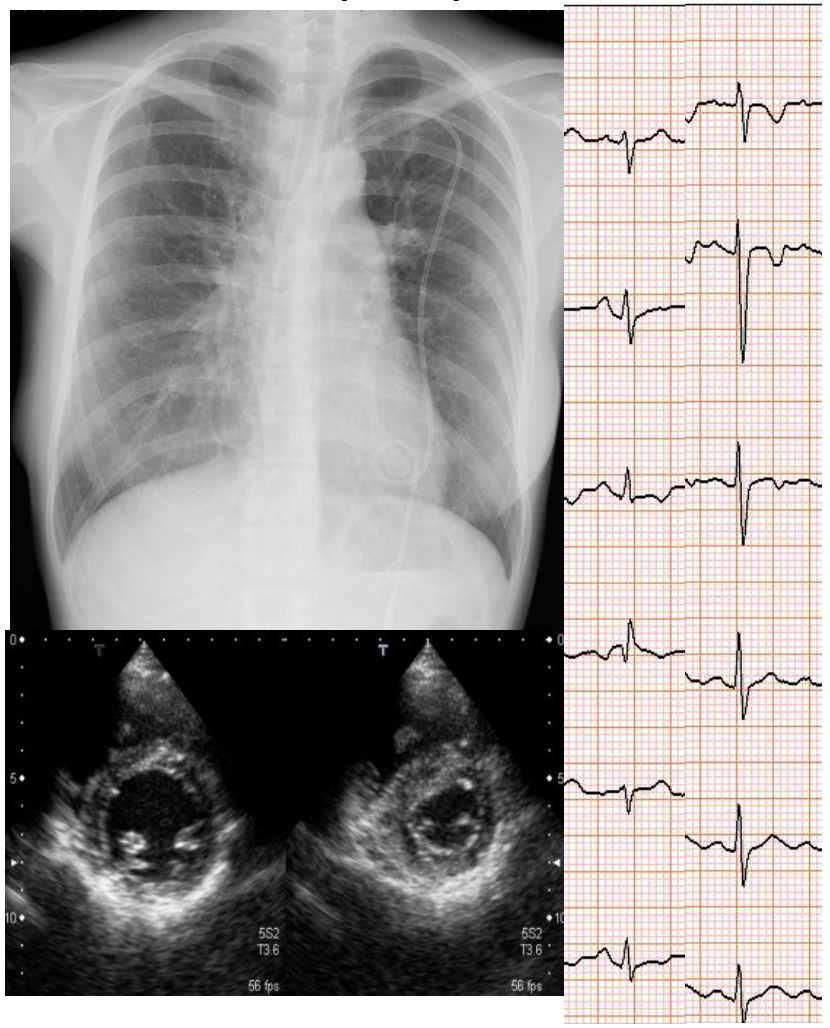
35/12(23) mmHg
6.0/4.2
2.2 WU

IPAH 33y.o. female

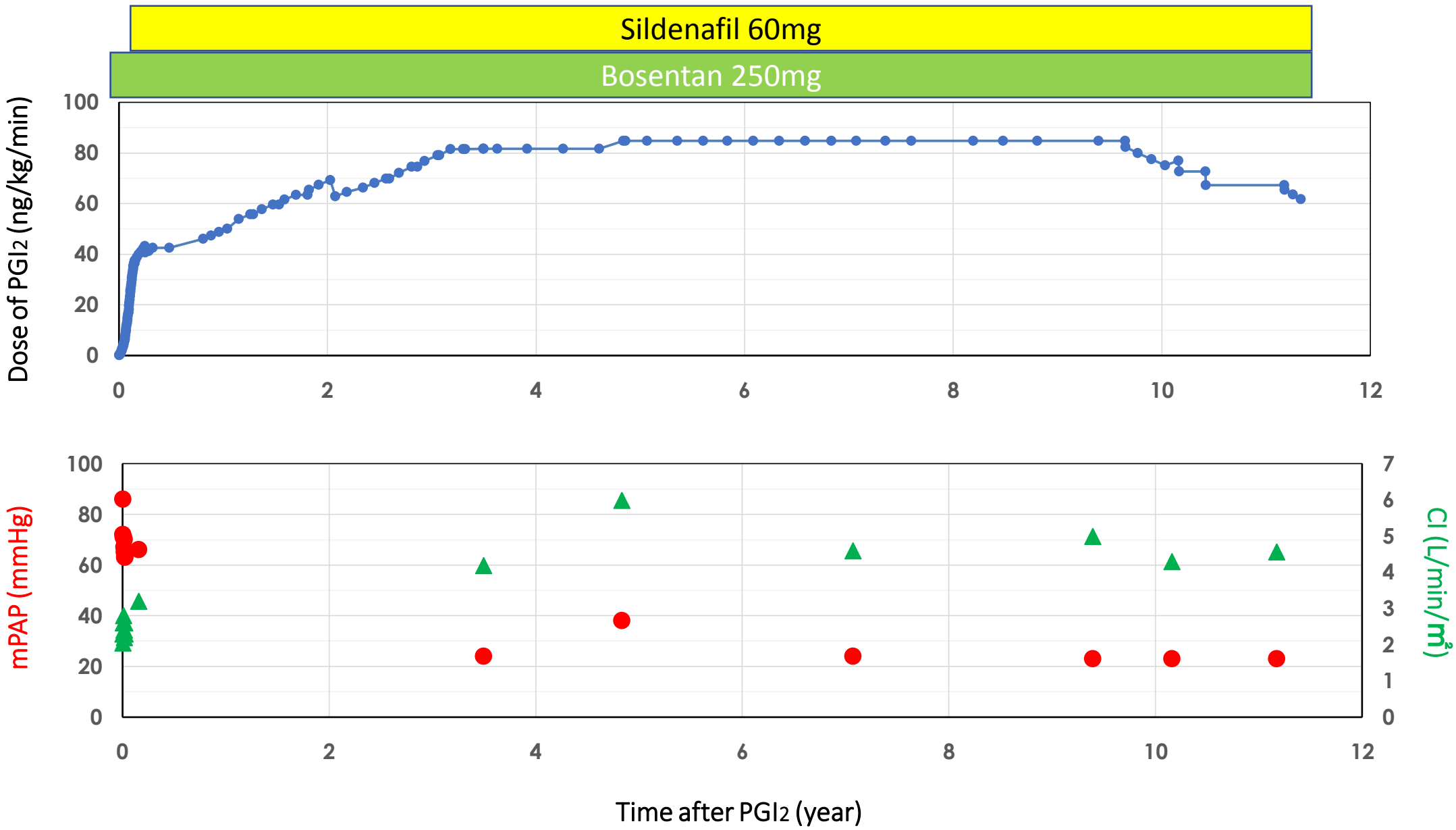
22/Nov/2007



19/Mar/2011



Clinical course（33 y.o. Female, IPAH）



Relation between Survival and Lowest mPAP Achieved after Medication

Clinical and hemodynamic data of survivors and non-survivors at baseline.

	Survivor ($n = 49$)	Non-survivor ($n = 7$)	P
Age, years	33 ± 18	25 ± 10	0.26
Male, *n* (%)	14 (29)	1 (14)	0.43
HPAH, *n* (%)	10 (20)	0 (0)	0.41
WHO functional class (I/II/III/IV)	3 (0/2/34/13)	4 (0/0/2/5)	<0.01
6MWD (m)	257 ± 166	103 ± 179	<0.05
BNP (pg/mL)	260 ± 307	705 ± 556	<0.01
Uric acid (mg/dL)	6.3 ± 2.0	6.7 ± 1.0	0.66
mPAP (mm Hg)	61 ± 17	62 ± 14	0.95
RAP (mm Hg)	8 ± 4	13 ± 9	<0.05
PCWP (mm Hg)	9 ± 3	10 ± 5	0.82
SvO_2 (%)	66.1 ± 8.7	65.4 ± 10.1	0.86
Cardiac index (L/min/m^2)	2.4 ± 0.9	2.4 ± 0.9	0.82
PVR (dyn·s/cm^5)	1391 ± 615	1375 ± 537	0.96
Heart rate (bpm)	74 ± 16	86 ± 15	0.07
SpO_2 (%)	97 ± 3	95 ± 3	0.08
Treatment			
Oral PGI_2	9 (18)	0 (0)	0.22
IV PGI_2	37 (76)	6 (86)	0.55
Dose of epoprostenol (ng/kg/min)	79.6 ± 43.2	54.0 ± 47.8	0.19
ERA	34 (69)	4 (57)	0.52
PDE5 inhibitor	28 (57)	1 (14)	<0.05
Monotherapy	10 (20)	3 (43)	0.24
Combination therapy	38 (78)	4 (57)	0.24
Number of PAH-targeted drugs: 2	16 (33)	4 (57)	0.21
Number of PAH-targeted drugs: 3	22 (45)	0 (0)	<0.05
Warfarin	11 (22)	2 (29)	0.72
Oxygen therapy	46 (94)	7 (100)	0.50

Values other than WHO functional class are expressed as mean ± SD. WHO functional class is presented as the median and number of patients in each class. HPAH: hereditary pulmonary arterial hypertension, 6MWD: 6-miute walk distance, BNP: brain natriuretic peptide, mPAP: mean pulmonary arterial pressure, RAP: right atrial pressure, PCWP: pulmonary capillary wedge pressure; SvO_2: mixed venous oxygen saturation; PVR: pulmonary vascular resistance, SpO_2: oxygen saturation, PGI_2: prostacyclin; IV: intravenous; ERA: endothelin receptor antagonist, and PDE5: phosphodiesterase type 5.

