Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης
Α΄ Καρδιολογική Κλινική ΑΧΕΠΑ
Ιατρείο Πνευμονικής Υπέρτασης

Presentation of a patient case in CTEPH

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Conflicts of interest

Honoraria and/or research grants from Actelion, MSD, Elpen Pharmaceuticals, Bayer, GSK, Galenica, Lilly, Pfizer

Female
58y

Background

- **2009**
  - Diagnosed with multiple myeloma
  - Multiple chemotherapy cycles until today (thalidomide derivatives)
  - Vague history of a possible DVT episode (received LMWH)
- **2010**
  - Autologous bone marrow transplantation
- **2016**
  - Enrolled in 2 clinical trials (plitidepsin, daratumumab)
- **Aug 2016**
  - Progressive dyspnea and syncopal episode.
- **Mar 2017**
  - Admitted with severe PH, signs of right heart failure and low cardiac output
  - Inotropes iv
  - Stabilised
  - Balloon atrial septostomy procedure

RHC - BAS

Πιέσεις (mmHg):	Αρχική	μετά 7/8 mm μπαλόνι	μετά 10 mm μπαλόνι- Τελική
Σφύξεις :	91/min	92/min	92/min
Δεξιος κόλπος:	(14)	(11)	(10)
Αριστερός κόλπος:	(7)	(7)	
Κορεσμός σε O2 αιμ. αριστερού κόλπου (%):	**97.2**	85.1	86.1
Κλίση πίεσης (ΔΚ-ΑΚ)	(7)	(4)	
Ενσφήνωση:			
Πνευμονική αρτηρία :	65/32 (43)	64/29 (42)	63/30 (41)
Κορεσμός σε O2 πνευμονικής(%)	**45.9**	**43.6**	**41**
Αορτή:	108/51(69)		116/75 (93)
Αριστερά κοιλία:	**124/6/14**	**112/6/11**	**120/6/10**
Κορεσμός σε O2 αρτηρίας(%):	**93.9**	**91.6**	**89.4**
ΚΛΟΑ (συστηματική) L/min:	3.15	3.15	3.12
ΚΛΟΑ (πνευμονική) L/min:	2.94	2.82	2.64
Διαφυγή δεξιά> αριστερά	**0.20**	**0.33**	**0.43**
Πνευμονικές αντιστασεις (dyn sec cm-5):	980 (12 WU)		
Περιφερικές αντιστάσεις (dyn sec cm-5):	1397 (17 WU)		

ΣΥΜΠΕΡΑΣΜΑ

Σοβαρού βαθμού πνευμονική υπέρταση.
Επιτυχής δημιουργία επικοινωνίας δεξιού-αριστερού κόλπου , χωρίς εμφανή αιμοδυναμική βελτίωση, με περιορισμένη πτώση του κορεσμού του αρτηριακού αίματος.

