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Solubility of helium, argon, and sulfur hexafluoride in human blood measured by mass spectrometry

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Hlastala MP, Meyer M, Riepl G, Scheid P. Solubility of helium, argon, and sulfur hexafluoride in human blood measured by mass spectrometry. Undersea Biomed Res 1980; 7(4):297–304.—A method has been developed to measure the solubility coefficients of gases in liquids by respiratory mass spectrometry. A sample (2.5 ml) of the test liquid, equilibrated with a test gas mixture, is injected into a sealed flask (~140 ml) for extraction by equilibration. The reequilibrated gas phase in the flask is analyzed by a mass spectrometer. Separately, an equal volume (2.5 ml) of the equilibrating test gas mixture is injected into a larger sealed flask (~11 liter) where it is mixed and then analyzed by the mass spectrometer. Solubility in the liquid is calculated from the ratio of mass spectrometer readings in both flasks and the ratio of flask volumes. The ratio of volumes of the small and the large flasks is made similar to the gas/liquid partition coefficient whereby the mass spectrometer readings in both become similar. With this approach, errors due to amplifier and mass spectrometer nonlinearity are greatly attenuated. The method was used to measure the solubility of helium, argon, and sulfur hexafluoride in distilled water, human plasma, and human blood.

solubility	mass spectrometry
blood	helium
plasma	argon
inert gases	sulfur hexafluoride

The measurement of solubility coefficients in blood of gases with low solubility has been subject to errors related to sensitivity and nonlinearity of analyzer-recorder systems. With the development of a new double-injection method (1) and the use of a highly sensitive respiratory mass spectrometer, it is now possible to overcome these limitations. A simple modification of that method allows measurement of the solubility coefficients of low-solubility gases in blood with a high degree of accuracy. A review of the literature reveals a surprising dearth of data for the blood solubility of helium (He, an important gas in diving) and argon (Ar). Most calculations of tissue and pulmonary gas exchange use the helium solubility in dog blood of Hawkins and Shilling (2) and argon solubility in water of Behnke and Yarbrough (3). Such usage is inadequate for some gases because of large differences between solubilities in water and blood, and large blood solubility differences between animal species and even among individuals. The purpose of this study was to provide a simple and accurate method for the measurement of the solubility coefficient of low solubility gases and to provide previously unavailable data for the solubility of He and Ar in human blood.

PRINCIPLE OF TECHNIQUE

Consider a liquid sample (volume, V) that is equilibrated with an inert gas at a partial pressure, P_0. The amount, M_g, of test gas in the sample is given by:

$$M_g = \alpha \cdot V \cdot P_0 \tag{1}$$

where α is the solubility coefficient of the test gas in the liquid.

The liquid sample is transferred into a gas-tight vessel (volume, V_1) containing only nitrogen with no test gas. A new equilibrium is approached for the test gas between the blood and gas phases, as described by the following mass balance relationship:

$$\alpha \cdot V \cdot P_0 = [\alpha \cdot V + \beta_g(V_1 - V)]\, P_1 \tag{2}$$

where P_1 is the new equilibrium partial pressure; β_g is the capacitance coefficient of the gas in the gas phase (for all ideal gases identical at 0.881 ml (STPD) · ml^{-1} (BTPS) · atm^{-1} at 37°C; calculated from Piiper et al. (4)).

Calculation of α from direct measurement of P_0 and P_1 would be subject to analysis error caused by the 1000- to 100,000-fold ratio of P_0 to P_1 for gases of low solubility. In the method of Meyer and Scheid (1) the injection into V_1 is repeated, replacing the liquid with an identical volume of the equilibrating test gas mixture. This provides a measurable concentration of test inert gas that is quantitatively similar to P_1 for gases of gas/liquid partition coefficient (λ) near unity (e.g., acetylene in blood).