Clinical and hemodynamic data before and after treatment.

	Baseline	Follow-up	P
Age, years	32 ± 17		
WHO functional class (I/II/III/IV)	3 (0/1/38/17)	2 (0/38/15/3)	<0.01
6MWD (m)	234 ± 174	378 ± 114	<0.01
BNP (pg/mL)	313 ± 372	67 ± 156	<0.01
Uric acid (mg/dL)	6.4 ± 1.9	6.2 ± 1.7	0.70
mPAP (mm Hg)	63 ± 15	35 ± 10	<0.01
RAP (mm Hg)	8 ± 4	5 ± 4	<0.01
PCWP (mm Hg)	9 ± 3	8 ± 4	0.31
SvO_2 (%)	66.2 ± 8.9	77.2 ± 5.7	<0.01
Cardiac index (L/min/m^2)	2.3 ± 0.8	3.5 ± 0.9	<0.01
PVR (dyn·s/cm^5)	1473 ± 600	481 ± 421	<0.01
Heart rate (bpm)	76 ± 17	82 ± 18	0.09
SpO_2 (%)	97 ± 3	98 ± 3	0.14

Abbreviations are as stated in Table 1. Data were evaluated in 56 patients except for hemodynamic parameters, that were evaluated in 43 patients who underwent follow-up right-heart catheterization >3 months after initial catheterization at our hospital.

Ogawa A et al.
LifeSciences118(2014)414–419.

Initiation Timing of Parenteral PGI_2 -patients' characteristics (1)-

	Early group (n=13)	Late group (n=11)	P
Age at Dx (y.o.)	28.5 ± 8.3	24.6 ± 11.6	
male/female	3/10	4/7	
IPAH/HPAH	1/12	1/10	
WHO Functional Class (II/III/IV)	0/11/2	1/7/3	
BNP (pg/ml)	338 ± 448	382 ± 328	0.79
RHC at Dx			
mPAP (mmHg)	59.8 ± 11.8	64.7 ± 14.9	0.38
CI ($L/min/m^2$)	2.3 ± 0.6	2.3 ± 0.6	0.77
PVR ($dynes \cdot sec \cdot cm^{-5}$)	1305 ± 434	1313 ± 528	0.97

Mean ± SD

Unpublished data.

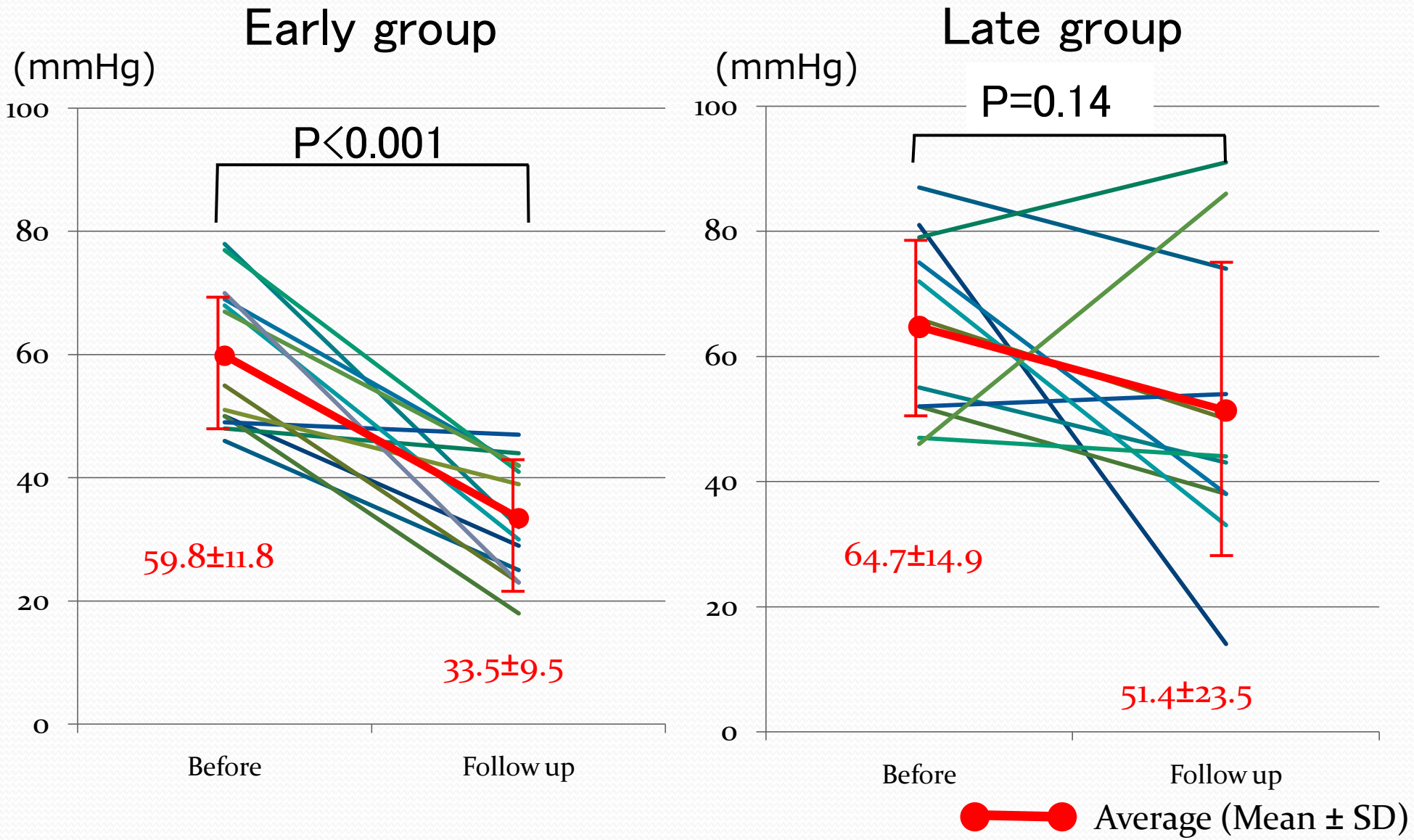
Initiation Timing of Parenteral PGI_2 -patients' characteristics (2)-

	Early group (n=13)	Late group (n=11)	P
Therapy duration (y)	7.3 ± 3.0	6.9 ± 2.8	0.78
ERA/PDE5I～PGI_2 (day)	39.1 ± 53.4	642.2 ± 361.1	
Epo/Tre	12/1	11/0	
Dosage of PGI_2 (ng/kg/min)	82.4 ± 39.3	73.3 ± 48.2	0.61
Oral drugs			
ERA	12	10	
PDE5I	10	6	
Mono(ERA or PDE5I)	4	4	
Dual(ERA + PDE5I)	9	6	

