Pulmonary Hypertension in Pregnancy

- Chair: Nadine Sauvé
- Speakers:
  - Respirology: Dr Mitesh V. Thakrar (University of Calgary)
  - Obstetric Medicine: Dr Ellen Harrison (Albert Einstein College of Medicine, Montefiore Medical Center, New York)
  - MFM: Dr Meena Khandelwal (Cooper Medical School of Rowan University, New Jersey)
  - Anesthesiology: Dr Lorraine Chow (Foothills Medical Centre, Calgary)

Pulmonary Hypertension & Pregnancy

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Disclosures

- I have received travel grants from Actelion Pharmaceuticals, Eli Lily, Bayer, and GSK
- I have received speaking honorariums from InterMune
- I have served on advisory boards with Boehringer Ingelheim, Actelion Pharmaceuticals, and Bayer

Objectives

- Review the different types of pulmonary hypertension, the diagnostic and treatment algorithm, and prognosis
- Review the normal hemodynamic changes associated with pregnancy
- Review the safety of medications used in treating pulmonary arterial hypertension during pregnancy & breast feeding

Definitions

- Pulmonary Hypertension (PH) is defined as a mean pulmonary artery pressure (mPAP) of greater than 25 mmHg

- Pulmonary Arterial Hypertension (PAH) is defined as PH plus a normal pulmonary capillary wedge pressure (PCWP <15 mmHg) and Pulmonary Vascular Resistance > 3 Wood Units

- PVR = (mPAP-PCWP)/CO

Hoeper et al. JACC 62 (25) Dec 24, D42-50

Classification of Pulmonary HTN

GROUP 1

GROUP 2

GROUP 3

GROUP 4

GROUP 5

1. Pulmonary arterial hypertension (PAH)

- 1.1 Idiopathic
- 1.2 Heritable
  - 1.2.1 BMPR2 mutation
  - 1.2.2 Other mutations
- 1.3 Drugs and toxins induced
- 1.4 Associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease (Table 6)
  - 1.4.5 Schistosomiasis

1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

1''. Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease

- 2.1 Left ventricular systolic dysfunction
- 2.2 Left ventricular diastolic dysfunction
- 2.3 Valvular disease
- 2.4 Congenital / acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
- 2.5 Other

3. Pulmonary hypertension due to lung diseases and/or hypoxia

- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental lung diseases (Web Table III)

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

- 4.1 Chronic thromboembolic pulmonary hypertension
- 4.2 Other pulmonary artery obstructions

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms

- 5.1 Haematological disorders
- 5.2 Systemic disorders
- 5.3 Metabolic disorders
- 5.4 Others

Galie N et al. Eur Heart J. Aug 29, 2015

Pulmonary Hypertension

Frequency of presentation, by subclassification

1. Pulmonary Arterial Hypertension

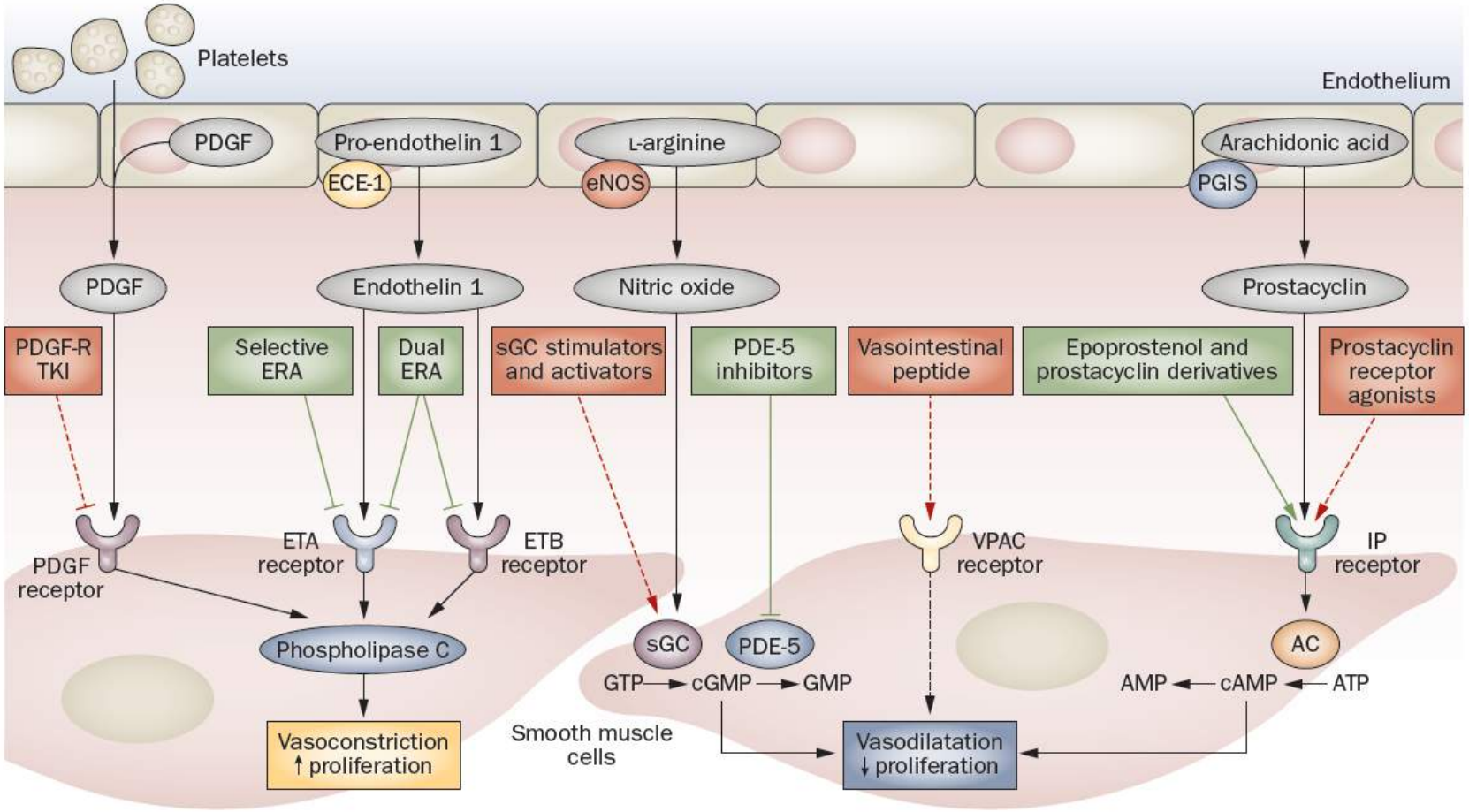
2. PH with Left Heart Disease

3. PH with Lung Disease/Hypoxemia

4. PH due to Chronic Thrombotic and/or Embolic Disease

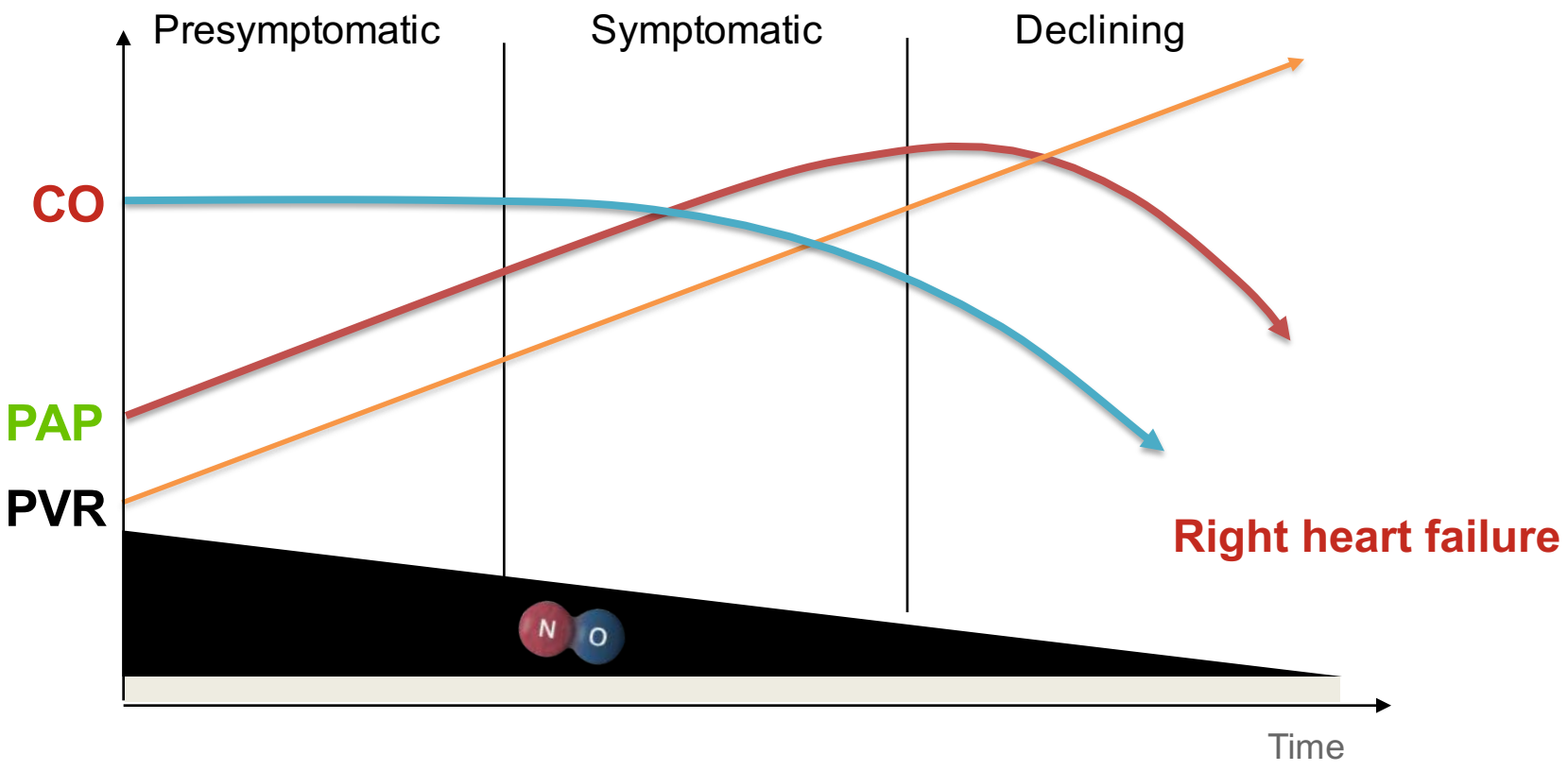
5. Miscellaneous

PAH Pathophysiology



O'Callaghan DS *et al. Nat Rev Cardiol* 2011;8:526–38.

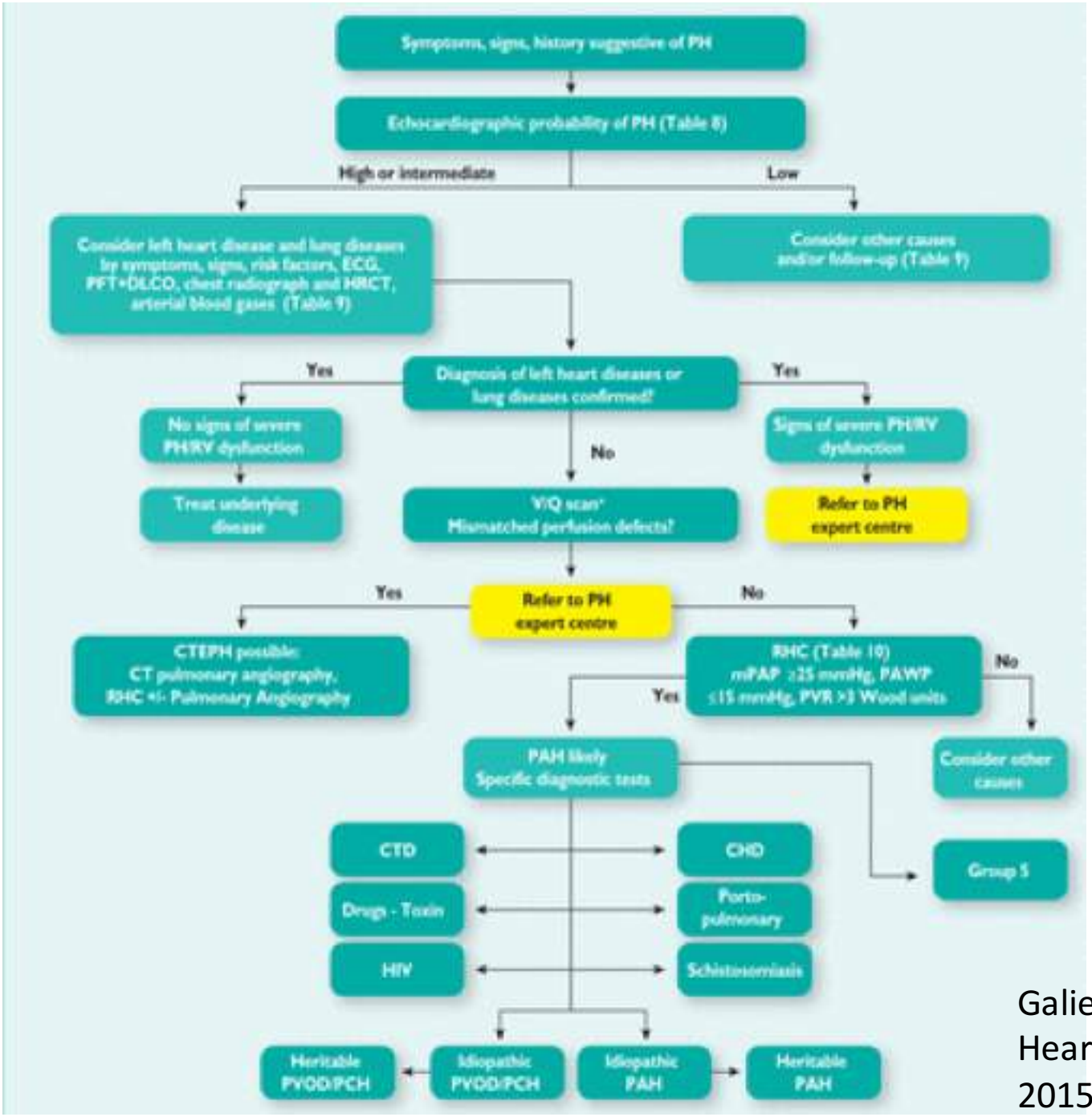
Endothelial dysfunction worsens as PH disease progresses



PVR = (mPAP-PCWP) / CO

CO, cardiac output; NO, nitric oxide; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance.

