Orthodeoxia and postural orthostatic tachycardia in patients with pulmonary arteriovenous malformations: a prospective 8-year series

Santhirapala V, Chamali B, McKernan H, Tighe HC, Williams LC, Springett JT, Bellenberg HR, Whitaker AJ, Shovlin CL

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Study populations

258 consecutive patients with radiologically-proven PAVMs were prospectively and newly recruited June 2005-January 2013. Demographics are provided in Table1. The series excludes any patient seen between May 1999-May 2005, findings for which have been previously reported,[1] and precipitated the current series. Full details of the structured clinic assessments are provided elsewehere:[2,3] All data reported are from the presentation assessment. Oxygen saturations (SaO2) and heart rate were measured by pulse oximetry (Ohmeda Biox 3900, Boulder, Colorado) while breathing room air. Additionally, 221 PAVM patients had same day spirometry evaluations, and 230 PAVM patients had same day blood tests: full blood counts were measured on XE Series Analysers (Sysmex, UK) and biochemical indices including serum iron, transferrin saturation index (T*f*SI) and ferritin Ci1600 Architect Analysers (Abbott Diagnostics, Ireland).

Control groups were generated retrospectively from other individuals who had been evaluated in the clinical service between April 2000 and September 2013. Controls were selected if they had no evidence of PAVMs on a dedicated thoracic CT scan, and no current/recent pregnancy or concurrent cardiorespiratory pathology or treatments anticipated to influence SaO_2 or pulse. Inclusion within these groups was determined by final diagnostic status, blinded to postural measurements. The main control group comprised 40 individuals (24 women, and 16 men aged 19-66 (median 45.5)ys in whom PAVMs and/or HHT had initially been considered diagnostic possibilities. They had undergone standard SaO_2/CT evaluations as part of clinical work up. Subsequent investigations had revealed alternate causes for their symptoms (haemoptysis, stroke, transient ischaemic attack), with HHT either not suspected clinically, or not present in their branch of the family by pedigree or mutational studies. A second control group comprised 87 individuals who had definite hereditary haemorrhagic telangiectasia (HHT)[4] but no evidence of PAVMs on dedicated thoracic CT scans. These 53 women and 34 men ranged in age from 19-79 (median 44)ys.

Study methodologies

The potential imprecision of pulse oximetry measurements is well recognised. To improve precision, measurements were made continuously for 10 minutes in both supine and erect postures, recorded at one minute intervals. All except one individual with PAVMs completed the full evaluation. Individual SaO_2 and heart rate measurements at minutes 7, 8, 9 and 10 were compared to evaluate intrapatient variability, and demonstrated high reproducibility (Table 2). For the evaluations presented in this study, the mean values from minutes 7, 8, 9 and 10 were used for final comparisons, and to generate the differences in SaO_2 or pulse between supine and erect postures**.** Data from one control outlier (change in pulse of $25min^{-1}$ recorded as a fall on standing) was excluded.

The reported exercise tolerance for patients reviewed between 2005-2010 was assigned to the Medical Research Council (MRC) Dyspnoea scale,[5] blinded to all other patient parameters.[2] Normal individuals with no dyspnoea except on extreme exertion were classified as Grade 1a if they were highly athletic individuals participating in intense sporting activity at least three times per week. Grade 1b represented normal (dyspnoeic only on strenuous exertion); Grades 2-5 progressively lower exercise tolerance.[2] The primary clinician's awareness of interim analyses in late 2010 implied these data could not be assigned to the 2010-2013 cohort in an unbiased manner.[2] Arterial oxygen content (CaO_2) on air was calculated by 1.34*haemoglobin *SaO_2, where 1.34mls is the empirically determined amount of oxygen carried per gram of haemoglobin.[6]

STATA IC version 12 (Statacorp, Texas) and GraphPad Prism 5 (Graph Pad Software Inc, San Diego) were used to calculate distributions of participant-specific variables, to perform comparisons between groups, and to generate graphs. Two group comparisons were by Spearman rank or Mann Whitney; three group repeated measures comparisons by Friedman with post-test Dunns corrections. Univariate and multivariate regression analyses were performed in STATA IC version 12 (Statacorp, Texas).

