Bubble growth and mechanical properties of tissue in decompression

R. D. VANN and H. G. CLARK

Department of Biomedical Engineering and F. G. Hall Environmental Research Laboratory, Duke University, Durham, North Carolina 27706

Vann, R. D., and H. G. Clark. 1975. Bubble growth and mechanical properties of tissue in decompression. Undersea Biomed. Res. 2(3):185-194. – A survey of decompression literature leads to the conclusion that when tissue is subjected to gaseous supersaturation, pre-existing gas micronuclei grow into the gas bubbles which are routinely observed in decompression studies. These micronuclei may originate from mechanically induced *tribonucleation* or cavitation within joints. A new tissue model for decompression sickness based upon failure theory in rubber is proposed. The model shows theoretically that pre-existing sea-level nuclei can be stabilized at depth by elastic forces in tissue. These same elastic forces restrain the growth of nuclei when supersaturation occurs. Mechanical stress will lower the gaseous supersaturation required for growth of nuclei. Gaseous supersaturation, mechanical stress, and the elastic properties of various tissues interact to produce unbounded bubble growth leading to tissue lesions when combined gaseous and mechanical supersaturation exceeds a threshold value. The recommendation is made that the high levels of supersaturation generally used for the decompression of men be reduced.

supersaturation	tribonucleation	bubble growth
gas micronuclei	mechanical stress	shear modulus
gas bubbles	decompression	failure theory

The presence of the gas phase within the body has long been implicated as the primary cause of physical symptoms of decompression sickness such as *chokes, bends,* and various CNS manifestations (Behnke 1951). Recent evidence (Philp, Inwood, and Warren 1972) indicates that the blood gas interface also contributes to the formation of microthrombi, blood sludging, and lipid emboli. It would thus appear desirable to avoid the formation of any gas at all, including the *silent* intravascular bubbles which can be detected with ultrasound equipment (Spencer and Clark 1972) but which do not give rise to pain.

The conditions under which gas leaves solution and forms bubbles are not well understood. Studies by Gent and coworkers (Gent and Lindley 1958; Denecour and Gent 1968; Gent and Tompkins 1969a, 1969b; Gent and Mainecke 1970; Gent 1970) on the mechanics of bubble growth in rubber have suggested a new approach to the problem. In the course of the following discussion, relevant decompression literature will be reviewed[1] and a new theoretical model for tissue in decompression based upon Gent's work will be considered.

[1] The work of Buckles (1968), Strauss (1974), and Strauss and Kunkle (1974) will not be covered here. The authors believe that these aspects of bubble growth would be more properly dealt with in a discussion of inert gas exchange.

NUCLEATION DE NOVO

Ordinary water in a glass contains a great many small gas micronuclei which adhere to cracks in the vessel walls and to solid particles floating in the bulk of the liquid. Free micronuclei having radii (r) less than a critical value cannot exist in bulk liquid. Increased internal pressure due to surface tension (γ), given by Laplace's Law, $2\gamma/r$, causes them to dissolve. At radii above the critical radius, the pressure due to surface tension is negligible and the nuclei are stable. Micronuclei having dimensions of less than this critical radius may be stabilized in cracks and crevices by surface tension due to changes in curvature of the gas-liquid interface (Harvey, Barnes, McElroy, Whitely, Pease, and Cooper 1944).

A liquid which contains micronuclei cannot sustain supersaturation without bubble growth occurring. However, if the liquid is subjected to hydrostatic pressure of about 100 atm (Harvey, Barnes et al. 1944), the micronuclei are driven into solution and subsequent levels of supersaturation must be very great before new gas bubbles will form.

What is the mechanism by which stable gas nuclei are formed in a liquid which is initially free of nuclei? Apfel (1972) describes W. Doring's theory of homogeneous nucleation. The random thermal motions of the liquid molecules generate submicroscopic cavities which collapse almost instantly under normal conditions due to attractive intermolecular forces. If, however, the liquid is placed in a hydraulic cylinder and subjected to negative pressure (i.e. tensile stress), a pressure of between -100 and -1000 ATA (Harvey, Barnes et al. 1944) will counteract the intermolecular forces and cause the thermally generated cavaties to expand to a stable size.

Negative pressure of great magnitude can also be generated by dissolving gas in a liquid, subjecting the liquid to very high hydrostatic pressure to dissolve nuclei, and then reducing the pressure. Negative pressure of this nature is commonly known as supersaturation. Kenrick, Wismer, and Watt (1924) were able to saturate a water solution with nitrogen to over 100 atm without forming bubbles.