Adapted from: Domenighetti G. *Swiss Med Wkly* 2007;137:331–6.
Schermuly R *et al. Expert Opin Invest Drugs* 2011;20:567–76.



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History & Physical

- History: Non-specific, and difficult to tease out from normal pregnancy
  - Dyspnea, Chest Pain, Presyncope, Edema
  - WHO Class
  - PAH typically worsens/presents in pregnancy during weeks 20-24 as hemodynamic physiologic changes peak then (Olsson K. Semin Respir Crit Care Med 2013;34:681–688.)
- Physical Exam:
  - Precordial – Loud P2, RV Heave, TR, S3/4
  - Vol O/L – Edema, Ascites, Pulsatile Liver, JVP ↑

WHO Functional Classes

B. World Health Organization functional assessment classification	
Class I:	Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
Class II:	Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class III:	Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class IV:	Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right-heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

http://www.medscape.org/viewarticle/544175; accessed October 22, 2015

Echocardiography

Peak tricuspid regurgitation velocity (m/s)	Presence of other echo 'PH signs'[a]	Echocardiographic probability of pulmonary hypertension
≤2.8 or not measurable	No	Low
≤2.8 or not measurable	Yes	Intermediate
2.9–3.4	No	
2.9–3.4	Yes	High
>3.4	Not required	

A: The ventricles[a]	B: Pulmonary artery[a]	C: Inferior vena cava and right atrium[a]
Right ventricle/ left ventricle basal diameter ratio >1.0	Right ventricular outflow Doppler acceleration time <105 msec and/or midsystolic notching	Inferior cava diameter >21 mm with decreased inspiratory collapse (<50 % with a sniff or <20 % with quiet inspiration)
Flattening of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/or diastole)	Early diastolic pulmonary regurgitation velocity >2.2 m/sec	Right atrial area (end-systole) >18 cm^2
	PA diameter >25 mm.	

$RVSP = 4(TRV^2) + RAP$

Galie N et al. Eur Heart J. Aug 29, 2015

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	PA diameter >25 mm.	

TAPSE < 18 mm

$RVSP = 4(TRV^2) + RAP$

Galie N et al. Eur Heart J. Aug 29, 2015

Echo in pregnancy

- Still a valuable screening tool
  - Non-invasive, no radiation, cheap, quick
- IVC may not be well seen with gravid uterus
  - Needed to calculate RVSP
- Good correlation with RHC
- But false positives do occur

Olsson K. Semin Respir Crit Care Med 2013;34:681–688.

Ancillary Tests

- ECG – Right axis, Rt heart strain pattern
- PFT – Isolated reduced DLCO
- CXR – Enlarged PA
- HRCT – Normal or mosaic attenuation
- Sleep Study
- Abdo U/S
- CMR
- NT-Pro-BNP
- Complete labs, incl HIV and CTD
- 6 Minute Walk Test (6MWT)

Galie N et al. Eur Heart J. Aug 29, 2015

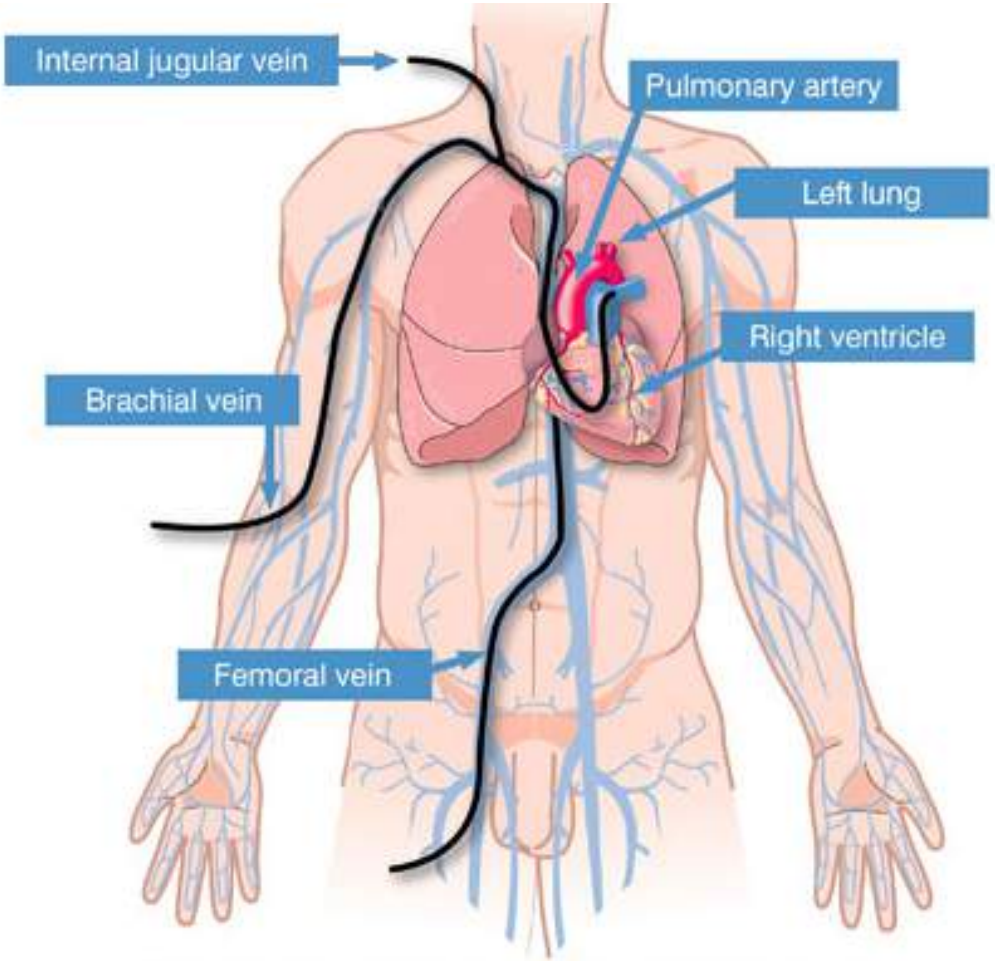
RHC & NO Challenge

- Gold standard and needed to confirm diagnosis of PAH

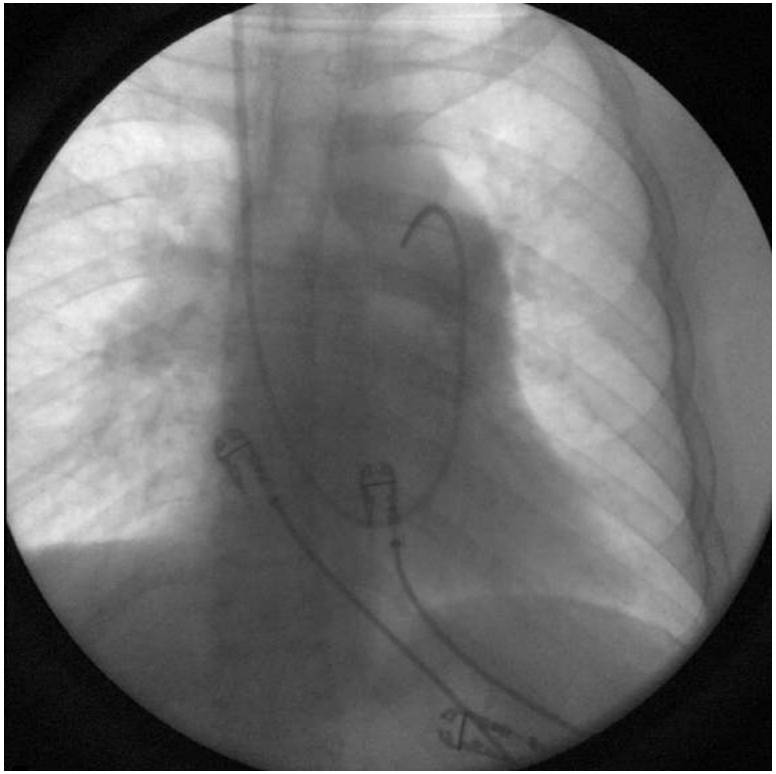
- Definition – mPAP > 25, PCWP < 15, PVR > 3
- PVR = (mPAP-PCWP)/CO
- CO via thermodilution or Fick

- Vasoreactivity – 20 ppm NO x 5 min
  - Absolute fall in mPAP < 40, minimum Δ mPAP of 10, and stable/increased CO.

Right Heart Cath



Standard approaches for catheter access



Galié et al. *Eur Heart J* 2009.

Treatment

			WHO-FC II		WHO-FC III		WHO-FC IV	
Calcium channel blockers			I	C[d]	I	C[d]	-	-
Endothelin receptor antagonists	Ambrisentan		I	A	I	A	IIb	C
	Bosentan		I	A	I	A	IIb	C
	Macitentan[e]		I	B	I	B	IIb	C
Phosphodiesterase type 5 inhibitors	Sildenafil		I	A	I	A	IIb	C
	Tadalafil		I	B	I	B	IIb	C
	Vardenafil[g]		IIb	B	IIb	B	IIb	C
Guanylate cyclase stimulators	Riociguat		I	B	I	B	IIb	C
Prostacyclin analogues	Epoprostenol	Intravenous[e]	-	-	I	A	I	A
	Iloprost	Inhaled	-	-	I	B	IIb	C
		Intravenous[g]	-	-	IIa	C	IIb	C
	Treprostinil	Subcutaneous	-	-	I	B	IIb	C
		Inhaled[g]	-	-	I	B	IIb	C
		Intravenous[f]	-	-	IIa	C	IIb	C
		Oral[g]	-	-	IIb	B	-	-
	Beraprost[g]		-	-	IIb	B	-	-
IP receptor agonists	Selexipag (oral)[g]		I	B	I	B	-	-

Galie N et al.
Eur Heart J.
Aug 29, 2015

Treatment

In Canada

Approval Pending

			WHO-FC II		WHO-FC III		WHO-FC IV	
Calcium channel blockers			I	C[d]	I	C[d]	-	-
Endothelin receptor antagonists	Ambrisentan		I	A	I	A	IIb	C
	Bosentan		I	A	I	A	IIb	C
	Macitentan[e]		I	B	I	B	IIb	C
Phosphodiesterase type 5 inhibitors	Sildenafil		I	A	I	A	IIb	C
	Tadalafil		I	B	I	B	IIb	C
	Vardenafil[g]		IIb	B	IIb	B	IIb	C
Guanylate cyclase stimulators	Riociguat		I	B	I	B	IIb	C
Prostacyclin analogues	Epoprostenol	Intravenous[e]	-	-	I	A	I	A
	Iloprost	Inhaled	-	-	I	B	IIb	C
		Intravenous[g]	-	-	IIa	C	IIb	C
	Treprostinil	Subcutaneous	-	-	I	B	IIb	C
		Inhaled[g]	-	-	I	B	IIb	C
		Intravenous[f]	-	-	IIa	C	IIb	C
		Oral[g]	-	-	IIb	B	-	-
	Beraprost[g]		-	-	IIb	B	-	-
IP receptor agonists	Selexipag (oral)[g]		I	B	I	B	-	-

Galie N et al.
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Adjuncts

- Diuretics
- Oxygen
- Anticoagulation (warfarin)
- Digoxin
- Exercise

Galie N et al. Eur Heart J. Aug 29, 2015

Monitoring

	At baseline	Every 3–6 months[a]	Every 6–12 months[a]	3–6 months after changes in therapy[a]	In case of clinical worsening
Medical assessment and determination of functional class	+	+	+	+	+
ECG	+	+	+	+	+
6MWT/Borg dyspnoea score	+	+	+	+	+
CPET	+		+		+[b]
Echo	+		+	+	+
Basic lab[c]	+	+	+	+	+
Extended lab[d]	+		+		+
Blood gas analysis[e]	+		+	+	+
Right heart catheterization	+		+[f]	+[g]	+[h]

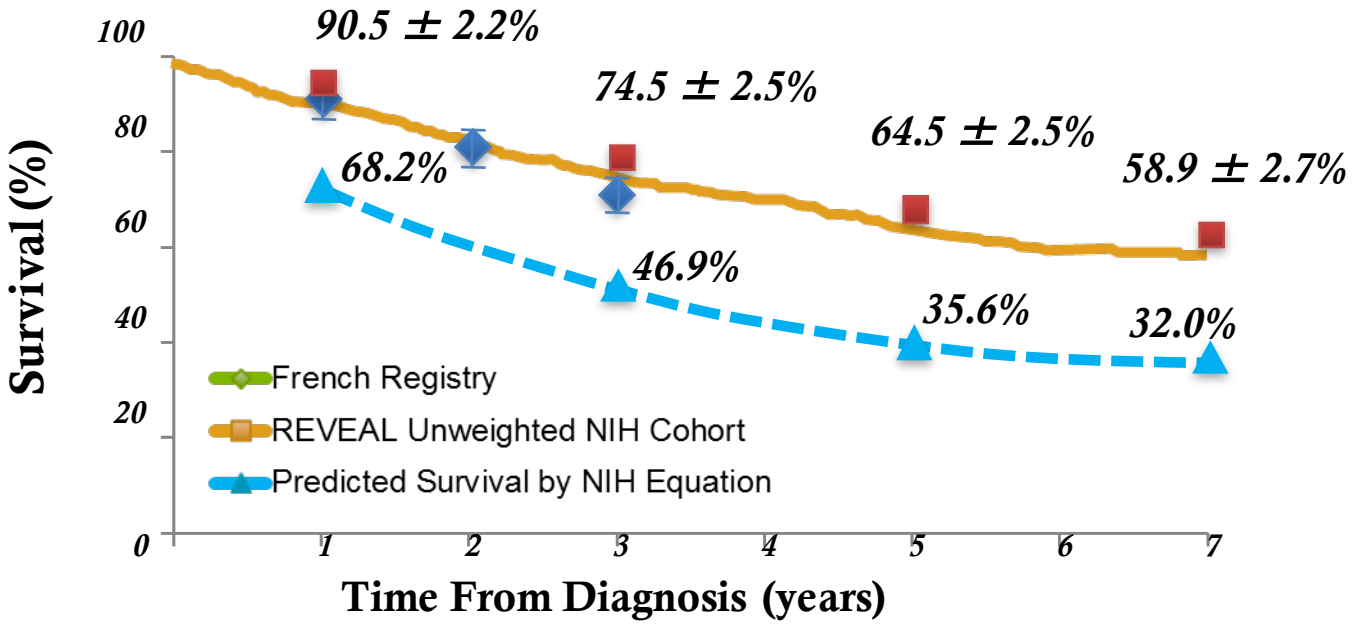
Galie N et al. Eur Heart J. Aug 29, 2015