Mean ± SD

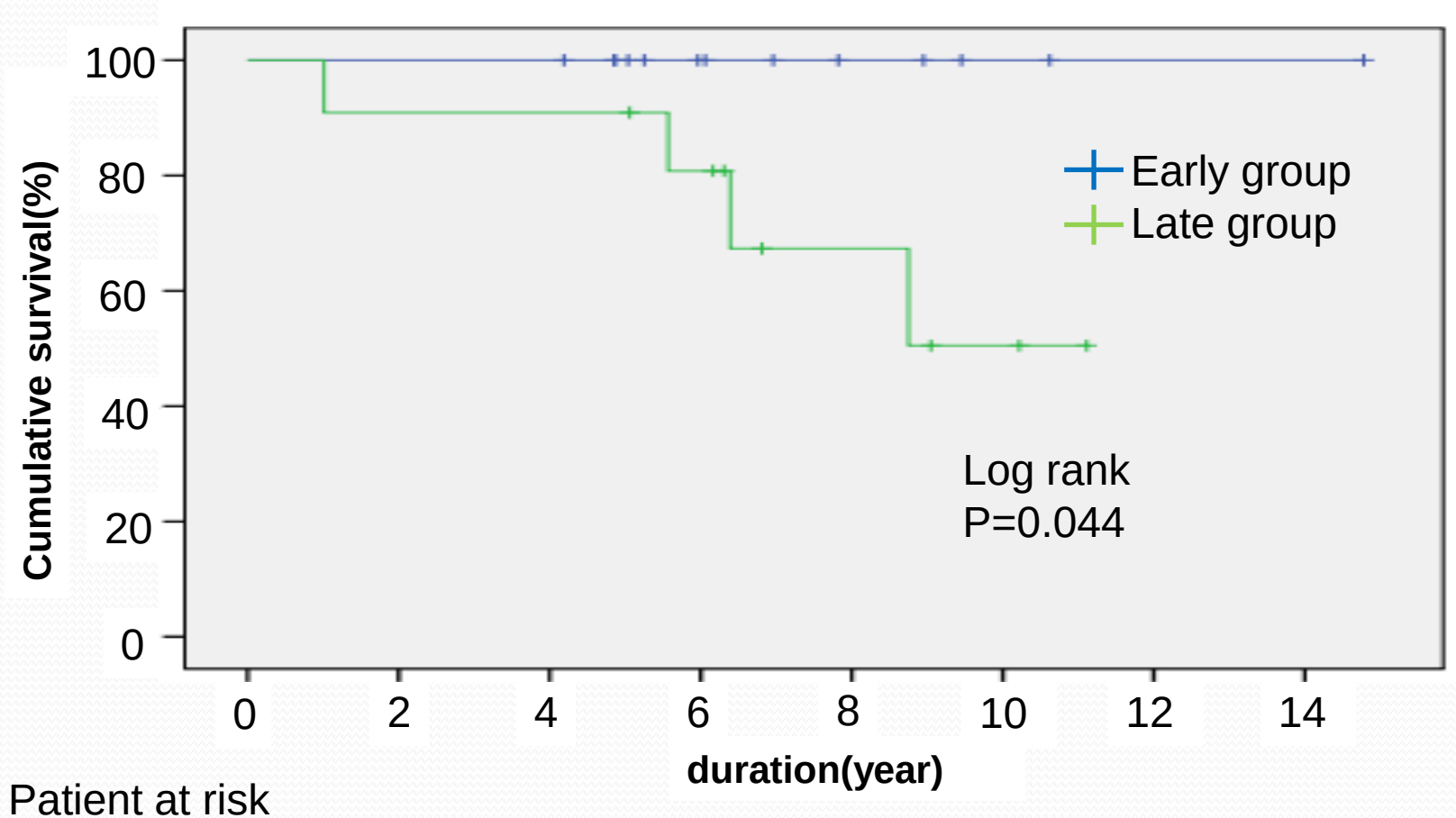
Unpublished data.

Changes in mPAP



Unpublished data.

