Hemoglobin Is a Vital Determinant of Arterial Oxygen Content in Hypoxemic Patients with Pulmonary Arteriovenous Malformations

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Abstract

Rationale: Pa_{O_2} and Sa_{O_2} are commonly measured in respiratory practice, but arterial oxygen content (Ca_{O_2}) refers to the volume of oxygen delivered to the tissues per unit blood volume. Ca_{O_2} is calculated from Sa_{O_2} and the hemoglobin concentration in blood, recognizing that each gram of hemoglobin can transport approximately 1.34 ml of oxygen when fully saturated.

Objectives: To prospectively evaluate serial changes in Ca_{O_2} in humans, incorporating and excluding dynamic changes to oxygenation and hemoglobin parameters that may occur during life.

Methods: A cohort of 497 consecutive patients at risk of both hypoxemia and anemia were recruited. The patients had radiologically proven pulmonary arteriovenous malformations (PAVMs), which result in hypoxemia due to right-to-left shunting, and concurrent hereditary hemorrhagic telangiectasia, which placed them at risk of iron deficiency anemia due to recurrent hemorrhagic iron losses. Presentation Sa_{O_2} (breathing room air, by pulse oximetry), hemoglobin, red cell and iron indices were measured, and Ca_{O_2} calculated as $Sa_{O_2} \times$ hemoglobin $\times$ 1.34 ml/g. Serial measurements were evaluated in 100 cases spanning up to 32.1 (median, 10.5) years.

Results: Presentation Ca_{O_2} ranged from 7.6 to 27.5 (median, 17.6) ml/dl. Ca_{O_2} did not change appreciably across the Sa_{O_2} quartiles. In contrast, hemoglobin ranged from 5.9 to 21.8 g/dl (median, 14.1 g/dl), with a linear increase in Ca_{O_2} across hemoglobin quartiles. After PAVM embolization and an immediate increase in Sa_{O_2}, hemoglobin fell and Ca_{O_2} was unchanged 1.6–12 (median, 4) months later. When hemoglobin fell because of iron deficiency, there was no change in Sa_{O_2}. Similarly, when hemoglobin rose after iron treatment, there was no change in Sa_{O_2}, and the expected Ca_{O_2} increment was observed. These relationships were not evident during pregnancy when hemoglobin fell, and PAVMs usually deteriorated: in pregnancy Sa_{O_2} commonly increased, and serial Ca_{O_2} values (incorporating hemodilution/anemia) more accurately reflected deteriorating PAVM status. An apparent fall in Ca_{O_2} with age in females was attributable to the development of iron deficiency. There was an unexplained increase in Ca_{O_2} with age in follow-up of males after embolization.

Conclusions: Hemoglobin/Ca_{O_2} should be further incorporated into oxygenation considerations. More attention should be given to modest changes in hemoglobin that substantially modify Ca_{O_2}.

Keywords: aging; anemia; hemorrhage; iron; pregnancy

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Although respiratory medicine guidance focuses on Pa_{O_2}, and/or oxygen saturation (Sa_{O_2}, the percentage of hemoglobin binding sites occupied by oxygen), the most relevant term for oxygen transport to the tissues is the arterial oxygen content (Ca_{O_2}), expressed as milliliters of oxygen per unit blood volume. When breathing room air, almost all of the oxygen in the bloodstream is transported bound to hemoglobin, and each gram of hemoglobin can transport approximately 1.34 ml of oxygen when fully saturated (1). Ca_{O_2} can therefore be calculated as hemoglobin $\times$ Sa_{O_2} $\times$ 1.34/100 (1). Reduced Ca_{O_2} demands higher cardiac output to maintain tissue oxygen delivery, most commonly recognized for anemia (2, 3); The co-operative binding of oxygen to hemoglobin, and resultant sigmoid shape of the oxygen dissociation curve, are recognized factors that serve to enhance delivery of oxygen from hemoglobin to the tissues. Beyond this, with the exception of specific settings such as intensive care, anesthesia, and elite sports, respiratory practice does not seem to integrate hemoglobin into usual oxygenation considerations.

An instructive and clinically important condition for exploring Ca_{O_2} contributions from oxygen and hemoglobin is provided by pulmonary arteriovenous malformations (PAVMs). PAVMs affect approximately 1 in 2,600 individuals (4), although they remain poorly emphasized by physician education programs (5). PAVMs lead to lower Pa_{O_2} (and hence lower Sa_{O_2}) due to right-to-left shunting of pulmonary arterial blood through the abnormal vessels, resulting in impaired gas exchange (6–8). Patients can preserve their exercise capacity despite very low Pa_{O_2}/Sa_{O_2}, through secondary erythrocytic and hemodynamic compensatory responses, assuming their hematological and cardiorespiratory systems operate normally (9–13). Polycythemia (high hemoglobin and hematocrit) can be so exuberant that patients may occasionally develop symptoms of hyperviscosity and require venesection (14). PAVM treatment, most commonly by embolization (8, 15–18), is important to reduce neurological sequelae due to paradoxical emboli, such as ischemic stroke and cerebral abscess (19–21). Successful embolization results in sustained increases in Pa_{O_2} and Sa_{O_2}, but surprisingly few patients notice incremental benefit in exercise tolerance after PAVM embolization, even after major improvements in Sa_{O_2} (10–13).

