## SUPPLEMENTARY MATERIALS

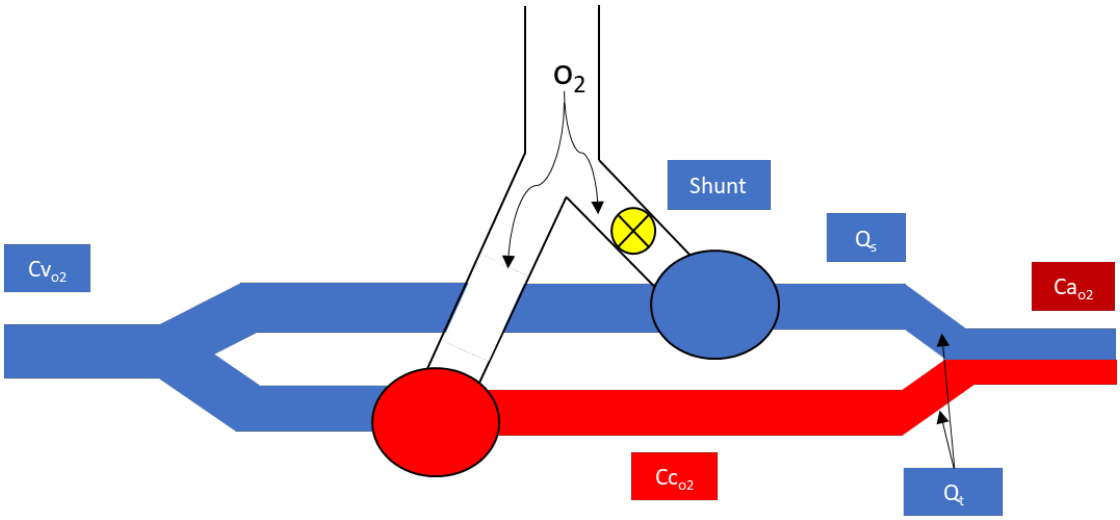


**Figure S1.** Determining the shunt fraction.

Where:

$Q_t$ - total pulmonary blood flow

$Q_s$ - blood flow through the shunt area

$Ca_{O2}$ - oxygen content of the arterial blood

$Cv_{O2}$ – oxygen content of the venous blood

$Cc_{O2}$ – oxygen content of blood that undergoes gas exchange

With a shunt, a fraction of the total blood returning to the lungs does not undergo gas exchange and this blood has a content of $O_2$ equal to that of mixed venous blood. The oxygen content of the arterial blood ($Ca_{O2}$) is a weighted average of the $O_2$ content of the shunted blood and the oxygen content of the blood that undergoes gas exchange. The oxygen content of the shunted blood is calculated as the fraction of shunted blood flow compared to total blood flow ($Q_s/Q_t$) times $O_2$ content of venous blood ($Cv_{O2}$). The oxygen content of blood undergoing gaseous exchange is calculated as the remaining fraction ($1 – Q_s/Q_t$) multiplied by the $O_2$ content of blood that undergoes gas exchange ($Cc_{O2}$). Therefore, we can derive the following equations:

$$Ca_{O2} = [Q_s/Q_t \times Cv_{O2}] + [(1- Q_s/Q_t) \times Cc_{O2}]$$

By manipulating the formula, the shunt fraction can be calculated as

$$Q_s/Q_t = (CcO_2 – Ca_{O2}) \div (Cc_{O2} – Cv_{O2})$$

Due to deoxygenated blood returning to the left atrium from the Thebesian veins and the bronchial circulation of the airways, there is a normal (anatomical) shunt of ~5% in normal individuals. This also contributes ~10 mmHg to the A-a gradient in adults.

**Table S1.** Search strategy.

**Web of Science**
#1 AND #2 AND #3 AND #4
TS="orthodeoxia" OR TI="orthodeoxia" OR AB="orthodeoxia"
TS="platypnea" OR TS="platypnoea" OR TI="platypnea" OR TI="platypnoea" OR AB="platypnea" OR AB="platypnoea"
TS="disease" OR TI="disease" OR AB="disease"
TS="syndrome" OR TI="syndrome" OR AB="syndrome"