Long term survival

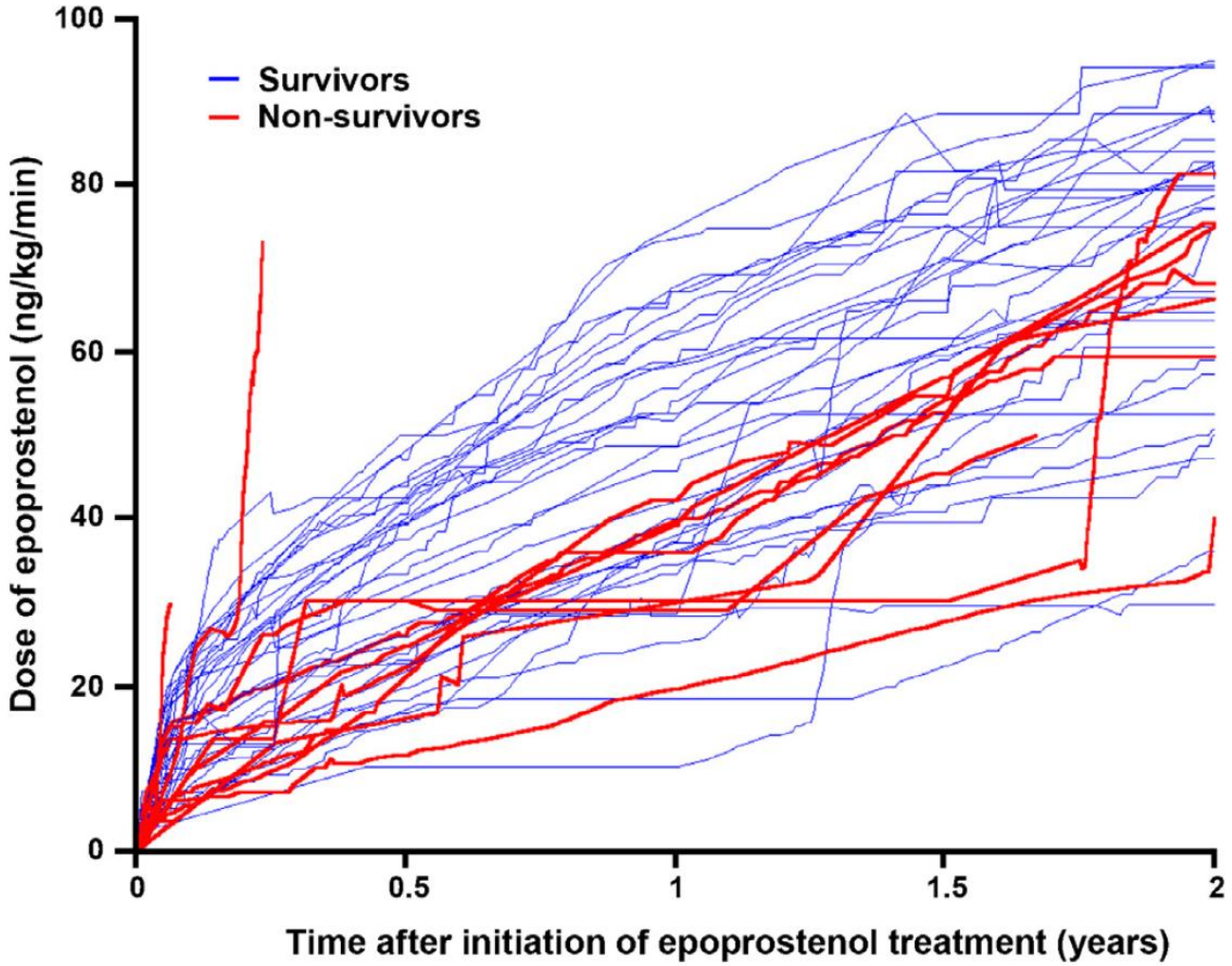


Patient at risk

Early	13	13	13	7	4	2	1	1
Late	11	10	10	8	4	2	0	0

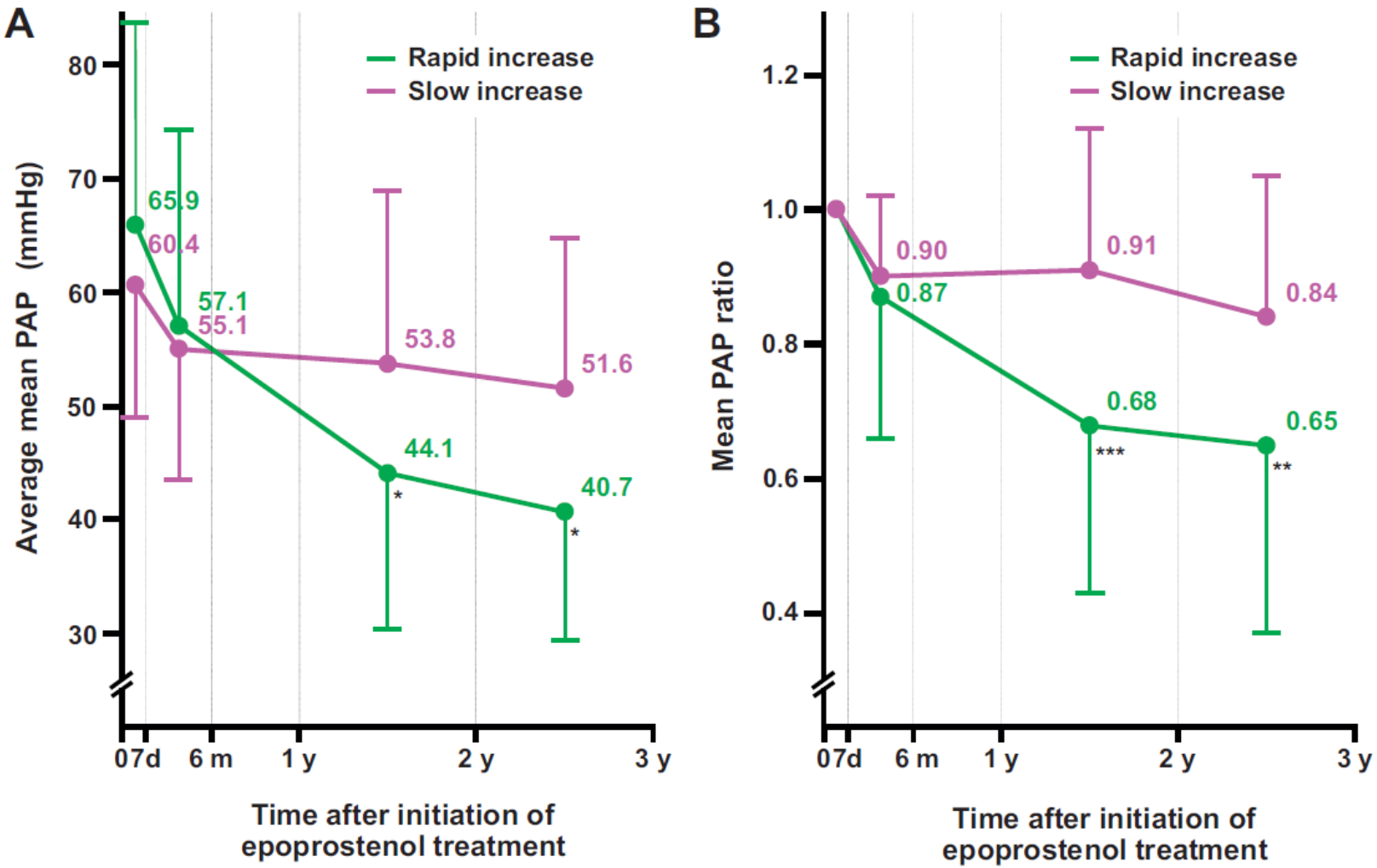
Unpublished data.

Dosing of Epoprostenol in Patients Treated in OMC and Okayama University Hospital



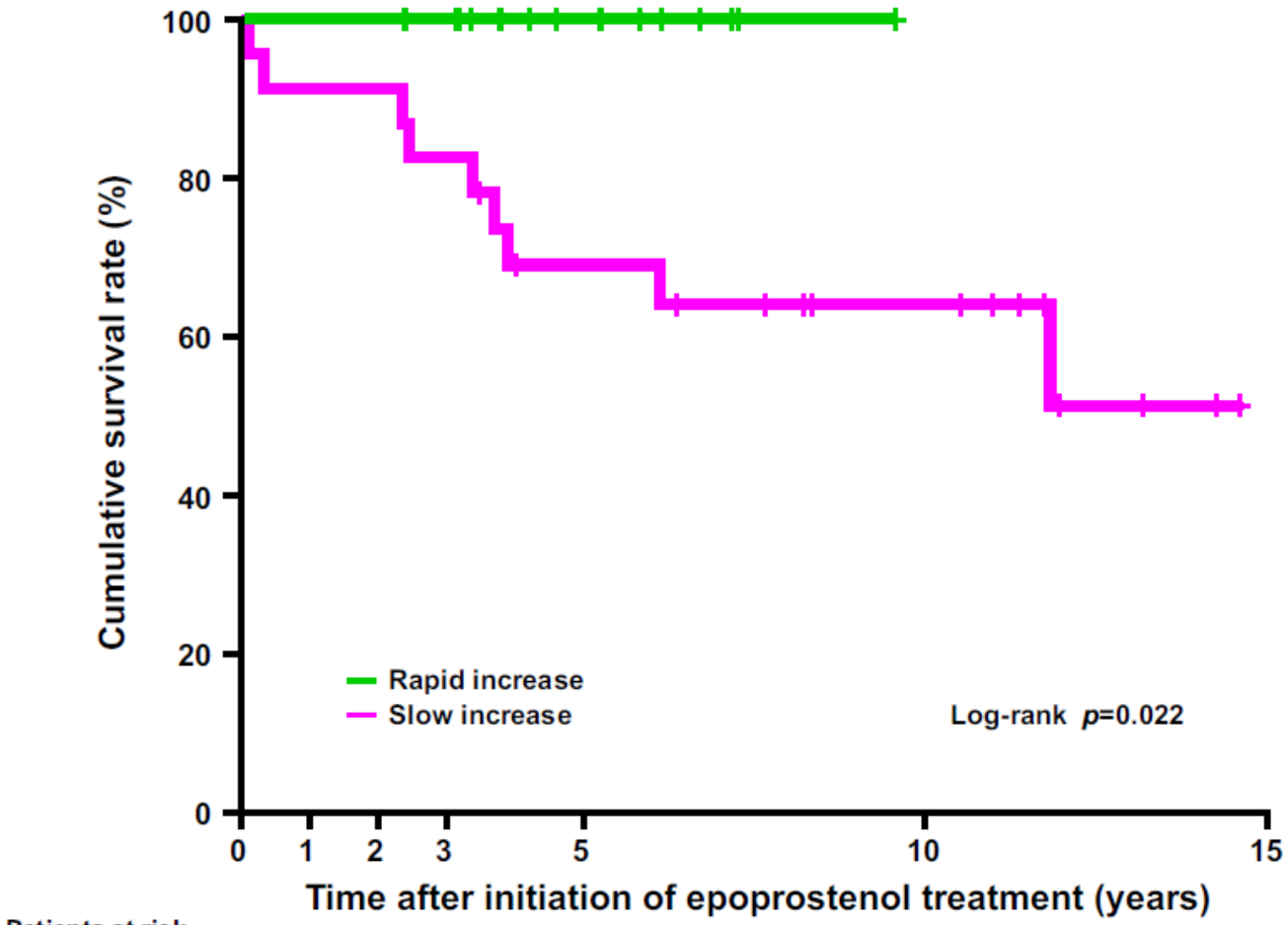
Tokunaga N, et al. J Cardiol. 2016 Dec;68(6):542-547.

Relation between Changes in mPAP and Increasing Pace of Epoprostenol



Tokunaga N, et al. J Cardiol. 2016 Dec;68(6):542-547.

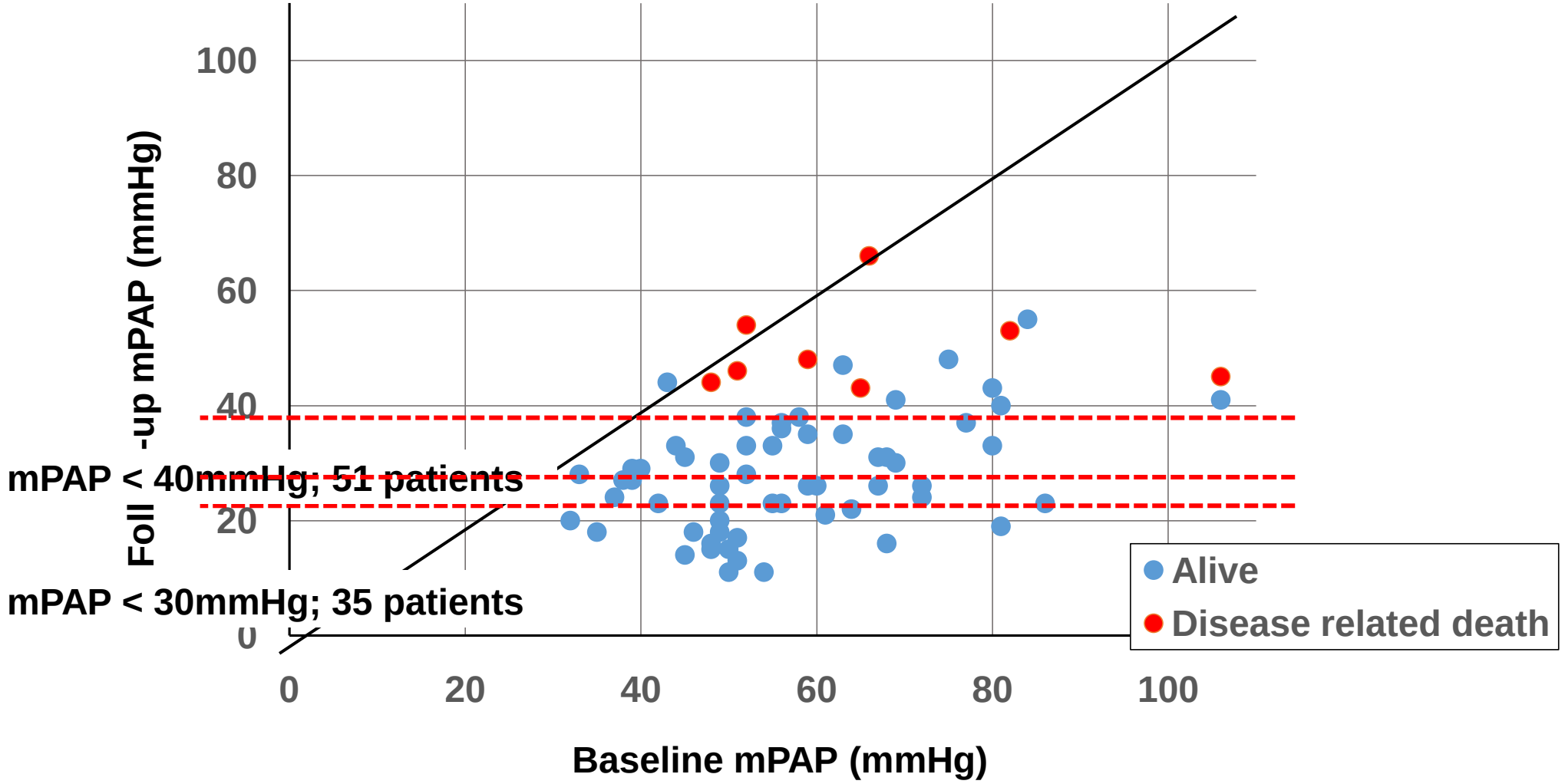
Relation between Patients' Survival and Increasing Pace of Epoprostenol