If mechanically generated negative pressures are called *mechanical supersaturation* (ΔP_m) and dissolved gas negative pressures are called *gaseous supersaturation* (ΔP_g) the total supersaturation (ΔP) of a system will be

$$\Delta P = \Delta P_m + \Delta P_g. \tag{1}$$

The greatest gaseous supersaturation that can be achieved safely in diving can be calculated to be about 4.8 atm on a no-decompression dive to 200 fsw. If the body behaved like denucleated water and required a ΔP for de novo nucleation of 100 to 1000 atm, then a ΔP_g of 4.8 atm would be insufficient to cause bubbles to form. Although ΔP_g is certainly augmented by ΔP_m resulting from muscular tension or as a consequence of Bernoulli's law in the circulatory system, some investigators (Harvey, McElroy, Whiteley, Warren, and Pease 1944; Albano 1970) have concluded that these mechanisms are insufficient to produce a ΔP of 100 to 1000 atm.

Hills (1967) has suggested that only very low levels of ΔP may be necessary to cause nucleation at interfaces between lipid and aqueous media, but experiments by Evans and Walder (1969) and Apfel (1972) have shown that such interfaces are of little consequence.

Upon consideration of the high levels of supersaturation necessary to achieve de novo nucleation and the low levels which are apparently generated in diving, it seems likely that the undissolved gas present during decompression originates from pre-existing micronuclei.

EVIDENCE FOR PRE-EXISTING NUCLEI

Several experiments have been performed which give indirect evidence of the presence of nuclei. Albano (1970) reports that in 1942 Aggazzotti and Ligabue measured volume changes of compressed dog tissue and found much larger decreases than would be expected if the tissue were free of the gas phase. Using their data and assuming tissue has the same compressibility as water, Albano calculated that gas fractions are present in dog tissue as listed in Table I.

TABLE I

Gas phase in tissue

Tissue	Gas Fraction* 10^5 x ml gas/ml	N 10^{-7} x nuclei/ml	V 10^7 x ml/nucleus	d Inter-nuclear distance
Myocardium	6.7	0.55	1.82	70
Liver	16.6	1.38	0.73	52
Gastrocnemius muscle	39.7	3.31	0.30	38
Brain	49.4	4.12	0.243	36

*from Albano (1970)

Dean (1944) calculated that a stable gas nucleus in water at 20°C has a radius of 1.42μ. Although in tissue the stable radius would be smaller, we can use 1.42μ to estimate the distance between nuclei (d), the tissue volume per nucleus (V), and the number of nuclei per ml of tissue (n). If the distance between capillaries is taken to be 40-100μ and the capillary length to be 200μ, Albano's figures give 0.5 to 65 nuclei in a tissue annulus served by one capillary.

Evans and Walder (1969) have also conducted an experiment which suggests the existence of nuclei within living tissue. They subjected groups of 50 transparent shrimp to decompressions from 1 ATA to 0.079 ATA. One group had been previously treated at a positive pressure of 389 ATA for 2 min to reduce the number of nuclei, if any were present. A second group was not pressure treated. Upon decompression of the pressure-treated group, bubbles were observed to form in four shrimp. In the nontreated group, bubbles were observed in 48 out of 50. A third group was pressure treated and then subjected to electrical stimulation before decompression to produce muscular activity. Of 50 shrimp, 16 developed bubbles.

The implications of these experiments are clear. There are micronuclei present within shrimp under normal conditions. These nuclei are to a large extent dissolved and reduced in size when shrimp are pressurized. Muscular activity promotes the formation of new nuclei.

THE ORIGIN OF NUCLEI

While the above experiments do suggest that small gas nuclei are present within biological organisms, they by no means constitute conclusive proof. A particularly interesting and yet

unanswered question concerns the origin of the nuclei–if, in fact, they do exist. For de novo nucleation to occur in the absence of large overall supersaturations, there must be an amplification of local mechanical stresses.

Ikels (1970) investigated a mechanical nucleation mechanism proposed by Hayward (1967) and called *tribonucleation.* According to this theory, large local mechanical supersaturations (ΔP_m) are generated when two closely opposed surfaces are separated in a liquid. Hayward's theory shows that the magnitude of the supersaturation is directly proportional to the product of the liquid viscosity and the velocity of separation of the surfaces.

Ikels (1970) rolled a steel ball down the side of an inclined, liquid-filled test tube. Olive oil and various glycerol-water mixtures were used to vary the liquid viscosity. In separate experiments, nitrogen, argon, and helium were dissolved in the liquid at ambient pressure and the test tube with the ball in place was centrifuged to remove nuclei. The apparatus was then decompressed and the ΔP_g at which the bubbles first formed was noted. Depending on the velocity-viscosity product and the type of dissolved gas, Ikels found that supersaturations of from 0.1 to 0.9 atm were required to form bubbles de novo on the path down which the ball rolled.

