



Portopulmonary Hypertension

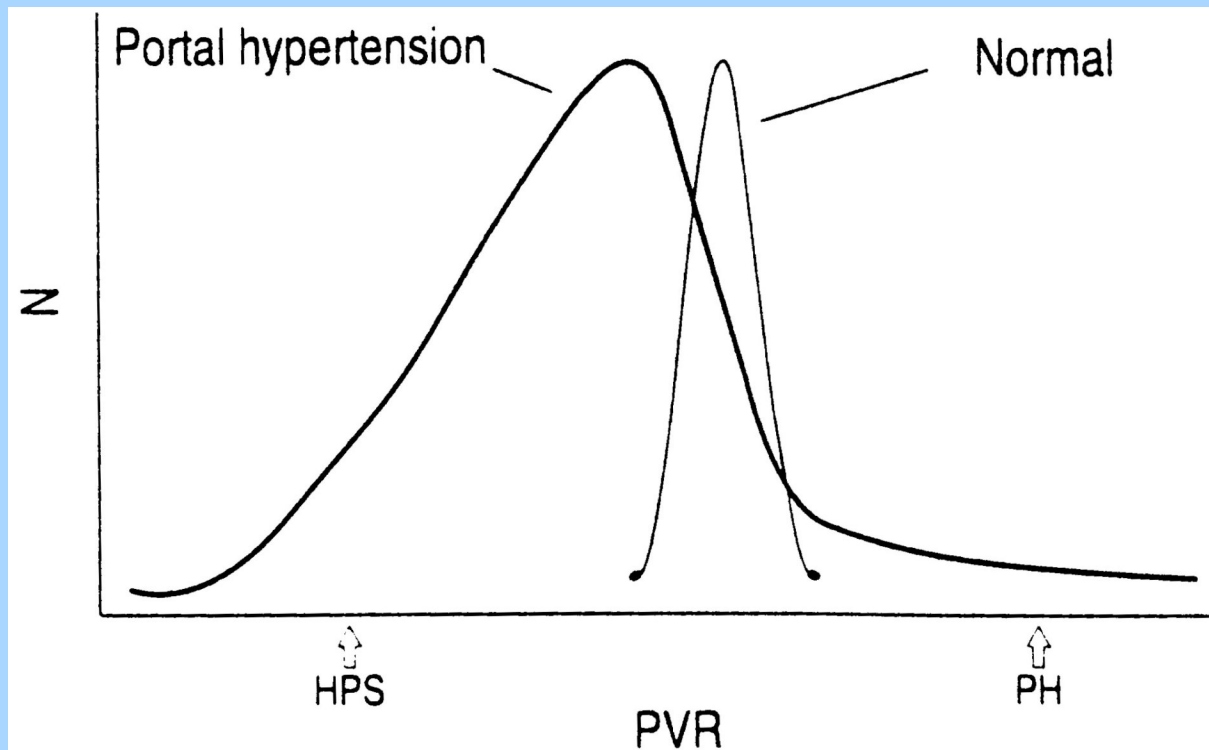
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28.02.08

Definition from PPHTN

- Liver diseases causing clinical portal hypertension
- mPAP > 25 mmHg (right heart catheterism)
- PCWP < 15 mmHg
- PVR > 240 dyn·s⁻¹·cm⁻⁵

PVR in Patients with portopulmonary Hypertension & with hepatopulmonary syndrome



28%

2-4%

Hervé et al, Eur Respir J 1998

Portopulmonary Hypertension

Prevalence with cirrhosis:

Autopsie-Study : **0,73%** *McDonnel et al, Am Rev Respir Dis 1983;127:437*

Studies based on catheterism : **10/507 = 2%**

*Hadengue et al,
Gastroenterology 1991;100:520*

2/43 = 4,7%

*Sen et al,
Indian J Gastroenterol 1999;18:158*

10/322 = 3,1%

Yang et al, J Gastroenterol 2001;36:181

liver transplant-candidates **8/257 = 3,5%**

Taura et al, Ansth Analg 1996;83:675

15/362 = 4%

Castro et al, Mayo Cli Proc 1996;71:543

Portopulmonary Hypertension

Clinical presentation:

Symptoms essentially if PAPm (> ca. 40 mm Hg):

Dyspnea on exertion	92%
Deasiness on exertion	24%
Chest pain	13%
Hemoptysis	8%
Right heart insufficiency	22%

Serie with 76 patients *Hadengue et al, Gastroenterology 1991*

Water retention : leg edema, Anasarque, neck veins distension ,Ascitis

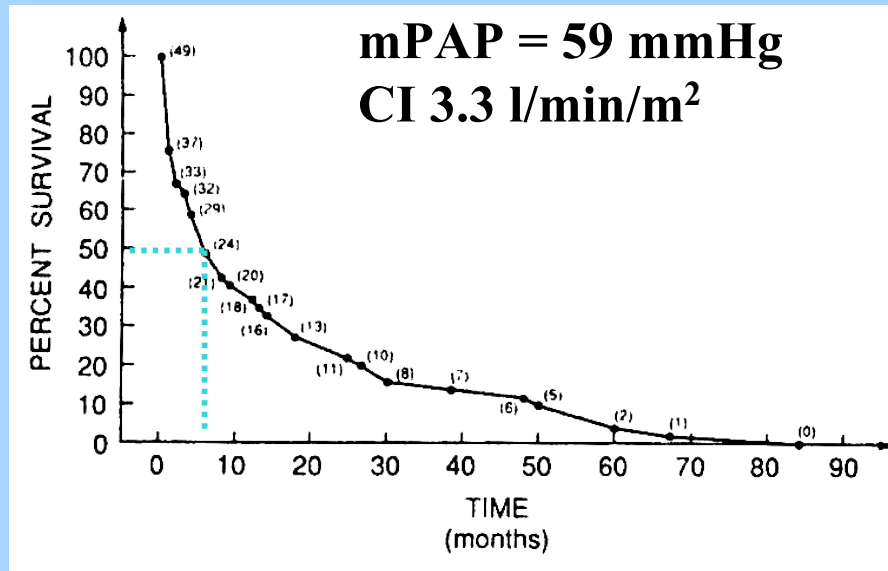
Stages in PPHTN

	(Norm)	Mild	Moderate	Severe	
mPAP	(15-24)	25-34	35-45	>45	mmHg
PVR	(< 240)	240 – 500	500 – 800	> 800	dyn·s⁻¹·cm⁻⁵