RESULTS:

Table 1: Demographics of the 258 PAVM Patients

Binary variables	***N*** §	***Present***	***%***	
Hereditary haemorrhagic telangiectasia	258	239	92.6	
Gender (female)	258	169	61.5	
Ever smoked	240	87	36.3	
Continuous variables	***N*** §	***Range***	***Median***	***IQR***
Age (yr)	258	16-90	48	36, 61
Body mass index (kg/m^2)	220	16.6- 46.3	26.3	23.0, 29.7
FEV1 (L)	221	1.0-5.2	2.9	2.4, 3.6
FEV1 (% predicted^)	221	36-127	94	83, 104
FEV1/VC (%)	221	38-99	78	73, 83
SaO_2 supine at presentation (%)	257	81.5-100	95.3	92.8, 96.5
Pulse supine at presentation (min^{-1})	257	45-110	74	66, 81
SaO_2 erect at presentation (%)	257	78-99	95	91.8, 96.3
Pulse erect at presentation (min^{-1})	257	52.3-142	89	80, 99
Change in SaO_2 on standing (%)	257	-11 to 7.5	-1	-2.3, 0.5
Change in pulse on standing (min^{-1})	257	-2.5 to 49	14.25	10.5, 21.3
Haemoglobin (g/dL)	230	5.9-20.9	14.1	12.7, 15.5
Serum iron (µmol/L)	214	0-64	14	7, 19
Transferrin saturation index (T*f*SI*, %)*	214	0-79	23	12,32
Ferritin (ug/L)	176	0-409	30	15, 63
Supine CaO_2 (mls/dl)	229	7.7-24.8	18.2	16.1, 19.6
Erect CaO_2 (mls/dl)	229	7.6-22.9	17.9	16.1-19.3
Change in CaO_2 on standing	229	-2.8 to 1.11	-0.16	-0.47, 0.07

§N, number of datasets; values <258 imply that data was not available for a subgroup of patients. Note one patient could not complete the 10 minutes standing, and their incomplete pulse oximetry assessments were not included in the final calculations. IQR, interquartile range. FEV1, forced expiratory volume in one second. VC, vital capacity. CaO_2: arterial oxygen content on air, calculated by SaO_2*Hb*1.34/100.[6]

Table 2: Variability of pulse oximetry measurements in 257 PAVM patients

	Overall	4 replicate measurements
SaO_2 erect (%): mean (SD)	93.3 (4.6)	0.44 (0.39)
SaO_2 supine (%): mean (SD)	94.5 (3.0)	0.50 (0.52)
Pulse erect (min^{-1}) : mean (SD)	89.9 (14.2)	2.8 (1.9)
Pulse supine (min^{-1}): mean (SD)	73.4 (11.1)	2.5 (1.9)

The first column presents the mean and standard deviation for SaO_2 and pulse in the two postures overall. The second column presents the standard deviations (SD) of the four replicate values for SaO_2 and pulse in the two

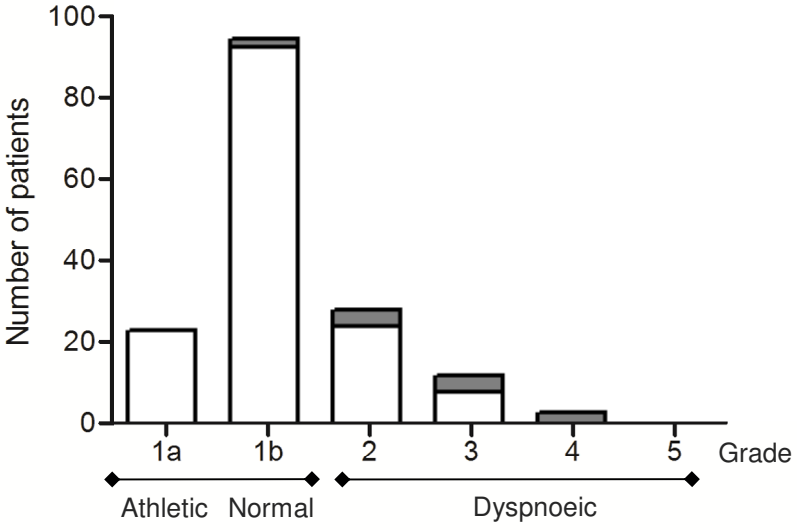
postures, calculated for each individual dataset within the respective group. Note that one patient was unable to complete measurements due to dizziness.