Ikels speculates that tribonucleation may occur within the body in the joints, in blood vessels which collapse and separate, or at sites where tendons and muscles slide across bone. However, the model is not sufficiently developed to predict whether tribonucleation can cause bubbles to develop in the body at sea-level pressure.

A phenomenon which may be either tribonucleation or growth of pre-existing nuclei was described by Bradley and Vorosmarti (1974). It is particularly attractive because it involves those sites most often afflicted with decompression pain, the joints. Knuckles and other joints are often observed to pop or crack at sea level. This condition is accentuated at elevated hydrostatic pressures. The cause of joint sounds has been shown by Unsworth, Dowson, and Wright (1971) to be the formation and collapse of cavitation bubbles within joint capsules. If these bubbles are not rapidly reabsorbed (*see next section*) or if they should become stabilized in irregularities at fluid-tissue interfaces, they most certainly will grow in size when the surrounding medium is supersaturated during decompression. Furthermore, since the forces responsible for cavitation are transmitted to the articular cartilage, it is possible that cavitation might occur within the cartilage itself. The resulting nuclei could be stabilized for long periods of time, as will subsequently be shown.

NEGATIVE SUPERSATURATION AND THE INSTABILITY OF GAS NUCLEI IN BODY LIQUIDS

Harvey, Barnes et al. (1944) define gaseous supersaturation as

$$\Delta P_g = \Sigma P_i - P \tag{2}$$

where P is the hydrostatic pressure and the P_i are the tensions of the dissolved gases. In the body, gaseous supersaturation depends upon the local tensions of nitrogen, oxygen, carbon dioxide, and water vapor. These tensions are determined by the composition of the breathing mixture and metabolic rate. Hills (1966) was the first to derive an expression for ΔP_g and

to measure it experimentally. A less elegant but simpler estimation of the magnitude of ΔP_g will be made below for venous blood.[2]

Large changes in inspired oxygen partial pressure produce much smaller changes in venous gas tensions. Here venous CO_2 tension (P_{vCO_2}) and O_2 tension (P_vO_2) will be assumed constant at 45 mm Hg. Considering, for the moment, only those conditions in which the body is saturated with respect to inert gas, the venous nitrogen tension (P_{vN_2}) is given by

$$P_{vN_2} = F_{IN_2}(P - P_{H_2O}) \tag{3}$$

where F_{IN_2} is the inspired nitrogen fraction and P_{H_2O} is the vapor pressure of water. Converting from mm Hg to atm and substituting into Harvey's definition of ΔP_g, one can determine that

$$\Delta P_g = (F_{IN_2} - 1)\ P - 0.0618 F_{IN_2} + 0.1816.$$

While breathing air at any pressure (P), $F_{IN_2} = 0.79$. Thus,

$$\Delta P_g = -0.21\ P + 0.1328.$$

While breathing nitrogen-oxygen mixes at sea level, P = 1 ATA and $F_{IN_2} = 1 - F_{IO_2}$. Thus,

$$\Delta P_g = -0.9382 F_{IO_2} + 0.1198.$$

Inspection of these equations in the ranges of F_{IN_2} (or F_{IHe}, etc.) and P that are encountered during diving indicates that there is a negative gaseous supersaturation in venous blood at all times. This negative supersaturation increases linearly with both P and F_{IO_2}. A negative ΔP_g will also exist in other parts of the body, but its magnitude will be somewhat different as the oxygen and carbon dioxide tensions will vary. Tissues which are not saturated with inert gas will have larger negative supersaturations than predicted by the above equations. Negative supersaturation is the driving force which causes dissolved inert gas to pass from the tissues into the blood and which forces undissolved bubbles into solution during decompression (Hills 1969).

Harvey, Whiteley, McElroy, Pease, and Barnes (1944) were generally unable to find bubbles in blood withdrawn from animals and decompressed in clean, nuclei-free glassware. As a result, they concluded that "gas nuclei are not free in blood and are not associated with any solid constituents of the blood." Since blood experiences negative supersaturation when it passes through the venous system, any nuclei which have not been removed by the lungs would presumably dissolve. This should be true for other body fluids also. Thus, the bubbles which Harvey, McElroy et al. (1944) were routinely able to observe in vivo in the vena cava of decompressed cats probably originated in tissue rather than in blood.

Philp et al. (1972) have observed increases in the number of circulating endothelial cells in the blood of decompressed rats. This is consistent with the occurrence of mechanical damage to the vasculature caused by gas bubbles entering the blood from the tissues.