Ο ιατρός

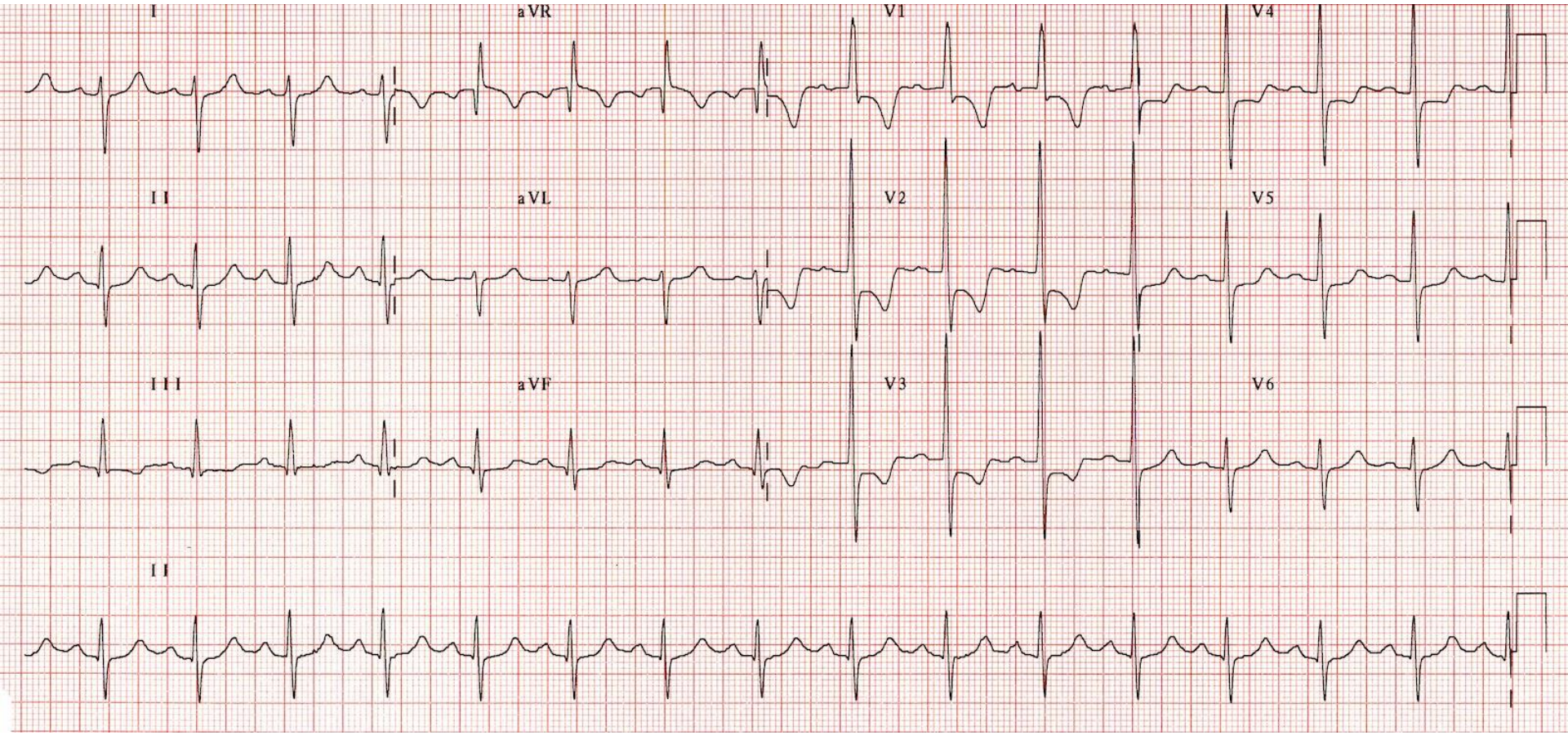
Σ Χατζημιλτιάδης

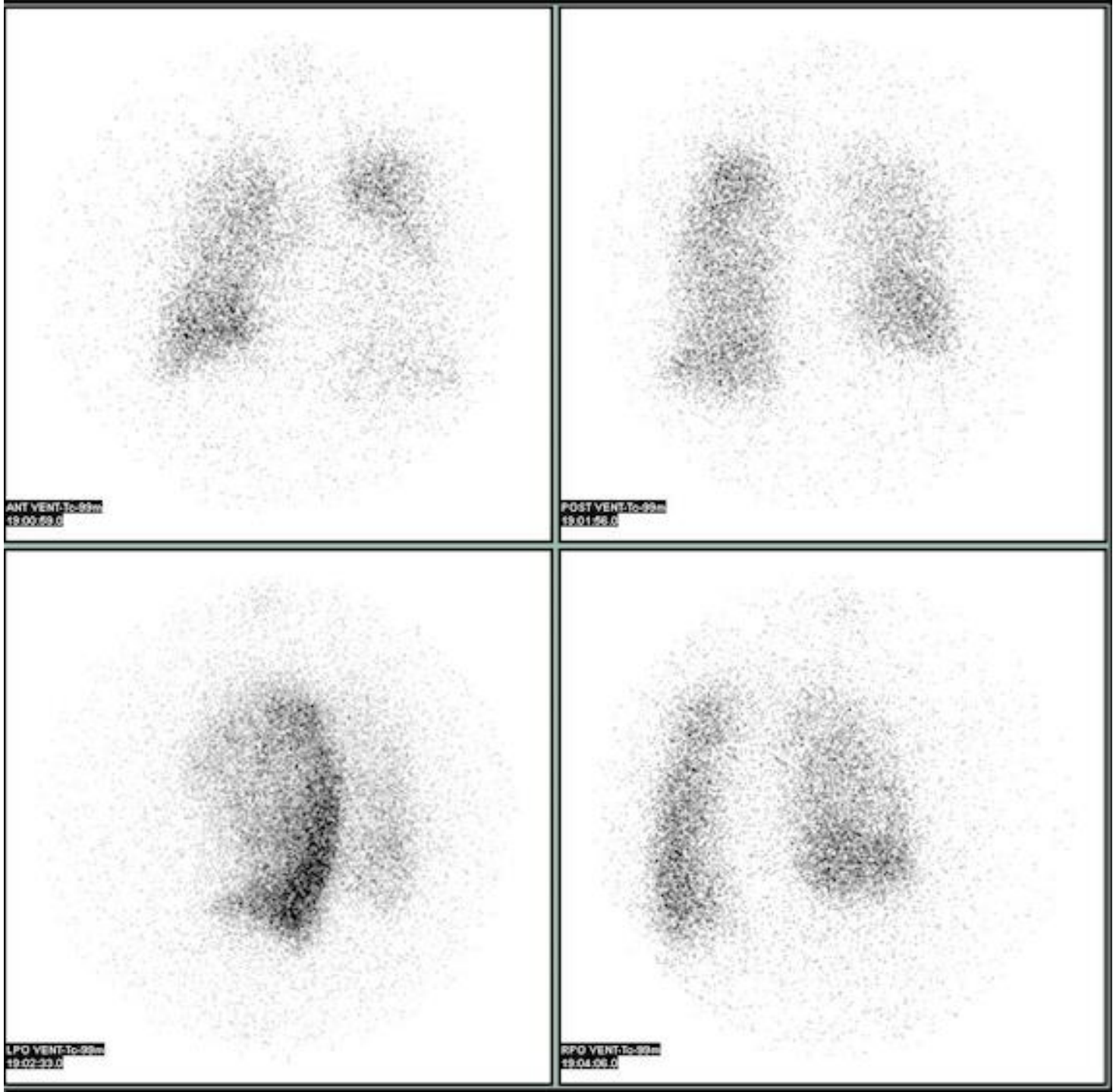
Assessment 2017

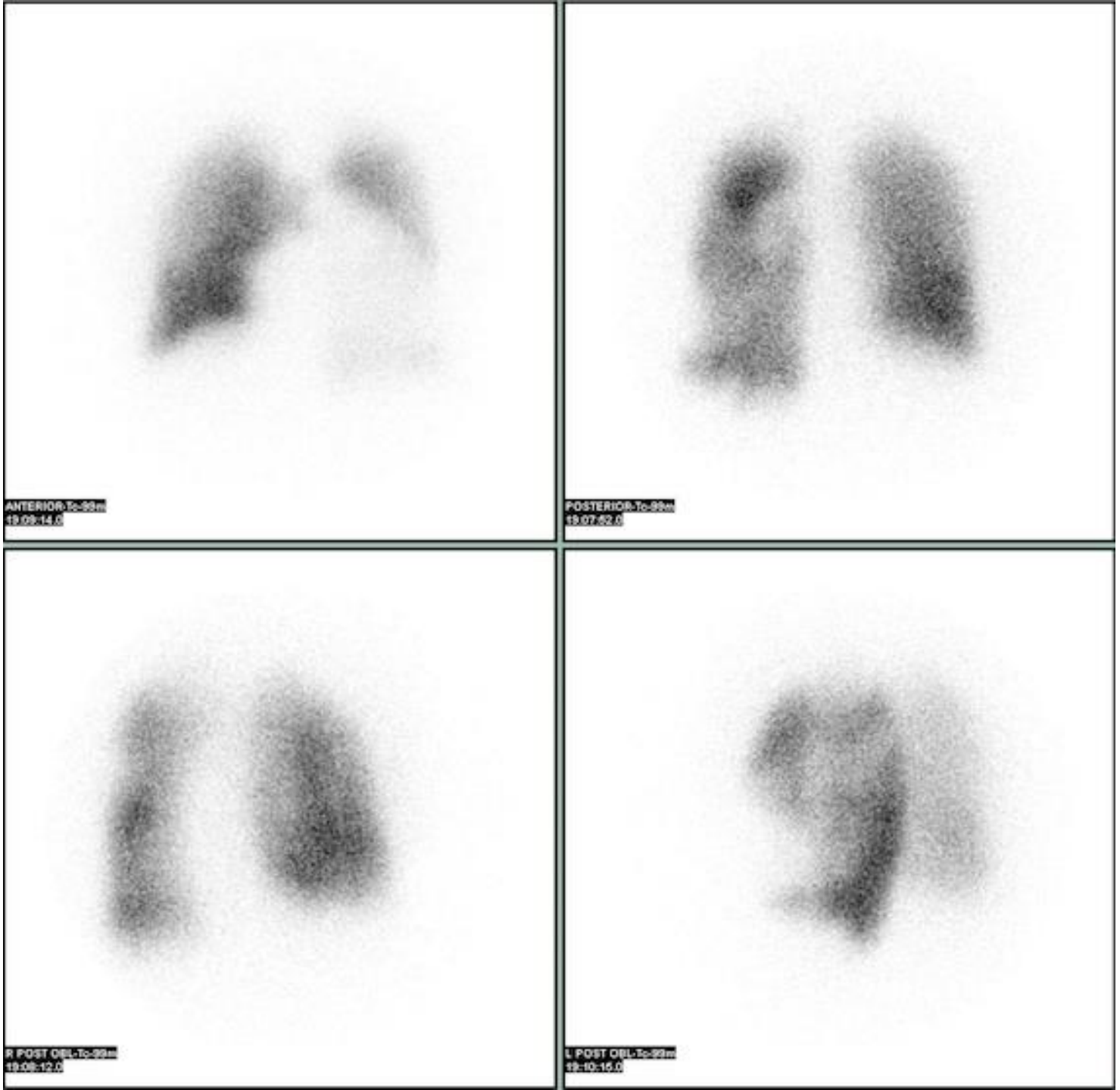
- Dyspnoea in mild exertion
- WHO class III
- SAT 92%, no clubbing
- HR 88/min,
- BP 110/80mmHg
- Loud P2
- No ascites/ mild peripheral edema