Monitoring/Treatment Goals

Determinants of prognosis* (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope†	Repeated syncope†
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 slope ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/l	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

Galie N et al. Eur Heart J. Aug 29, 2015

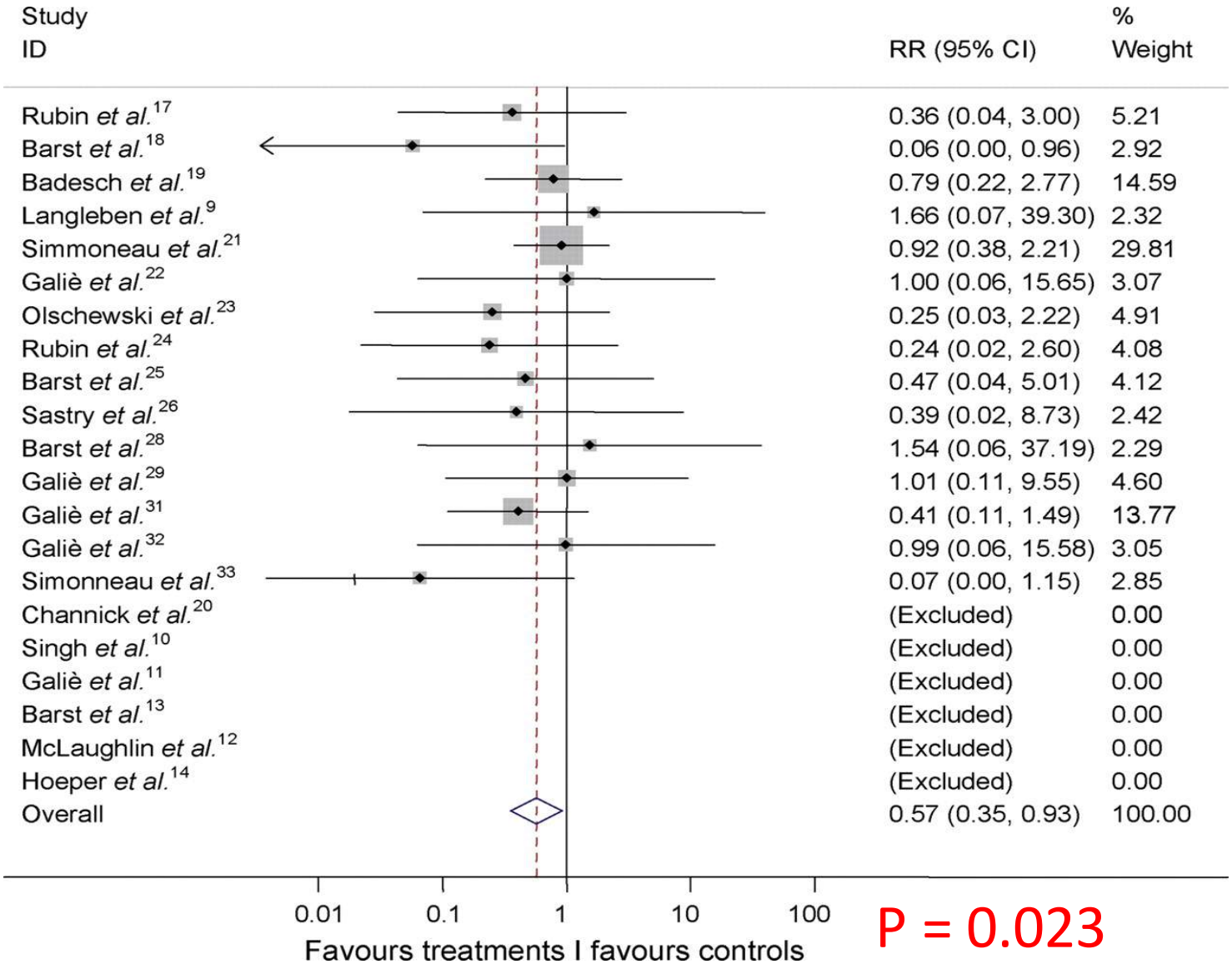
Although Outcomes Have Improved Over the Past 15 Years, Long-term Prognosis of PAH Remains Suboptimal



No. at risk*: 279 377 390 388 328 240 153 88

Benza RL et al. Chest. 2012;142:448-456

Cumulative RR of death with PAH Tx



P = 0.023

N Galie et al, Eur H J 2009;30:394

Prognosis in Pregnancy

Table 16

Recommendations for general measures

Recommendations	Class[a]	Level[b]
It is recommended that PAH patients avoid pregnancy	I	C

(Presentation of de novo PAH is also common in pregnancy, accounting for up to 55% of cases in female PAH patients)

Galie N et al. Eur Heart J. Aug 29, 2015

Olsson K. Semin Respir Crit Care Med 2013;34:681–688.

Prognosis in Pregnancy

- Mortality of PAH patients who become pregnant is high
- Early reports of 30-56% maternal mortality (before PAH specific therpies) and 11-13% fetal mortality
- More contemporary reports – 12-33% maternal mortality, worsening WHO class, low fetal mortality (but SGA common), 62% pregnancy success rate

Olsson K. Semin Respir Crit Care Med 2013;34:681–688.

Prognosis in Pregnancy

- Right heart cath data may provide prognostic information
- Pre-medical Rx – CI > 4, RAP < 10, PVR < 12.5 associated with improved survival
- Recent registry data suggests improved outcomes if PVR < 6.25
- Patients who died or were transplanted had increased mPAP and PVR and lower CI

Roberts NV & Keast PJ. Anaesth Intensive Care 1990;18(3):366–374

Jais et al Eur Respir J 2012; 40: 881–885

Hemodynamics in Pregnancy

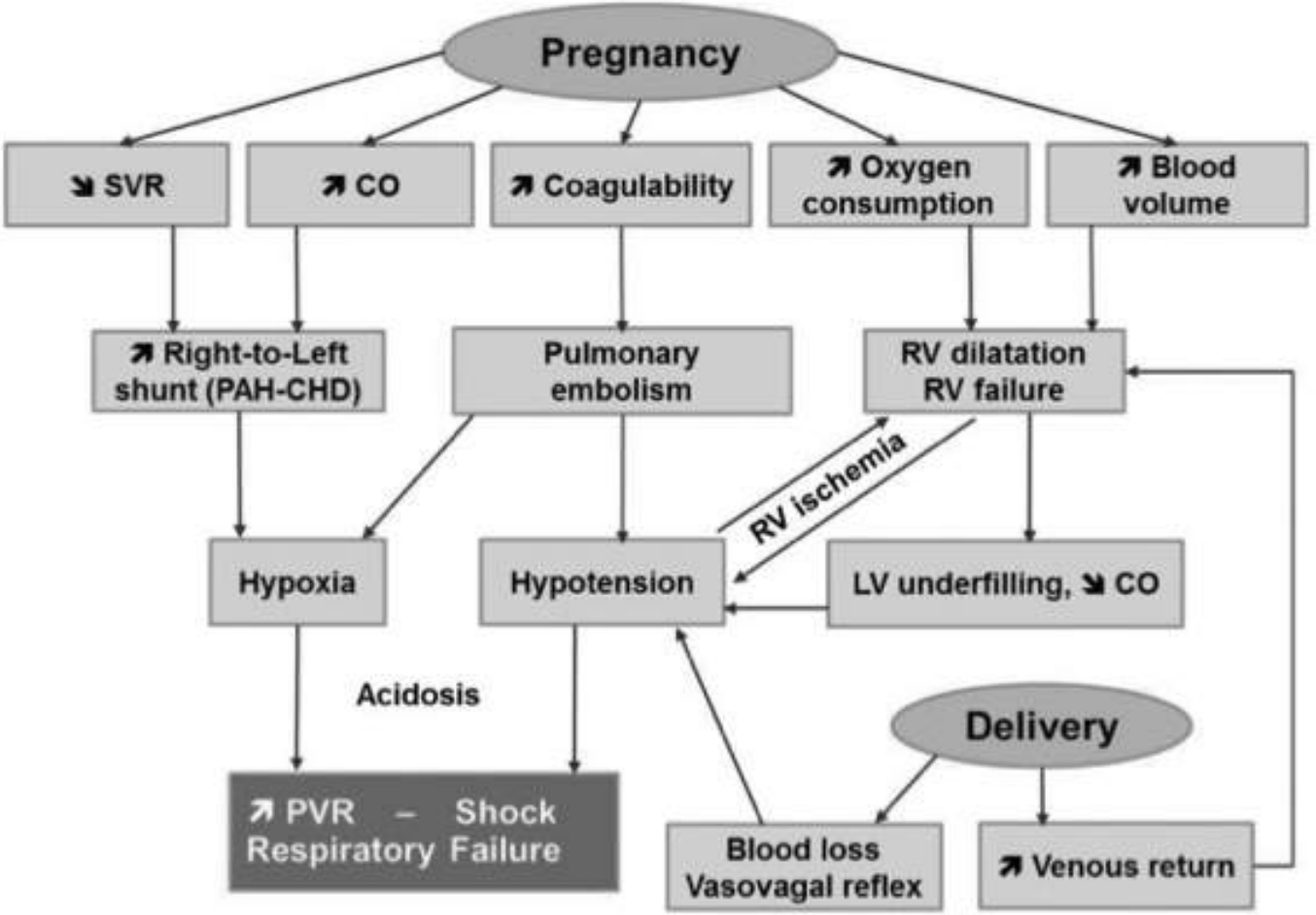


Fig. 1 The physiologic response to pregnancy in pulmonary hypertension. (Reproduced with permission from Hsu, C. H. and John Wiley and Sons.)

PAH Therapies in Pregnancy

Medication	Grade in Pregnancy	Safe in Breastfeeding (Y/N)
Epoprostinol	B	No info
Treprostinil	No human data	No info
Sildenafil	B	No info
Tadalafil	B	No info
Bosentan	X	No info
Ambrisentan	X	No info
Macitentan	X	No info
Riociguat	X	No info
Warfarin	X	Safe to use
Furosemide	C	Contraindicated*
Spironolactone	C	Probably safe
Metalozone	B	Probably safe

Briggs ; Drugs In Pregnancy and Lactaction 8th edition

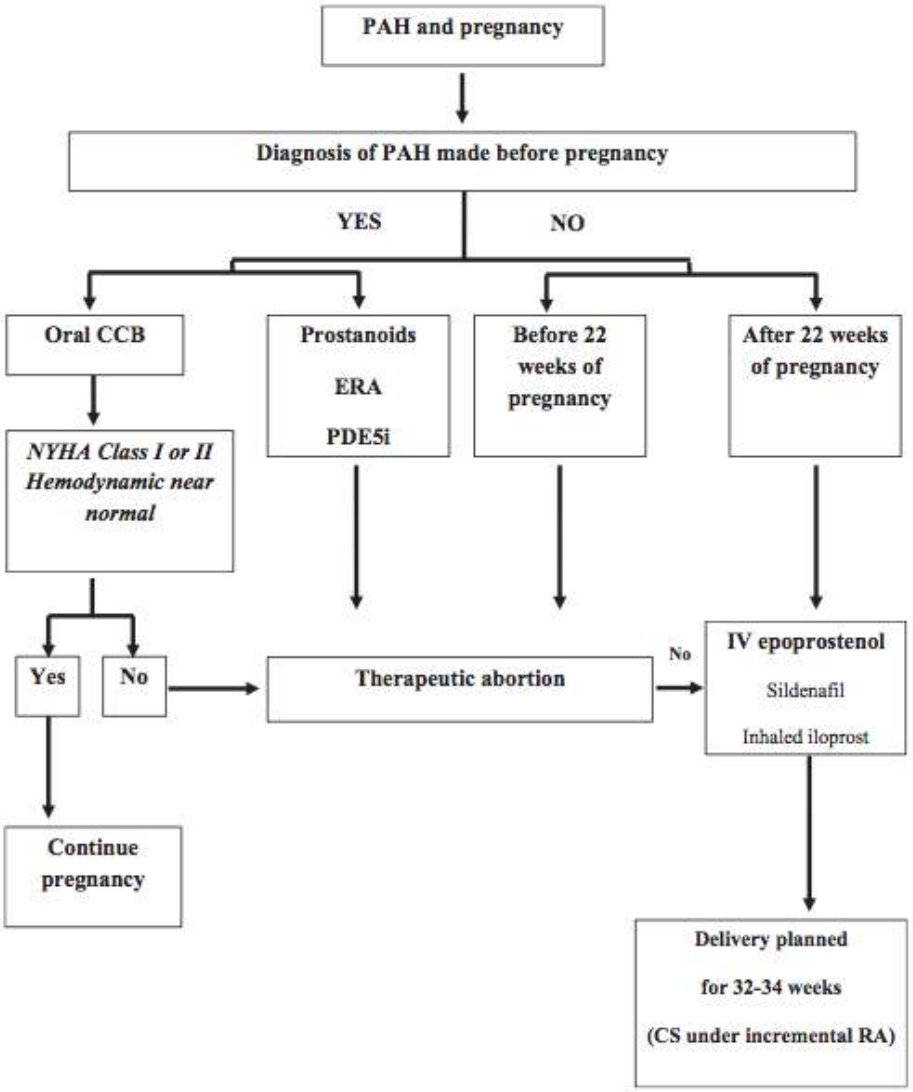
Objectives

- Review the different types of pulmonary hypertension, the diagnostic and treatment algorithm, and prognosis
- Review the normal hemodynamic changes associated with pregnancy
- Review the safety of medications used in treating pulmonary hypertension during pregnancy & breast feeding

General Approach

- Maximize pulmonary vasodilation to maximally decrease PVR
- Epoprostinol +/- sildenafil
- Anticoagulation – change to LMWH or UFH
- Multi-disciplinary peri-partum care, ideally in a PAH centre.