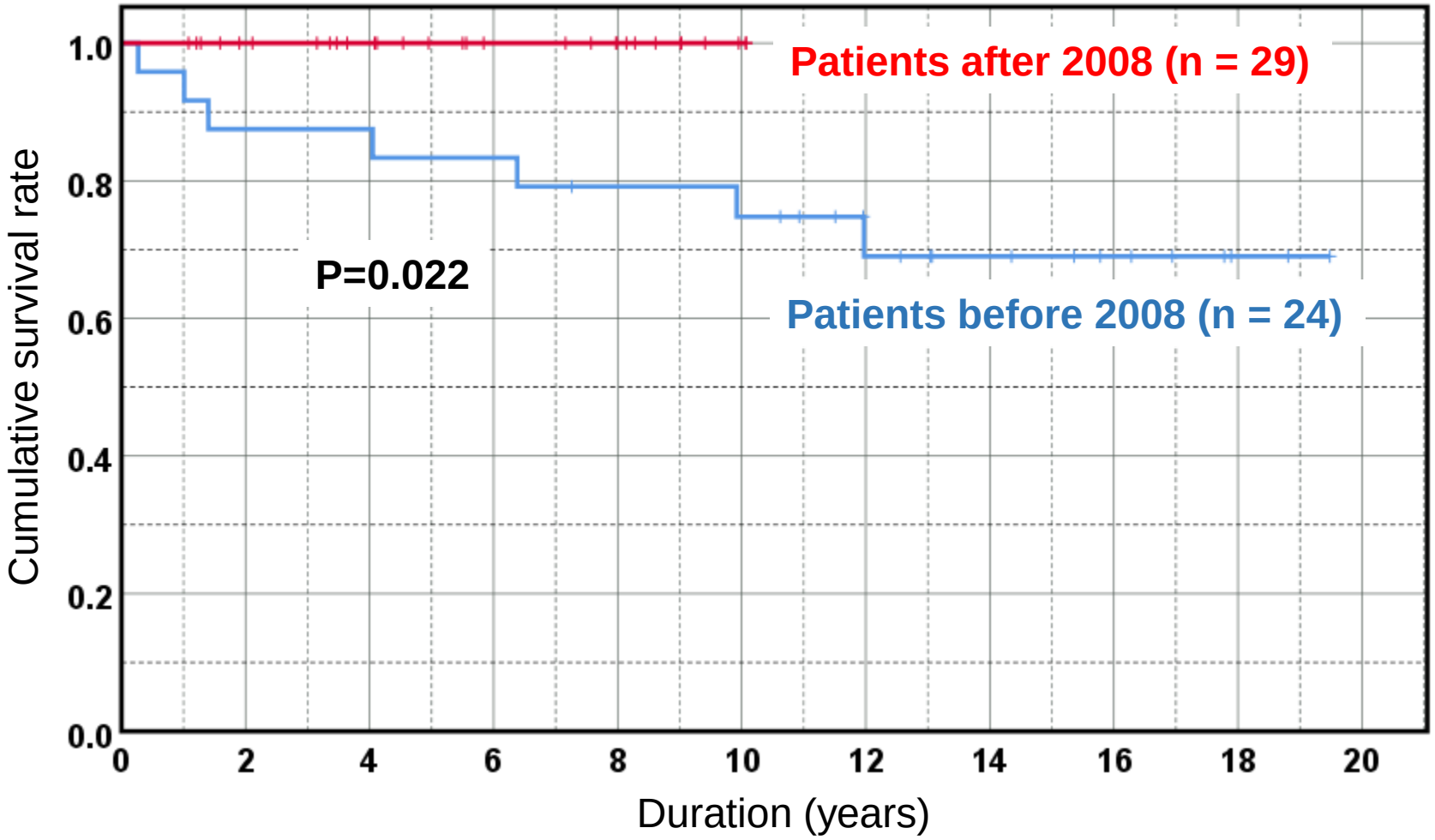
Tokunaga N, et al. J Cardiol. 2016 Dec;68(6):542-547.

Changes of mPAP in I/H PAH patients

(Apr 1999 – Mar 2019, n = 67)

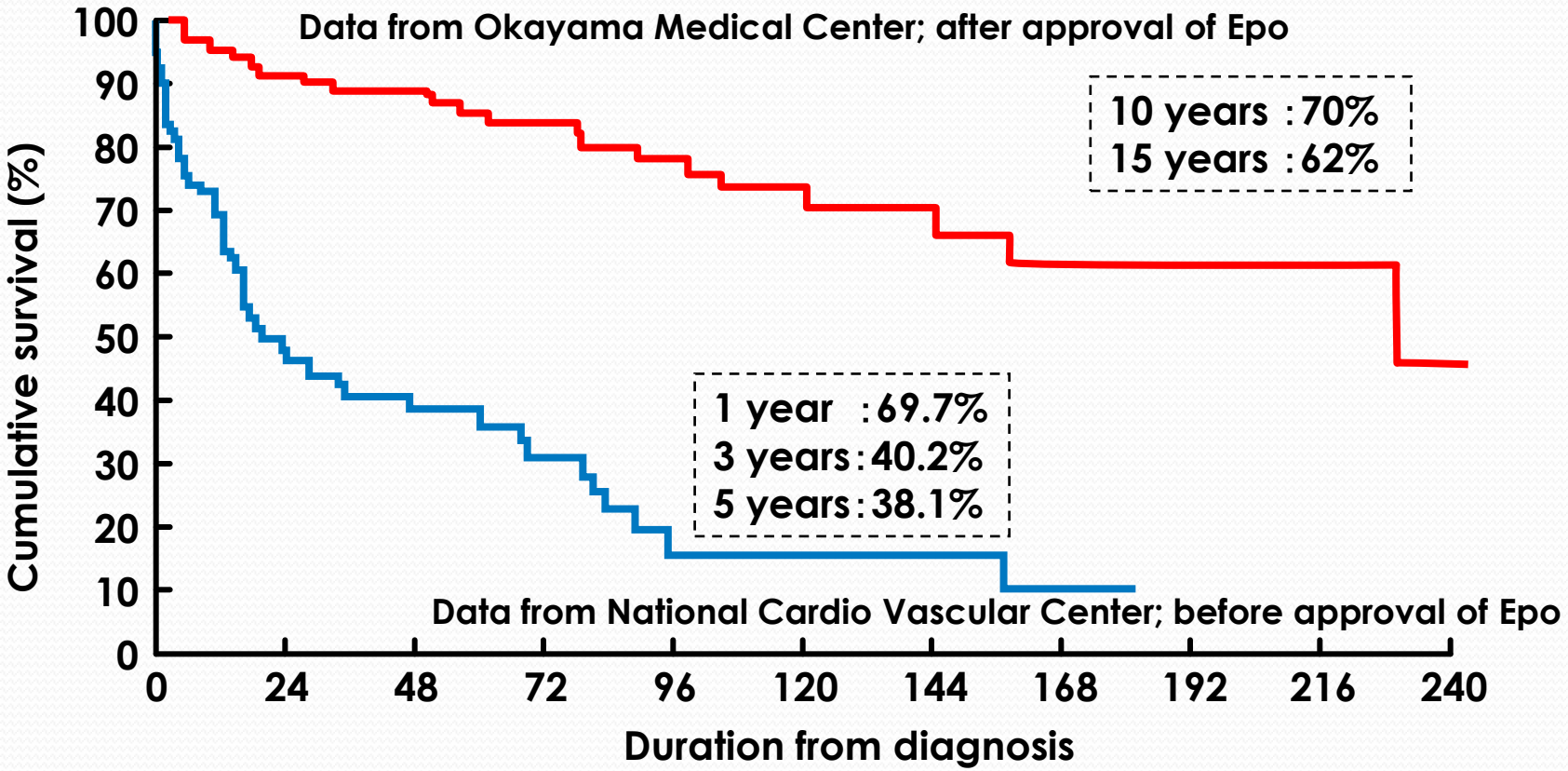


Transplant free survival of patients with I/H PAH treated with parenteral PGI_2 in OMC (Apr 1999 – Sep 2018, n = 53) End point = disease related death



Unpublished data.