Little was known about longer term serial changes in the compensatory demands and mechanisms that maintain Ca_{O_2}. Although patients with PAVMs may by chance have other cardiorespiratory conditions that impact on adaptive responses to hypoxemia, the problem most commonly present is iron deficiency due to underlying hereditary hemorrhagic telangiectasia (HHT) (21, 22). HHT is present in the majority of cases of PAVMs, although the surprisingly high prevalence of PAVMs (4) reminds us that single PAVMs can occur sporadically, in the absence of HHT. HHT leads to iron deficiency as a result of chronic bleeding (predominantly nosebleeds, with smaller proportions of patients experiencing significant gastrointestinal bleeding). Although iron handling appears normal as evidenced by hepcidin analyses (23), underreplacement of iron through the diet depletes body iron stores, requiring iron supplementation, and sometimes blood transfusions for severe anemia. Thus many patients with PAVMs have both hypoxemic and anemic tendencies, providing an instructive, clinical model to examine relative contributions of oxygen and hemoglobin to the volume of oxygen transported per unit blood volume.

The goal of this observational study was to examine Ca_{O_2} in patients with PAVMs over prolonged time periods, incorporating and excluding the dynamic changes to oxygenation and hemoglobin parameters that occur over lifetimes. Some of the results of these studies have been previously reported in the form of abstracts (24–26).

Methods

This study was conducted in accordance with the amended Declaration of Helsinki. The Hammersmith and Queen Charlottes Local Research Ethics Committee (LREC 2000/5764) approved the protocol.

Study Population and Assessments

Four hundred and ninety-seven consecutive and unselected patients with radiologically proven PAVMs and HHT were recruited prospectively between May 1999 and January 2013. The cohort included patients who had first presented to the same institution from 1984, and had been assessed using broadly comparable methods (27–31).

Pulmonary function testing included measurement of Sa_{O_2} by pulse oximetry (Ohmeda Biox 3900; Ohmeda, Boulder, CO) while breathing room air, for 10 minutes in supine and erect postures. Sa_{O_2} was recorded each minute, and the mean Sa_{O_2} was calculated for each posture across minutes 7–10. The erect Sa_{O_2} value was used for calculations in this article, because this better reflects right-to-left shunt size (measured supine) than Sa_{O_2} in other postures (27, 30, 31), and is more relevant for patients' daily activities.

Earlier in the series (between 1999 and 2006), same-day right-to-left shunt measurements were routinely made, using established nuclear medicine departmental protocols (27–31). After injection of ^{99m}Tc-labeled albumin macroaggregates, the right-to-left shunt was quantified by the proportion of radioactive tracer detected over the right kidney (posterior view), adjusted for dose injected, and assuming the right kidney receives 10% of cardiac output (kidney dose method) (27–32). Because of the cerebral images (27), acute reports of migraine precipitation (27, 33), and further validations of oxygen methodologies (10, 27), routine right–left shunt measurements were phased out after 2006.

From 1999, blood tests were taken at standardized times to minimize variability due to diurnal variation in iron levels (34, 35), and were drawn in the semirecumbent or supine position. Complete (full) blood counts including hemoglobin and red cell indices (mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC]) were measured with XE series analyzers (Sysmex UK Ltd, Milton Keynes, UK). Routine biochemical indices including serum iron and transferrin saturation index (T*f*SI) were measured on Ci1600 Architect analyzers (Abbott Diagnostics, Sligo, Ireland). Ferritin was also measured routinely after 2005–2006 analyses demonstrated associations between iron treatment and/or iron deficiency with venous thromboemboli (36, 37), and pulmonary hypertension (38; C. L. Shovlin, J. E. Jackson, and E. Kulinskaya [2006], unpublished).

Where indicated, embolization of PAVMs was performed as described elsewhere (8, 15, 39–42), generally during standardized 48-hour admissions, when pulse oximetry measurements were made on the day before, and on the day after, embolization. Embolization was not indicated in the remainder primarily due to

PAVMs with feeding arteries too small for treatment—these were followed up over time, providing the basis of the serial analyses described, with many patients requiring further embolization in later years because of interim PAVM growth, recanalization, or methodological advances (8, 15, 16, 39–44). Throughout, pulmonary artery pressures were measured in patients undergoing embolization, recorded by a centrally placed catheter before contrast injection (8, 15, 42). Follow-up assessments were performed according to local clinical policies.