**Medline (PubMed)**
#1 "syndrome"[MeSH Terms] OR "syndrome"[Title/Abstract] OR "disease"[MeSH Terms] OR "disease"[All Fields]) AND (1949/1/1:2023/5/8[pdat])
#2 "platypnoea"[Title/Abstract] OR "platypnea"[Title/Abstract]) AND (1949/1/1:2023/5/8[pdat]
#3 "orthodeoxia"[Title/Abstract]) AND (1949/1/1:2023/5/8[pdat]
#4 (("syndrome"[MeSH Terms] OR "syndrome"[Title/Abstract] OR "disease"[MeSH Terms] OR "disease"[All Fields]) AND 1949/01/01:2023/05/08[Date - Publication]) AND (("platypnoea"[Title/Abstract] OR "platypnea"[Title/Abstract]) AND 1949/01/01:2023/05/08[Date - Publication]) AND ("orthodeoxia"[Title/Abstract] AND 1949/01/01:2023/05/08[Date - Publication])) AND (1949/1/1:2023/5/8[pdat])

**Ebscohost (CINAHL)**
S1 "syndrome"
S2 "disease"
S3 TI (platypnea OR platypnoea)
S4 AB (platypnea OR platypnoea)
S5 TI orthodeoxia
S6 AB orthodeoxia
S7 S1 AND S2 AND S3 AND S4 AND S5 AND S6

**Table S2.** Reason for exclusion of articles.

| Study | Reason for exclusion |
|---|---|
| 1. Aboussouan LS et al, 2000 | Review article |
| 2. Afonson L et al, 2010 | Wrong study design |
| 3. Agrawal A et al. 2017 | Review article |
| 4. Agrawal G et al, 2008 | Wrong population |
| 5. Akagi T et al, 2021 | Wrong study design |
| 6. Akin E, et al. 2014 | Review article |
| 7. Almange C, et al. 2002 | Review article |
| 8. Anzola GP et al, 2002 | Review article |
| 9. Athavale T et al, 2021 | Wrong study design |
| 10. Baptista R et al, 2011 | Full article not accessible |
| 11. Barbero C et al, 2016 | Full article not accessible |
| 12. Bertaux G et al, 2007 | Wrong study design |
| 13. Bhan A et al, 2011 | Review article |
| 14. Bottiroli M et al, 2020 | Full article not accessible |
| 15. Brittl JA, 1996 | Wrong publication type |
| 16. Buchhilz S et al, 2012 | Review article |
| 17. Butt W, 2015 | Editorial |
| 18. Byrd RP et al, 1992 | Full article not accessible |
| 19. Cetiner N et al, 2021 | Wrong population |
| 20. Chen GPW et al, 2005 | Review article |
| 21. Cheng TO, 1999 | Editorial |
| 22. Cheng TO, 2002 | Letter |
| 23. Cheng TO, 2002 | Letter |
| 24. Cheng TO, 2004 | Full article not accessible |
| 25. Cheng TO, 2007 | Letter |
| 26. Cho KK et al. 2021 | Review article |
| 27. Choussat A et al, 2003 | Wrong population |
| 28. Corno AF et al, 2022 | Review article |
| 29. Correa PCRP, 2020 | Editorial |
| 30. Cruz-Gonzalez I et al, 2008 | Review article |
| 31. Cruz-Gonzalez I et al, 2009 | Review article |
| 32. Darremont O et al, 1992 | Full article not accessible |
| 33. Das BB et al, 2020 | Review article |
| 34. De Vecchis R et al, 2016 | Retraction |
| 35. De Vecchis R et al,2016 | Duplicate |
| 36. De Vecchis R et al. 2017 | Review article |
| 37. Debeaumont D et al, 2016 | Wrong outcome |
| 38. Delgado G et al, 2004 | Full article not accessible |
| 39. Desouza KA et al, 2009 | Full article not accessible |
| 40. Devendra GP et al, 2012 | Wrong population |
| 41. Drighil A et al, 2007 | Review article |
| 42. Dundon BK et al, 2008 | Full article not accessible |
| 43. Dvoretskiy LI et al, 2020 | Review article |
| 44. Eicher JC et al, 2005 | Wrong study design |
| 45. Fallesen CO et al, 2013 | Full article not accessible |
| 46. Fazio G et al, 2010 | Wrong study design |