Improved Survival of Japanese Patients with I/H PAH



中西 宣文：“Ⅱ肺高血圧症 疫学と予後”新目でみる循環器病シリーズ16. 肺循環障害 第1版 メジカルビュー社：45, 2007[L20071217077]より改変

Reversal of pulmonary vascular remodeling after unilateral lung transplantation (40y.o. female)

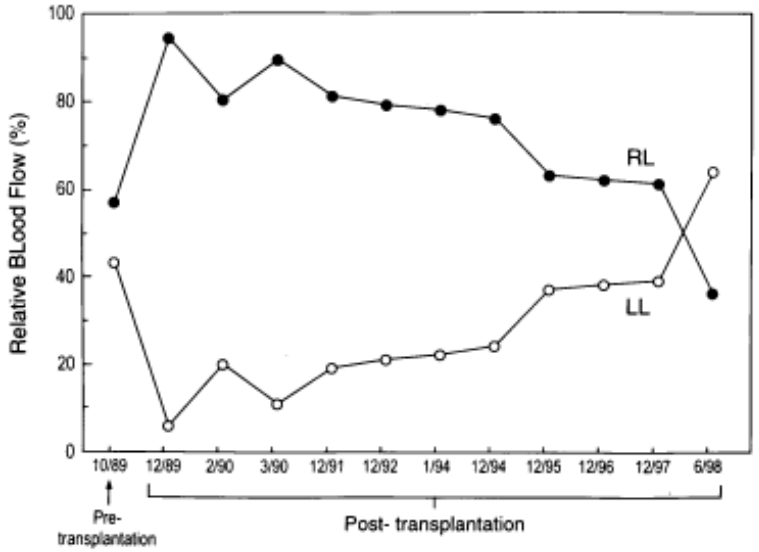


FIGURE 1 Lung perfusion scans demonstrating the relative blood flow between the native (left) and transplant (right) lungs.

Levy NT et al. J Heart Lung Transplant. 2001 Mar;20(3):381-4.

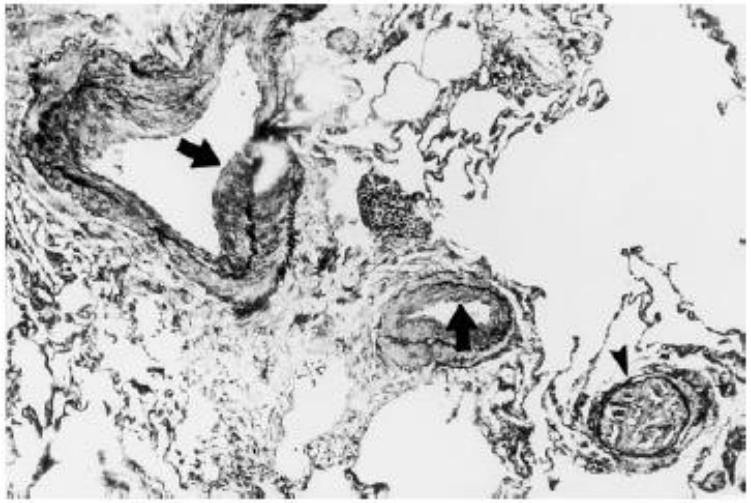


FIGURE 3 Explanted lung. Marked intimal arterial thickening (arrows). Plexiform lesion (arrowhead).

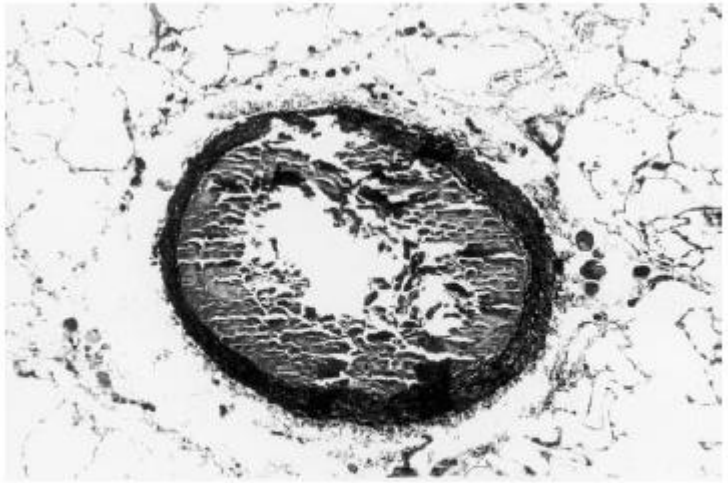


FIGURE 5 Left native lung. There is no evidence of intimal thickening. (VVG × 100).

Haemodynamic unloading reverses occlusive vascular lesions in severe pulmonary hypertension

Kohtaro Abe[1], Masako Shinoda[2], Mariko Tanaka[2,3], Yukimitsu Kuwabara[2], Keimei Yoshida[2], Yoshitaka Hirooka[1], Ivan F. McMurtry[4,5,6], Masahiko Oka[4,5,6†*], and Kenji Sunagawa[7†]

[1]Department of Advanced Cardiovascular Regulation and Therapeutics, Center for Disruptive Cardiovascular Medicine, Kyushu University, Fukuoka 811-1347, Japan; [2]Department of Cardiovascular Medicine, Kyushu University Graduate School of Medicine, Fukuoka 812-8582, Japan; [3]Division of Anesthesiology and Critical Care Medicine, Kyushu University Graduate School of Medicine, Fukuoka 812-8582, Japan; [4]Department of Pharmacology, University of South Alabama Mobile, 307 N University Blvd #130, Mobile, AL 36608, USA; [5]Department of Internal Medicine, University of South Alabama Mobile, 307 N University Blvd #130, Mobile, AL 36608, USA; [6]Center for Lung Biology, University of South Alabama Mobile, 307 N University Blvd #130, Mobile, AL 36608, USA; and [7]Therapeutic Regulation of Cardiovascular Homeostasis, Center for Disruptive Cardiovascular Medicine, Kyushu University, Fukuoka 811-1347, Japan