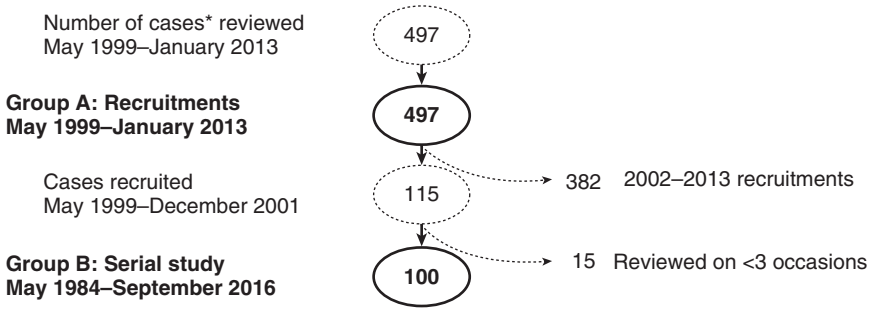

Figure 1. Study flow chart. *Cases in which pulmonary arteriovenous malformations were confirmed by imaging (thoracic computed tomographic scan and/or angiography), recruited prospectively from May 1999. Note that 70 had been first reviewed at earlier time points.

Statistical Analyses

All presentation data available for all 497 patients with PAVM are reported, and referred to as group A. For the purposes of this study, serial data were also evaluated. Serial measurements were accrued in order of presentation, and by the 115th case it became clear that the most informative, long-term measurements were to be found within the earlier presenting group. Diminishing follow-up periods and data sets in more recent years (*see* Figure E1 in the online supplement) were attributable to reduced intensity of follow-up, in addition to more recent first reviews. For the purposes of the current article, serial data were examined in the first 100 patients reviewed on at least three occasions, referred to as group B (Figure 1, Figure E1). Overall, this cohort provided up to 32.1 (median, 10.5) years of follow-up. Where three serial reviews were not performed, this was generally because of patient preference for follow-up in more local health care settings.

Ca_{O_2} (ml/dl) was calculated as $Sa_{O_2} \times$ hemoglobin $\times$ 1.34/100, where Sa_{O_2} was expressed as a percentage, and 1.34 ml is the empirically determined amount of oxygen carried per gram of hemoglobin (1). Iron deficiency was assigned as absent ("0") if ferritin, iron, and T*f*SI were all clearly in the normal range (ferritin $>$ 20 μg/L, serum iron $>$ 11 μmol/L, and T*f*SI $>$ 20%), and present ("1") if ferritin was less than 15 μg/L (45). After earlier hematinic validations (10), iron deficiency was also assigned as present ("1") for individuals with both iron and T*f*SI clearly subnormal ($<$7 μmol/L and $<$20%, respectively); subnormal mean MCV ($<$80 fl), MCH ($<$27 pg), and MCHC ($<$32 g/dl); or if clearly subnormal MCV ($<$78 fl), MCH ($<$26 pg), or MCHC ($<$31 g/dl). For quartile analyses, assignment of Sa_{O_2} and hemoglobin to overlapping quartiles was performed in order of recruitment, blinded to all other variables.

In group B, to facilitate automated exclusion of data sets where changes in iron status or broader physiology would be predicted to confound Ca_{O_2} analyses, each time point was also categorized according to the presence of such a confounder. Thus any embolization, venesection, blood transfusion, use of supplementary oxygen, use of iron (oral or intravenous iron), or pregnancy was recorded. If any of these, or iron deficiency, had changed since the patient's previous measurements, the time point was also categorized by a new "changed" variable. Data sets were selected for examination of changes on iron treatment, blinded to Sa_{O_2}/Ca_{O_2}, if the hemoglobin had risen by 1 g/dl as a result of iron therapy and no further PAVM treatment was required. For examination of responses to iron deficiency, blinded to Sa_{O_2}/Ca_{O_2}, data sets were selected if the hemoglobin had fallen by 1 g/dl or more, was associated with a change in MCV of at least 2 fl, with no PAVM treatment in the preceding year.

STATA IC version 12 (StataCorp, College Station, TX) and GraphPad Prism 5 (GraphPad Software Inc, San Diego, CA) were used to calculate distributions of participant-specific variables, to perform comparisons between groups, and to generate graphs. Two group comparisons

Table 1. Serial study (Group B) patient demographics

	n	Median	IQR	Range
Oxygen saturation (Sa_{O_2}),%	1,275	940	89–96	59–100
Right-to-left shunt, % cardiac output	248	6.45	6.45	3.65–48.8
Hemoglobin, g/dl	825	14.3	12.4–15.8	6.1–23.7
Hematocrit, %	781	0.43	0.39–0.47	0.22–0.67
Mean corpuscular volume (MCV), fl	785	89.3	84.1–92.9	60.3–122
Mean corpuscular hemoglobin (MCH), pg	711	29.2	26.5–30.8	15.5, 30.8
MCHC, g/dl	772	32.4	30.9–33.5	23.3–36.2
Platelets, $\times 10^9$/dl	779	263	222–328	73–593
Serum iron, μmol/L	342	9.5	5–17	1–63
Serum transferrin saturation index (T*f*SI), %	264	16	7–30	2–81
Ferritin, μg/L	135	21	9–39	1–533
C-reactive protein (CRP), IU/ml	191	3	1.9–5.5	0–106
Prothrombin time (PT), s	516	10.9	10.5–11.6	9–54.6*
Activated partial thromboplastin time (APTT), s	510	26	25–28	9.8–61*
Thrombin time (TT), s	476	15	13.4–16.0	10–22
Fibrinogen, g/L	334	2.85	2.35–3.43	0.7–4.92