In the present study, where gases with low solubility were evaluated, a second flask of bigger volume, V_2, was used for gas injection. Reequilibration in the larger vessel is determined by mass balance in a manner equivalent to Eq. *2*:

$$\beta_g \cdot V \cdot P_0 = \beta_g \cdot V_2 \cdot P_2 \tag{3}$$

where P_2 is the new equilibrium partial pressure. Equations *2* and *3* are combined to eliminate P_0 and solved for the solubility coefficient:

$$\alpha = \beta_g \left(1 - \frac{V}{V_1}\right) \Bigg/ \left(\frac{P_2}{P_1}\cdot\frac{V_2}{V_1} - \frac{V}{V_1}\right) \tag{4}$$

from which the gas/liquid partition coefficient, $\lambda = \alpha/\beta_g$, may be obtained.

METHODS

Heparinized blood was obtained from six healthy, nonsmoking subjects by venipuncture. A portion of the blood was centrifuged at 13,000 rpm for 10 min to obtain plasma. Aliquots of whole blood were analyzed for hematocrit by the microhematocrit technique and for hemoglobin by the ferricyanide technique. Total lipid and protein concentration in plasma were determined spectrophotometrically by the sulfophosphovanillin reaction and Biuret techniques, respectively. Aliquots (3 ml) of either whole blood, plasma, or distilled water were equilibrated for 30 min (He with Ar) or 60 min (SF_6 with Ar) in a rotating tonometer (model 273, Instrumentation Laboratory, Paderno, Dugnano, Italy) at 37°C with a humidified gas mixture that was provided by precision gas mixing pumps (301 a-F, Wösthoff, Bochum, Germany). The first set of experiments was performed using 30% Ar and 70% He and the second set with 30% Ar and 70% SF_6.

A liquid sample (V = 2.5 ml) was anaerobically collected from the tonometer with a gas-tight Hamilton syringe and injected into the small gas vessel (V_1 = 139.5 ml) through a septum after flushing with pure nitrogen. The small gas vessel was immersed in a water bath maintained at 37°C. The liquid sample was mixed well with a magnetic stirrer. For the He and Ar measurements, the samples were equilibrated for 10 min (complete equilibration after 5 min); for the SF_6 and Ar measurements, the samples were equilibrated for 50 min (complete equilibration after 30 min). The partial pressure in the gas phase of the vessel P_1 was measured with a modified Varian M3 mass spectrometer (5) sampling at a rate of 3.7 ml/min. A linear drop in partial pressure due to a drop in total vessel pressure with sampling was corrected by linear extrapolation to the beginning of the sampling period.

Then, after flushing the large gas vessel (V_2 = 11,475 ml) with nitrogen, a sample of the equilibrating gas mixture (partial pressure, P_0) was injected with the same Hamilton syringe (V = 2.5 ml) used for liquid injection. A large magnetic stirrer bar assisted gas mixing in the large vessel. Equilibrium partial pressure, P_2, was measured by mass spectrometry. The liquid solubility (α) was calculated from Eq. *4* and is reported in ml (STPD) · ml^{-1} · atm^{-1}.

RESULTS

The α values obtained with simultaneous measurement of Ar and He and of Ar and SF_6 in whole human blood and in human plasma are listed in Tables 1 and 2, respectively. The α_{Ar} values determined simultaneously with He and SF_6 are not statistically different. The mean values, obtained by averaging all measurements in all subjects, are summarized in Table 3 for solubility coefficients of SF_6, He, and Ar in plasma and blood, along with values in distilled water. The α_{Ar} values are averages from determinations with He and SF_6.