Porto-pulmonary Hypertension

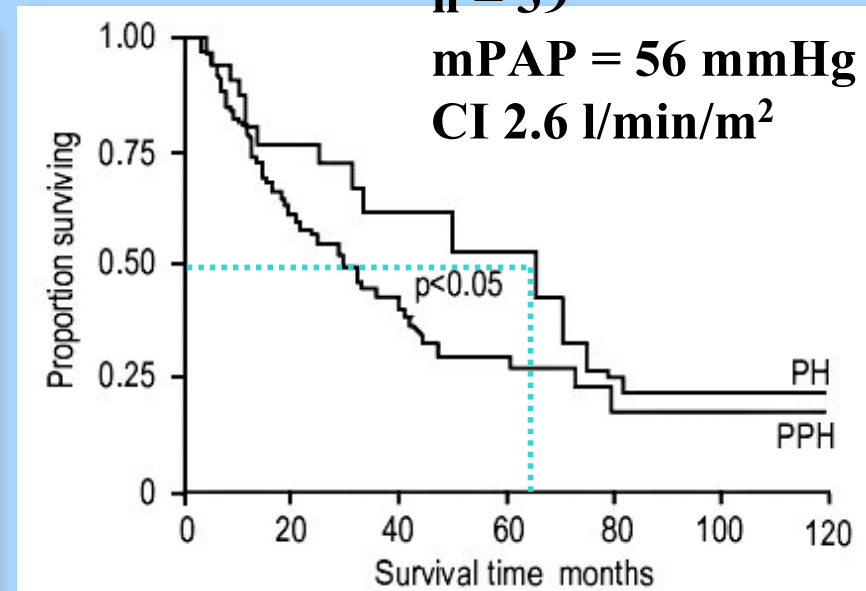
Prognosis from severe PPHT

n = 49
mPAP = 59 mmHg
CI 3.3 l/min/m²



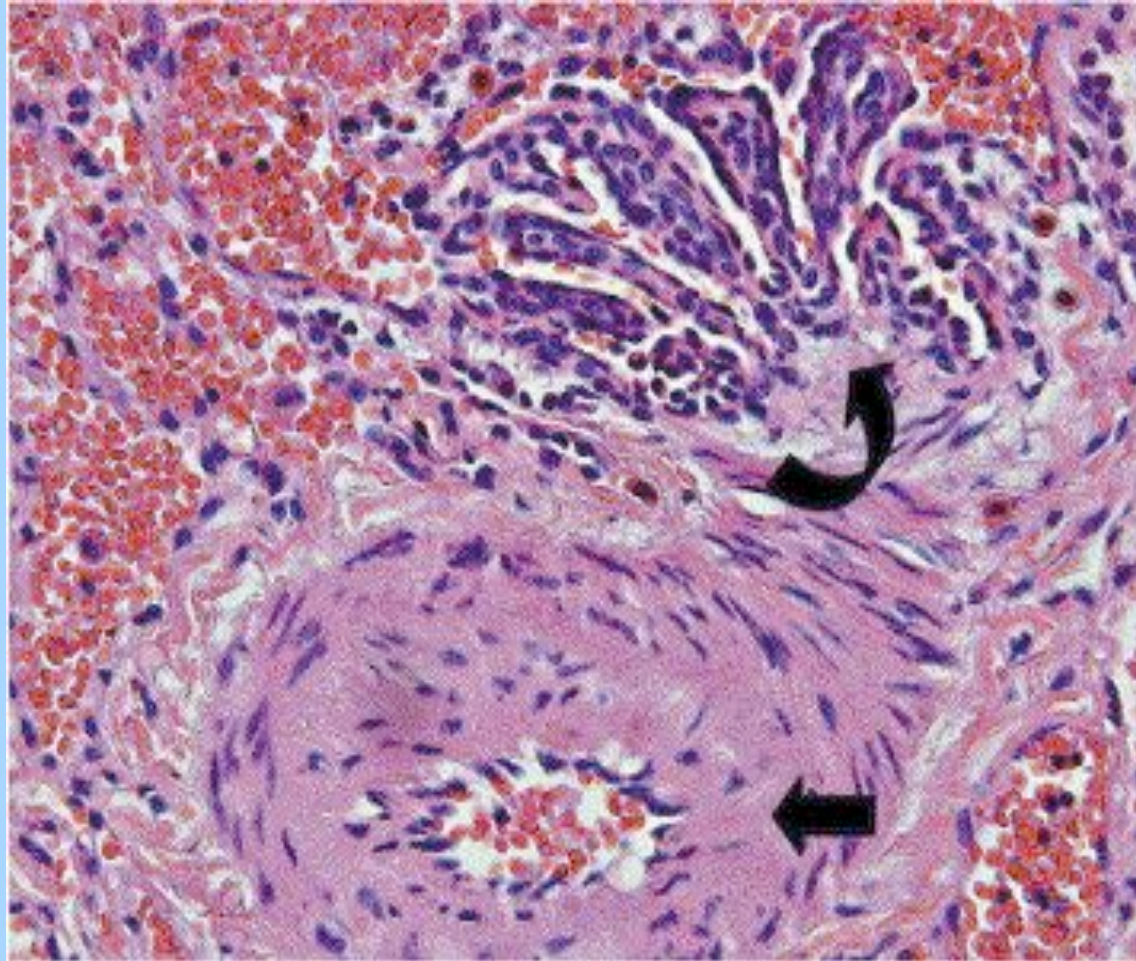
Robalino *et al.* JACC 1991

n = 39
mPAP = 56 mmHg
CI 2.6 l/min/m²



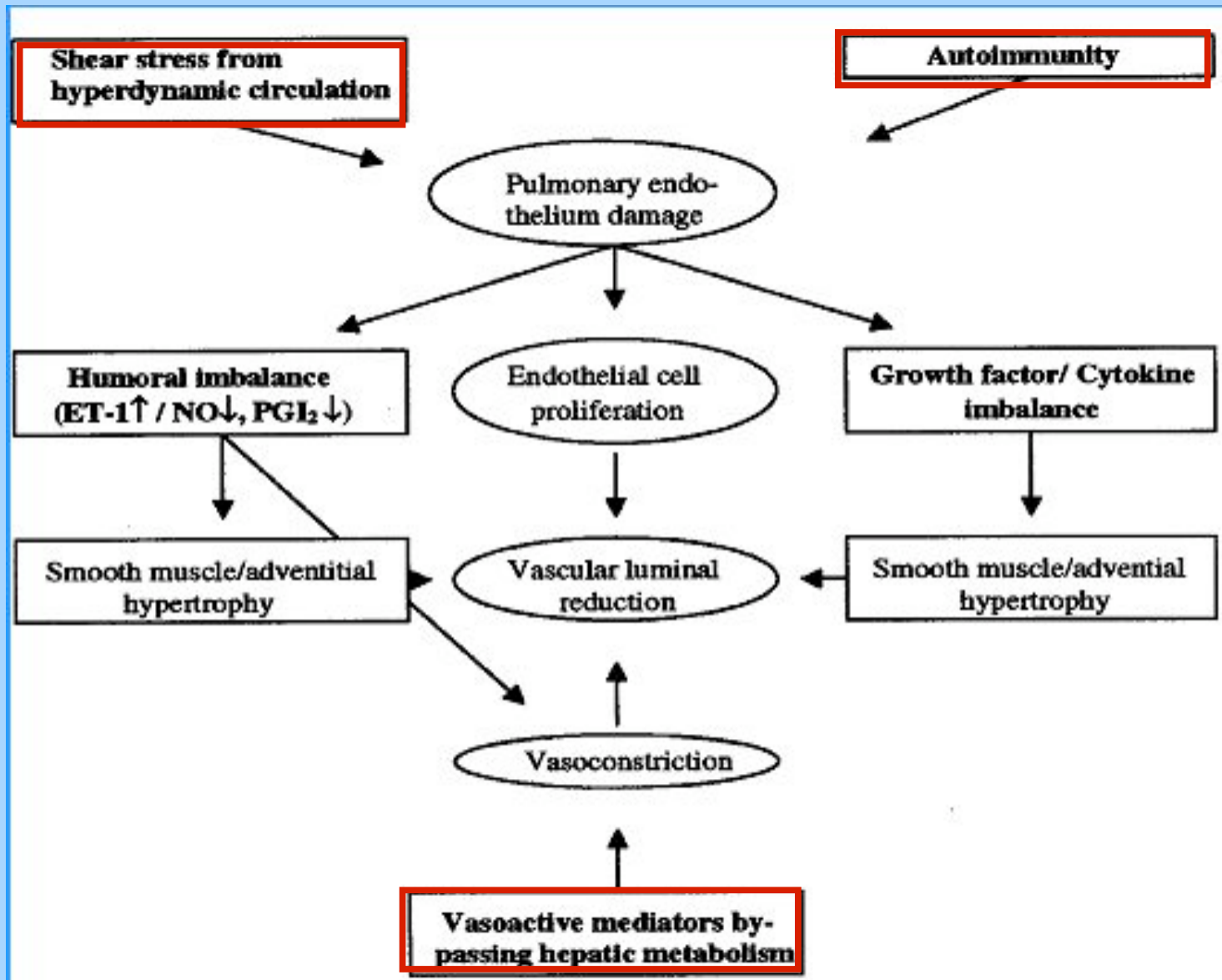
Hervé *et al.* ERJ 1998

Proliferative pulmonary vasculopathy in severe PPHTN