Definition of abbreviations: IQR = interquartile range; MCHC = mean corpuscular hemoglobin concentration; n = number of data points recorded in the 100 patients.
Demographics are provided for all values across the serial analyses. Iron measurements were not specifically made earlier in the series, but iron deficiency could be evaluated by red cell indices at many more time points (*see* METHODS).
*Higher values accounted for by warfarin (Coumadin) treatment.

were by Mann–Whitney (unpaired) or Wilcoxon matched-pairs signed rank test (paired data). Three or more group comparisons were performed by Kruskal–Wallis with posttest Dunn's corrections. Univariate and multivariate linear, logistic, and quantile regression analyses were performed in STATA IC version 12 (StataCorp), using normal quantile plots to select the most normally distributed variable to use as the dependent (outcome) variable.

Results

Patient Demographics

In all 497 patients (group A), the median age was 47 (interquartile range [IQR], 35–60) years. Of these, 302 (60.8%) were female. High proportions experienced neurological complications of PAVMs including ischemic stroke (61, 12.3%), brain abscess (48, 9.7%), and migraines (172, 34.7%). More than one-quarter (137, 28%) were using oral iron supplements, with fewer receiving intravenous iron, blood transfusions, supplementary oxygen, or venesection (Table E1).

The 100 patients studied in the serial analyses (group B; Table 1) were marginally younger (median age, 42 [IQR, 27–51.5] yr), with a similar proportion of females (n = 64). Two had required venesections, and three used supplementary oxygen. Fifty-four patients (54%) displayed indices of iron deficiency on at least one occasion, 40 used oral iron supplements, 3 required intravenous iron, and 6 were transfused regularly. Over the full period of follow-up, they had a total of 231 embolization treatments (range, 0–10; median, 2; IQR, 1–3). In total, the serial cohort provided a median follow-up of 10.5 years (maximum, 32.1 yr; 65 data sets; Figure E1).

Arterial Oxygen Content at Presentation

Presentation Sa_{O_2} ranged from 59 to 100% (median, 94.75%; Figure 2A). However, Ca_{O_2} did not change appreciably across the Sa_{O_2} quartiles (Figure 2B). In contrast, Ca_{O_2} was determined primarily by hemoglobin, which ranged from 5.9 to 21.8 g/dl (median, 14.1 g/dl; Figure 2C): there was a clear, linear increase in Ca_{O_2} across the hemoglobin quartiles (Figure 2D).

Regression analyses contrasted the magnitude of the improvement in Ca_{O_2} for each 1g/dl rise in hemoglobin, versus each 1% rise in Sa_{O_2} (Figure E2, Table E2). In crude analyses, each 1g/dl rise in hemoglobin was associated with a 1.10-fold (95% confidence interval [CI], 1.06–1.15) increase in Ca_{O_2} ($P < 0.0001$). Again, the association between Sa_{O_2} and Ca_{O_2} was less pronounced, with crude and hemoglobin-adjusted regression coefficients of 0.06 (95% CI, 0.01–0.10; $P = 0.018$) and 0.21 (95% CI, 0.20–0.21; $P < 0.0001$), respectively.

Serial Assessment of Arterial Oxygen Content

Embolization treatment of PAVMs resulted in an immediate increase in Sa_{O_2} that was sustained in the next few days, and on first subsequent follow-up 2–12 (median, 4.4)