| | |
|---|---|
| 47. Gaber R et al, 2012 | Wrong population |
| 48. Gaspardone A et al, 2008 | Review article |
| 49. Gautier-Brun et al, 2002 | Review article |
| 50. Gelernter-Yaniv L et al, 2008 | Wrong study design |
| 51. Gibbons CH et al, 2005 | Wrong outcome |
| 52. Giblet JP et al, 2020 | Wrong outcome |
| 53. Giblett JP et al. 2019 | Review article |
| 54. Giombolini C et al, 2005 | Full article not accessible |
| 55. Gonnah AR et al, 2022 | Review article |
| 56. Graves J et al, 2007 | Full article not accessible |
| 57. Hampton T et al, 2021 | Wrong population |
| 58. Harrow AS et al, 1989 | Wrong study design |
| 59. Hayasaka T et al, 2020 | Wrong population |
| 60. Haziza F et al, 2003 | Full article not accessible |
| 61. Ho WJ et al, 1999 | Wrong study design |
| 62. Ilkhanoff L et al, 2005 | Wrong population |
| 63. Irwin B et al, 2012 | Review article |
| 64. Jan JS et al, 1996 | Full article not accessible |
| 65. Kedia G et al, 2008 | Review article |
| 66. Kerut et al, 2001 | Review article |
| 67. Khiangte B et al, 2020 | Wrong study design |
| 68. Knapper JT et al. 2014 | Review article |
| 69. Koekkoek WAC et al, 2018 | Full article not accessible |
| 70. Kohashi Y et al, 2021 | Full article not accessible |
| 71. Kolte D et al, 2021 | Review article |
| 72. Krassas A et al, 2020 | Wrong study design |
| 73. Krowka MJ et al, 1987 | Wrong population |
| 74. Layoun ME et al, 2017 | Review article |
| 75. Legras A et al, 1999 | Wrong outcome |
| 76. Lisignoli V et al, 2007 | Wrong outcome |
| 77. Liu LY et al, 2022 | Wrong outcome |
| 78. Lombardi M et al. 2022 | Review article |
| 79. Lopez gaston OD, 2005 | Full article not accessible |
| 80. Love A et al, 2022 | Full article not accessible |
| 81. Malbrain ML et al, 1995 | Full article not accessible |
| 82. Meier B et al, 2018 | Wrong outcome |
| 83. Merino Argumanez C et al, 2014 | Full article not accessible |
| 84. Meyers C et al, 1998 | Wrong outcome |
| 85. Mojadidi MK et al. 2019 | Review article |
| 86. Muratori M et al, 2016 | Wrong outcome |
| 87. Naeije R et al, 2003 | Wrong population |
| 88. Nagata T et al, 2002 | Wrong study design |
| 89. Nedeltchev K et al, 2003 | Wrong study design |
| 90. Oldani S et al, 2021 | Wrong population |
| 91. Onorato E et al, 2003 | Wrong study design |
| 92. Pati V et al, 2014 | Wrong population |
| 93. Pieri P et al, 2020 | Full article not accessible |
| 94. Piovanelli B et al, 2014 | Wrong outcome |

| | |
|---|---|
| 95. Pristipino C et al, 2021 | Review article |
| 96. Rajendram et al, 2020 | Review article |
| 97. Rao PS, 2004 | Wrong study design |
| 98. Reynard C et al, 2005 | Full article not accessible |
| 99. Rigatelli et al, 2010 | Review article |
| 100. Rigatelli G et al, 2006 | Wrong study design |
| 101. Robin ED et al, 1997 | Review article |
| 102. Rodrigues P et al, 2012 | Review article |
| 103. Rodriguez-Roisin R et al 2008 | Review article |
| 104. Rodriquez-Roisin et al, 2018 | Review article |
| 105. Saenz-Gomez J et al, 2015 | Wrong population |
| 106. Sagar VVSS et al, 2022 | Wrong population |
| 107. Saharan S et al, 2022 | Wrong population |
| 108. Salick M et al, 2022 | Wrong outcome |
| 109. Salsa-Pacheco JL et al. 2021 | Review article |
| 110. Santhirapala V et al, 2014 | Wrong study design |
| 111. Seed G, 2011 | Letter |
| 112. Shahid M et al, 2019 | Wrong population |
| 113. Simpson B et al, 2021 | Wrong population |
| 114. Somers C et al, 2000 | Full article not accessible |
| 115. Sorribas Rubio PL et al, 2016 | Full article not accessible |
| 116. Surmely JF et al, 2007 | Wrong population |
| 117. Suzuki H et al, 2006 | Wrong population |
| 118. Thomson JD et al, 2013 | Wrong population |
| 119. Timmermans C et al, 1993 | Full article not accessible |
| 120. Tobis JM et al, 2016 | Wrong population |
| 121. Tobis JM, 2016 | Editorial |
| 122. Valenti et al, 2010 | Review article |
| 123. Varsano et al, 2011 | Foreign language |
| 124. Vitarelli A et al, 2019 | Review article |
| 125. Wahl A et al, 2001 | Review article |
| 126. Werlang ME, et al, 2016 | Wrong study design |
| 127. Yalonetsky S et al, 2006 | Wrong outcome |
| 128. Yang CY et al, 2018 | Wrong outcome |
| 129. Zanchetta M et al, 2005 | Review article |
| 130. Zier LS et al, 2016 | Review article |