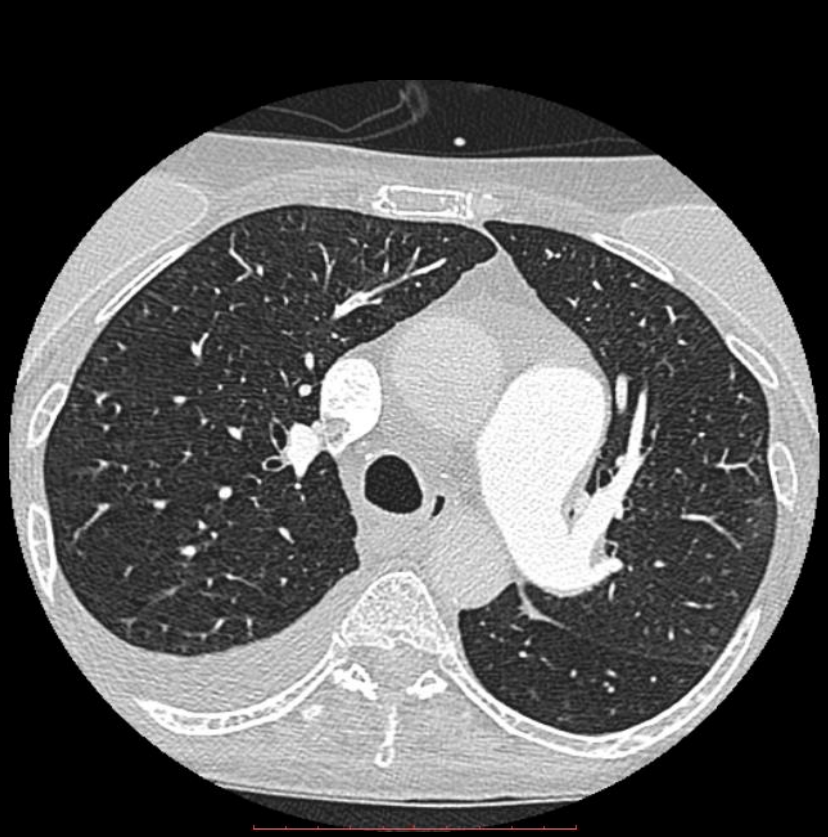
6MWT (without oxygen)		
	Pre	Post
SpO2	89	78
HF	85	125
Borg	2	8
Total walked distance 227m		