General Approach



Olsson K. Semin Respir Crit Care Med 2013;34:681–688.

Pulmonary Hypertension in Pregnancy Obstetric Medicine

Ellen A Harrison
Albert Einstein College of Medicine
Montefiore Medical Center

No Disclosures or Conflicts of interest

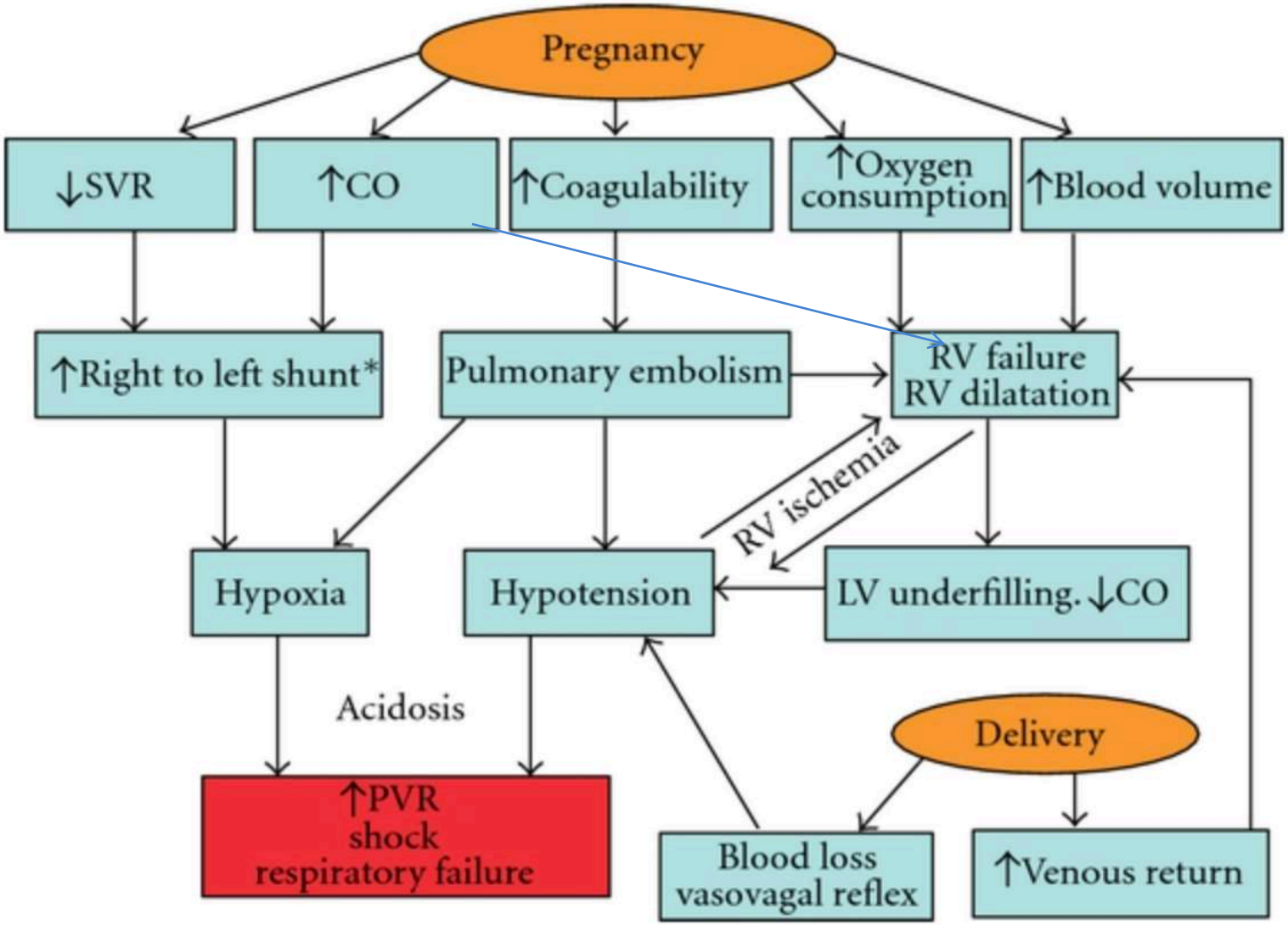
* Medical care during and after pregnancy
* Current assessments of mortality

Safest Pregnancy is No Pregnancy

Antepartum Care
Women with Known PHTN

- Prevention
- Early detection
- Intervention

Response to Pregnancy in Pulmonary Hypertension



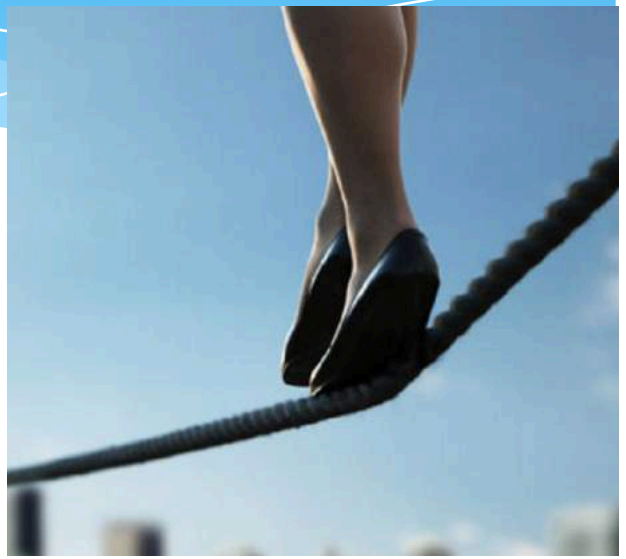
Bassily-Marcus, A PHTN in Pregnancy: Critical Care Management"
Pulmonary Medicine 2012

Interventions Matched to Elements that Provoke Deterioration

* Plasma volume
* Increased O2 demand
* Increased CO
* Hypercoagulability

* Abnormal Pulmonary Vascular Resistance

Increased Plasma Volume



* Tightrope
  * Excess volume with increased right heart and PA pressures, congestion, decrease in RV wall perfusion, impingement on LV cavitary volume, decreased CO;
  * Underfilled RV: low preload with decreased CO
* Limit excess sodium intake
* Diuretics
  * Choice of agent
    * Furosemide commonly recommended
    * Avoid Spironolactone
* Attend to conditions with volume loss

Increased CO and O2 demand

* Avoid anemia
* Maintain adequate oxygenation
* Infection
  * Immunization
  * Avoid exposure
  * Prompt treatment
  * Antipyretics
* Limit activity

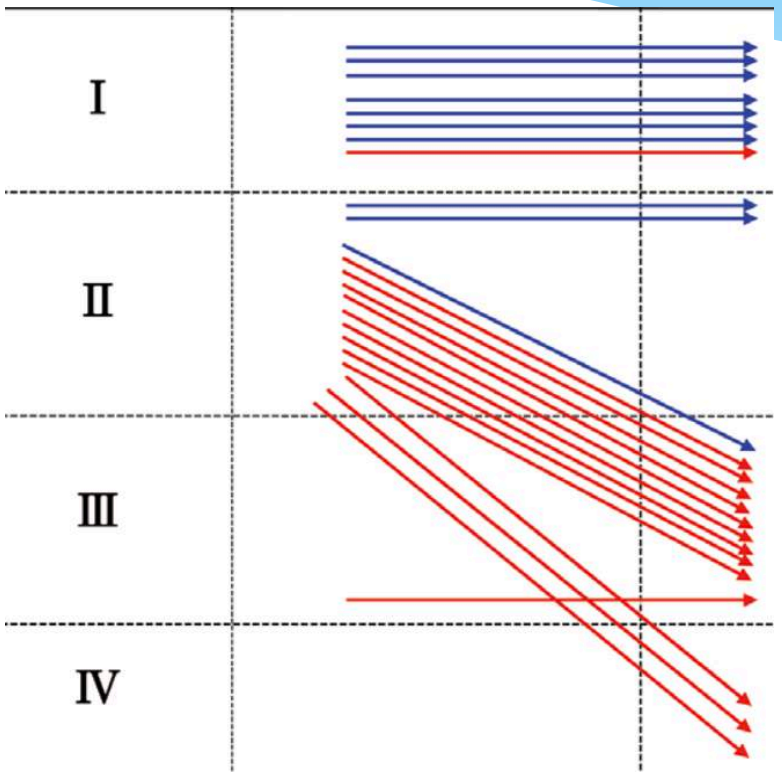
Hypercoagulability

* Risk of peripheral venous thrombosis and pulmonary embolism as well as pulmonary vascular thrombosis
* Anticoagulation
  * Widely used
  * Patient selection
  * LMWH
  * Intensity
  * Timing

Direct therapy of Increased Pulmonary Vascular Resistance

Maternal Evaluation During Antenatal Care

Change in NYHA Class from Early to Late Pregnancy

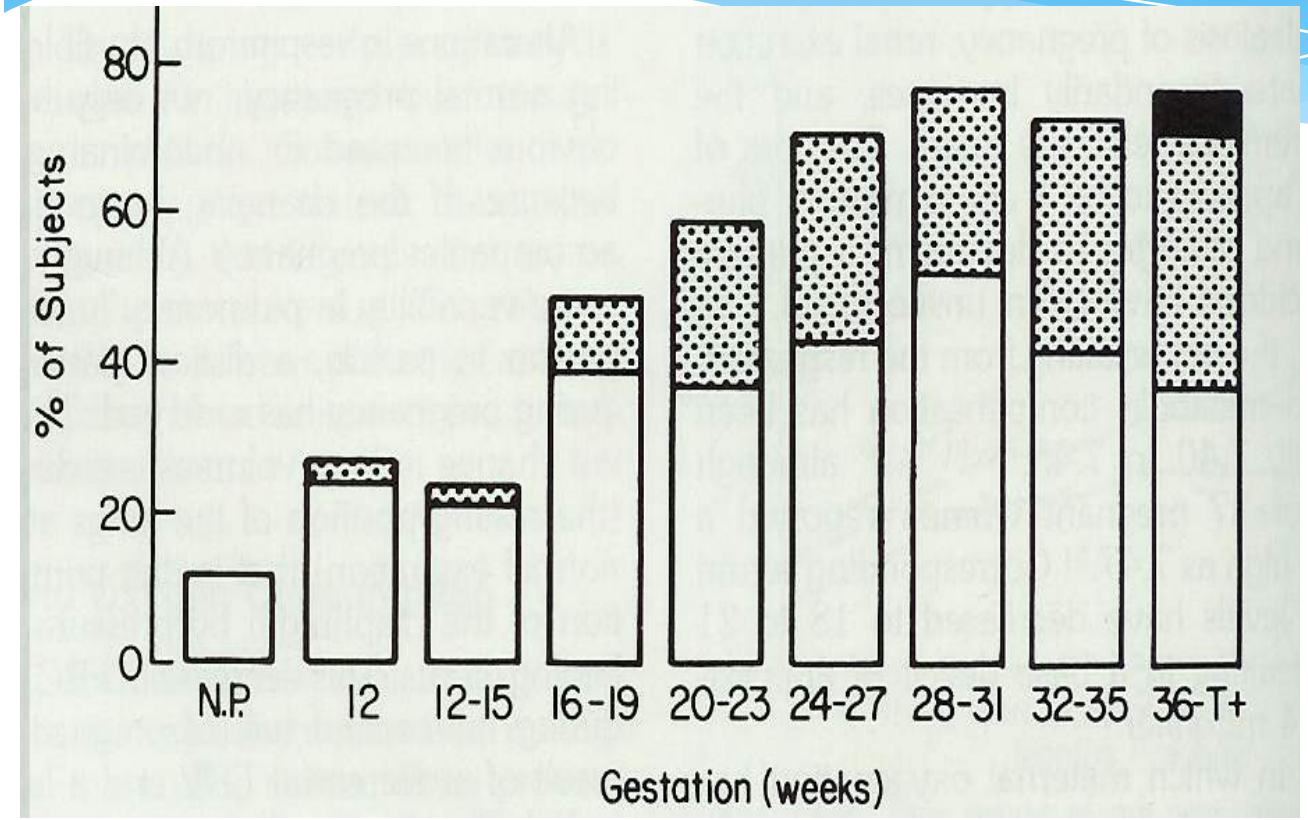


Katsuragi S Circ J 2012; 76:2249

Symptoms overlap with common pregnancy complaints

* Dyspnea on Exertion

Dyspnea in normal pregnancy



* White =dyspnea on climbing hills or > 1 flight
* Dotted = dyspnea with 1 flight, routine housework, or walking even pace on level ground
* Black = dyspnea on slight exertion or at rest