**Table S3.** Summary of included studies.

| **Items** | **Summary** |
|---|---|
| **Study design** | N = 337 |
| Case report | 302 |
| Case series | 35 |
| **Year of publication** | N = 337 |
| 1979 | 1 |
| 1984 | 1 |
| 1985 | 1 |
| 1989 | 1 |
| 1990 | 1 |
| 1991 | 1 |
| 1992 | 1 |
| 1995 | 2 |
| 1996 | 1 |
| 1997 | 3 |
| 1999 | 3 |
| 2000 | 3 |
| 2001 | 4 |
| 2003 | 4 |
| 2004 | 7 |
| 2005 | 6 |
| 2006 | 3 |
| 2007 | 5 |
| 2008 | 5 |
| 2009 | 11 |
| 2010 | 5 |
| 2011 | 16 |
| 2012 | 15 |
| 2013 | 10 |
| 2014 | 22 |
| 2015 | 20 |
| 2016 | 15 |
| 2017 | 19 |
| 2018 | 15 |
| 2019 | 32 |
| 2020 | 29 |
| 2021 | 40 |
| 2022 | 27 |
| 2023 | 8 |

**List S1.** Included articles.


1. Magois E, Aubry P, Andrejak C, Peltier M, Saidi L, Rey C, et al. "On and off" hypoxaemia. Rev Mal Respir. 2011;28: 668–671. doi:10.1016/j.rmr.2010.11.004

2. Mathew U, Mittal A, Vyas S, Ray A. Interstitial pneumonia with autoimmune features and platypnea-orthopnea syndrome. BMJ Case Rep. 2019;12. doi:10.1136/bcr-2019-230948

3. Salvotti F, Poiatti F, Bressa S, Montani G, Nardin M, Rizzoni D. Platypnoea-orthodeoxia syndrome in COVID-19. Eur J Case Rep Intern Med. 2021;8:002849. doi:10.12890/2021_002849

4. Surridge A  Aujayeb A. AJ. Platypnoea and orthodeoxia in the hepatopulmonary syndrome. BMJ Case Rep. 2019; 12: e231499. doi:10.1136/bcr-2019-231499

5. Aayilliath K A, Singh K, Ray A, Wig N. Platypnoea–orthodeoxia syndrome in COVID-19. BMJ Case Rep. 2021;14: e243016. doi:10.1136/bcr-2021-243016

6. Walker-Jacobs A, Mota B, Hajjar K, Abdul-Samad O, Sankaran P. Platypnoea-orthodeoxia syndrome and hemidiaphragm paralysis. BMJ Case Rep. 2022;15: e248502. doi:10.1136/bcr-2021-248502

7. Tamura Y, Sakamoto T. Platypnoea–orthodeoxia syndrome induced by short-term weight loss: a case series. Arzanauskaite M, Sinning C, Voges I, McNaughton E, Chakir M, editors. Eur Hear J Case Rep. 2020;4: 1–6. doi:10.1093/ehjcr/ytaa498

8. Bouros D, Agouridakis P, Tsatsakis A, Askitopoulou E, Siafakas NM. Orthodeoxia and platypnoea after acute organophosphorus poisoning reversed by CPAP: a newly described cause and review of the literature. Respir Med. 1995;89: 625–628. doi:10.1016/0954-6111(95)90232-5

9. Vasant J, Jones S, Easaw J. Platypnoea-orthodeoxia syndrome. BMJ Case Rep. 2011; 2010–2012. doi:10.1136/bcr.11.2010.3559

10. Vânia Rodrigues, Tiago Gomes, Adriana Santos Silva, Rita Rocha, Ana Ferrão. Platypnoea-Orthodeoxia Syndrome: An Intriguing Diagnosis. Eur J Case Rep Intern Med. 2019;6: 001030. doi:10.12890/2019_001030

11. Gama e Castro A, Luz A, Oliveira F, Brochado B, Santos R, Alexandre A, et al. Platypnoea orthodeoxia syndrome and patent foramen ovale closure: single-centre experience and long-term follow-up. Hear Lung Circ. 2022;31: 1547–1552. doi:10.1016/j.hlc.2022.07.003