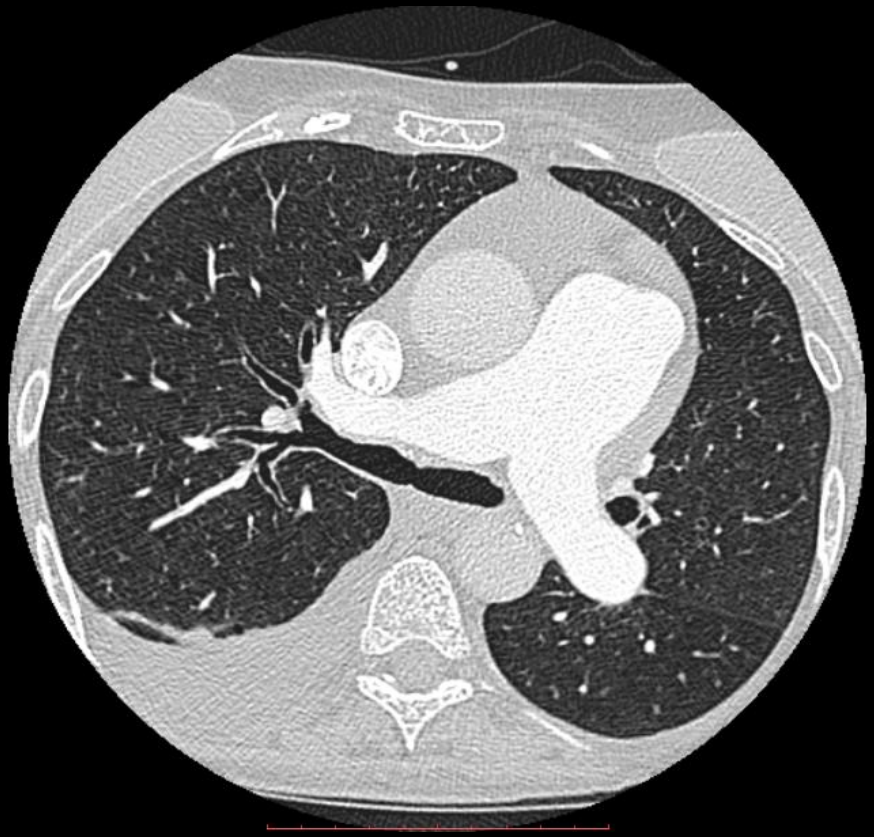
ECG




ANT VENT-Tc-99m
POST VENT-Tc-99m
LPO VENT-Tc-99m
RPO VENT-Tc-99m


ANTERIOR Tc-99m
19:09:14.0
POSTERIOR Tc-99m
19:07:52.0
R POST OBL Tc-99m
19:08:12.0
L POST OBL Tc-99m
19:10:16.0



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Se: 8
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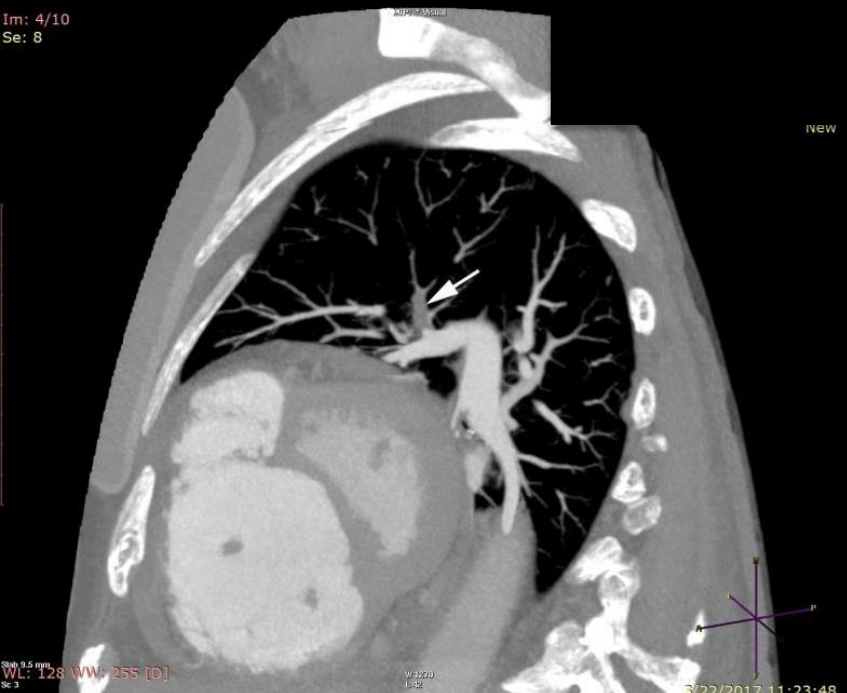
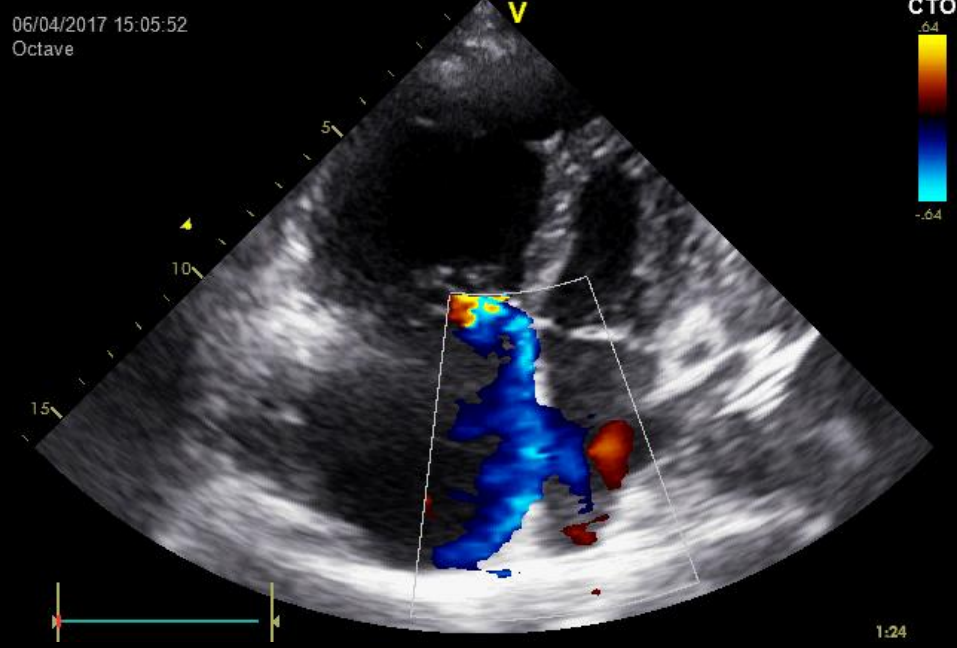
3/22/2017 11:23:48


Im: 2/10
Se: 8


Im: 4/10
Se: 8
WL: 128 WW: 255 [D]