Milne Postgrad Med J 1979; 55:318

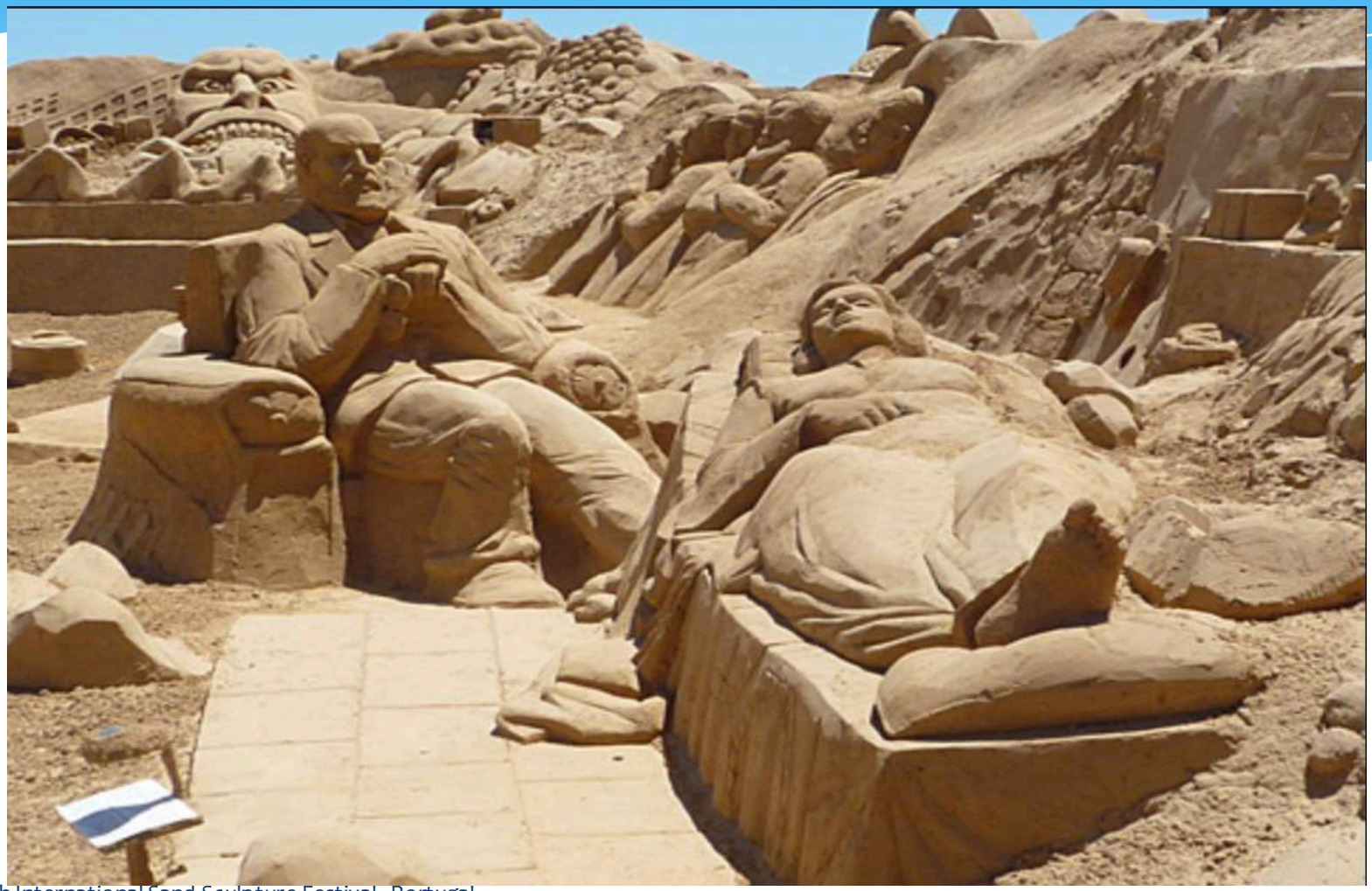
PHTN Symptoms overlap with common pregnancy complaints

* Dyspnea on Exertion
* Fatigue
* Edema
* Palpitations with or without exertion
* Dizziness, Presyncope or Syncope
  * precipitated by exertion?
* Chest Pain

* Disproportion
* Progression
* Severity
* Exertional onset
* Low threshold to investigate further

Symptoms at Rest are Late Manifestations

Symptoms at Rest are Late Manifestations



R.Haworth International Sand Sculpture Festival, Portugal

Signs to elicit Antenatal Exam

* Heart Rate, Respiratory Rate, Blood Pressure
* Oxygen saturation
* JVD, HJR
* CV: RV heave, loud P2, RS3,adequacy of pulses
* Liver: size, tenderness, pulsatility
* Edema, Ascites, Abdominal Discomfort
* Exercise tolerance:
  * 6 min walk…
  * Ad hoc

6 minute walk test

Structured repeated mild exertion

Laboratory Testing

* Liver tests: transaminases
* Creatinine
* Electrolytes
* CBC : hemoglobin
* Oxygen Saturation

* BNP

* Troponin
* Lactate/anion gap

Echocardiography

* Verify finding of PHTN determined echocardiographically by Right Heart Catheterization **
    - before acting on a new diagnosis
    - before recommending termination
    - before starting vasoactive drugs

1/3 of new referrals for PHTN based on echo were not substantiated by RHC in 2 studies

Temporary conditions can alter PA pressure

Accuracy of RVSP on echo in pregnancy (and other high output states) questioned

Penning S. Am J Obstet Gynecol, 184 (2001), p. 1568. Wylie B. J Perinat Med 2007;35:497

Table II. Individual pulmonary artery pressures as measured by echocardiography and catheterization

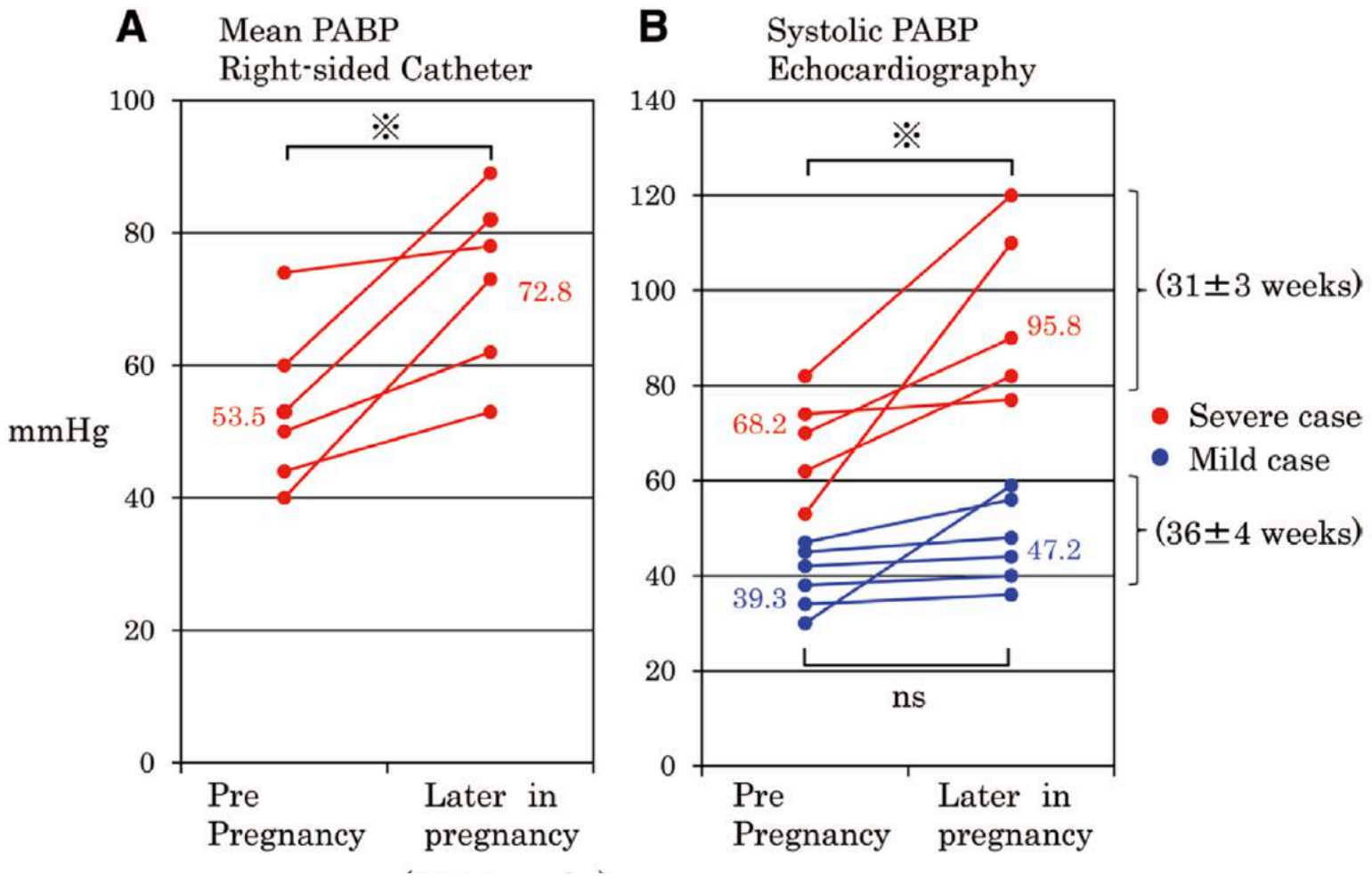
Patient No.	*Echo pulmonary artery systolic pressure (mm Hg)*	*Catheter pulmonary artery systolic pressure (mm Hg)*
1	77	68
2	57	25
3	70	18
4	52	27
5	78	70
6	68	55
7	54	77
8	144	126
9	52	134
10	49	52
11	33	25
12	40	34
13	46	15
14	110	116
15	71	52
16	40	55
17	43	19
18	15	54
19	55	36
20	37	38
21	47	41
22	42	30
23	50	80
24	40	42
25	27	35
26	43	32
27	55	25

Penning S. Am J Obstet Gynecol, 184 (2001), p. 1568

Imaging: Echocardiography

* Standard of care: Serial evaluation
* Attention to RA, RV, Intraventricular septum, RVSP
* Part of global assessment
* Expected magnitude of change

Change in Pulmonary Arterial Systolic Pressure During Pregnancy



Katsuragi S Circ J 2012; 76:2249

De Novo Diagnoses in Pregnancy and Puerperium

* Common !!!!
* Weiss study
  * 81% Eisenmengers with PHTN dx'd pre pregnancy
  * Primary PHTN 15% prepregnancy, 52 %preg, 22% pp
* Pieper study (2014) majority of deaths in de novo cases

* Strategy to find these cases
  * Attention to suggestive symptoms
  * Focus: underlying diseases associated with PHTN
    * i.e. Hemolytic anemias, HIV, systemic sclerosis

Pieper,P Best Practice & Research ObGyn 2014; 28:579. WeissBM JACC 1998; 31:1650

Strategies in Antenatal Care
Maternal

* Close surveillance by Expert Multidisciplinary Team
* Activity
* Anemia
* Infection
* Volume control
* Electrolyte control
* Oxygenation
* Anticoagulation
* Vasodilator therapies
* Primary Disease
* Planning for delivery and postpartum care
* Termination of pregnancy

Advisability of Pregnancy

* Consideration
  * Maternal mortality
    * Related to pregnancy
    * Life expectancy independent of pregnancy
  * Success of pregnancy/wellbeing of offspring
  * Ability to care for child
* Preconception counseling
* If pregnant, discussion of risks and consideration of termination

Mortality
What do we know?

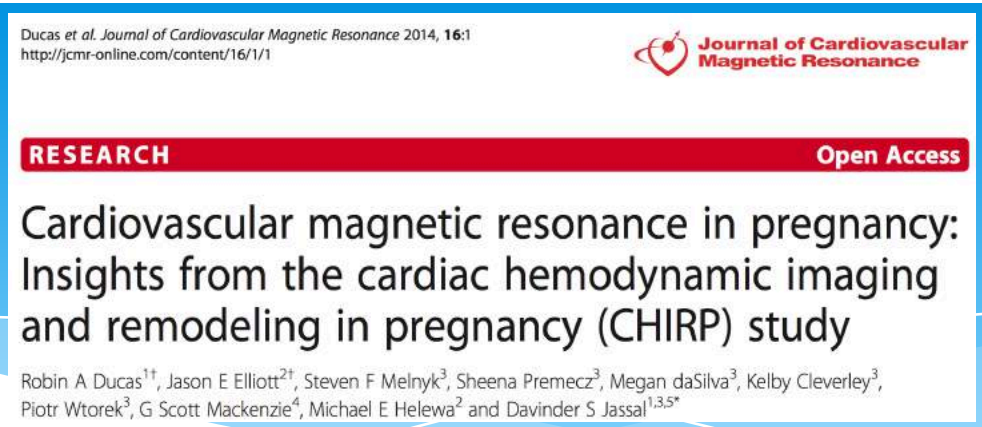
* Timing Primarily post partum
* Causes
* Incidence
  * Changing with time. Why?
* Predictive factors

Causes of Death/Transplant

* R heart failure
* Venous Thromboembolism
* Arrhythmia
* Intractable
* Massive event or smaller event superimposed on preexisting pathology
* Sudden death

Postpartum Physiology
Contribution to Decline in RV Function

* Increase in Pulmonary Vascular Resistance
* Intravascular volume
  * Beyond the immediate peripartum shifts in fluid, ongoing mobilization of fluid from third space
* Maximum hypercoagulability
* Decrease in RV mass



* 34 normal pregnant women
* Studied in third trimester and at least 3 months postpartum

* LV Mass by CMR 179 +/- 5 gms TM3
  * 121 +/- 5 gms pp

* RV mass by CMR 71 +/- 6 gms TM3
* 51 +/- 5 gms pp
* Inferred a 40% increase in RV mass in pregnancy with pp regression
* ? A contributor to propensity for postpartum RV deterioration

Ducas J Cardiovasc Magnetic Res 2014;16:1

Postpartum management

* Intensive Care
* Fluid management
  * Diuretics, management of blood loss
* Hemodynamic monitoring
* Anticoagulation
* Electrocardiographic Monitoring
* Echocardiography
* Continuation/Initiation of pulmonary vasodilator therapy
* Inotropic support; availability of bridge to transplant

Changing Incidence of Mortality

Best Practice & Research Clinical Obstetrics and Gynaecology

ELSEVIER

journal homepage: www.elsevier.com/locate/bpobgyn

9

Pregnancy and pulmonary hypertension

Petronella G. Pieper, MD, PhD, Cardiologist [a,*],
Heleen Lameijer, MD, Research Doctor [b],
Elke S. Hoendermis, MD, PhD, Cardiologist [b]

Table 4
Mortality in women with pulmonary hypertension: comparison of three reviews.