Dyspnoea in 165 PAVM patients by modified MRC dyspnoea grade

The dypsnoea grading system for the 165 patients first assessed between 2005-2010 was derived from the MRC dyspnoea scale.[5] The distributions of oxygen saturation (SaO_2) and arterial oxygen content (CaO_2) across these dyspnoea grades are presented elsewhere:[2] There was no clear relationship with SaO_2, but patients with higher dyspnoea grades had lower CaO_2 (defined as SaO_2* haemoglobin*1.34/100).[2,6]

There was also a striking correlation with comorbidities unrelated to PAVMs (online supplementary Figure 1). For these 165 patients, 15 (9.1%) had significant co-existing disease, including eight (4.8%) with obstructive spirometry due to either asthma or COPD; one with emphysema and previous bullectomy; two with severe pulmonary arterial hypertension; one with obstructive sleep apnoea, and three with congestive cardiac failure or severe cardiac valvular disease. No PAVM patient had severe (Grade 4/5) dyspnoea without significant co-existing cardio-pulmonary disease (online supplementary Figure 1).

Figure 1: Dyspnoea in 165 PAVM patients by modified MRC dyspnoea grade

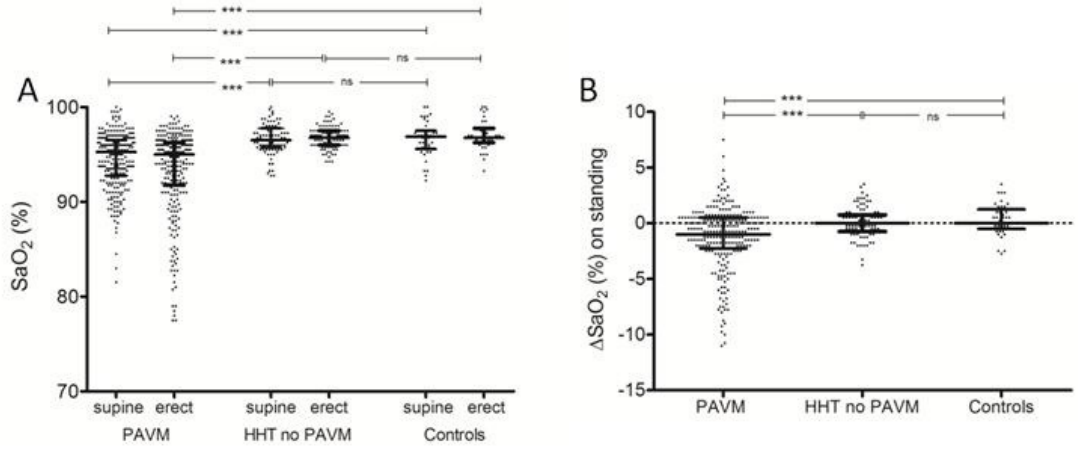


Legend: Grey bars indicate individuals with significant co-existing cardiopulmonary disease. Note that Grade 1 (normal) is separated into 1a (highly athletic individuals participating in intense sporting activity at least three times per week), and 1b (normal). Grades 2-5 represent dyspnoea up a hill (Grade 2); after a mile on the flat (Grade 3); after a few minutes (~100m, Grade 4), and at rest or on minimal effort (Grade 5).

Postural changes in SaO_2 in individuals with and without CT evident PAVMs.