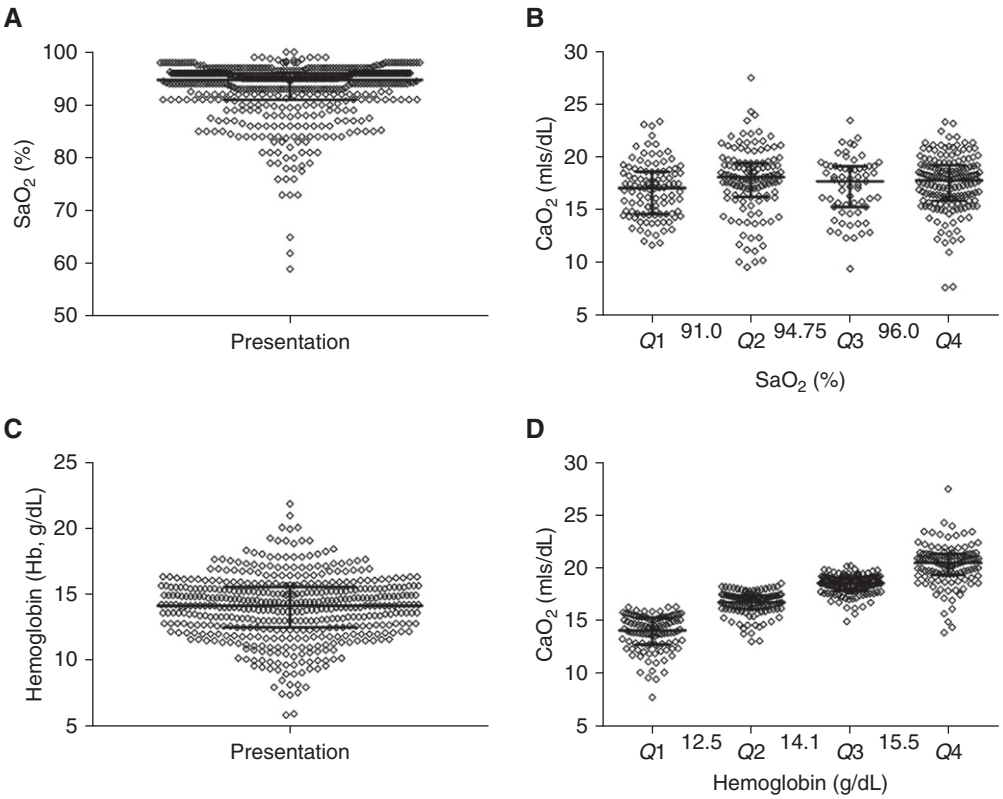

Figure 2. Presentation oxygenation indices in Group A, the 497 consecutive patients with pulmonary arteriovenous malformations. (*A*) Sa_{O_2} (n = 471). (*B*) Arterial oxygen content (Ca_{O_2}) across the four Sa_{O_2} quartiles ($P = 0.028$ by Kruskal–Wallis, n = 440). (*C*) Hemoglobin (n = 462). (*D*) Ca_{O_2} across the four hemoglobin quartiles ($P < 0.001$ by Kruskal–Wallis, n = 440). *Error bars* indicate median and interquartile range.

months later (Figure 3A). After successful embolization, the hemoglobin tended to fall (median, 14.4 g/dl, compared with 14.8 g/dl pre/periembolization). As result, there was minimal change in Ca_{O_2} at first follow-up 1.6–12 (median, 4) months after embolization (17.9 ml/dl compared with 17.8 ml/dl; $P = 0.92$) (Figure 3B).

We speculated that a fall in hemoglobin due to iron deficiency may be accompanied by a rise in Sa_{O_2}, mirroring the changes on embolization treatment. However, there was no change in Sa_{O_2} when hemoglobin fell on the development of iron deficiency, and Ca_{O_2} reflected the hemoglobin increment (Figure 4A).

Similarly, when patients were started on iron therapy, hemoglobin increased (median increase, 2.95 g/dl; $P < 0.0001$), but Sa_{O_2} was unchanged ($P = 0.57$), and again, Ca_{O_2} reflected the hemoglobin increment (Figure 4B).

Arterial Oxygen Content Spanning Pregnancy

Pregnancy also often resulted in increased Sa_{O_2}: of the 13 pregnancies in which Sa_{O_2} was recorded mid-pregnancy (Figure E3), Sa_{O_2} rose in 8 (61.5%). Figure 5A illustrates one pregnancy with particularly pronounced right-to-left shunting (such that the individual was on the steep part of the oxygen dissociation curve). However, there was commonly a fall in Sa_{O_2} postpartum (documented in 11 of 16 pregnancies [69%]), at all severities of right-to-left shunting (Figure E3). Furthermore, of nine pregnancies with post-pregnancy computed tomographic scanning or angiography, PAVM growth was confirmed in seven (77.8%), implying the transient pregnancy-related Sa_{O_2} rises did not reflect improvements in PAVM status as for the postembolization group (Figure 3A). Earlier articles (46–48) have speculated on possible mechanisms to account for gestational rises in Sa_{O_2} but did not refer to the hemodilution and anemia that commonly develop during pregnancy (49). As demonstrated in Figure 5B, serial Ca_{O_2} values, which incorporate hemoglobin changes, more accurately reflected deteriorating PAVM status than Sa_{O_2} in isolation.

Longer Term Trends in Ca_{O_2}

Longer term trends in Ca_{O_2} were examined across the years after embolization, when PAVMs may recanalize, recur, or enlarge, resulting in greater right-to-left shunting, and lower Sa_{O_2}. In addition, Pa_{O_2} and Sa_{O_2} fall because of chest wall and lung parenchymal age–related changes that reduce efficiency of ventilation and gas exchange. In group B, there was a tight linear relationship between the right-to-left shunt measured by technetium scans, and erect Sa_{O_2} with no evident sex difference (Figure 6A). In serial evaluations, erect Sa_{O_2} tended to fall between embolizations, and this expected finding was similar in males and females (Figure 6B).

Across all data sets, Ca_{O_2} also appeared to fall with age in females (Figure 6C), but this was almost fully attributable to the development of iron deficiency: the fall in age became barely significant once the data sets indicating iron deficiency were removed (Table E4). Using the single longest follow-up time period for each patient in whom iron deficiency was not present, the difference between males and females for the average change in Ca_{O_2} per annum was not statistically significant (Figure 6D). For some males in the series, however, there appeared to be a possible overshoot in erythrocytic compensations, (Figure 6C) and overall, Ca_{O_2} tended to increase over years of follow-up postembolization in males (Figure 6C, Table E4).