12. Cho K, Kempton H, Roy D. Cardiac Platypnoea-orthodeoxia syndrome – supine and upright transoesophageal echocardiography. Hear Lung Circ. 2021;30: e88–e90. doi:10.1016/j.hlc.2021.01.006

13. Mano D, Campos P, Vale B, Pinto A. Stroke and respiratory failure: mind the shunt! Eur J Case Rep Intern Med. 2021;8: 003094. doi:10.12890/2021_003094

14. Long MT, Grate J, Bradley K V. Postoperative hemidiaphragmatic paralysis and platypnea–orthodeoxia syndrome. Indian J Crit Care Med. 2021;25: 951–953. doi:10.5005/jp-journals-10071-23934

15. Kubler P. Platypnoea-orthodeoxia syndrome. Heart. 2000;83: 221–223. doi:10.1136/heart.83.2.221

16. Asami-Noyama M, Harada M, Hisamoto Y, Kobayashi T, Oishi K, Edakuni N, et al. Platypnea-orthodeoxia syndrome in a patient with ongoing COVID-19. Respirol Case Rep. 2022;10: e01009. doi:10.1002/rcr2.1009

17. Zanoni N Frizzelli A, Longo F, Accogli R, Chetta AA. LC. Platypnea-Orthodeoxia Syndrome after SARS-CoV-2 interstitial pneumonia: an overview and an update on our patient. Acta Biomed. 2022;93: e2022015. doi:10.23750/abm.v93i1.11814

18. Buikema JW van GPP. Platypnea-orthodeoxia syndrome. Ned Tijdschr Geneeskd. 2010;154: A2613.

19. Kumar V, Bhushan D, Sahoo BH, Hegde A. Platypnea-orthodeoxia Syndrome: An Important Cause of Morbidity in Post Coronavirus Disease Patients. Indian J Crit Care Med. 2022;26: 401–402. doi:10.5005/jp-journals-10071-24126

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26. Rigatelli G, Bacich D, Zuin M, Braggion G, Dell'Avvocata F. Cardiac pump-induced platypnea-orthodeoxia. Eur Hear J Cardiovasc Imaging. 2019;20: 603. doi:10.1093/ehjci/jey228

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Platypnea and orthodeoxia associated with Pneumocystis jiroveci and Cytomegalovirus pneumonia: a case report. J Med Case Rep. 2009;3: 9319. doi:10.1186/1752-1947-3-9319

28. Fontes CP, Fonseca SB, Santos M. Platypnoea-orthodeoxia syndrome: the importance of the patient's posture for diagnosis. BMJ Case Rep. 2021;14: e243210. doi:10.1136/bcr-2021-243210

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453–454. doi:10.7861/clinmedicine.16-5-453

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**Table S4.** Treatment options.

| **Treatment** | **n (%)** |
|---|---|
| Percutaneous closure of PFO | 395 (67) |
| Conservative management | 52 (9) |
| Open surgical closure of PFO | 38 (6) |
| Oxygen and physiotherapy | 29 (5) |
| Percutaneous closure of ASD | 23 (4) |
| Open surgical closure of ASD | 16 (3) |
| Steroids | 5 (1) |
| Immunosuppression/chemotherapy | 4 (0.7) |
| Anticoagulation | 3 (0.5) |
| Other surgical repairs | 3 (0.5) |
| Liver transplantation | 3 (0.5) |
| Surgical closure of PAVM | 3 (0.5) |
| Surgical thrombectomy | 2 (0.3) |
| Device occlusion of AVM | 2 (0.3) |
| Serial balloon dilatation | 1 (0.2) |
| Atropine, pralidoxime, mechanical ventilation | 1 (0.2) |
| Percutaneous drainage of liver cyst | 1 (0.2) |
| Pericardiectomy | 1 (0.2) |
| Increased intravascular volume | 1 (0.2) |
| Laxative | 1 (0.2) |
| Delivery of baby | 1 (0.2) |
| AVF ligation | 1 (0.2) |
| Embolization of PAVF | 1 (0.2) |
| Closure of PLSVC | 1 (0.2) |

Abbreviations: PFO, patent foramen ovale; ASD, atrial septal defect, PAVM, pulmonary arteriovenous malformation; AVM, arteriovenous malformation; AVF, arteriovenous fistula; PAVF, pulmonary arteriovenous fistula; PLSVC, persistent left superior vena cava.