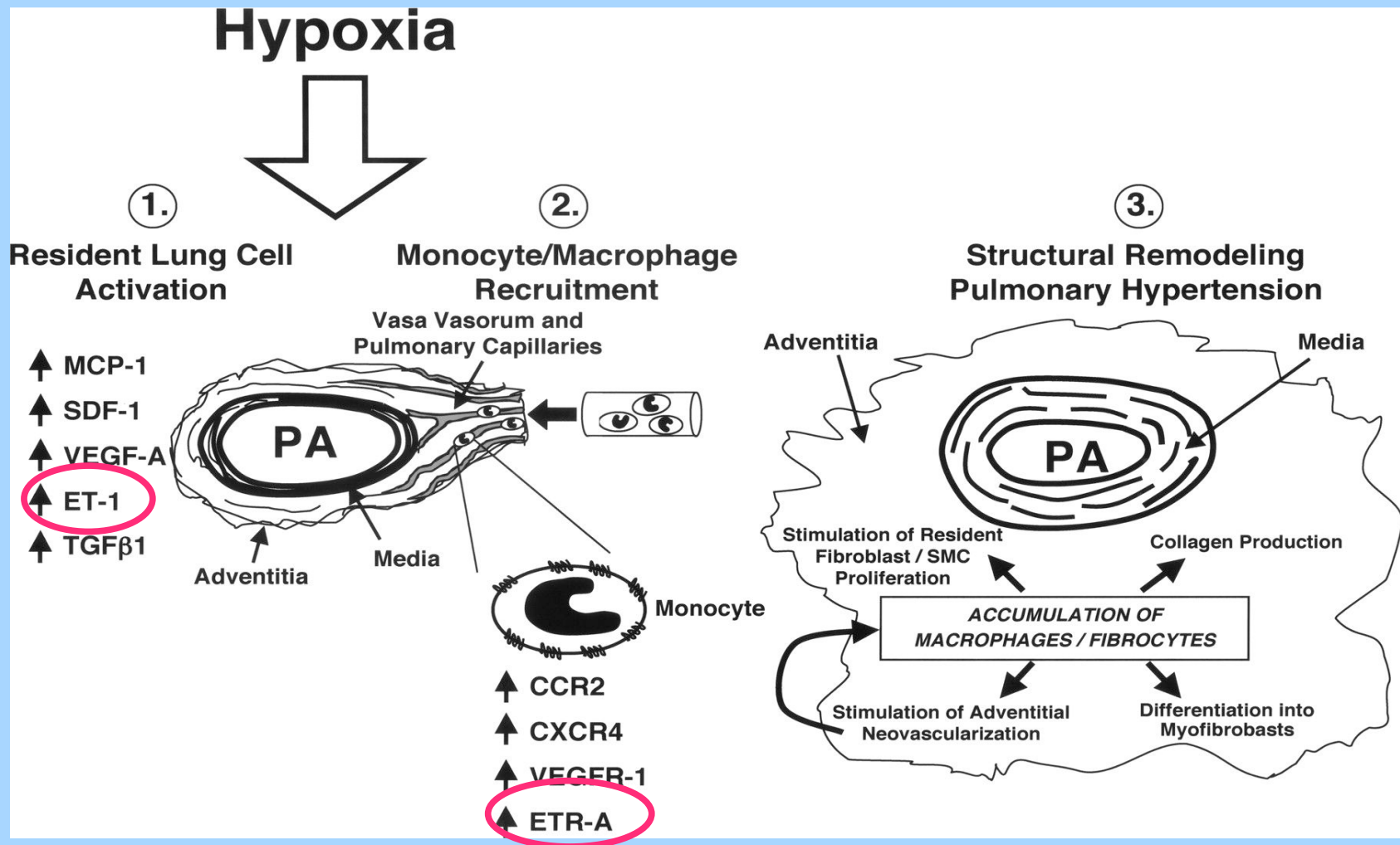


Hoeper MM, Lancet. 2004;363:1461-8

Pathophysiology of PPHTN

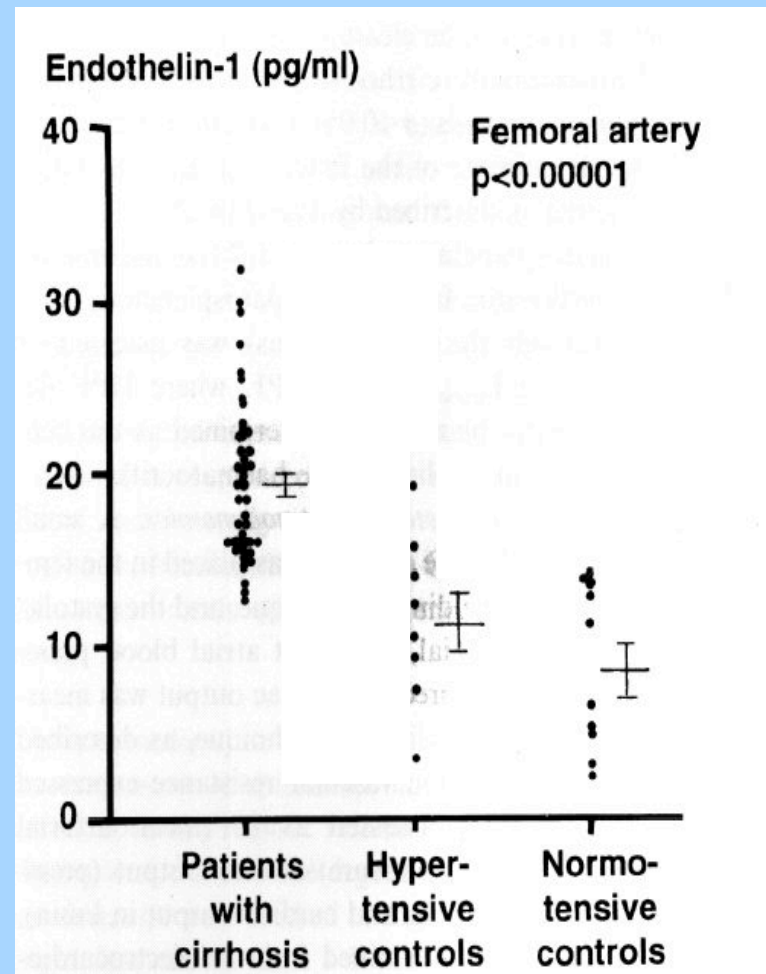


Hypoxie und Progress der PPHTN



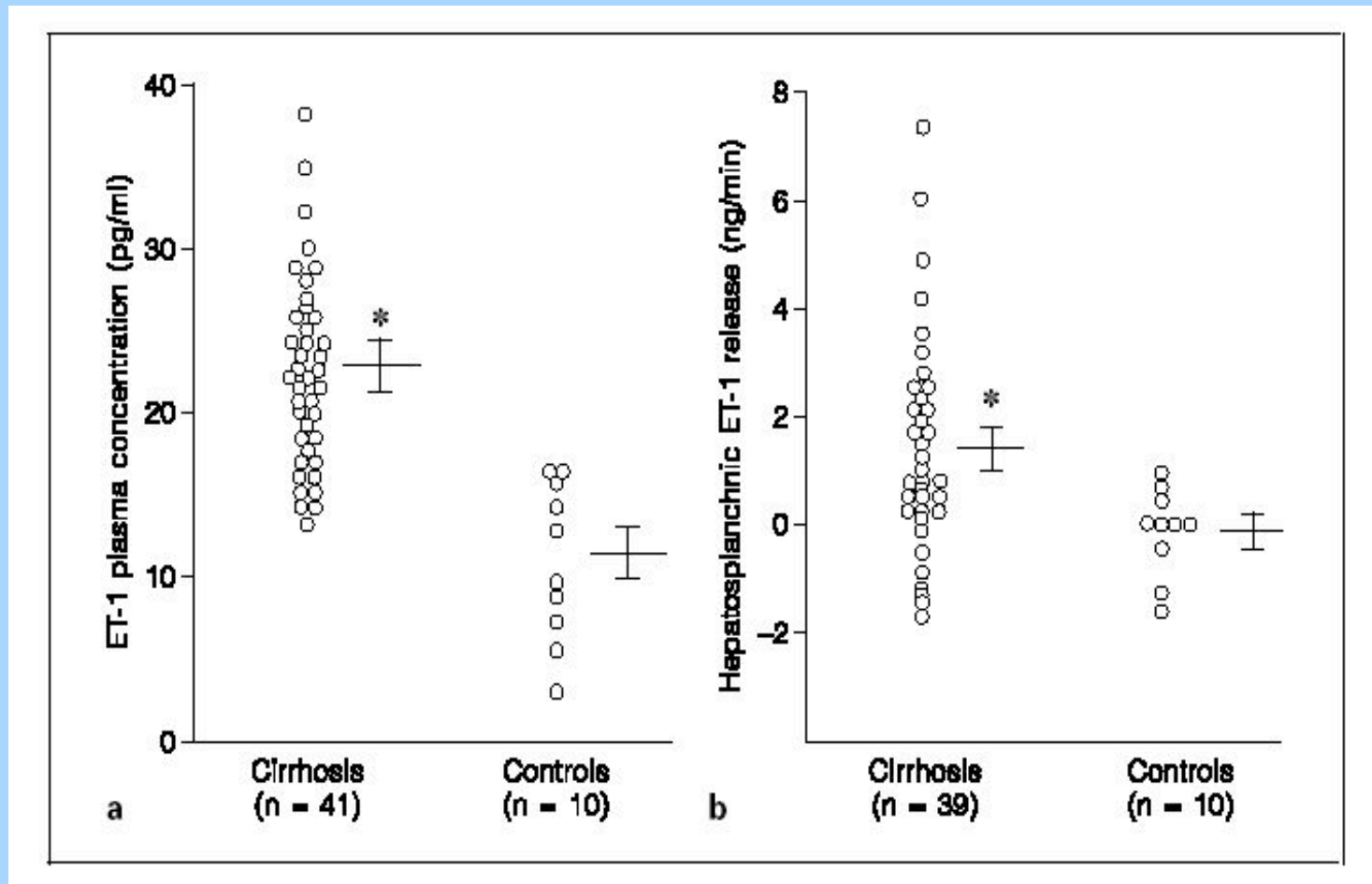
Stenmark KR, et al., J Appl Physiol 2005;98:715-21

Patients with Liver cirrhose have elevated arterial Endothelin-1 Plasmatic concentrations