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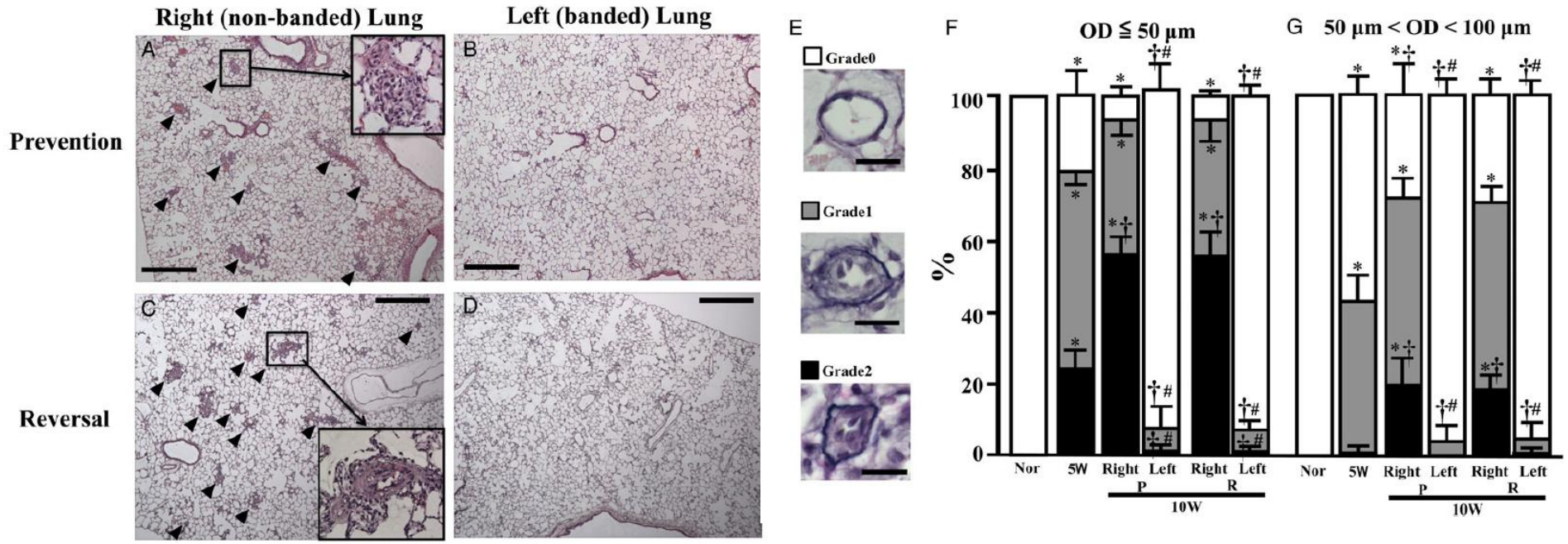
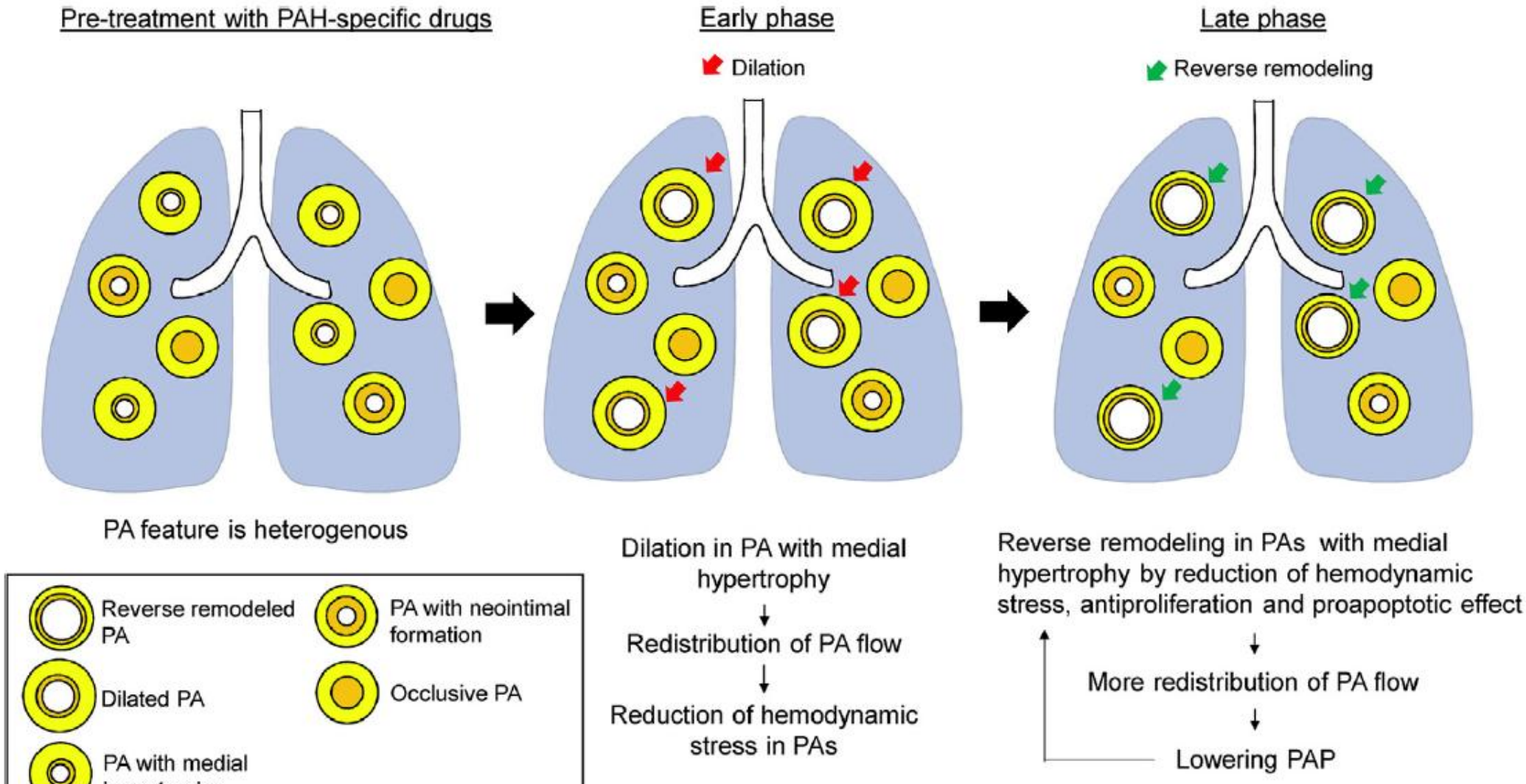
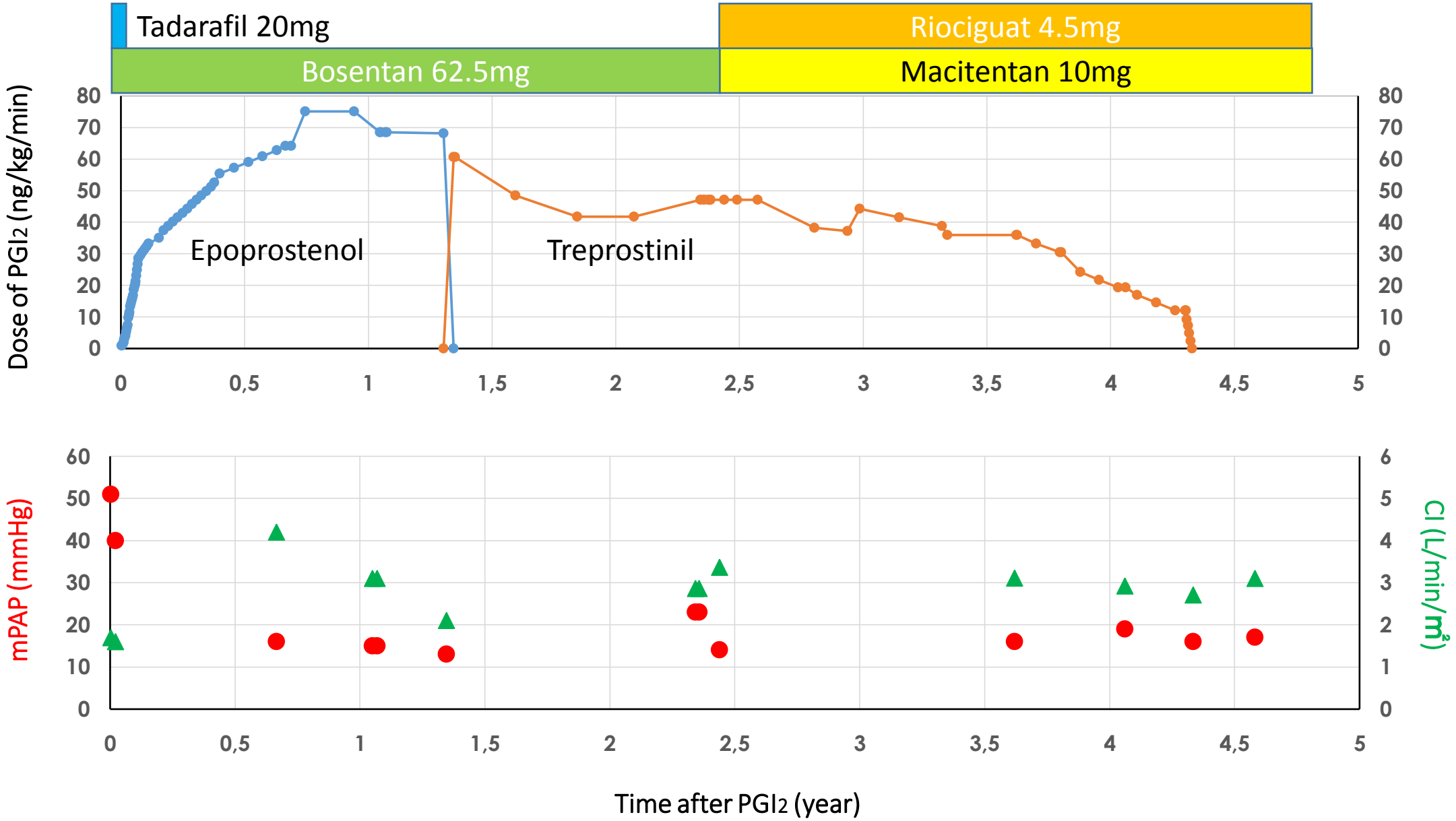


Speculated pathological change treated with PAH-specific drugs to maximally lowering PAP.