Im: 9/10
Se: 8
MIP: * Visual


06/04/2017 15:08:34
Octave
V
CTO
5
10
5
1:55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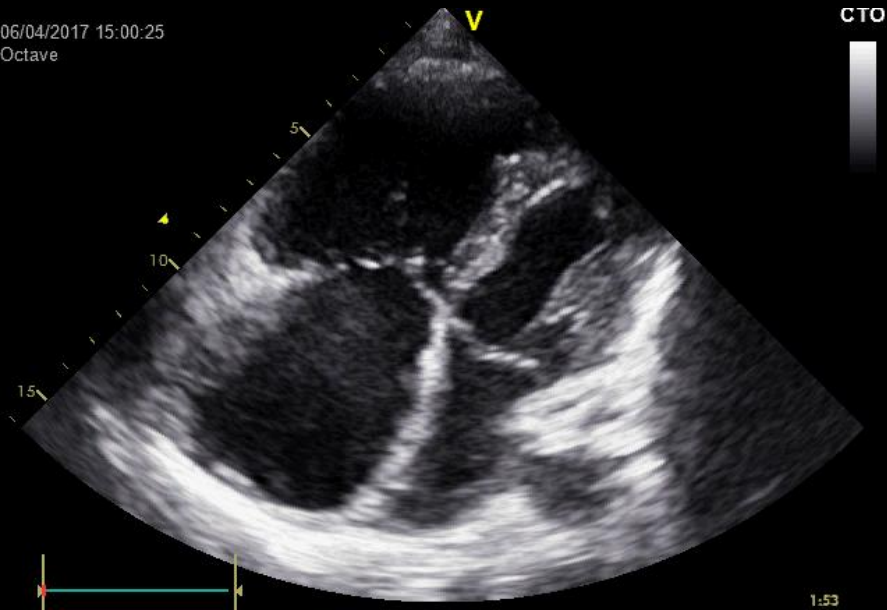
Octave
V
CTO
.64
-.64
5
10
15
1:24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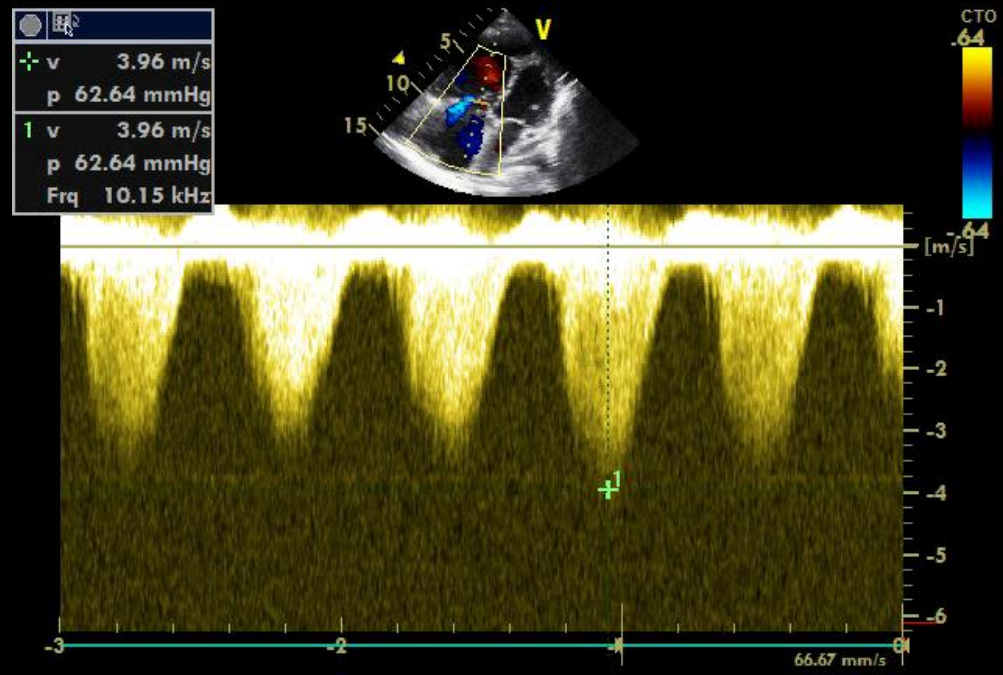
Octave
V
CTO
5
10
15
1:53


v 3.96 m/s
p 62.64 mmHg
1 v 3.96 m/s
p 62.64 mmHg
Frq 10.15 kHz
V
5
10
15
CTO
.64
-.64
[m/s]
-1
-2
-3
-4
-5
-6
-3
-2
66.67 mm/s

- 3 months of anticoagulation
- No improvement
- WHO III
- NTproBNP 4200

- Operability assessment: Inoperable disease due to distal disease with disproportionate findings from imaging and hemodynamics

- BP 105/50
- Started on riociguat 1 mg tid uptitrated to 2 mg tid

Chronic thromboembolic pulmonary hypertension

Recommendations	Class	Level
In PE survivors with exercise dyspnoea, CTEPH should be considered.	IIa	C
Life-long anticoagulation is recommended in all patients with CTEPH.	I	C
It is recommended that in all patients with CTEPH the assessment of operability and decisions regarding other treatment strategies be made by a multidisciplinary team of experts.	I	C
Surgical PEA in deep hypothermia circulatory arrest is recommended for patients with CTEPH.	I	C
Riociguat is recommended in symptomatic patients who have been classified as having persistent/recurrent CTEPH after surgical treatment or inoperable CTEPH by a CTEPH team including at least one experienced PEA surgeon.	I	B
Off-label use of drugs approved for PAH may be considered in symptomatic patients who have been classified as having persistent/ recurrent CTEPH after surgical treatment or inoperable CTEPH by a CTEPH team including at least one experienced PEA surgeon.	IIb	B
Interventional BPA may be considered in patients who are technically non-operable, or carry an unfavourable risk-benefit ratio for PEA.	IIb	C
Screening for CTEPH in asymptomatic survivors of PE is currently not recommended.	III	C

BPA - ballon pulmonary angioplasty; CTEPH = chronic thromboembolic pulmonary hypertension; PE = pulmonary embolism; PEA = pulmonary endarterectomy.

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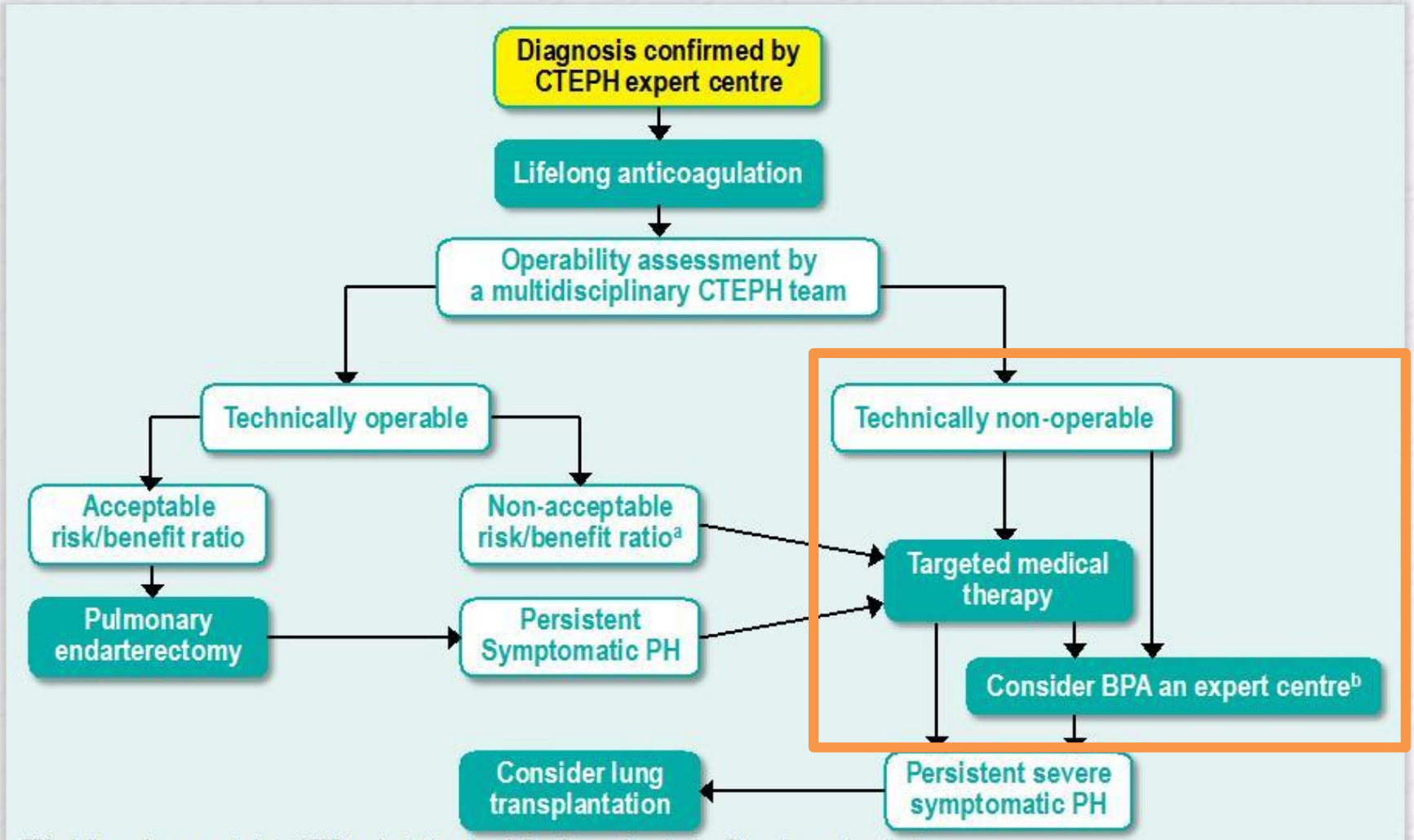
www.escardio.org