Patients with CT-proven PAVMs were more hypoxaemic than controls in both postures (Figure 2A). There was no trend for the control or HHT groups to exhibit orthodeoxia (Figure 2B).

Figure 2: Postural SaO_2 assessments in PAVM patients and controls

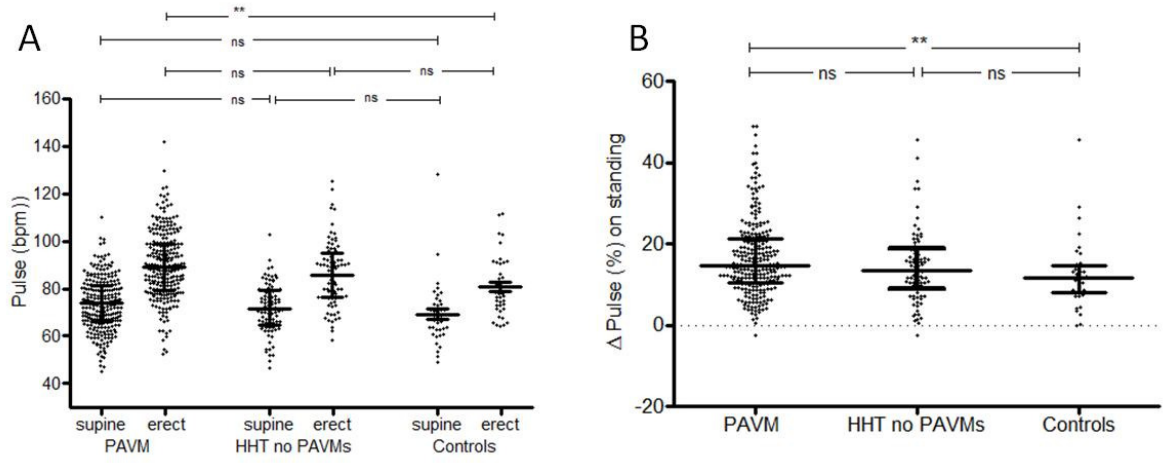


Legend: Comparison of SaO_2 values in patients with and without PAVMs: PAVM patients (n=257), HHT patients with no CT scan evidence of PAVMs (n=87) and controls (n=40). **A)** Absolute SaO_2 values in supine and erect postures. **B)** Postural changes. Error bars represent median and interquartile range. P values were calculated by Kruskal Wallis and Dunn's post test. ***: p<0.001, ns: not significant.

Postural tachycardia in individuals with and without CT evident PAVMs.

The supine heart rate was no different in patients with and without CT-proven PAVMs (Figure 3A). However, the pulse was consistently higher after assuming the erect posture in all three groups (Figure 3A, Figure 3B), particularly in younger individuals: On average for each year of life added, the postural tachycardia diminished by 0.61 min^{-1} in controls (p=0.011), 0.57 min^{-1} in HHT patients with no evidence of PAVMs on CT (p=0.001), and 0.75 min^{-1} in the PAVM group (p<0.0001). Age alone explained only 18.7% of the variance in postural tachycardia in PAVM patients. Overall postural tachycardia was more pronounced in PAVM patients than in controls (Figure 3B).