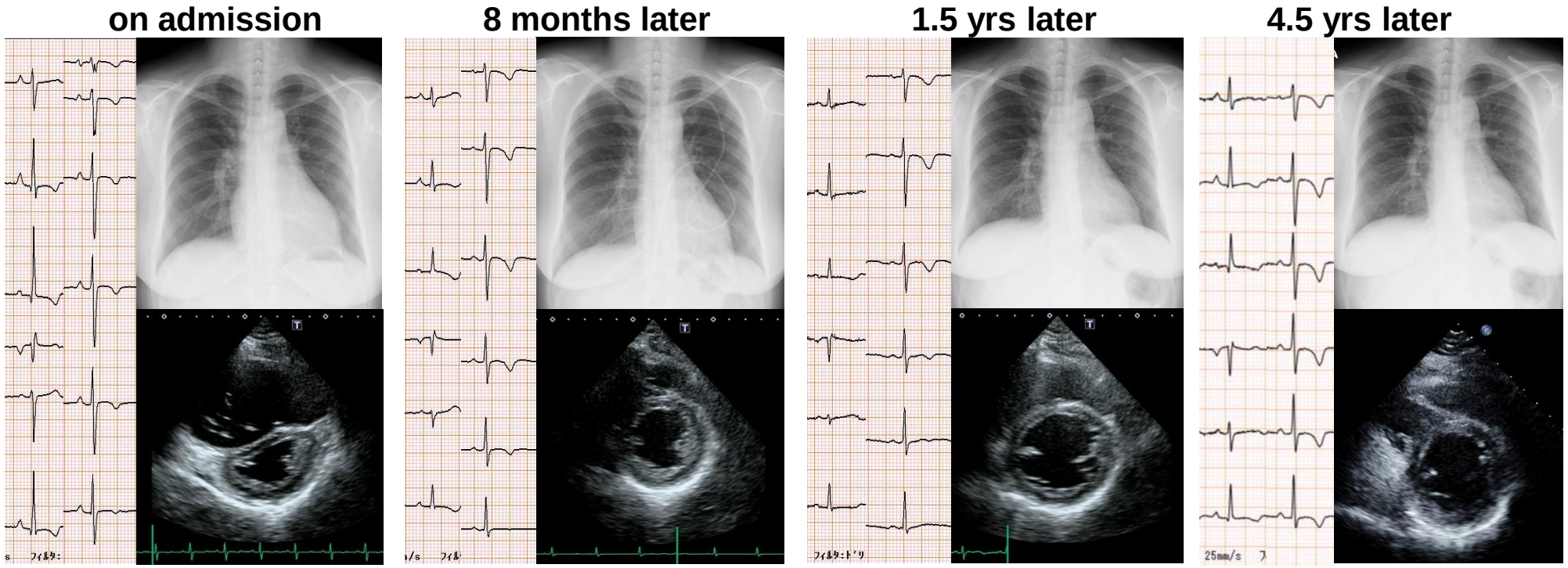


Akagi S, **Matsubara** H, Nakamura K, Ito H.
J Cardiol. 2018 Jun 10. pii: S0914-5087(18)30137-0. doi: 10.1016/j.jjcc.2018.04.014.

Clinical course（31y.o. Female, IPAH）

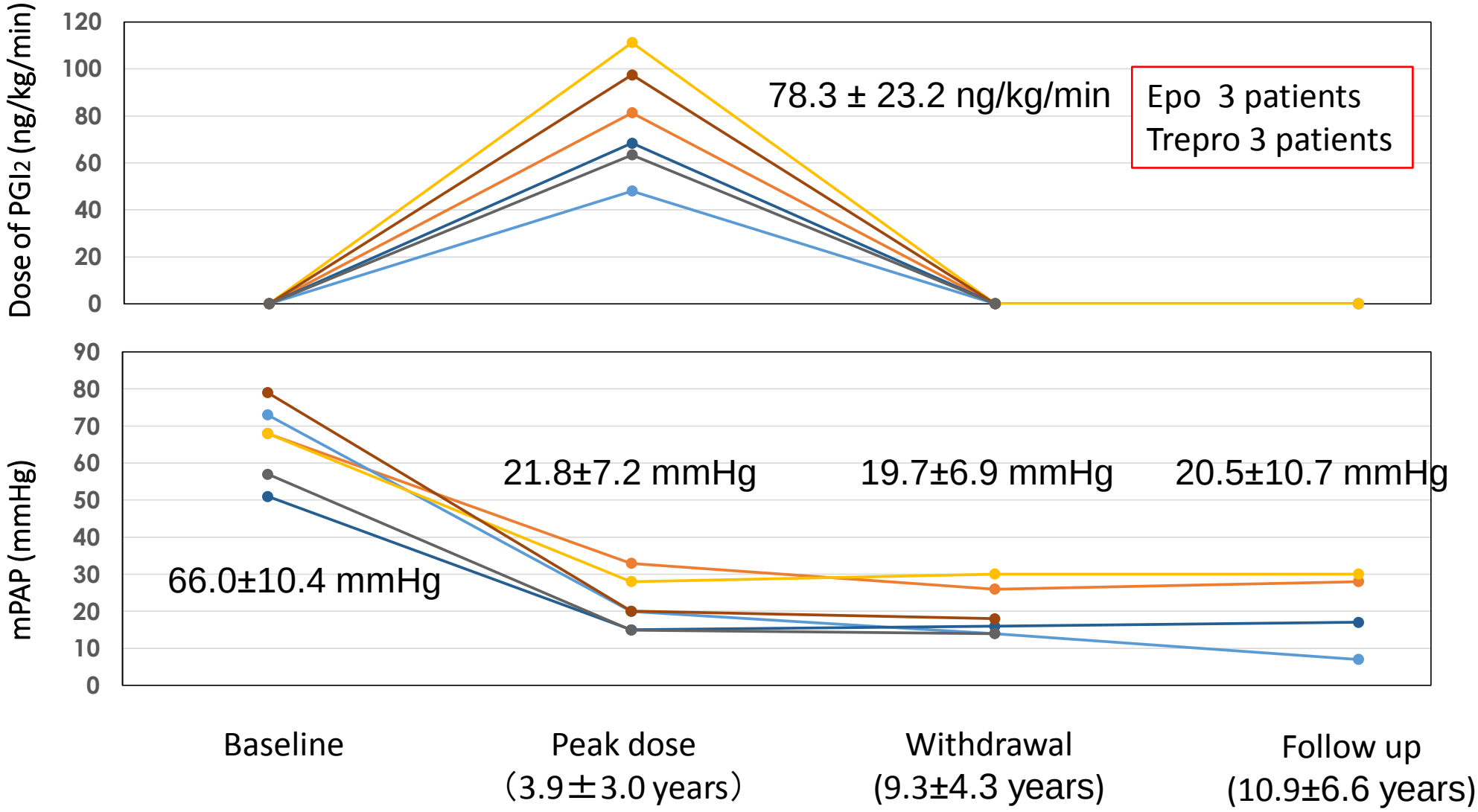


31 y.o. female (IPAH)



	on admission	8 months later	1.5 yrs later	4.5 yrs later
FC	VI	II	I	I
6MWD (m)	80	330	400	-
BNP (pg/ml)	312.6	<5.8	9.6	10.3
PAP (mmHg)	77/33 (51)	24/11 (16)	20/12 (16)	26/4 (14)
CI (L/min/㎡)	1.7	4.2	3.1	2.7
PAH-targeted drug	-	epoprostenol 68.4 ng/kg/min bosentan 62.5 mg/day	treprostinil 60.6 ng/kg/min bosentan 62.5 mg/day	macitentan 10 mg/day riociguat 4.5 mg/day

Withdrawal from parenteral PGI_2
(IPAH 5 cases, HPAH 1 case)



Unpublished data.

Summary

- Lowering mPAP could be a treatment goal of I/H PAH patients.
- Early initiation and quick up-titration of parenteral PGI_2 with upfront combination use of other oral drugs would be the key for success.
- By achieving improvement of hemodynamics, I/H PAH patients can survive more than 15 years without experiencing deterioration.
- Parenteral PGI_2 could be safely stopped after achieving normalization of patients' hemodynamics.