European Heart Journal 2016:37;67–119 -doi:10.1093/eurheartj/ehv317
European Respiratory Journal 2015 46: 903-975;

- Improved
- 6MWT 303m
- NTproBNP 2100
- Still WHO III

- Waiting list for BPA

Treatment algorithm for chronic thromboembolic PH



BPA = balloon pulmonary angioplasty; CTEPH = chronic thromboembolic pulmonary hypertension; PH = pulmonary hypertension.
[a]Technically operable patients with non-acceptable risk/benefit ratio can be considered also for BP[illegible]; [b]In some centres medical therapy and BPA are initiated concurrently.

European Heart Journal 2016:37;67–119 -doi:10.1093/eurheartj/ehv317
European Respiratory Journal 2015 46: 903-975;

Any data in Greece?

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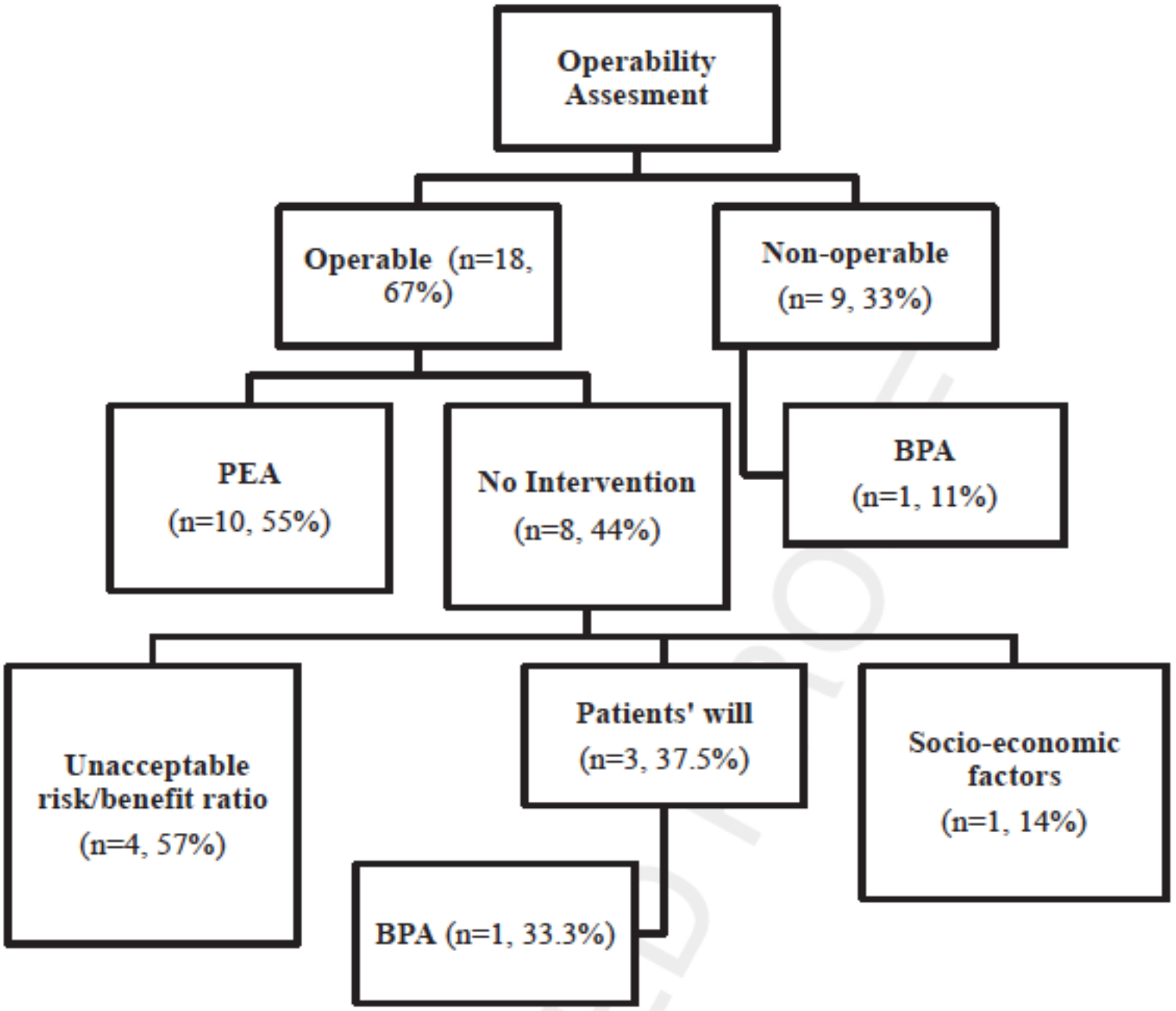
ORIGINAL ARTICLE

Epidemiology and management of chronic thromboembolic pulmonary hypertension: experience from two expert centers

Table 1 Basic demographic and clinical characteristics of study population.