	Weiss et al. [1] (1978–1996)	Bedard et al. [3] (1997–2007)	Current systematic review (1998–2013)
Total mortality	48/125 (38%)	18/73 (25%)	12/77 (16%)
Mortality, IPAH	8/27 (30%)	5/29 (17%)	3/32 (9%)
Mortality, CHD-PAH	26/73 (36%)	8/29 (28%)	7/30 (23%)
Mortality, oPH	14/25 (56%)	5/15 (33%)	2/15 (13%)

CHD-PAH, pulmonary arterial hypertension associated with congenital heart disease; IPAH, idiopathic pulmonary arterial hypertension; oPH, other cause of pulmonary hypertension.

Two subsequent studies : n=12 16.7% mortality Duarte . Chest. 2013 May;143(5):1330
Jais n=20 15% mort & 5% heart transplant European Respiratory Journal 2012, 40:881

Why might mortality be decreasing?

* More advanced patients foregoing pregnancy
* More mild cases recognized: increased echo use
* Change in distribution of underlying etiology

* More patients referred to specialized centers
* Better antepartum care; earlier recognition of problems
* Improved management of L&D, Anesthesia, puerperal care (TBD)
* Targeted vasodilator therapies for PHTN

Counseling: Prediction of maternal outcome

* Trends to improved outcomes with current care
* No reliable predictor of individual outcome to inform counseling
  * trends toward better outcome with milder disease and with idiopathic disease
* More current outcome data needed

* No change in current recommendations about avoiding pregnancy

PULMONARY HYPERTENSION

OBSTETRIC MANAGEMENT

Meena Khandelwal, M.D.

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Division of Maternal Fetal Medicine

CMSRU DISCLOSURE

- *In accordance with the ACCME Essentials and Standards, everyone involved in planning and presenting this CMSRU educational lecture has no relevant commercial relationships or conflicts of interest.*
- *There is no commercial support for this program.*

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OBJECTIVES

- *7. Develop an individualized antepartum plan for obstetrical management.*
- *8. Plan carefully with the multidisciplinary team the intrapartum management required, including the mode of delivery (vaginal vs. cesarean-section) and cautions about certain medications (cervical ripening, oxytocin, hemabate, ergots, etc.).*

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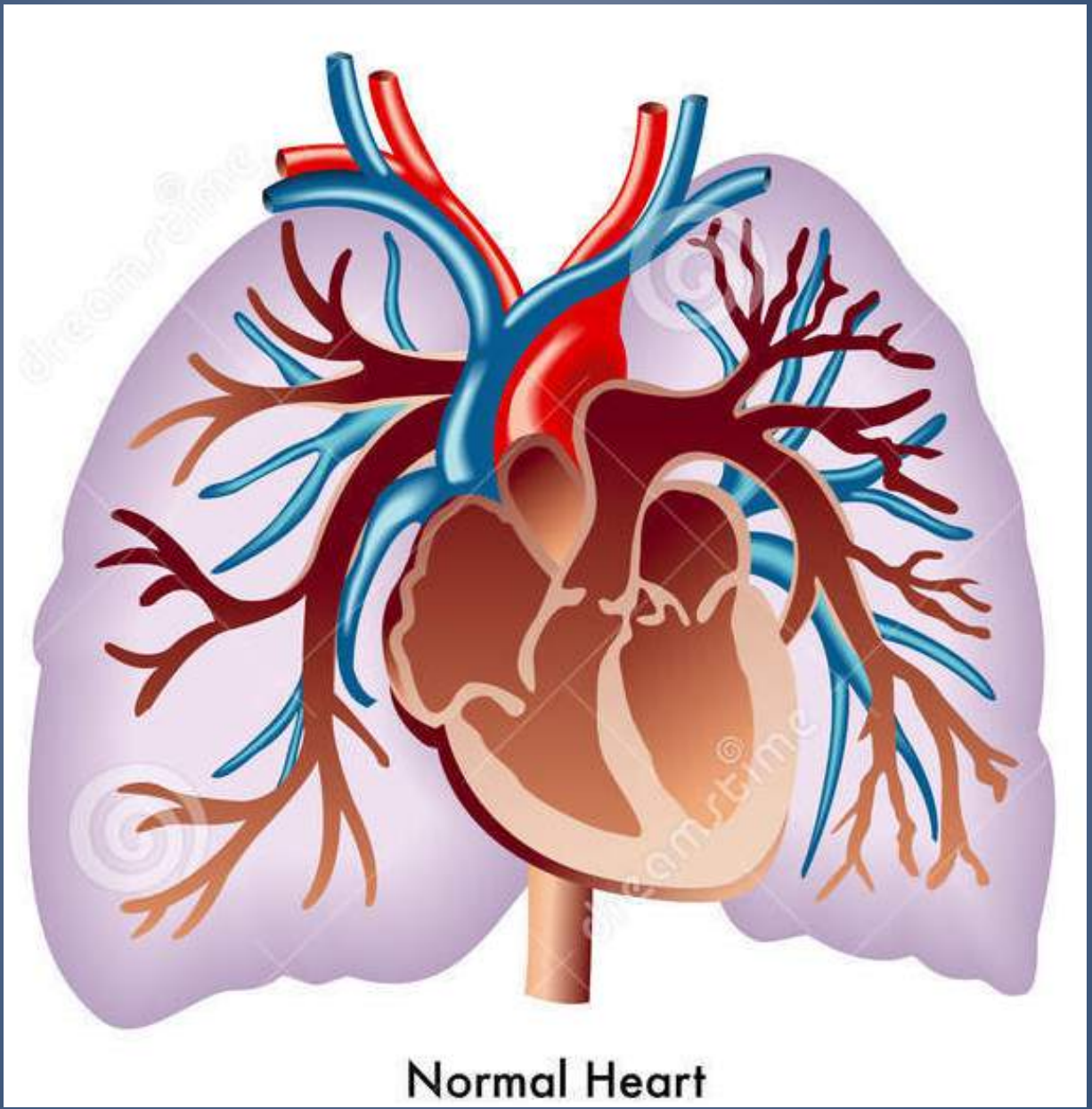

Normal Heart

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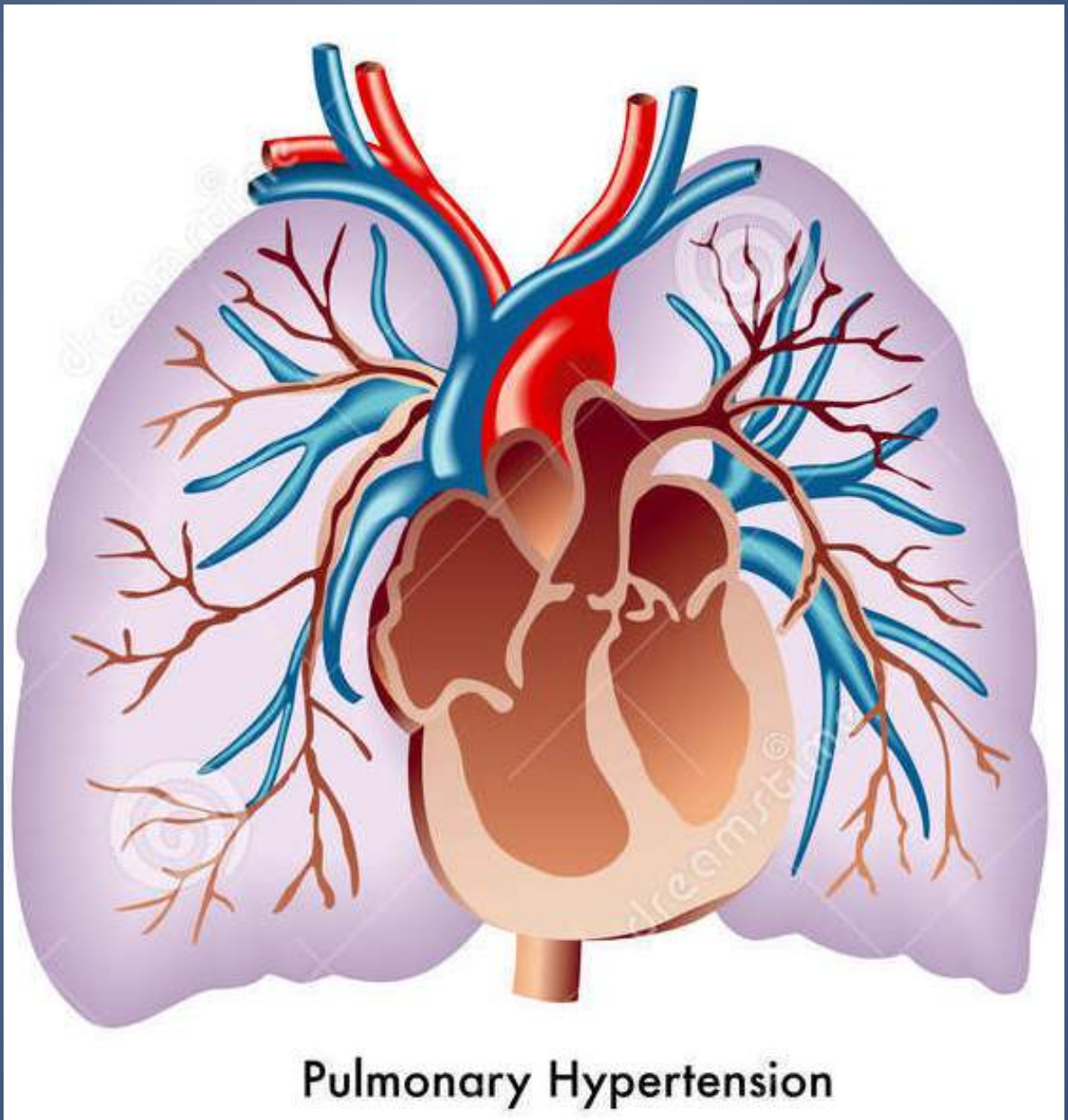

Pulmonary Hypertension

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CONSEQUENCES

- a fixed obstructive cardiopulmonary lesion
  - similar to severe aortic or mitral stenosis
  - If ↑ preload → CHF (right-sided)
  - If ↓ preload → ↓ CO, vasoconstriction, CV collapse
- CRITICAL to get it

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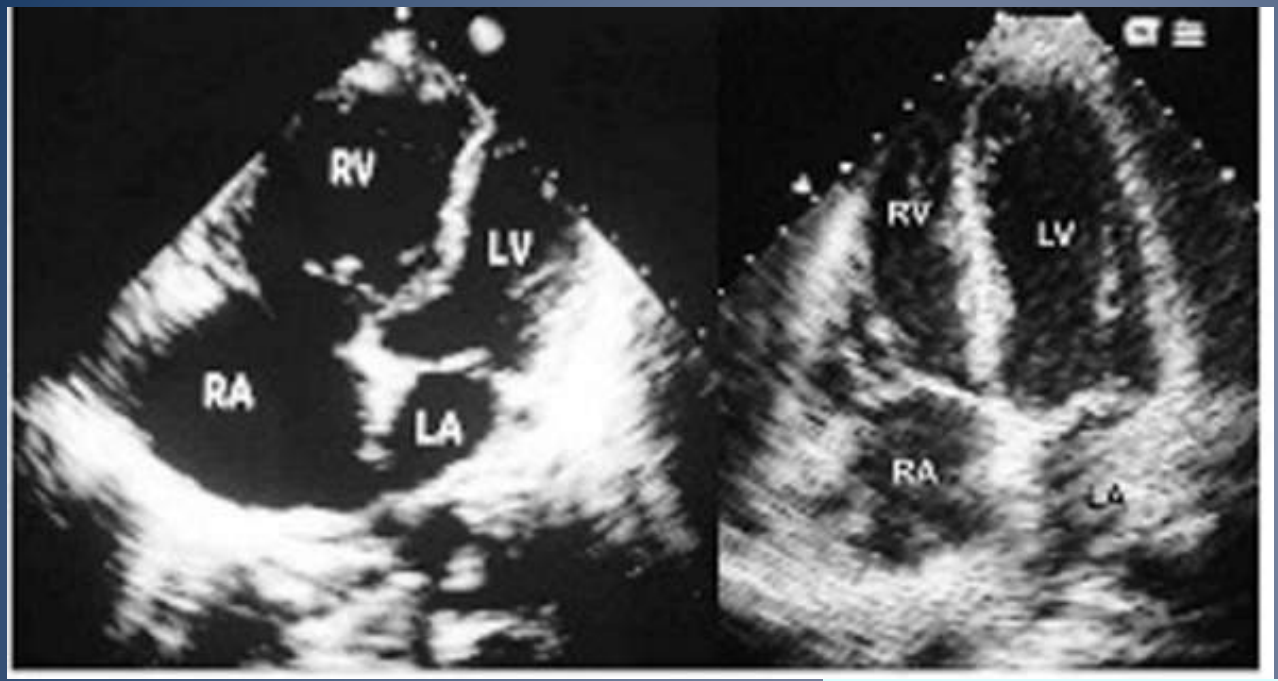
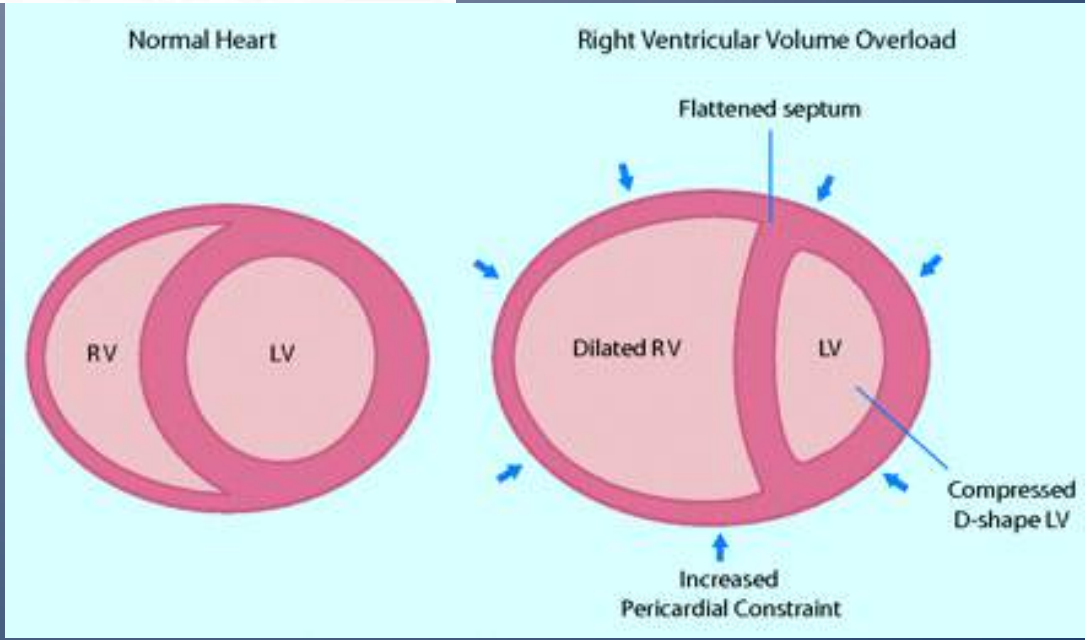