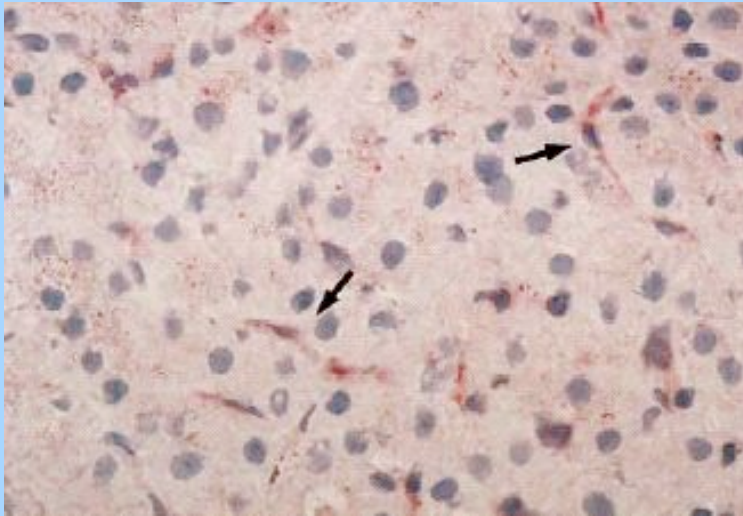
Gerbes AL et al., Hepatology 1995;21:735-739

Splanchnic spill-over and increased levels of Endothelin-1 plasmatic concentrations in Patients with liver cirrhosis

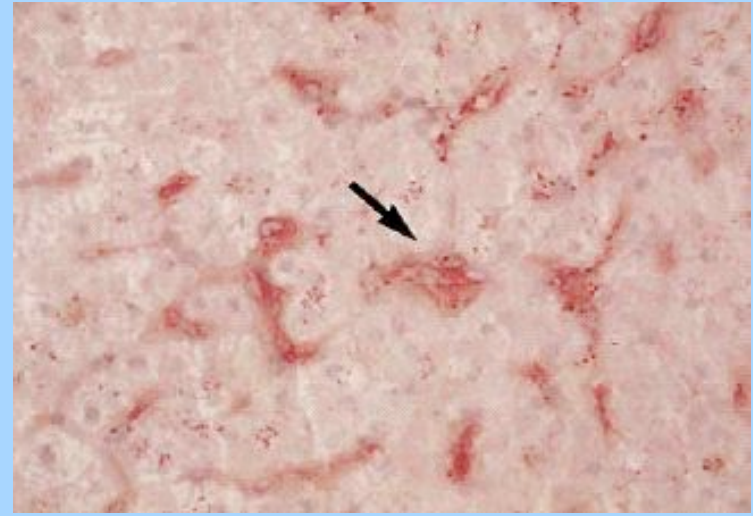


Gerbes AL, Gülberg V, Digestion 1998;59(suppl 2):8-10
Moeller S et al., J Hepatol 1995;23: 135-144