Characteristics	Total (n=27)	Operable (n=18)	Nonoperable (n=9)	p-value
Female sex	16(59)	9(50)	7(78)	0.16
Age, years	59.3 ± 15.1	54.1 ± 13.7	70.1 ± 12.5	0.07
BMI, kg/m^2	28.5 ± 5.4	28.1 ± 4.8	29.4 ± 6.6	0.54
Smoking	14(52)	9(50)	5(55)	0.78
NYHA (III/IV)	20(74)	13(72)	7(28)	0.75
6MWD, m	297.5 ± 134.6	306.1 ± 140.5	279.3 ± 128.2	0.65
Dyspnea	26(96)	17(94)	9(100)	1.00
Edema	8(30)	5(27)	3(33)	1.00
Chest pain	3(33)	5(27)	4(44)	0.42
Syncope	2(7)	2(11)	0	-
Fatigue	26(96)	17(94)	9(100)	1.00
Palpitations	10(37)	6(33)	4(44)	0.68

Values represent absolute count (percentage) or mean ± standard deviation.
BMI: Body mass index, NYHA: the New York Heart Association, 6MWD: 6-Min Walk Distance.



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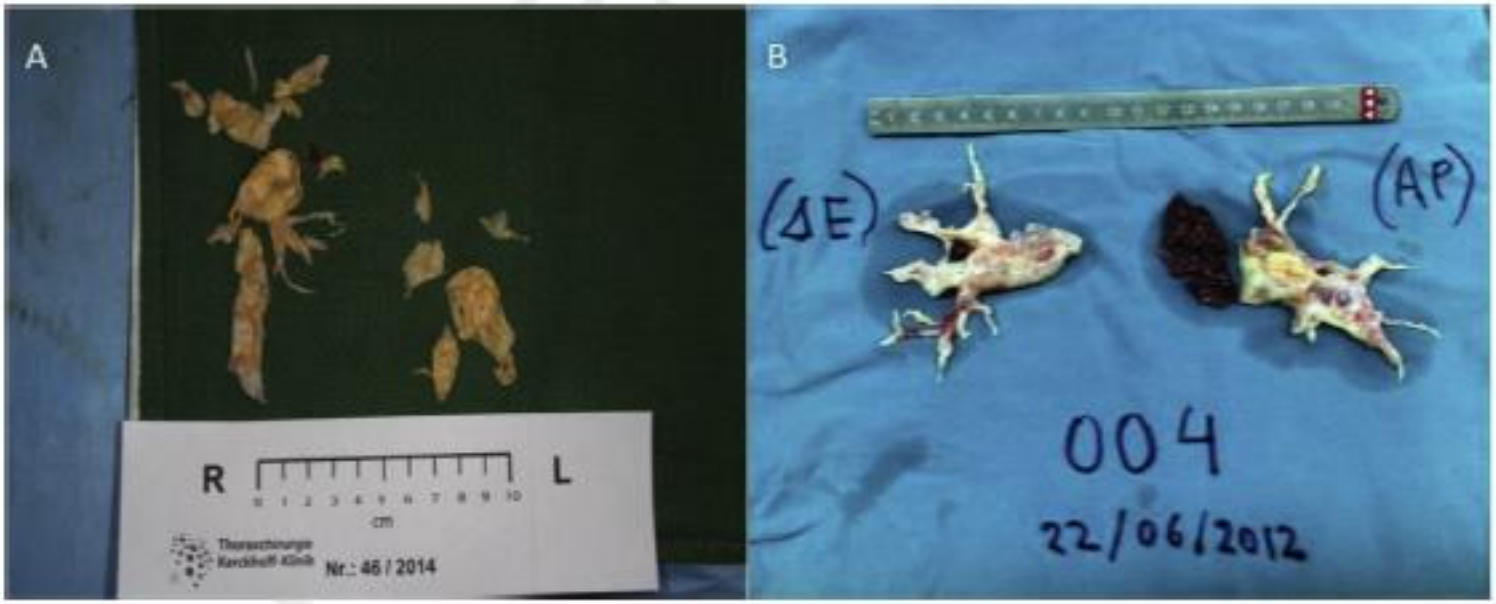

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Table 2 Risk factors for CTEPH in the study cohort.

Risk factors	Total N=27	Operable N=18	Nonoperable N=9	p-value
History of PE	22(82)	13(72)	9(100)	0.14
Recurrent	5(19)	4(22)	1(11)	0.64
Massive	5(19)	5(28)	0	-
Previous DVT	6(22)	5(28)	1(11)	0.63
Associated conditions at diagnosis	24(89)	15(83)	9(100)	0.52
Thrombophilic disorder	11(41)	10(55)	1(11)	0.04
Lupus anticoagulation	2(7)	2(11)	0	-
Protein C deficiency	2(7)	2(11)	0	-
Factor V Leiden	4(15)	4(22)	0	-
Prothrombin gene mutation	2(7)	1(5)	1(11)	-
Antithrombin III	1(3)	1(5)	0	-
Previous major surgery	4(15)	4(22)	0	-
History of cancer	2(7)	2(11)	0	-
Thyroid disorder	2(7)	1(5)	1(11)	-
Noninsulin DM	5(19)	2(11)	3(33)	0.30
Splenectomy	3(11)	1(5)	2(22)	0.25
Coronary artery disease	3(11)	2(11)	1(11)	-
Varicose veins	4(15)	3(17)	1(11)	-
Obesity	7(26)	4(22)	3(33)	0.65
Chronic venous insufficiency	3(11)	3(17)	0	0.53
Prolonged hospitalization	4(15)	3(17)	1(11)	-
Fracture	1(3)	1(5)	0	-
Family history of DVT/PE	1(3)	1(5)	0	-
Congestive heart failure	1(3)	1(5)	0	-
VA shunt	1(3)	1(5)	0	-
Inflammatory bowel disease	0	0	0	-
Infection of VA shunt /pacemaker	1(3)	1(5)	0	-
History of AF/flutter	2(7)	1(5)	1(11)	-
Other conditions				
Systemic hypertension	14(52)	9(50)	5(55)	1.00
COPD	4(15)	2(11)	2 (22)	-
Sleep apnea	1(3)	0	1(11)	-
Contraceptive pills	1(3)	1(5)	0	-

Table 3 Diagnostic evaluation of study cohort.