TABLE 1

SOLUBILITY OF ARGON AND HELIUM (37°C) DETERMINED WITH 70% HE, 30% AR MIXTURE

Subject	Hct	Hb, g/dl	Total Proteins, g/dl	Total Lipids, mg/dl	α_{He}		α_{Ar}	
					Plasma	Blood	Plasma	Blood
M.H.	46	15.2	6.8	838	0.00755 ±0.00014	0.00707 ±0.00009	0.02525 ±0.00074	0.02814 ±0.00080
F.S.G.	42	16.2	9.2	740	0.00737 ±0.00007	0.00700 ±0.00010	0.02400 ±0.00030	0.02606 ±0.00035
G.R.	45	16.8	8.5	701	0.00765 ±0.00003	0.00696 ±0.00012	0.02429 ±0.00022	0.02543 ±0.00040
G.M.	44	15.5	7.7	686	0.00765 ±0.00010	0.00707 ±0.00011	0.02469 ±0.00062	0.02655 ±0.00057
T.S.	45	15.2	7.9	1026	0.00749 ±0.00011	0.00695 ±0.00008	0.02473 ±0.00042	0.02656 ±0.00027
C.H.	46	16.1	8.3	758	0.00761 ±0.00017	0.00701 ±0.00009	0.02489 ±0.00061	0.02671 ±0.00043
Mean ± SEM	44.7 ± 0.6	15.8 ± 0.3	8.1 ±0.3	791.5 ± 51.7	0.00755 ±0.00004	0.00701 ±0.00002	0.02464 ±0.00018	0.02658 ±0.00037

Mean solubility coefficients (± SD) in ml (STPD) · ml^{-1} · atm^{-1}; n = 6 (5 in one case) for each set.

TABLE 2

SOLUBILITY OF ARGON AND SULFUR HEXAFLUORIDE (37°C) DETERMINED WITH 70% SF_6, 30% AR MIXTURE

Subject	Hct	Hb, g/dl	Total Proteins, g/dl	Total Lipids, mg/dl	α_{SF_6} Plasma	α_{SF_6} Blood	α_{Ar} Plasma	α_{Ar} Blood
M.H.	47	15.6	8.3	821	0.00441 ±0.00026	0.00591 ±0.00032	0.02446 ±0.00023	0.02788 ±0.00064
F.S.G.	40	13.6	8.1	644	0.00481 ±0.00055	0.00555 ±0.00033	0.02441 ±0.00043	0.02607 ±0.00039
G.R.	44	13.9	6.9	649	0.00505 ±0.00009	0.00664 ±0.00040	0.02551 ±0.00051	0.02767 ±0.00022
G.M.	47	16.4	7.3	640	0.00439 ±0.00026	0.00569 ±0.00035	0.02423 ±0.00053	0.02704 ±0.00062
T.S.	46	16.3	7.0	1240	0.00620 ±0.00046	0.00649 ±0.00030	0.02515 ±0.00040	0.02717 ±0.00037
C.H.	40	15.1	7.2	670	0.00478 ±0.00020	0.00569 ±0.00047	0.02499 ±0.00050	0.02740 ±0.00058
Mean ± SEM	44.0 ± 1.3	15.2 ± 0.5	7.5 ±0.2	777 ± 97	0.00494 ±0.00027	0.00600 ±0.00019	0.02479 ±0.00020	0.02721 ±0.00026

Mean solubility coefficients (± SD) in ml (STPD) · ml^{-1} · atm^{-1}; $n = 6$ (5 in two cases) for each set.

TABLE 3

SUMMARY OF ALL SOLUBILITY COEFFICIENTS (37°C) MEASURED IN STUDY

Gas	H_2O	n	Plasma	n	Blood	n
SF_6	0.00348 ±0.00003	30	0.00494 ±0.00027	35	0.00600 ±0.00019	36
He	0.00846 ±0.00002	32	0.00755 ±0.00004	36	0.00701 ±0.00002	36
Ar	0.02665 ±0.00012	72	0.02472 ±0.00013	71	0.02689 ±0.00023	71

Mean solubility coefficients (± SEM) in ml (STPD) · ml^{-1} · atm^{-1}.