Discussion

We have demonstrated that in the chronically adapted state, hemoglobin is a vital determinant of arterial oxygen content (Ca_{O_2}). In patients with PAVMs, evaluation of arterial oxygenation in isolation can be spuriously reassuring, particularly if there is concurrent pregnancy, anemia, or iron deficiency. Impaired erythropoiesis due to iron deficiency was identified as the key determinant of Ca_{O_2}, in males and in females. In this cohort, Ca_{O_2} appeared to decrease with age only because of concurrent iron deficiency.

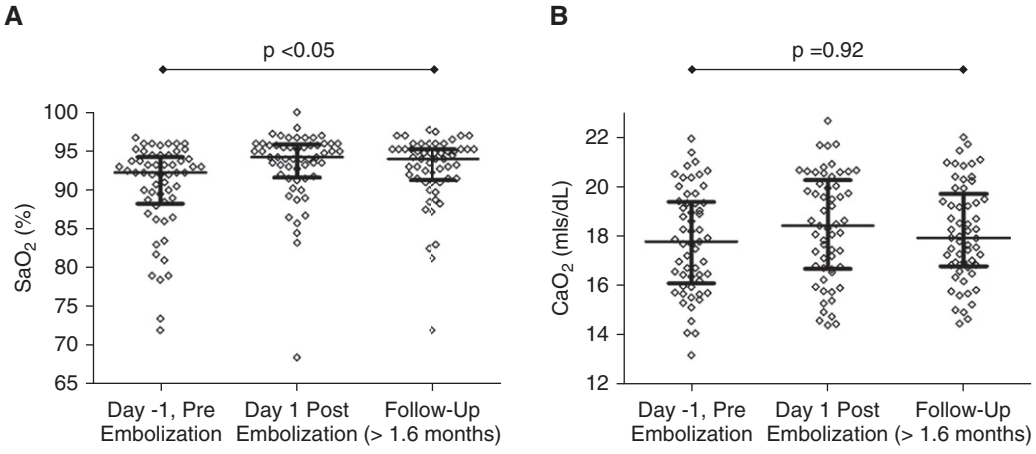

Figure 3. Periembolization changes in oxygenation indices. (*A*) Sa_{O_2} (%), immediately preembolization (Day-1), immediately postembolization ("Day 1" range, 0–3 d), and at first follow-up. Dunn's posttest correction calculated the *P* value for the difference in Sa_{O_2} between follow-up (median, 94.0%) and preembolization (median, 92.3%). (*B*) Ca_{O_2} (ml/dl) immediately preembolization (Day-1), immediately postembolization (Day 1, range, 0–3 d, using same hemoglobin), and at first follow-up 1.6–12 (median, 4.4) months later. *Error bars* indicate median and interquartile range. The 57 data sets exclude embolization when one of the time points was associated with significant iron deficiency and a hemoglobin less than or equal to 11 g/dl.