Immunohistochem :expression from ET-1 in sound and cirrhotic Liver subjects

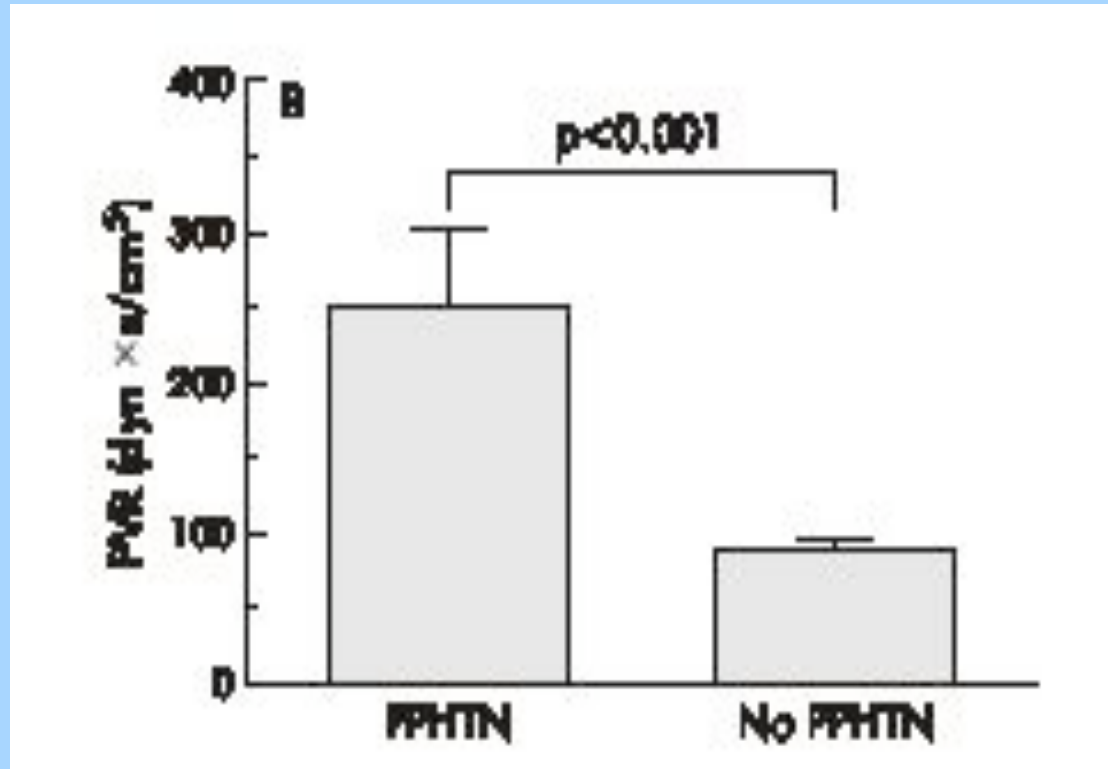


**Controls: discrete staining in
area of sinusoidal cells
(cytoplasm)**



**Strong staining in area of sinusoidal
cells from cirrhotic nodules**

Enhanced ET-1 Plasmatic concentration in Patients with PPHTN

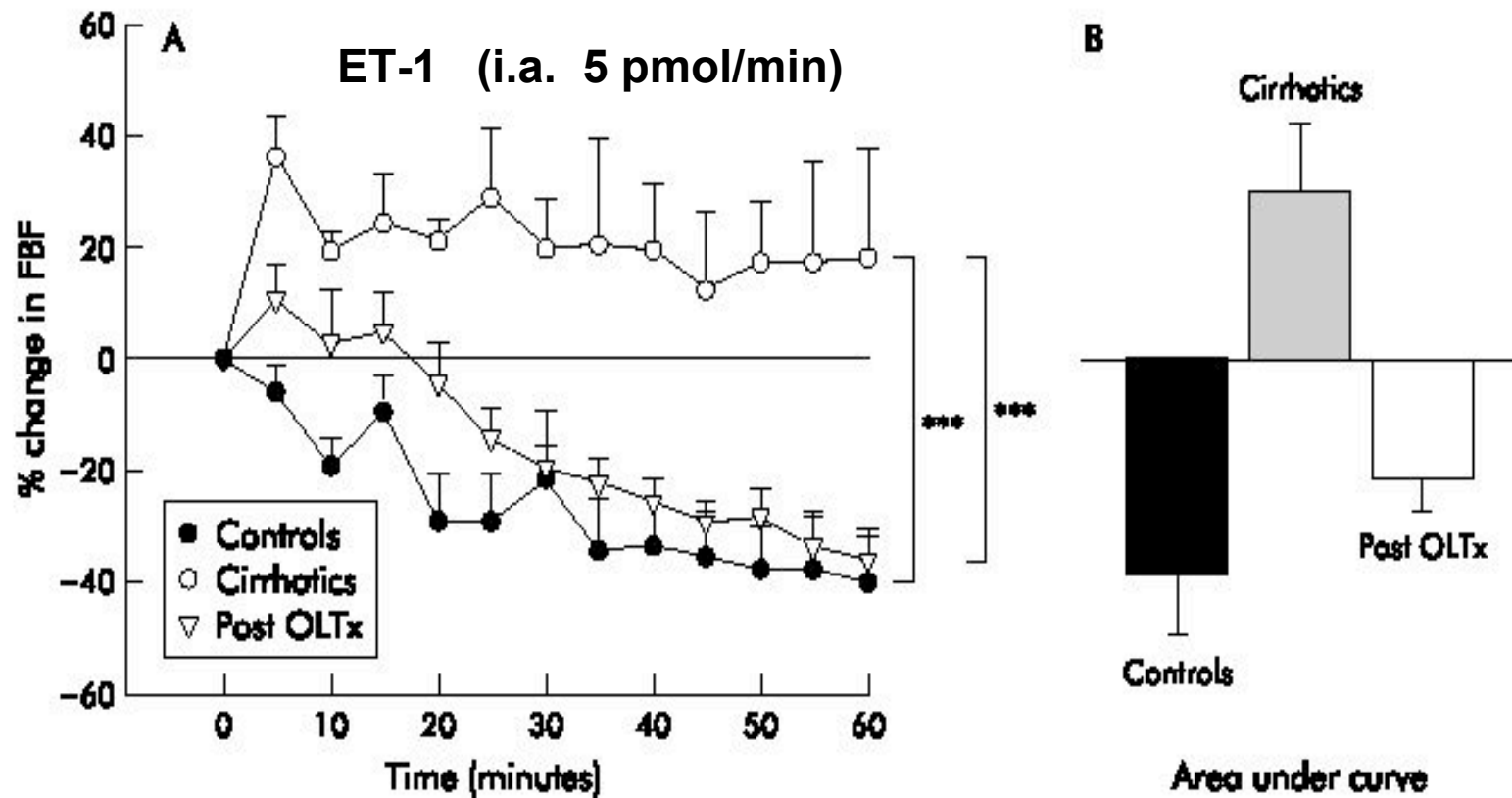


ET-1 (pg/ml) 3.04 ± 0.40

1.98 ± 0.12

Benjaminov FS, et al. Gut
2003;52:1355-62

The „Endothelin-Paradox“ with decompensated Liver cirrhosis



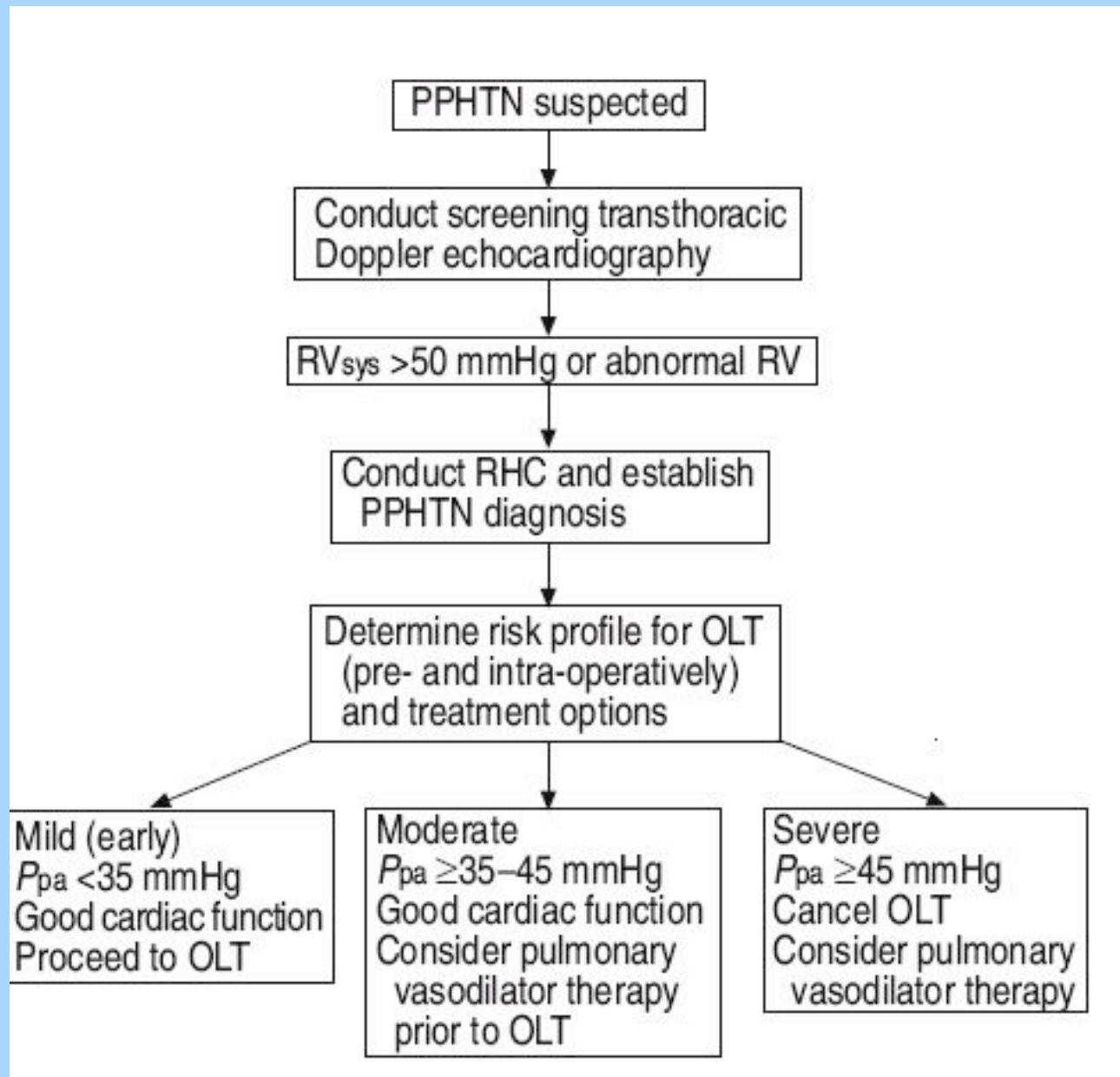
With endstage cirrhosis ,ET-1 produces vasodilatation in forearm at a dose that causes marked vasoconstriction in controls

Vaughan RB, et al. Gut 2003;52:1505–10

Endothelin in the Pathophysiology from portopulmonary Hypertension

- Vasoconstriction (ET_{A+B})
- Acting in vasculature remodelling (ET_{A+B})
- experimental cirrhose:
 - Increased ET-Plasmatic concentration
 - Increased hepatic ET-Expression
 - Reduction from portal pressure with ET-Antagonists
- Patients mit Liver cirrhose:
 - Increased ET-Plasmatic concentrations
 - hepato-splanchnic spill-over

Clinical work-up of Portopulmonary Hypertension



ERS TASK FORCE PHD,
Eur Respir J 2004; 24:861

Therapeutic strategies in PPHTN

pro

con

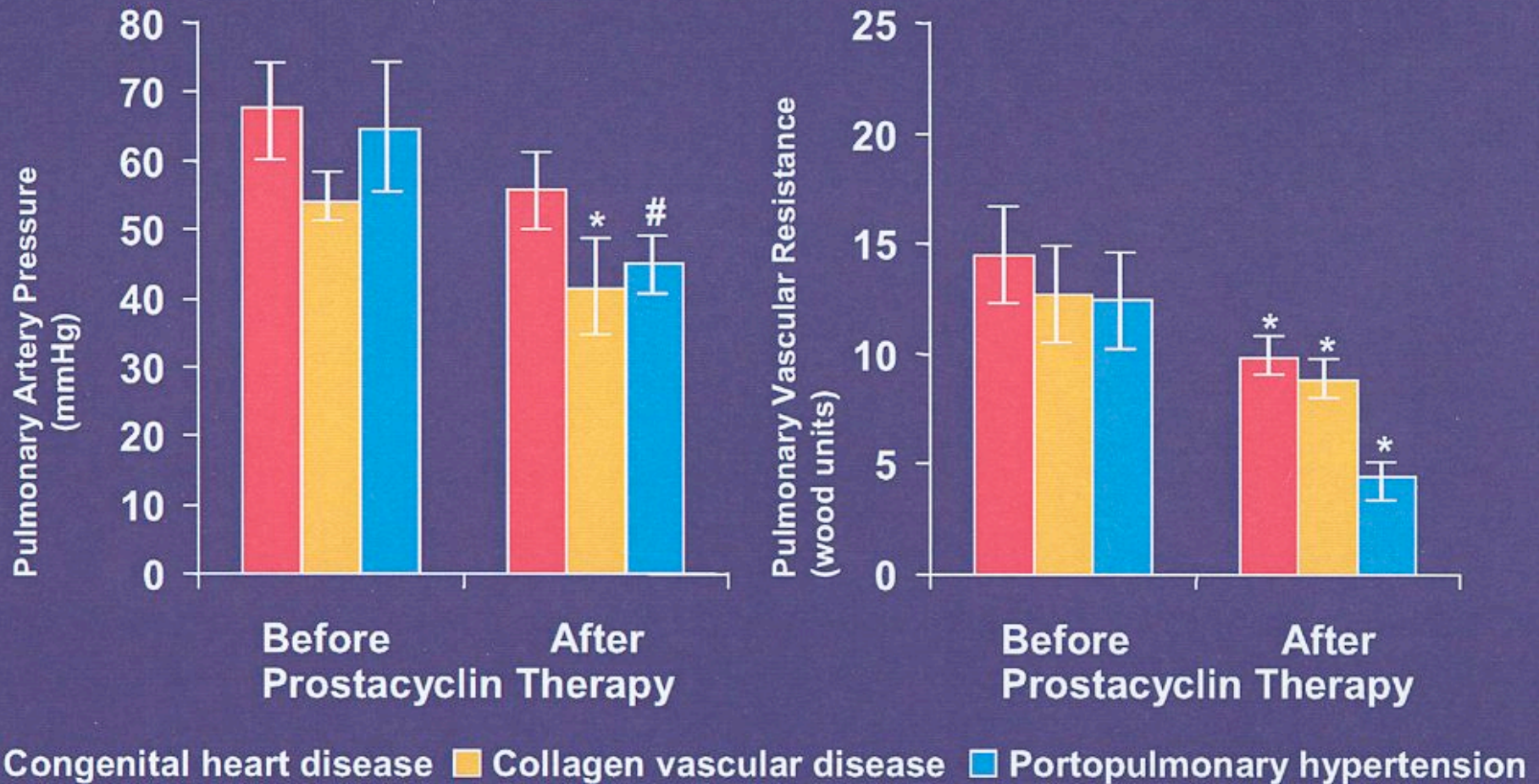
	<i>pro</i>	<i>con</i>
Liver transplantation	curative	Contraindication in severe PPHTN with moderate PPHTN only after improvement with treatment
Ca-Antagonisten		Aggravation from systemic Haemodynamic, increased portal HT
β -Blocker \pm Nitrate	Simultaneous decrease from portal Hypertension	Cardial decompensation with severe PPHTN Worsening of PPHTN
Prostaglandin (-derivate)	Well establish with other forms of PPHTN Hemodynamic improvement ;survival?	Decrease from thrombocytes function, with increased risk of bleeding (?)
Endothelin- Antagonists	Improved survival in open studies (Child A)	Hepatotoxicity ? (Transaminasenanstieg bei 10 – 12 % der Patienten)
Phosphodiesterase inh	Hemodynamic improvement ;survival?	Aggravation from systemic Haemodynamic ?