Diagnostic tests	Total (N=27)	Operable (N=18)	Nonoperable (N=9)	p-value
Right heart catheterization	27(100)	18(100)	9(100)	-
mRAP, mmHg	8.0(3.0-21.0)	8.0(4.0-16.0)	8.0(3.0-21.0)	0.73
mPAP, mmHg	44.6 ± 8.7	45.3 ± 8.4	43.3 ± 9.6	0.58
PCWP, mm Hg	10.0(5.0-14.0)	9.5(5.0-14.0)	10.0(10.0-13.0)	0.24
PVR, Wood Units	8.5 ± 3.3	8.9 ± 3.0	7.7 ± 3.8	0.42
CI, $L/min^{-1}/m^{-2}$	2.6 (1.5-5.0)	2.6(1.7-5.0)	2.6(1.5-4.9)	0.66
SVO_2, %	65.3 ± 8.3	66.5 ± 8.1	62.3 ± 8.8	0.29
Echocardiography	27(100)	18(100)	9(100)	-
RVSP, mmHg	78.6 ± 20.9	76.1 ± 17.3	83.2 ± 26.6	0.42
TR Vmax, m/s	4.10 ± 0.63	4.08 ± 0.45	4.15 ± 0.90	0.83
Abnormal RV contractility	22(81)	15(83)	7(78)	0.53
TAPSE, cm	1.97 ± 0.25	2.00 ± 0.26	1.86 ± 0.22	0.30
Dilated RV	25(92)	16(89)	9(100)	0.43
V/Q scintigraphy	24(89)	16(89)	8(89)	-
Only perfusion scan performed	8(33.3)	6(37.5)	2(25)	0.43
Pulmonary angiography	21(77.7)	15(83)	6(67)	-
Proximal lesions	13(62)	12(80)	1(16.7)	0.01
CT scan	25(93)	17(94)	8(89)	-
Proximal lesions	12(48)	12(70)	0	0.01
Dilation of bronchial arteries,	8(32)	5(29)	3(33.3)	1.00
Mosaic perfusion pattern (HRCT)	11(44)	5(29)	6(67)	0.20
Lung function tests	21(77.7)	13(72.2)	8(88.8)	-
DLCO (% pred)	70.7±10.7	71.0±8.4	70.2±14.2	0.87
FEV1(% pred)	88.6±21.4	92.5±23.3	82.2±11.7	0.29
FVC(% pred)	88.4±18.4	91.5±18.8	83.3±17.8	0.33
FEV1/FVC	1.0±0.1	1.0±0.1	0.9±0.1	0.69
TLC (% pred)	81.3±13	84.5±14.1	75.3±8.7	0.14

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Table 4 Conventional therapies at diagnosis and follow-up.

Conventional therapies	Total N=27	Operable N=18	Nonoperable N=9	p-value
At diagnosis				
Anticoagulation	25(93)	17(94)	8(88.9)	0.56
VKA	21(77.8)	13(72)	8(88.9)	0.28
NOAC	2(7)	2(11)	0	-
LMWH	2(7)	2(11)	0	-
O_2 therapy	12(44.4)	8(44.4)	4(44.4)	-
Diuretics	13(48.1)	9(50)	4(44.4)	-
At follow-up				
Anticoagulation	27(100)	18(100)	9(100)	-
VKA	20(75)	14(78)	6(66.7)	-
NOAC	5(18)	4(22)	1(11.1)	-
LMWH	2(7)	0	2(22.2)	-
O_2 therapy	6(22.2)	3(16.6)	3(33.3)	0.36
Diuretics	13(48.1)	8(44)	5(55.5)	0.69

Values represent absolute count (percentage).
VKA: Vitamin K antagonist, NOAC: non-vitamin K oral anticoagulant, LMWH: low-molecular-weight heparin.

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Table 5 Pulmonary hypertension-specific therapy at initiation and follow-up.

PH-specific therapy	Total N=27	Operable N=18	Nonoperable N=9	p-value
At initiation				
Phosphodiesterase type 5 inhibitor	11(40.7)	8(44.4)	3(33.3)	0.69
Endothelin receptor antagonist	4(14.8)	2(11.1)	2(22.2)	0.58
Prostacyclin analogue	1(3)	1(5)	0	-
Riociguat	4(14.8)	2(11.1)	2(22.2)	0.58
At follow-up				
Phosphodiesterase type 5 inhibitor	1(3)	0	1(11.1)	-
Endothelin receptor antagonist	2(7)	0	2(22.2)	-
Prostacyclin analogue	1(3)	0	1(11.1)	-
Riociguat	16(59.3)	10(55)	6(66.7)	0.58

Values represent absolute count (percentage).

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Conclusions

- Riociguat has received approval for use in the treatment of adults with persistent or recurrent CTEPH after surgical treatment, or inoperable CTEPH
- In some centers medical therapy and BPA are initiated concurrently
- Important to follow the ESC Guidelines!

2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism

The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC)

8.2 Pulmonary embolism and cancer

The overall risk of venous thromboembolism in cancer patients is four times as great as in the general population.[8] Although the largest absolute numbers of VTE episodes occur in patients with lung, colon, and prostate cancer, the relative risk for VTE is highest in multiple myeloma, brain, and pancreatic cancer (46-, 20-, and 16-fold increased vs. healthy controls, respectively).[439] In the metastatic stage, stomach, bladder, uterine, renal, and lung cancer are also associated with a high incidence of VTE.[17]

Patients receiving chemotherapy have a six-fold increase in the adjusted risk ratio for VTE compared with a healthy population.[8] Nevertheless, prophylactic anticoagulation is not routinely recommended during ambulatory anti-cancer chemotherapy, with the exception of thalidomide- or lenalidomide-based regimens in multiple myeloma.[440,441] LMWH or VKA are not effective in preventing thrombosis related to the use of permanent central venous lines in cancer patients.[441]

Acknowledgements
AHEPA University Hospital
Pulmonary Hypertension Unit

Thank you

Thanks

Risk factors from transition from PE to CTEPH

Associated condition	OR
VA shunt/infected leads [1, 2]	13.00 [2.5-129] and 76.4 [7.67-10350.62]
Splenectomy [1, 2, 3]	13.00 [2.7-127] and 17.87 [1.56-2438]
Recurrent VTE [1]	14.4 [5.40-43.08]
Thyroid replacement therapy [1]	6.1 [2.73-15.05]
Previous VTE [1]	4.52 [2.35-9.12]
Antiphospholipid antibodies /LA [1]	4.20 [1.56-12.21]
Survived cancer [1]	3.76 [1.47-10.43]
Inflammatory bowel disease [1, 2]	3.19 [0.74-16.03]
Blood groups non-0 [1,4]	2.09 [1.12-3.94]
Fibrinogen Aα Thr312Ala polymorphism [5]	1.68 [1.13-2.49]
HLA-B*5201 (Japan) [6]	2.14 [1.29-3.55]
HLA-DPB1*0202 (Japan) [6]	3.41 [1.71-6.74]