Figure 3: Postural pulse assessments in PAVM patients and controls



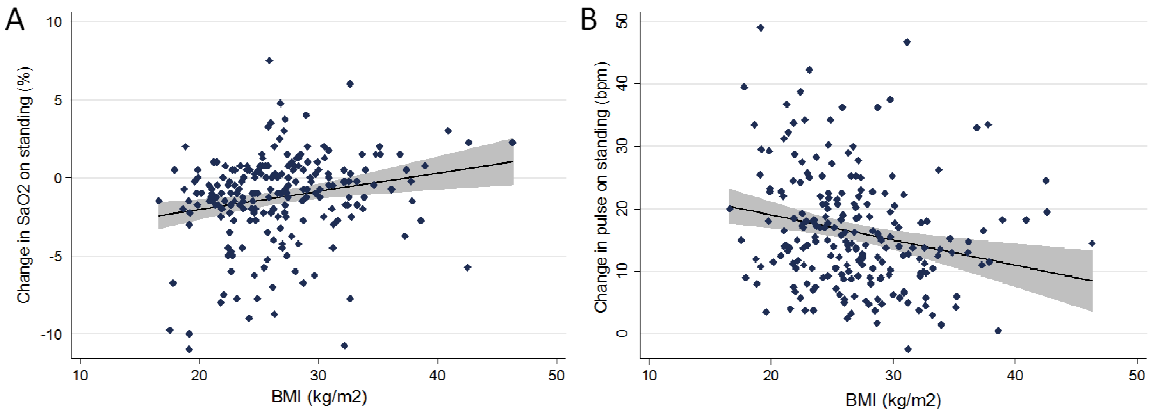
Legend: Three way comparison of heart rates (pulse) in PAVM patients and control groups. Comparison of **A)** absolute pulse and **B)** postural change in pulse in PAVM patients (n=257), HHT patients with no CT scan

evidence of PAVMs (n=87) and controls (n=40). Error bars represent median and interquartile range. P values were calculated by Kruskal Wallis and Dunn's post test. **: p<0.01, ns: not significant.

Obesity and postural changes in PAVM patients

In the general population, obese individuals have smaller total lung capacity attributed to greater compression of the chest wall and reduced diaphragmatic expansion.[7] Variable reports on SaO_2 have been described.[7] In the current study, PAVM patients with higher body mass index (BMI) tended to have lower supine SaO_2 for their erect SaO_2, and correspondingly less evidence of orthodeoxia (Figure 4A). Patients with higher BMI also demonstrated less pronounced postural tachycardia (Figure 4B). The associations remained evident once adjusted for age and gender (data not shown).

Figure 4: Postural data in 220 PAVM patients stratified by body mass index (BMI).

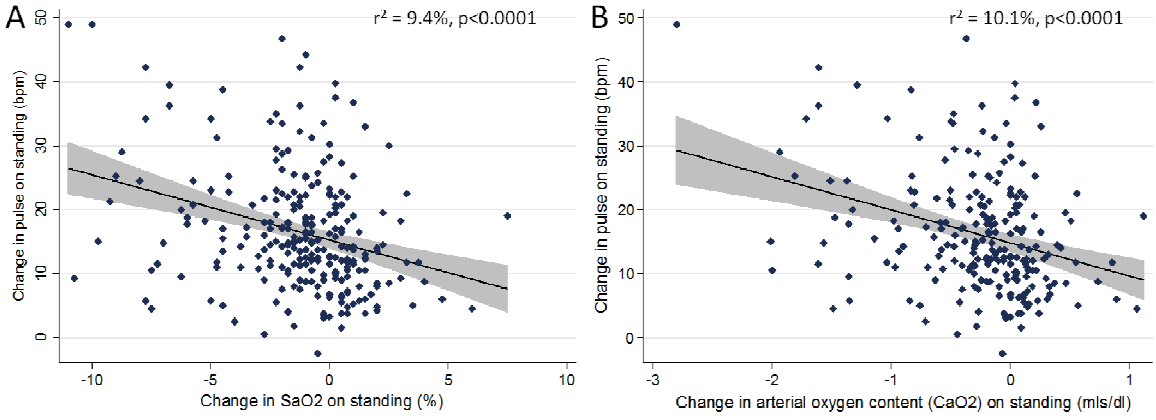


Legend: A) Change in SaO_2 on standing. Linear regression $r^2 = 4.4\%$, $p = 0.0017$. **B)** Change in pulse on standing. linear regression $r^2 = 4.9\%$, $p = 0.0010$.

Acute hypoxaemia and postural tachycardia in PAVM patients

Patients who demonstrated greater orthodeoxia tended to have more pronounced postural orthostatic tachycardia (Figure 5). The associations remained evident once adjusted for age, body mass index, haemoglobin, and all other parameters in online supplementary Table1 (data not shown).