MILD RV DILATION WITH SEPTAL FLATTENING

SEVERE RV DILATION WITH SEPTAL BOWING

Lakshmanadoss et al 2011 Card Res



Haddad et al 2008 Circulation

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GUIDELINES WITHOUT DATA:

- *Statement on pregnancy in pulmonary hypertension from the **Pulmonary Vascular Research Institute** Author(s): Anna R. Hemnes, David G. Kiely, Barbara A. Cockrill, Zeenat Safdar, Victoria J.Wilson, Manal Al Hazmi, Ioana R. Preston, Mandy R. MacLean, and Tim Lahm Source: Pulmonary Circulation, Vol. 5, No. 3 (September 2015), pp. 435-465 (USA)*
- ***Saudi Guidelines** on the Diagnosis and Treatment of Pulmonary Hypertension: Pregnancy in pulmonary hypertension. KHAN J, IDREES MM. Annals of Thoracic Medicine 2014;9:S108-12.*
- *2015 **ESC/ERS Guidelines** for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). GALIE N, HUMBERT M, VACHIERY JL, et al. European heart journal 2015.*
- *Pharmacologic therapy for pulmonary arterial hypertension in adults: **CHEST guideline** and expert panel report. TAICHMAN DB, ORNELAS J, CHUNG L, et al. Chest 2014;146:449-75.*
- *Treatment of pulmonary arterial hypertension (PAH): updated Recommendations of the **Cologne Consensus Conference** 2011. GHOFRANI HA, DISTLER O, GERHARDT F, et al. International Journal of Cardiology 2011;154 Suppl 1:S20-33. (Belgium)*

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EVERYONE AGREES

- *Pregnancy is contraindicated*
- *Recommend TOP 1st & early 2nd trimester*
  - *Has risks associated as well*
  - *Avoid GA*
    - *depress SV; ↑PVR with PPV; ↑PAP with intubation*
  - *Surgical D&E safest*
- *Contraception counseling MUST*

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ANTEPARTUM MANAGEMENT

- *Determine Functional AHA class*
  - *Risk assessment (echo, BNP, 6min Walk Test)*
  - *"Responder", Dx when, Syncope?, RAP, Cardiac Index*
- *Which PH group (etiology)*
- *Social support / help*
- *Clinic appointments (q1-4 weeks)*
- *Fetal U/S evaluations (qmonth)*
- *Care co-ordination*

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MULTIDISCIPLINARY TEAM

ESSENTIAL

- *Obstetrician/ MFM*
- *Obstetric Medicine*
- *Critical Care*
- *Anesthesia*
- *Neonatology*
- *Pulmonologist*
- *Cardiology*
- *Nursing (Ob & ICU)*
- *Respiratory Therapy*
- *Patient*
- *Her Family*
- *Nutritionist*
- *Social Worker*
- *Pharmacist*

PATIENT & FAMILY EDUCATION

Define Expectations

Triggers for delivery

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MANAGEMENT IN PREGNANCY

- *General Measures:*
  - *Avoid supine position*
  - ***Limit physical activity** yet supervised exercise rehabilitation therapy*
    - *Low-level graded aerobic exercise like **walking***
    - *Pulmonary rehabilitation*
  - *Low sodium diet*
  - *Influenza & Pneumococcal vaccination*
  - *Avoid tobacco exposure*

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MANAGEMENT IN PREGNANCY

- *General Measures:*
  - ***Avoid anemia***
  - *Avoid high altitude*
    - *Need O2 supplementation 2L/min if fly >1500m or PaO2 ≤ 60 mmHg (8kPa)*
  - *Avoid triggers of vasovagal syncope*
    - *Valsalva, standing, hypovolemia , tachycardia, hyperventilation & vasodilators*

In Pregnancy: encourage compression stockings

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MANAGEMENT IN PREGNANCY

- *Supportive therapy:*
  - *Oxygen to maintain O2 sats >90%*
  - *Anticoagulation (prophylactic LMWH)*
  - *Digoxin, if LV dysfunction*
  - *Diuretics, if needed*
- *Referral to High-Risk Specialized Center*
  - *Genetic counseling (for idiopathic / heritable PAH)*

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PAH-SPECIFIC THERAPY: PA VASODILATORS

- *Augmentation of PAH therapy*
  - *Calcium-channel blockers (only in 'responders')*
    - *Nifedipine, Amlodipine, Diltiazem*
  - *Prostacycline analogs*
    - *Epoprostenol (IV)*
    - *Iloprost (IV or inhaled)*
    - *Treprostinil (oral, s/c, Inhaled, IV)*
    - *Beraprost (oral)*

COMBINATION THERAPY

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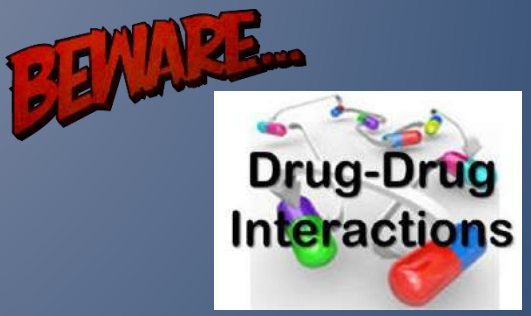
PAH-SPECIFIC THERAPY: PA VASODILATORS

- *Augmentation of PAH therapy*
  - *Phosphodiesterase type 5 inhibitors:*
    - *Sildenafil (tid)*
    - *Tadalafil (qd)*
    - *Verdenafil (bid)*
- *Not used in pregnancy*
  - *Guanylate cyclase stimulators*
    - *Riociguat*



H2 blockers
Anti-fungals

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PAH-SPECIFIC THERAPY: PA VASODILATORS

- ☻ *Not used in pregnancy*
  - ➢ *Endothelin Rc antagonists*
    - ❖ *Bosentan*
    - ❖ *Ambrisentan*
    - ❖ *Macitentan*
    - ❖ *Sitaxentan*
  - ➢ *Prostacyclin IP receptor agonist*
    - ❖ *Selexipag (oral)*

MODE OF DELIVERY

- ***Vaginal***
  - *PROs*
    - *Fewer infections*
    - *Reduced blood loss*
    - *Lower TE risk*
    - *Less abrupt hemodynamic changes*
  - *CONs*
    - *Lack of predictability*
    - *Prolonged, difficult, painful labor - DETRIMENTAL*
- ***Cesarean***
  - *PROs*
    - *Planned during the day when all medical resources available*
    - *Avoiding 'emergency'*
    - *TL at the same time*
  - *CONs*
    - *Sudden changes in fluid balance (auto-transfusion)*
    - *Postpartum recovery prolonged with pain and delayed ambulation*

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TIMING OF DELIVERY

- *Individualized*
  - *32-36 weeks*
- *Balance*
  - *Sufficient fetal maturity*
  - *Avoiding maternal decompensation*
  - *Avoiding unplanned emergency delivery*
  - *Favorable cervix*
- *Effective Analgesia imperative*

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DELIVERY CARE PLAN

- *All meds should continue*
  - *When to start IV Prostacyclin analog*
  - *When to hold and restart anticoagulants*
- *Where?*
  - *L&D vs Main OR vs Hybrid room*
- *Exaggerated left lateral tilt*
- *How much fluid bolus reasonable*
  - *Esp prior to regional anesthesia*
  - *Or for fetal HR abnormality*

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PERIPARTUM MONITORING

- *ECG*
- *Pulse oximetry*
- *Arterial Line*
- *Jugular venous line* (***CVP monitoring***)
- *Non-invasive CO monitoring* (*Vigileo, Echo*)
- *Ins / Outs*
  - *Fluids have to be JUST RIGHT*

- *Fetal monitoring*

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Avoid S-G catheter ➲ ↑ complications

DELIVERY CARE PLAN

- *Ob Drugs OK to use*
  - *Oxytocin; **Cytotec** (E1); Prepidil/Cervidil (E2)*
  - *AVOID Hemabate (F2α)*
- *Avoid Valsalva / pushing*
  - *Shorten 2nd stage with operative delivery*
  - *Atropine in the room; 2 i.v. lines*
- *Contingency Plans*
  - *If CD needed*
  - *If decompensation occurs*
    - *Vasopressin or Noradrenaline*
    - *Dobutamine*

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POSTPARTUM MANAGEMENT

- *Most maternal deaths occur 2nd to 30th day*
  - *RV failure*
    - *Fluid overload (autotransfusion)*
    - *Excessive ↑ PVR*
    - *Adverse effects of Oxytocin*
    - *Inadequate preload (hemorrhage)*
  - *Thromboembolism*

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POSTPARTUM MANAGEMENT

- *Misoprostol 800 mcg rectally prophylactic*
- *ICU monitoring*
  - *Variable time 48hrs-1wk*
- *Maximal pulmonary vasodilator therapy* (↓ *RV afterload*)
- *Maintenance of appropriate RV pre-load* (*maintain sufficient SVR for adequate coronary perfusion*)
  - ***Avoid excessive diuresis***
  - *Vasopressin or Norepinephrine as vasopressors*
- *Anticoagulation* (*prophylactic*)
- *Promote breast-feeding*

& skin-to-skin

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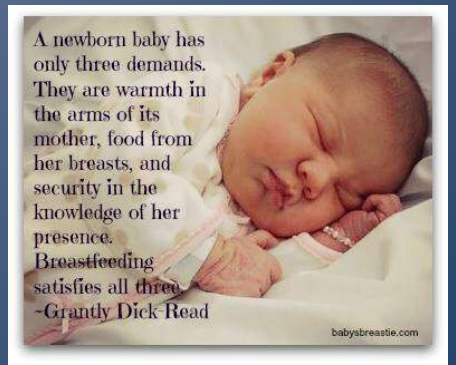


PRECONCEPTION OR POST-PARTUM CONTRACEPTION COUNSELLING

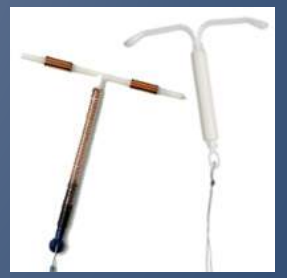
? Which one ?

CONTRACEPTIVE CHOICES

- ~~*Oral combination pills*~~
  - *Estrogen with increased risk of TE*

- *Progesterone-only pill*
  - *OK but Bosentan reduces efficacy*
  - *Cannot be used alone*

- *Progesterone (Levonorgestrel) IUD*
  - *Occasionally causes vasovagal reaction upon insertion (poorly tolerated)*
  - *Copper IUD – avoid due to menorrhagia*



- *Emergency contraception (Levonorgestrel)*
  - *Safe with 1% failure rate if used within 72 h*

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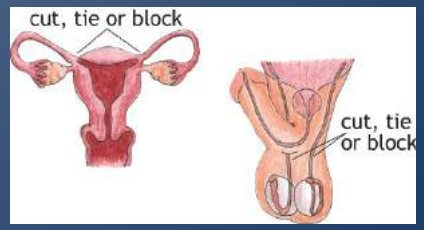
CONTRACEPTIVE CHOICES

- ✓ ☻ ***Barrier contraceptives***
  - ➢ *Safe BUT effect unpredictable*
- ✓ ☻ ***Progesterone subdermal implant***
  - ➢ *Safe as LA insertion*
- ☻ ***Hysteroscopic sterilization*** *(Essure)*
  - ➢ *Risk of vasovagal*
- ☻ ***Sterilization***
  - ~~➢ *Avoid laparoscopy*~~
  - ✓ ➢ *Minilaparotomy – under regional*
  - ➢ *At time of cesarean delivery*
  - ✓ ➢ ***Partner vasectomy****: under LA, 20x fewer complications, 10 to 37-fold lower failure rate, 3x cheaper*



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Primum non nocere

First DO NO HARM!