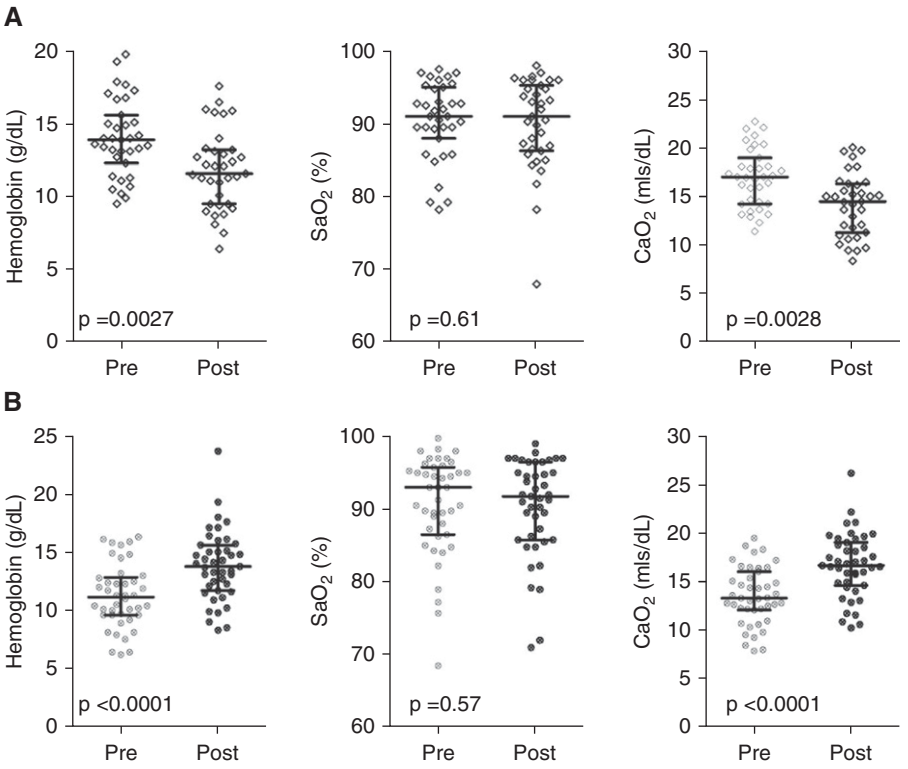

Figure 4. Dynamic changes in Ca_{O_2} due to iron deficiency and treatment. (*A*) Effects of decreased hemoglobin due to iron deficiency: 35 paired data sets. (*B*) Effects of increased hemoglobin due to iron therapy: 43 paired data sets. Median and interquartile range are illustrated, and *P* values were calculated by Wilcoxon matched-pairs signed rank tests.

Strengths of the study include the unique single-institution cohort offering insights into extreme phenotypes of hypoxemia and anemia, studied in high numbers for such a rare condition. Rigorous phenotyping over decades allowed data sets to be selected according to specific questions to address. Limitations include the absence of invasive measurements of blood gases and cardiac output. There is no reason from the genetic basis of the majority of PAVMs (usually pathogenic DNA sequence variants in *ENG*, *ACVRL1*, or *SMAD4* [50, 51]), iron handling (52), or generally circulatory principles (22), why these Ca_{O_2} findings should not apply to other patients with hypoxemia, although it is clear that replication in wider patient groups would be valuable. Usually, HHT is seen in a detrimental context (53). However, it is not known whether hypoxemic patients without underlying HHT will be able to sustain the high cardiac outputs required (2, 3, 22, 54–56), as do patients in the HHT/PAVM cohort who may benefit from broader cardiovascular protection (38).

The findings support and extend previous studies looking at single and periembolization time points (7–13, 56). These demonstrated in separate series that in the months after successful PAVM embolization, patients reset to their prior Ca_{O_2} (10, 11, 13) and to their prior oxygen pulse (oxygen used/delivered) at peak exercise (11), and lose the hematological (10) and hemodynamic (56) compensatory responses they had previously employed. Outstanding and previously unanswered questions regarding primary changes in hemoglobin concentrations, and whether these influence Sa_{O_2}, appear to have been addressed, although the mechanism for the transient rises in Sa_{O_2} during pregnancy, despite interim growth of PAVMs, is still not evident. Further study may also helpfully address the severity of iron deficiency that

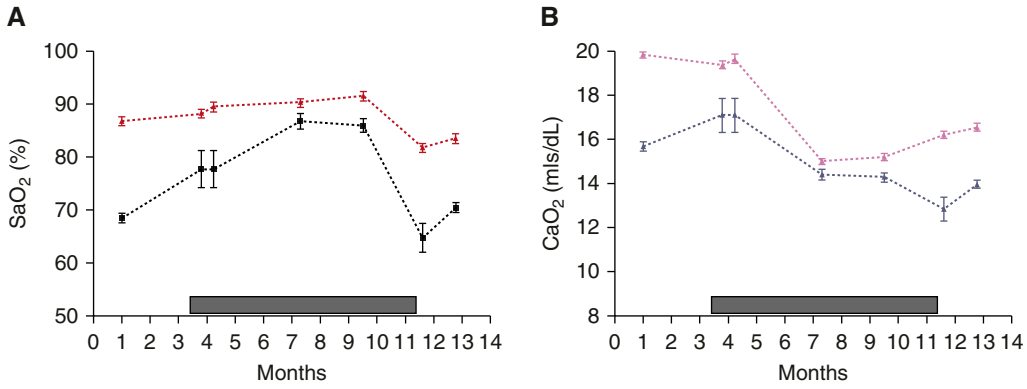

Figure 5. Changes in oxygenation indices across pregnancy. (*A*) Sa_{O_2} changes during pregnancy (*gray bar*) displaying supine (*red*) and erect (*black*) mean values, and 95% confidence intervals. Across this particular pregnancy, the right-to-left shunt increased from 31 to 40% of the cardiac output. Note the marked orthodeoxia before, and the striking increase in erect Sa_{O_2} during, pregnancy. (*B*) Ca_{O_2} changes during the same pregnancy (*gray bar*); shown are supine (*lilac*) and erect (*navy*) mean values, and 95% confidence intervals. The hemoglobin was 17.1 g/dl prepregnancy and 16.4 g/dl in early pregnancy but fell to 12.4 g/dl in later pregnancy, before increasing again postpartum. (For further examples, *see* Figure E3.)