DISCUSSION

The method applied in this study has certain advantages for the measurement of low solubilities. In principle, it can be used with any analysis and recording system. The use of a respiratory mass spectrometer allows simultaneous, rapid measurement of several inert gases. For these low solubilities the accuracy is usually limited by the sensitivity of the mass spec-

trometer because of small gas concentrations present. With the mass spectrometer used in this project the signal-to-noise ratios were 10:1 at 50 ppm for SF_6 and >100:1 at 160 ppm for He and Ar. The low signal-to-noise ratio for SF_6 was due to the limited mass range of the device, which made it necessary to measure a breakdown product of SF_6 at mass 54 with a signal of only 2.1% that of the highest peak (mass 127). This limit would vary for different mass spectrometer systems. With our system it was impossible to measure He and SF_6 at the same time in these low concentrations, so He and Ar were measured together, and then the mass spectrometer was retuned for measuring Ar and SF_6 together.

The key advantage of the method is that volumes of the two gas equilibrium vessels, for the liquid and the gas samples, can be adjusted to give similar concentrations in the gas phase after equilibration, thus avoiding problems with inherent alinearities in analyzer-recorder systems. If the injectate volume V is small compared with both V_1 and V_2, the partial pressures in both flasks, P_1 and P_2, become equal if the gas/liquid partition coefficient, $\lambda(=\alpha/\beta_g)$, equals the volume ratio V_1/V_2. In the present system, the vessel volume ratio was 0.0122, which constitutes a compromise between the partition coefficients of Ar, He, and SF_6. If, on the other hand, λ was determined from P_1 and equilibrating gas partial pressure, P_0, the system using the mass spectrometer and recorder would have to be linear over several decades.

It has been shown that inert gas solubility in blood is dependent on such factors as protein and lipid concentrations and hematocrit; such trends can be seen from Tables 1 and 2 in this study. The blood solubility is higher for SF_6 ($P<0.001$, paired t test) and Ar ($P<0.001$) and lower for He ($P<0.001$) than in plasma, thus indicating a hematocrit dependence for these gases. There is a significant positive correlation of α_{SF_6} (plasma) with plasma lipid concentration ($P<0.05$) and a significant negative correlation of α_{Ar} (plasma) with plasma protein concentration ($P<0.05$). Other relationships exist but are not significant at the $P = 0.05$ level. Because this study was designed to validate the methodology and to provide normal human blood solubility data, large variations of hematocrit and of lipid and protein concentration were not considered. Therefore precise determination of the variations of solubility with blood constituents is not warranted from the present data. It is apparent, however, that the data obtained in this study should not be applied in situations with abnormal blood lipid and protein.

The data obtained in this study fall within a range of values reported in the literature (Table 4). This range is large in some cases (α_{SF_6} in blood) and quite small in some cases (α_{He} in water). Clearly, one of the reasons for variability in blood solubility is interspecies variation due to differences in the blood constituents. Another reason is differences in technique and methodological errors, some of which were mentioned earlier in this paper. In the case of Ar there is no significant difference between α_{Ar} in water and in human blood. Therefore substitution of α_{Ar} (water) for α_{Ar} (blood) in calculations of Ar washout from tissues or from the lung would cause no error. On the other hand α_{He} (human blood) is only 83% of α_{He} (water) and 82% of α_{He} (dog blood) (2) and therefore use of any other data in calculations of human helium washout behavior is unwarranted. The most important factor to consider is any deviation of blood lipid or protein from normal, in which case solubility of the gas in question should be measured directly by using a method such as the one described in this study.