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RADIATION EXPOSURE AFTER RIGHT HEART CATHETERIZATION

- *United Nations Scientific Committee on the Effects of Atomic Radiation cites a typical value of ~7 mSv (<1 rad)*
- *Various reports vary from 2.3 to 22.7 mSv (≅ 0.2 to 2.2 rads)*
- *Decrease exposure by radial access rather than femoral*
- *ACOG – total amount of allowed radiation = 5 mSv*
  - *exposure <50 mSv is not associated with fetal loss or anomaly*
  - *5 mSv ↑s risk of congenital anomaly from 4.0% to 4.01%*
  - *chance of child developing cancer will ↑ from 0.07% to 0.11%*

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Einstein et al 2007 Circulation

Pulmonary Hypertension in Pregnancy

The Anesthesiologist's Perspective

North American Society of Obstetric Medicine Conference (NASOM)

November 15, 2015

Lorraine Chow, MD FRCPC

Foothills Medical Centre, Calgary

Disclosure

- I have nothing to disclose

Objectives

1. To discuss the effects of common anesthetic agents on pulmonary hypertension physiology
2. To highlight the goals of anesthesia in pulmonary hypertension patients
3. To discuss management of labour analgesia and anesthesia for Cesarean section
4. To describe some monitoring options in obstetric setting for patients with pulmonary hypertension
5. To identify treatment strategies of acute pulmonary hypertension crisis

PH in Pregnancy

- High mortality rate (30-56%)
- Majority occurs during labour or within 1 month PP
- Increase in blood volume, cardiac output, decrease in SVR (and PVR?)
- Labour and delivery → further increase CO and BP, especially during uterine contractions
- Following delivery → changes in preload ↑↓, SVR↑, PVR↓, contractility↓
- Hypercoagulable state

PH in pregnancy and anesthesia

- Peri-op period: can precipitate worsening PH, RV ischemia and RV dysfunction
- PPV can worsen PH
- RV, LV interplay
- RV coronary perfusion
  - RV failure → ↑RV end-diastolic pressure → decreased RV perfusion → RV ischemia → RV function↓
- Acute increase in PA pressure → RV failure
  - Hypercarbia, hypoxia, acidosis, noxious stimuli

Anesthetic goals:

- Maintain RV perfusion pressure
- Avoid abrupt increases in PVR
- SVR > PVR
  - Increase SVR
  - Decrease PVR
- Augment RV contractility

Anesthetic goals:

- Maintain RV perfusion pressure
- Avoid abrupt increases in PVR
- SVR > PVR
  - Increase SVR
  - Decrease PVR
- Augment RV contractility

Systemic vasopressors

Anesthetic goals:

- Maintain RV perfusion pressure
- Avoid abrupt increases in PVR
- SVR > PVR
  - Increase SVR
  - Decrease PVR
- Augment RV contractility

Systemic vasopressors

Pulmonary vasodilators

Anesthetic goals:

- Maintain RV perfusion pressure
- Avoid abrupt increases in PVR
- SVR > PVR
  - Increase SVR
  - Decrease PVR
- Augment RV contractility

Systemic vasopressors

Pulmonary vasodilators

Inotropes

Anesthetic goals, continued:

- Fluid management
- Avoid arrhythmia, noxious stimuli
- Side-effect of anesthetic agents, respiratory depression

Pre-operative evaluation

- Cause and severity of PH
- History
- Physical
- Investigations
  - RHC – accurate characterization of pulm press
  - LHC – if CAD or left-sided valvular dz suspected
  - ECG, CXR, Echo
- Continue all usual medications for PH
  - Avoid withdrawal symptoms

Intra-op management

- Inotrope augment of RV function
- Vasopressors
- Pulmonary vasodilators
- Pain control (and other noxious stimuli)
- Avoid respiratory depression (post-op as well)
- Maintain oxygenation
- Ventilator settings

Labour management

- Epidural – paramount importance
  - Maintain balance of SVR/PVR and avoid catecholamine surges from pain
- Minimize hemodynamic effect of labour
- Single-shot spinal – contra-indicated
- Oxytocin, methergine, prostaglandin → use with EXTREME CAUTION

C section management

- Maintain hemodynamic goals regardless of type
- Adequate level of anesthesia
- Anesthetic agents *may* depress myocardial contractility, decrease SVR, increase PVR, impair venous return
- GA Induction: etomidate, propofol, ketamine
  - Intubation → highly stimulating
- Epidural > spinal, low-dose CSE
- Weiss – review of OB outcomes over 18 years:
  - Similar outcomes with GA vs. regional for CS

Post-op (Post-partum) management

- Risk of worsening PH and RV ischemia
- Rebound PH when weaning from pulmonary vasodilators
- Decreased myocardial contractility
- Increased risk of thromboembolism
- Exaggerated pulmonary vascular reactivity
- Sudden decrease in blood volume after delivery
- Pain control → Epidural post-op

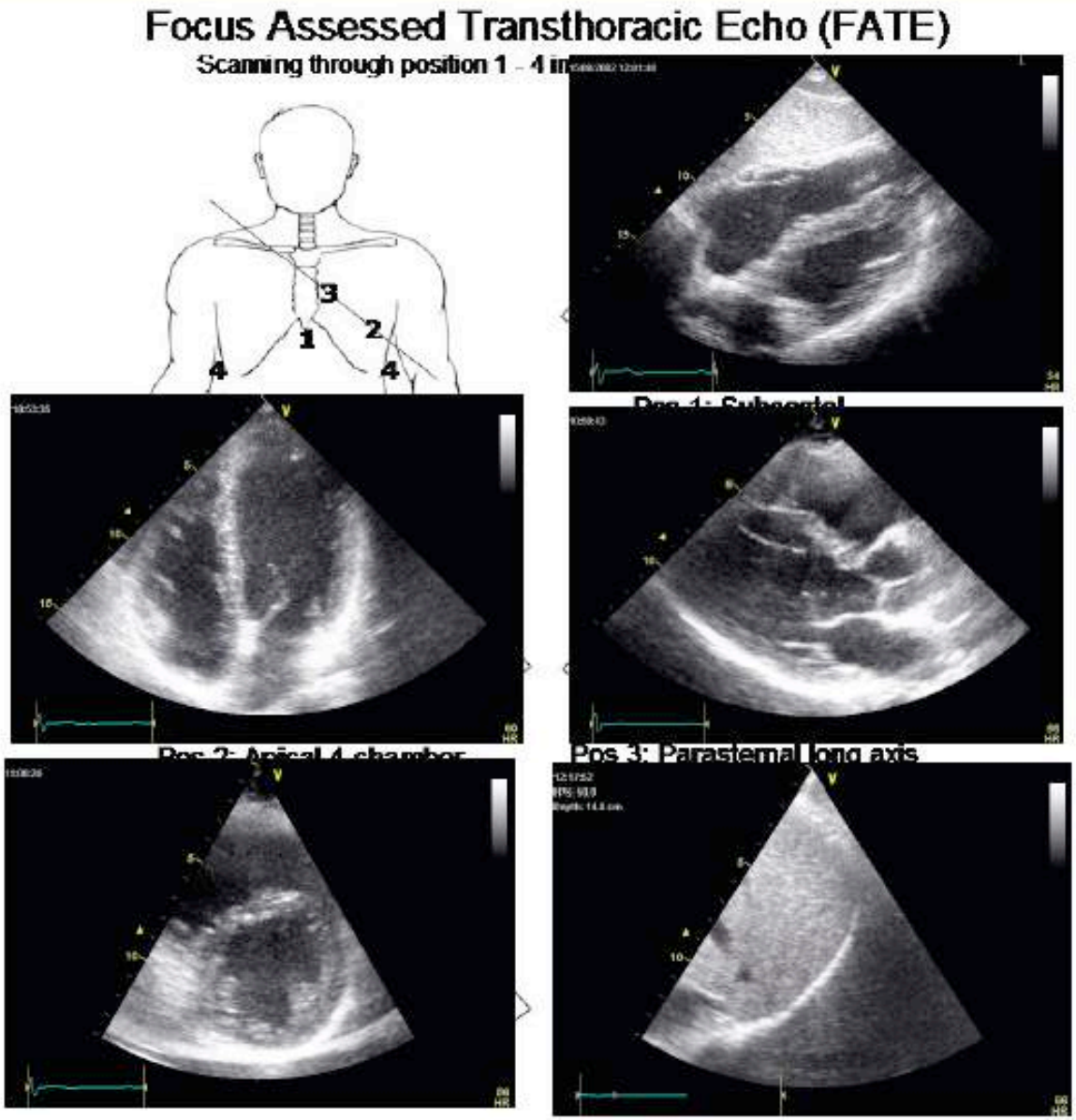
Monitoring

- Standard CAS monitoring
- Invasive blood pressure monitoring (arterial line)
- +/- Central venous line
- +/- PA catheter
- Transesophageal echo
- Transthoracic echo (bedside)
  - FATE, FOCUS

Focus Assessed Transthoracic Echocardiography (FATE):

- Emerging technology in OB anesthesia
- Non-invasive, validated, precise hemodynamic data
- RV dilation → loss of triangular shape
- RV size → assessed by calculating RV/LV end-diastolic area
- Paradoxical septal motion in systole
- Fluid status assessment (and assessment of fluid responsiveness)

The FATE card



Management of PH crisis

- ↑ SVR – NE, vasopressin (dopamine, epi)
- ↓ PVR
  - Stability systemic BP with pressors first
  - Pulmonary vasodilators
    - Inhaled NO
    - Inhaled prostacyclin (or analogs)
    - Oral (or parenteral) sildenafil
    - Inhaled milrinone
- Augment RV function
- ECMO if those measures fail

Inotropes

- Dobutamine – β1 agonist
- *Norephinephrine*
- Phosphodiesterase (PDE)-3 inhibitors
  - *Milrinone (IV and nebulized*)
- Levosimendan – Calcium sensitizing agent, positive inotrope and vasodilatory effects

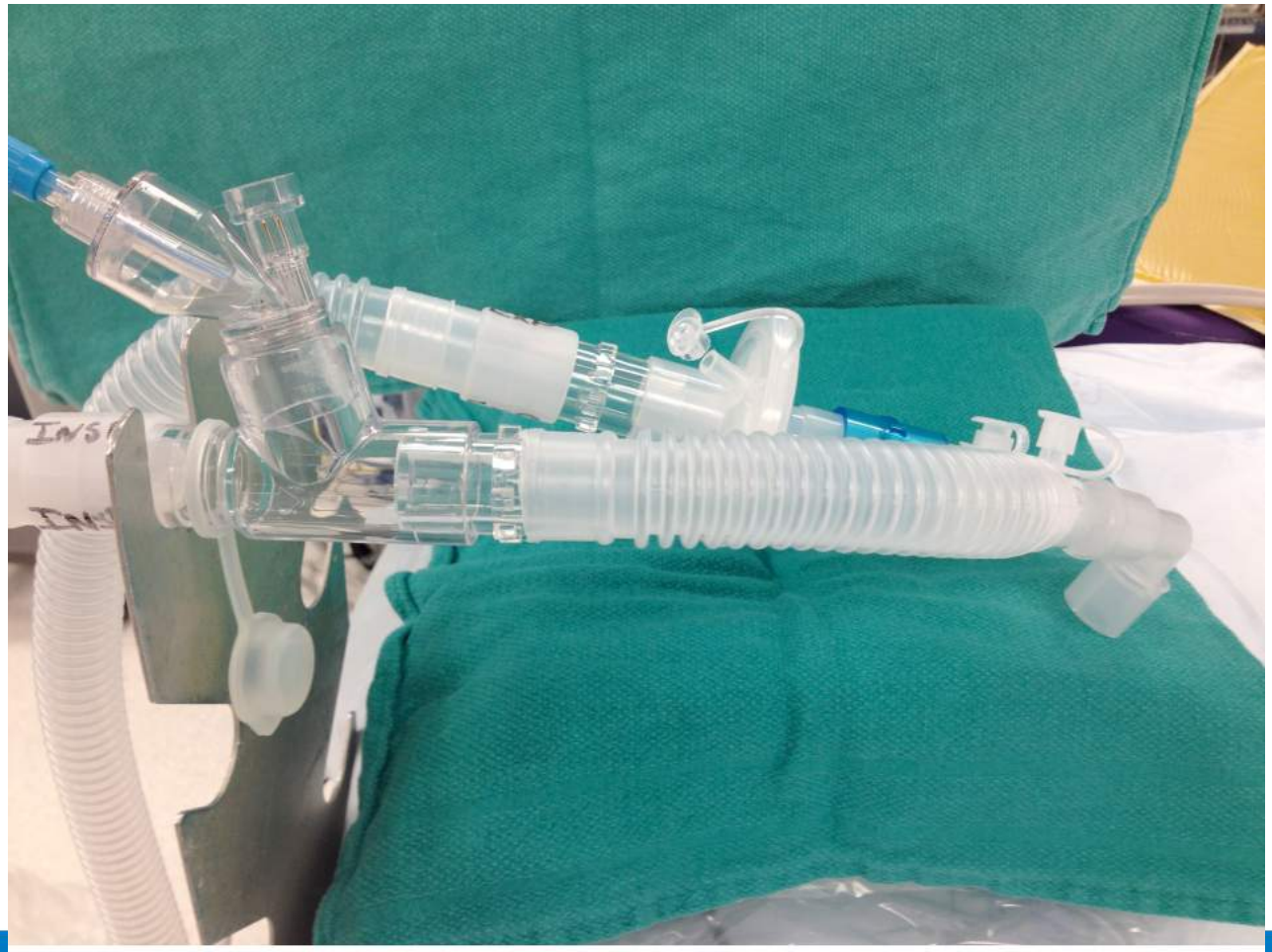
Vasopressors

- Norepinephrine
- Phenylephrine – direct alpha agonist
- Vasopressin – vasopressingergic (V1) receptor agonist

Pulmonary vasodilators

- Endothelin receptor antagonists (eg. Bosentan)
- Calcium channel blockers – nifedipine, amlodipine, diltiazem
- Prostacyclins and analogs (eg. Epoprostenol, trepostinil, iloprost)
  - *inhaled prostacyclin intraop*
- PDE-5 inhibitors (eg. Sildenafil)
- *Inhaled nitric oxide (iNO)*

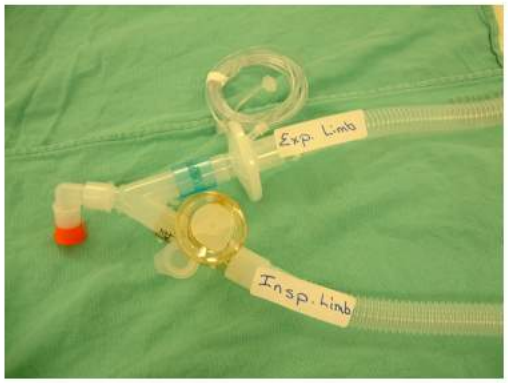
Nebulized epoprostenol (in circuit)



Inhaled Milrinone

FMC Ventilator Circuit Set-up
(Disposable Nebulizer)

FMC Ventilator Circuit Set-up
(Reusable Nebulizer)



PLC Ventilator Circuit Set-up
(Disposable Nebulizer)

QUESTIONS??

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Drug	Route of adminstration	Dose
Milrinone (PDE3 inhibitor)	IV or nebulized	0.25-0.75 mcg/kg/min (initial 50 mcg bolus optional) 2 mg diluted in 10 ml NS for 10-15 min
Dobutamine	IV	2-5 mcg/kg/min
Epoprostenol (Prostacyclin)	IV or inhaled	4-10 ng/kg/min
Nitric oxide	Inhaled	10-40 ppm
Iloprost (prostacylin analog)	Inhaled	5-10 mcg for 10-15 min