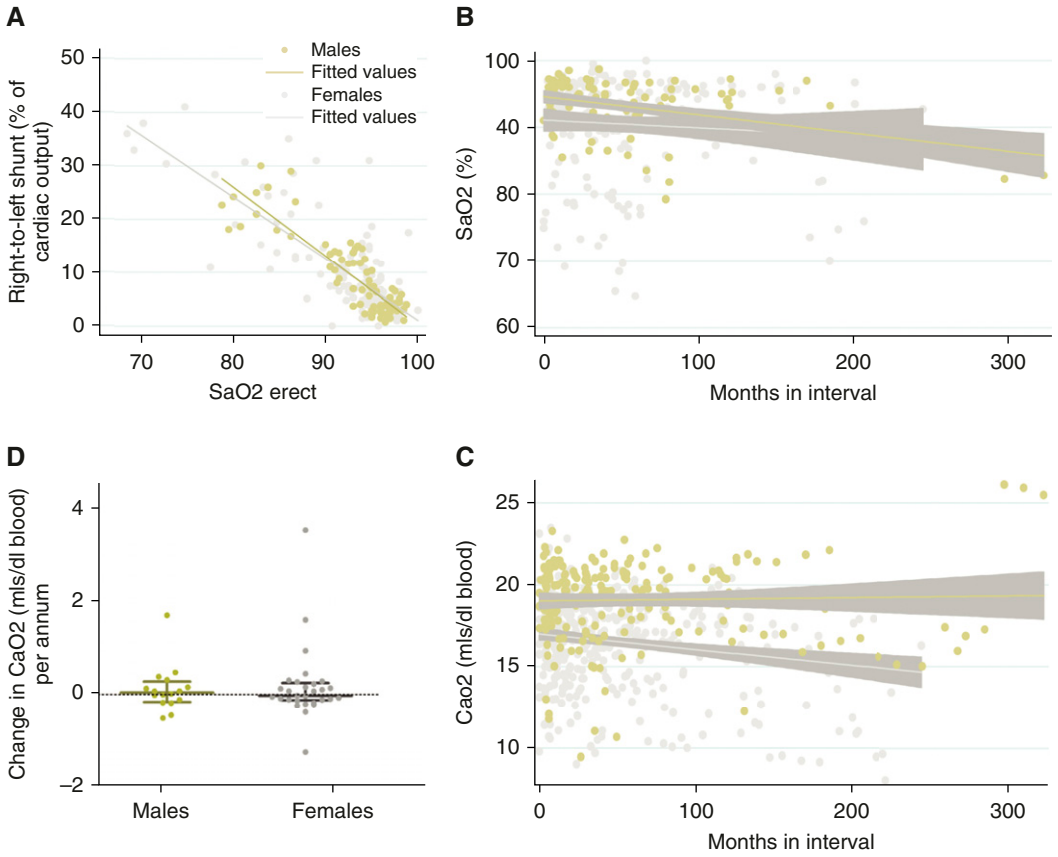

Figure 6. (*A*) Right-to-left shunt and associated Sa_{O_2} values across all group B data points, providing 151 female and 80 male data sets. Fitted values by linear regression (female coefficient, −1.15; $r^2 = 0.64$; $P < 0.0001$; male coefficient, −1.29; $r^2 = 0.76$; $P < 0.0001$); confidence intervals are not displayed for clarity. Further model details are provided in Table E3. (*B*) Sa_{O_2} (%) and (*C*) Ca_{O_2} (ml/dl) for females (*gray symbols*) and males (*khaki symbols*) in all consecutive group B data points. Data represent periods before and after that shown in Figure 2, such that the third ("follow-up") data point in Figure 2 would be represented by a $T = 0$ data point in (*B*) and (*C*). The 95% confidence intervals for linear regression are indicated: details of the regression models for (*C*) are provided in Table E4. (*D*) The mean change in Ca_{O_2} per annum, plotted for the longest time point for each individual for whom there was no influence from embolization, iron deficiency, iron treatment, or other stated confounders. The data were from the 15 males and 29 females in group B, who had at least a 1-year follow-up period that did not include embolization, iron deficiency, iron, transfusion, oxygen, or venesection treatments. Data represent the average change across 1.1–16.8 years of follow-up for males (median, 6.37 yr), and across 1.04–17.8 years of follow-up for females (median, 5.19 yr).

impacts on arterial oxygen content, and why for some individuals without pathological iron deficiency there may be a possible overshoot in erythrocytic compensations.

By focusing on Ca_{O_2}, clinicians will be able to avoid the pitfalls of using spuriously high and misleading Sa_{O_2}, particularly during pregnancy and anemic states. It is for others to determine whether this is sufficient to modify obstetric care protocols for women with severe hypoxemia in terms of oxygen supplementation. Arterial blood gas measurements of arterial Pa_{O_2} would reduce the confounding issues with anemic states, although it is not clear that their use would be justified for serial routine measurements, particular in light of patient preference to avoid such measurements. Judicious use of existing protocols for the detection and treatment of anemia and iron deficiency would seem wise, recognizing the recent data that iron supplementation is associated with rapid increases in serum iron after iron treatments (35), supranormal serum iron levels in iron recipients (20, 35, 55), and overzealous iron supplementation may increase HHT nosebleeds (35, 57), injure the endothelium (35, 59), and/or lead to greater frequency and severity of bacterial infections (20, 60).

In summary, for patients with PAVMs, and potentially all hypoxemic patients, further attention should be given to minor incremental changes in hemoglobin that substantially modify Ca_{O_2}. ■

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