Figure 5: Postural tachycardia in 257 PAVM patients stratified by acute oxygen changes



Legend: Change in pulse on standing stratified by **A)** Change in SaO_2 on standing; **B)** Change in arterial oxygen content (CaO_2) on standing. The crude regression coefficients and p values are displayed.

DISCUSSION

The questions addressed by this study were whether orthodeoxia was commonly present in PAVM patients, whether patients were symptomatic as a result, and if not, why this might be.

Where PAVMs are present in dependent portions of the lung, gravitational forces will increase flow through the right-to-left shunts, a phenomenon first noted by auscultation, and quantified using nuclear medicine perfusion scans using ^{99m}Tc-labelled albumin microspheres.[8] These scans calculated the gamma irradiation from particles reaching the right kidney, assuming this received 10% of the cardiac output, and allowing for attenuation, compared to the total dose received.[9] In clinical practice, the oxygen saturation (SaO_2) provides a convenient, non invasive assessment of the right-to-left shunt.[3,9,10] Orthodeoxia, a fall in arterial oxygenation on assuming the erect posture, is described in the PAVM literature, though its frequency has been questioned.

Orthodeoxia is also described for patients with patent foramen ovale and other intracardiac shunts.[11] We were intrigued by the apparent prevalence of the platypnoea-orthodeoxia syndrome in patients with patent foramen ovale (PFO), as despite clear evidence of orthodeoxia, the PAVM patients that we have reviewed do not report dyspnoea on standing, despite acute postural assessments being an integral part of their clinical assessment at our institution.

We have recently highlighted one of the primary mechanisms that help sustain tissue oxygen delivery in chronically hypoxaemic PAVM patients–a graded secondary erythrocytotic response which resolves following correction of hypoxaemia by embolisation of PAVMs.[2] As a result, despite often substantial increments in SaO_2, the majority of patients report no difference in exercise tolerance when re-evaluated several months after embolisation.[2]

Acute orthodeoxia could not be accompanied by a change in haemoglobin. We hypothesised that compared to the patients described in the literature with platypnoea-orthodeoxia syndrome, PAVM patients might be better able to utilise physiological compensatory methods. Considerations of the initial response to haemorrhage suggested an increase in heart rate might be one such potential compensatory mechanism, and the data in the current study would support such a hypothesis. Standing reduces venous return due to gravitational forces, with baroreceptors usually implicated in the activation of the sympathetic nervous system responsible for postural tachycardia. The PAVM patients remind of an additional potential increment from chemoreceptor activation. This appears to be relevant to the acute change: we have recently demonstrated no difference in heart rate at peak exercise in PAVM patients chronically adapted to their hypoxaemia, compared to the same patients retested several months after embolisation treatment had corrected hypoxaemia.[12]

Why the PAVM patients might be better able to mount compensatory responses to acute orthodeoxia than the symptomatic patients described in the literature is not clear. Increasing age was associated with less pronounced orthostatic tachycardia in all groups. The continuous nature of the right-to-left shunt, in contrast to PFO where right-to-left shunting is intermittent, may facilitate adaptation. We cannot exclude HHT-specific enhancement of orthostatic tachycardia, and this might be suggested in view of the intermediate phenotype of the HHT patients compared to PAVM patients and controls (Figure3). However, it is important to note that from published data,[13] and the endoglin (HHT1 bias) of the study population, it would be anticipated that at least half of this HHT 'non PAVM' group would have right-to-left shunting that would have been detectable by contrast echocardiography but not associated with PAVMs sufficiently large to be visualised on CT scans.