PPHT and Liver transplantation

**A PPHT
(mPAP >35 mmHG)
In Patients with an
End stage-Liver disease
Should be a contraindication**

Treatments for PoPAH

Pgl2 Therapy



* $p < 0.01$; # $p < 0.05$ compared with baseline

Prostacyclin (Flolan®) und Portopulmonary Hypertension

1.2 Hemodynamics under epoprostenol (8 ng/kg/min)

	05/97	10/97
PAP systolic/diastolic (mm Hg)	76/32	59/22
Mean PAP (mm Hg)	46	32
PVRI (225-315)	931	561
PCWP	9	7
Cardiac Output (l/min)	4.03	6.95
Systemic arterial pressure	108/80	113/81

Abbreviations: PAP, pulmonary artery pressure; PVRI, pulmonary vascular resistance index; PCWP, pulmonary capillary wedge pressure

Intravenous iloprost bridging to orthotopic liver transplantation in PPHTN

- 48 y old patient
 - Chronic hepatitis C with liver cirrhosis
 - Chronic alcohol abuse
 - PPHTN discovered pre-transplantation of liver (mPAP:50 mmHg)
- Treatment:
 - Iloprost i.v. x 3 months 200 µg/day
 - Iloprost i.v. x 4 months 300 µg/day

Hemodynamic values and 6' walking test (MWD) before and after orthotopic liver transplantation

	Pre-OLT		Post-OLT		
	Baseline	Iloprost	Iloprost		
			Day 1	Month 1	Month 4
HR (bpm)	68	64	80	89	68
BP (mmHg)	104/54	100/46	120/85	130/90	130/80
PVR (dyn.s.cm⁻⁵)	524	302	361		
RVSP (mmHg)	74		68	27	29
6MWD (m)	462	579	570	572	582

Bosentan in PPHT

Multicentric cases collection (Hannover, Dresden, Leipzig)

- **n = 11, Age 52 ± 9 years**
- **Child-A-cirrhose from various etiologies**
- **PPHT NYHA III-IV**
- **PAPm 53 ± 9 mmHg, PVR 944 ± 519 dyn**
- **Therapy with Bosentan > 1 year**

Bosentan in PPHT

Multicentric cases (Hannover, Dresden, Leipzig)

	Baseline		1 Year
6-min walking test	310 m	→	388 m
VO ₂ max (n=7)	12.6	→	16.6 ml/min/kg
PVR	944	→	635 dyn
Bilirubin	31	→	29 μmol/l

Long term therapy with Bosentan in cryptogenic Liver cirrhose and PAH (CHILD A)

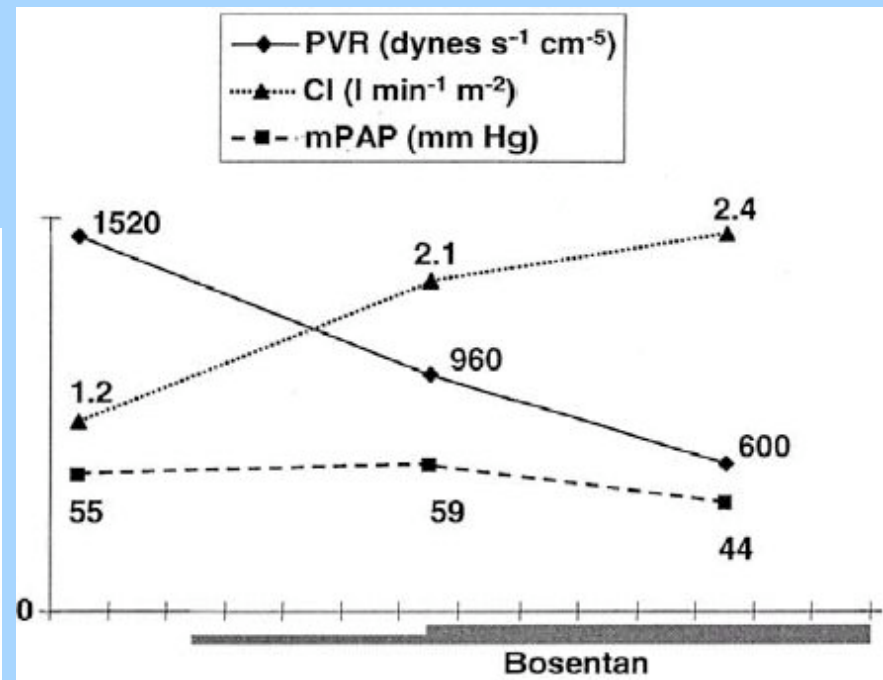
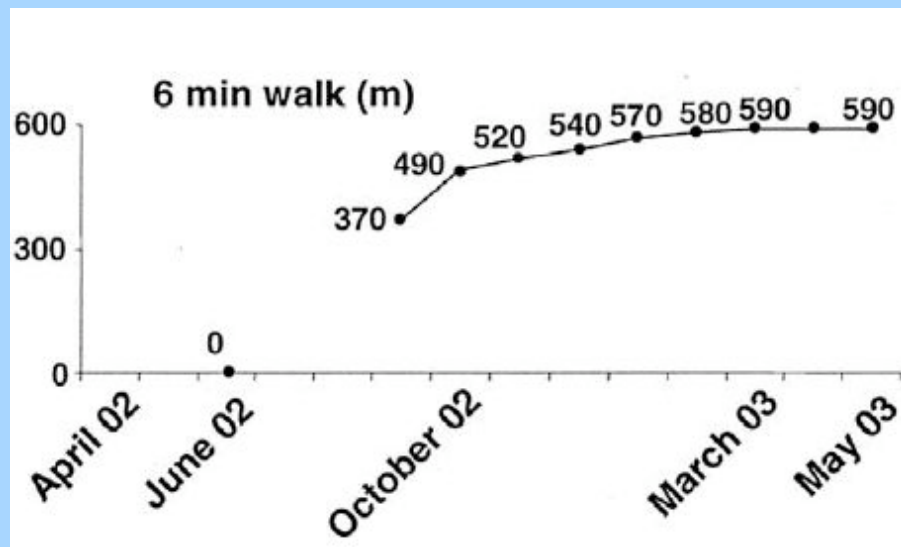
Parameters	baseline	After five months
PAPm	54	28
PVR	741	215
CI	2.6	4.3
SVR	1472	819
6 MWD	360	450
VO ₂ peak	14.1	18.2

PAP after a year of Iloprost-Monotherapy, after then 3 months from a combi-Therapie with Bosentan and finally 4 months Bosentan-Monotherapy in cryptogenic cirrhosis

Table 1. Hemodynamic measurements in several therapeutic regimens

	sPAP (mmHg)	dPAP (mmHg)	mPAP (mmHg)
Diagnosis	90	32	51
After stopping ilomedin therapy	88	29	52
During combination therapy with ilomedin and bosentan	63	21	37
During single bosentan therapy	65	23	39