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TABLE 4
COMPARISON WITH LITERATURE DATA FOR SOLUBILITY AT 37°C

Gas	Liquid	References	α ml (STPD) · ml^{-1} · atm^{-1}	
SF_6	Water**	Ashton et al. (6)	0.00426*	
		Power and Stegall (7)	0.00386	
		Meyer (8)	0.00362*	
		This study	0.00348	
	Dog Plasma	Young and Wagner (9)	0.00323†	
		Meyer et al. (10)	0.0039*	
	Human Plasma	Longo et al. (11)	0.00647	
		Young and Wagner (9)	0.00440†	
		This study	0.00494	
	Rat Blood	Levitt and Levitt (12)	0.0056	
		Truog et al. (13)	0.00830†	
	Rabbit Blood	Ohta et al. (14)	0.00718	
	Dog Blood	Wagner et al. (15)	0.00785†	
		Young and Wagner (16)	0.00809†	
		Meyer et al. (10)	0.0059	
	Human Blood	Longo et al. (11)	0.00671	
		Wagner et al. (15)	0.00529†	
		Edwards et al. (17)	0.0066	
		Dueck et al. (18)	0.00408†	
		This study	0.00600	
He	Water**	Lannung (19)	0.0084	
		Hawkins and Shilling (2)	0.0085	(38°C)
		Behnke and Yarbrough (3)	0.00821	(38°C)
		Lawrence et al. (20)	0.0085	
		This study	0.00846	
	Human Plasma	This study	0.00755	
	Rat Blood	Levitt and Levitt (12)	0.0094	
	Dog Blood	Hawkins and Shilling (2)	0.00877*	(38°C)
	Ox Blood	Hawkins and Shilling (2)	0.00877*	(38°C)
	Human Blood	Edwards et al. (17)	0.0075	
		This study	0.00701	
Ar	Water**	Lannung (19)	0.0264	
		Behnke and Yarbrough (3)	0.02593	(38°C)
		Lawrence et al. (20)	0.026	
		Ashton et al. (6)	0.02677*	
		Meyer (8)	0.02595*	
		This study	0.02665	
	Dog Plasma	Meyer et al. (10)	0.0211*	
	Human Plasma	This study	0.02472	
	Rabbit Blood	Ohta et al. (14)	0.0269	
	Dog Blood	Meyer et al. (10)	0.0224*	
		Meyer (8)	0.0226	
	Human Blood	Edwards et al. (17)	0.0264	
		This study	0.02689	

*Recalculated from the form of presentation in the original paper. **For a summary review of published values for SF_6, He, and Ar solubility in water, see Wilhelm et al. (21). †Gas volumes converted from ml BTPS in the original paper to ml STPD using the factor (volume STPD/volume BTPS) of 0.826 for 37°C.

Hlastala MP, Meyer M, Riepl G, Scheid P. La solubilité de l'hélium, l'argon, et du soufre-héxafluroide chez le sang humain mésurée par la spectrométrie de masse. Undersea Biomed Res 1980: 7(4):297–304.— Une méthode a été developée pour mésurer les coefficients de solubilité des gaz dans les liquides par la spectrométrie de masse respiratoire. Un échantillon (2.5 ml) de la liquide de l'examen, équilibrée avec une mélange de gaz expérimental, est injectée dans un flacon obturé (~140 ml) pour l'extraction par équilibration. La phase rééquilibrée de gaz dans le flacon est analysée par le spectromètre de masse. Séparément, un volume égal (2.5 ml) de la mélange de gaz expérimental équilibrant est injecté dans un flacon obturé plus grand (~11 litre) où il est melangé et puis analysé par le spectromètre de masse. La solubilité dans la liquide est calculée du rapport des cotes du spectromètre de masse dans tous les deux flacons et les rapports des volumes des flacons. Le rapport des volumes du flacon petit et du flacon grand a été fait semblable au coefficient gaz/liquide partition par lequel tous les deux cotes du spectromètre de masse deviennent semblables. Avec cette approche, les erreurs occasionnés par non-linéarité d'amplificateur et de spectromètre de masse sont fortement attenués. Cette méthode-ci a été utilisée pour mésurer la solubilité de l'hélium, de l'argon et du soufre-héxafluoride dans l'eau distilée, le plasma humain, et le sang humain.

solubilité
sang
plasma
gaz nobles
spectromètre de masse
hélium
argon
soufre-héxafluoride

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