Finally, the delineation of changes in a disease population often leads to suggestions that the assessments might be helpful in diagnostic or screening strategies. As emphasised in 1999,[14] and subsequently reiterated,[15] the detection of hypoxaemia by age-defined PaO_2, or SaO_2 from postural assessments, is insufficiently sensitive to be used as the sole diagnostic screening test for PAVMs. SaO_2 measurements do have substantial clinical utility in the serial investigations required in follow up of individual patients. It remains to be seen whether the evaluation of postural tachycardia will

be similarly beneficial, or merely a tool to better understand the physiological mechanisms that permit tolerance of acute changes in arterial oxygen content.

eREFERENCES

1. Shovlin CL, Jackson JE, Bamford KB, et al. Primary determinants of ischaemic stroke/brain abscess risks are independent of severity of pulmonary arteriovenous malformations in hereditary haemorrhagic telangiectasia. Thorax 2008: 63: 259-66

2. Santhirapala V, Williams LC, Tighe HC et al. Arterial oxygen content is precisely maintained by graded erythrocytotic responses in settings of high/normal serum iron levels, and predicts exercise capacity. An observational study of hypoxaemic patients with pulmonary arteriovenous malformations. PLoS One 2014 Mar 17;9(3):e90777.

3. Shovlin CL, Chamali B, Santhirapala V, et al. Ischaemic strokes in patients with pulmonary arteriovenous malformations and hereditary hemorrhagic telangiectasia: associations with iron deficiency and platelets. PLOS One 2014 Feb 19;9(2):e88812.

4. Shovlin CL, Guttmacher AE, Buscarini E, et al. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). Am J Med Genet 2000: 91: 66–7

5. Fletcher CM. Standardised questionnaire on respiratory symptoms: a statement prepared and approved by the MRC Committee on the aetiology of chronic bronchitis (MRC breathlessness score). BMJ 1960:2: 1665

6 . Pittman RN. Oxygen Transport. Chapter 4 in: Regulation of Tissue Oxygenation. San Rafael (CA) 2011: Morgan & Claypool Life Sciences. Available: http://www.ncbi.nlm.nih.gov/books/NBK54103

7. Salome CM, King GG, Berend N. Physiology of obesity and effects on lung function. J Appl Physiol. 2010;108:206-11.

8. Ueki T, Hughes JMB, Peters AM, et al. Oxygen and 99mTc-MAA shunt estimations in patients with pulmonary arteriovenous malformations: effects of changes in posture and lung volume. Thorax 1994;49:327-331.

9. Chilvers ER, Peters AM, George P, Hughes JMB, Allison DJ. Quantification of right to left shunt through pulmonary arteriovenous malformations using 99Tcm albumin microspheres. Clin Radiol 1989;39:611-614.

10. Thompson RD, Jackson J, Peters AM, Doré CJ, Hughes JM. Sensitivity and specificity of radioisotope right-left shunt measurements and pulse oximetry for the early detection of pulmonary arteriovenous malformations. Chest 1999; 115: 109-13

11. Rodrigues P, Palma P, Sousa-Pereira L. Platypnea-orthodeoxia syndrome in review: defining a new disease? Cardiology 2012;123:15-23. doi: 10.1159/000339872.

12. Howard LSGE*, Santhirapala V*, Murphy K et al. Cardiopulmonary exercise testing demonstrates maintenance of exercise capacity in hypoxemic patients with pulmonary arteriovenous malformations. Chest 2014 Mar 27. doi: 10.1378/chest.13-2988. [Epub ahead of print]

13. van Gent MW, Post MC, Snijder RJ, et al. Real prevalence of pulmonary right-to-left shunt according to genotype in patients with hereditary hemorrhagic telangiectasia: a transthoracic contrast echocardiography study. Chest 2010: 138; 833-9

14. Shovlin CL, Letarte M. Hereditary haemorrhagic telangiectasia and pulmonary arteriovenous malformations: issues in clinical management and review of pathogenic mechanisms. Thorax 1999;54:714-29.

15. Shovlin CL, Jackson JE, Hughes JMB. Pulmonary arteriovenous malformations and other pulmonary vascular disorders. Ch. 50 in Murray and Nadel's Textbook of Respiratory Medicine, 4th Edition, 2005. Eds. Mason RJ, Courtney Broaddus V, Murray JF, Nadel JA. (Elsevier Saunders, Philadelphia) Section L, Pt 50, 1480-1501