6 Min-walking test and Haemodynamic before and under Therapy with Bosentan in liver cirrhose and PAH (CHILD A)



Laboratory values in follow up under Bosentan

	-3 Months	-Day 4	Day 2	Day 5	Day 10	4 Months	5 Months	1 Year
Bilirubin (<1.00 mg/dL)	2.25	1.29	1.24	1.64	1.37	0.76	0.83	1.08
ALT/GPT (<45 U/L)	36	23	23	21	19	28	32	25
AST/GOT (<40 U/L)	52	35	35	31	33	35	40	29
aP (<135 U/L)	139	150	250	124	114	111	132	128
Albumin (3.5-5.0 g/dL)	4.7	4.5	4.1	4.1	4.1	5.1	5.1	4.5
INR (<1.3)	1.2	1.3	1.2	1.2	1.2	1.1	1.1	1.1
Creatinine (0.5-1.2 mg/dL)	1.1	1.1	1.2	0.9	0.9	1.0	1.0	0.8
BUN (9-50 mg/dL)	41	60	42	38	28	52	36	21

Ventilation	-3 Months ambient air	-Day 3 2 Liters O ₂ /min	Day 9 ambient air
pH	7.46	7.45	7.43
pO ₂ (mm Hg)	71	56	75
pCO ₂ (mm Hg)	35	26	36
HCO ₃ ⁻ (mmol L ⁻¹)	24	21	21

Bosentan added in severe right heart decompensation under iv Iloprost in OH associated PPHTN

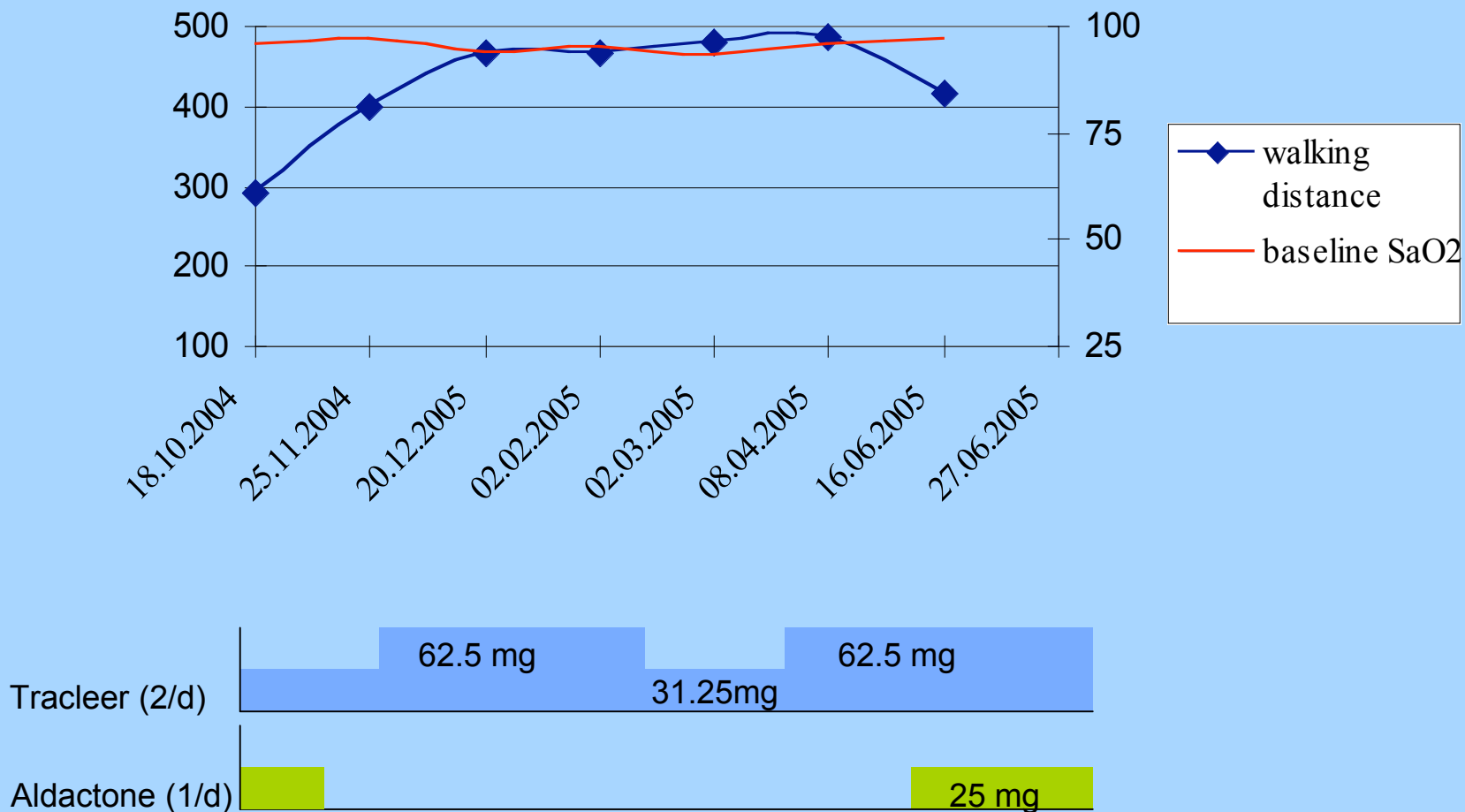
Parameters	June 2001 no therapy	June 2002 IV iloprost 3 ng/kg/min	Jan 2003 IV iloprost 3.5 ng/kg/min	Mar 2003 IV iloprost 4.7 ng/kg/min + bosentan	Jan 2005 IV iloprost 6 ng/kg/min + bosentan
CI (l/min/m ²)	1.4	2.2	1.2	1.9	3.1
RAP _m (mmHg)	25	5	26	13	5
PAP _m (mmHg)	66	49	59	55	48
PVR (dynes*cm*sec ⁻⁵)	1551	727	1545	975	516
RR _m (mmHg)	67	78	59	71	68
PCWP (mmHg)	9	7	8	7	6
HR (beats/min)	110	96	116	100	88

Case presentation from Be

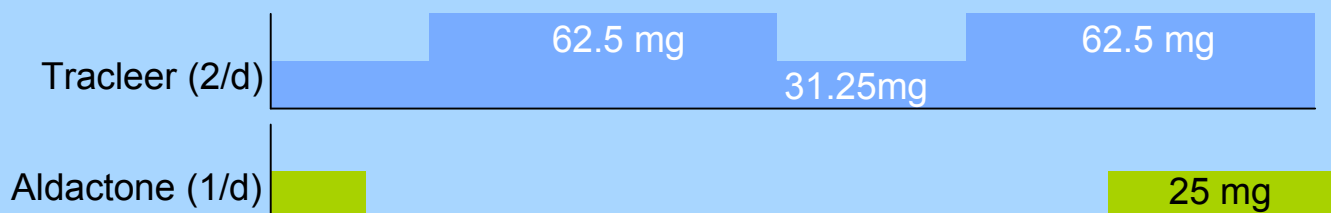
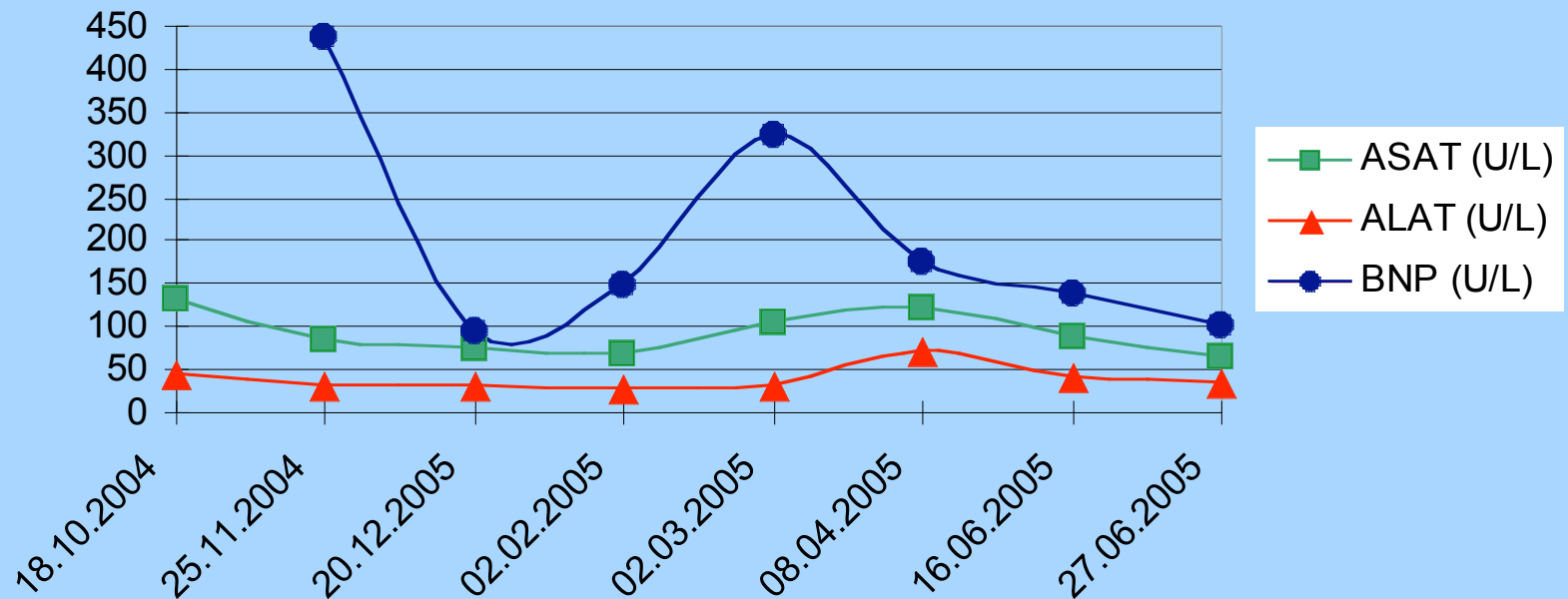
41 year old caucasian male patient
hospitalized with:

- Liver cirrhosis Child C (Child-Pugh Score 11pts)
- Chronic hepatitis C
- Alcohol abuse (stop 2004)
- Suspicion of hepato-renal syndrom

Clinical evolution and treatment



Progression of liver enzymes, BNP



Overall findings in case Be

Bosentan was effective

- Clinical Score has improved Child C ► Child B
- Improvement of renal clearance from 35 to 102 ml/min
- pO₂ improved from 63mmHg to 83mmHg
- BNP decreased (438pg/ml down to 93pg/ml)
- Right ventricular ejection vol. increased by 28ml (MRI)
- Cardiac output increased from 2.55 l/min to 4.5 l/s
- 6 min. walking distance improved by 195m

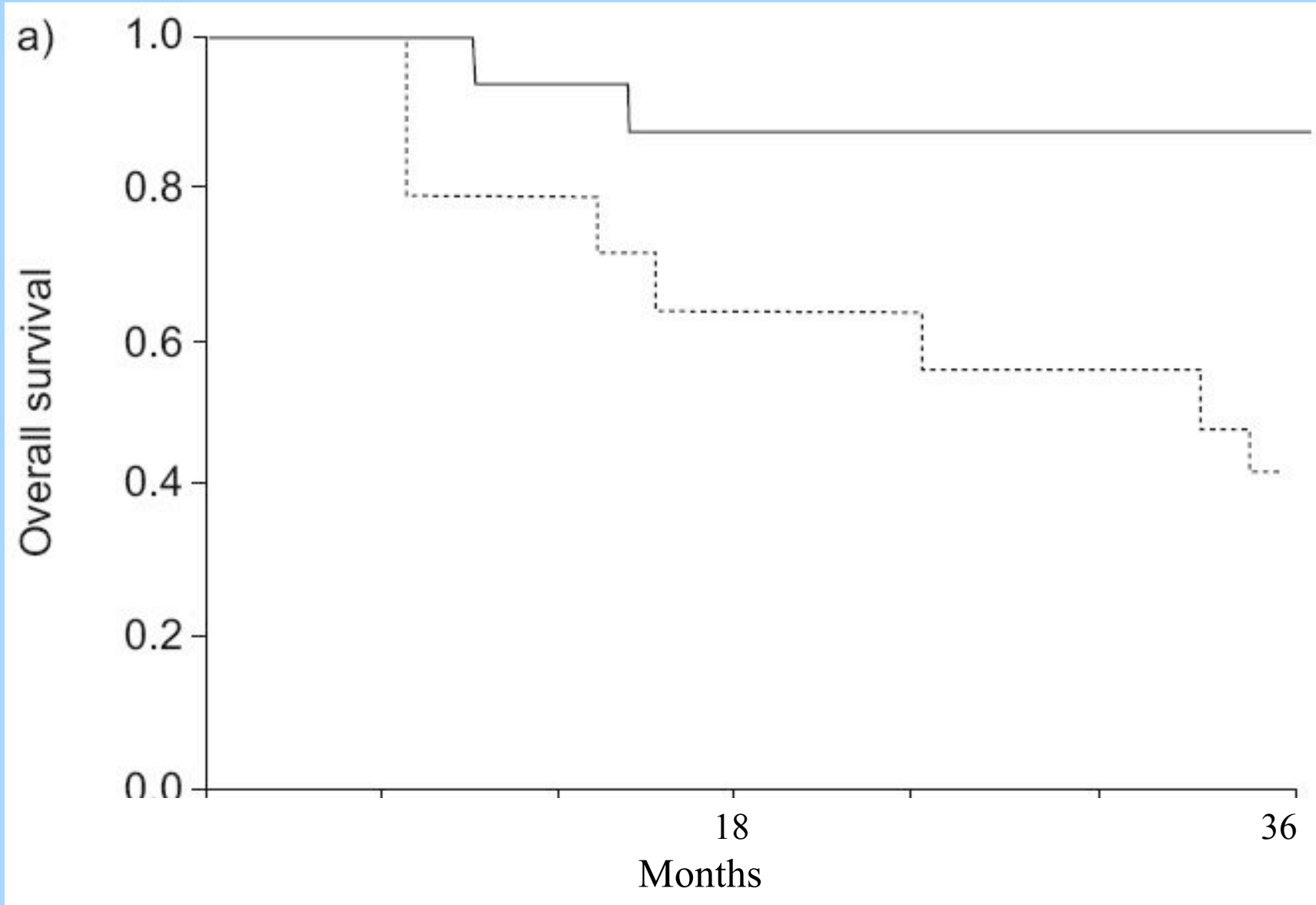
A slight worsening is occurring after 8 months of therapy

Bosentan or inhaled Iloprost for Portopulmonary Hypertension

	Iloprost group	Bosentan group	p-value
Subjects n	13	18	
Female/male n	8/5	9/9	0.717
NYHA II	1 (8)	0 (0)	0.419
NYHA III	12 (92)	16 (89)	1.0
NYHA IV	0 (0)	2 (11)	0.497
Age yrs	44 ± 8	48 ± 11	0.144
6-min walk distance m	343 ± 116	358 ± 101	0.435
RAP mmHg	6 ± 5	9 ± 6	0.204
\bar{P}_{pa} mmHg	51 ± 7	52 ± 7	0.832
CO L·min⁻¹	4.9 ± 1.6	4.6 ± 1.3	0.735
CI L·min⁻¹·m⁻²	2.6 ± 0.6	2.4 ± 0.6	0.352
PVR dyn·s·cm⁻⁵	812 ± 337	866 ± 422	0.866
S_{v,O₂} %	65 ± 9	62 ± 8	0.204
FVC % pred	94 ± 15	92 ± 17	0.882
FEV₁ % VC	75 ± 6	73 ± 10	0.250
DL_{CO} % pred	68 ± 16	60 ± 17	0.209

MM Hoepfer et al E R J 2007;30:1096

Bosentan or inhaled Iloprost for Portopulmonary Hypertension



MM Hoeper et al E R J 2007;30:1096

Bosentan or inhaled Iloprost for Portopulmonary Hypertension

	Iloprost [#]		Bosentan [†]	
	Baseline	6–18 months	Baseline	6–18 months
RAP mmHg	7 ± 6	11 ± 8	8 ± 6	4 ± 3
Change (p-value)	4 ± 11 (p=0.320)		-4 ± 5 (p=0.027)	
\bar{P}_{pa} mmHg	50 ± 10	53 ± 8	53 ± 8	45 ± 13
Change (p-value)	2 ± 8 (p=0.577)		-7 ± 13 (p=0.077)	
CO L·min⁻¹	4.8 ± 1.6	4.7 ± 1.7	4.4 ± 1.2	5.7 ± 1.3
Change (p-value)	0 ± 1.8 (p=0.765)		1.2 ± 1.1 (p=0.002)	
PVR dyn	828 ± 349	895 ± 351	925 ± 473	579 ± 261
Change (p-value)	73 ± 457 (p=0.413)		-345 ± 361 (p=0.008)	
Sv,O₂ %	65 ± 9	62 ± 11	61 ± 7	68 ± 5
Change (p-value)	-3 ± 13 (p=0.966)		6 ± 8 (p=0.005)	

MM Hoeper et al E R J 2007;30:1096

Medical Therapy from severe PPHTN

Data are still sparse from open studies

Prospective, controlled studies are needed

Biggest published series are with Bosentan

Bosentan for CHILD A is safe and efficient