[2] Negative supersaturation in blood is equivalent to the concept of *partial pressure vacancy* developed in the 1930's at the U.S. Navy Experimental Diving Unit, Washington, D.C. A lucid account of the concept, its development, and its application is given by Dr. A. R. Behnke in *The isobaric (oxygen window) principle of decompression.* (Transactions of the 3rd Ann. Conf. of the Marine Technology Society, 1967, San Diego. Published by MTS, Washington, D.C.)

STABILITY OF NUCLEI IN TISSUE

The investigations of Gent and his coworkers into the failure of soft elastic rubber (Gent and Lindley 1958; Denecour and Gent 1968; Gent and Tompkins 1969a, 1969b; Gent 1970; Gent and Mainecke 1970) may explain why nuclei which will dissolve in body liquid can be stable in tissue. They subjected transparent blocks of lightly vulcanized rubber to mechanical and gaseous supersaturations and observed that bubbles formed within the material at predictable mechanical stress levels and gas loadings. In his analysis, Gent assumed that there were pre-existing nuclei within the rubber and that these nuclei had radii of 10^{-5} cm or greater. His justification for this assumption was that his experimental observations could be predicted theoretically and were not consistent with the existence of smaller nuclei or de novo nucleation.

As an analytical model, Gent took a small cavity within an infinite elastic medium. The medium was assumed to be isotropic and to have the same surface properties as liquid. With these considerations, he gave an expression for the inflation pressure (P_{Inf}) in the cavity as a function of the cavity radius (Gent and Tompkins 1969a). Thus,

$$P_{Inf} = G\left[2.5 - 2\,(r/r_0)^{-1} - 0.5\,(r/r_0)^{-4}\right] + 2\gamma/r \qquad (4)$$

where r_0 is the cavity radius at the time of formation, r is any subsequent radius, and G is the shear modulus of the material. When r_0 is taken as 10^{-5} cm or greater, the surface pressure term ($2\gamma/r$) becomes negligible, and the inflation pressure is identical to the total supersaturation (ΔP) defined earlier. Figure 1 is a graph of

$$\Delta P/G = 2.5 - 2(r/r_0)^{-1} - 0.5\,(r/r_0)^{-4}.$$

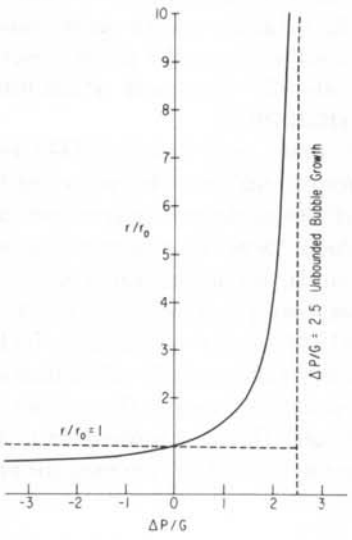

Fig. 1. The relationship between the total supersaturation, ΔP, and the radius, r, of a cavity in an elastic isotropic medium having a shear modulus, G. The cavity radius at the time of formation is r_0. Adapted from Denecour and Gent (1968).

When $r/r_0 = 1$, the inflation pressure is 0. At $r/r_0 < 1$, large decreases in P are required to produce small changes in the cavity radius. At $r/r_0 > 2$, small increases in P cause large increases of the radius. As P approaches 2.5 G, the radius becomes unbounded and the cavity expands infinitely, forming visible flaws in the rubber. The time course of the change in cavity radius is controlled by the rate of change of the hydrostatic pressure and the rate of gas diffusion into or out of the cavity. For materials having anisotropic properties and nonlinear stress-strain relationships, as is the case for many tissues, Gent's analysis does not apply in so simple a form but the general conclusions are the same.

There is a phenomenon similar to unbounded bubble growth in rubber which is more readily appreciated. When a toy balloon is inflated, the greatest pressure must be exerted while the balloon is still quite small. This is a critical pressure which, if maintained, would eventually lead to rupture of the balloon. A cavity in an extended elastic medium may be regarded as a balloon with an infinitely thick wall. The functional relationships between radius and inflation pressure for thin-walled and infinitely thick-walled balloons depend only upon the elastic properties of the material and contain no fitting constants. Denecour and Gent (1968) have experimentally verified these relationships. They are derived as special cases of the treatment of the symmetrical expansion of a thick spherical shell which can be found on page 103 in the treatise *Theoretical Elasticity* by Green and Zerna (1968). These authors apply the theory of finite deformation to a material which is homogeneous, elastically isotropic, and incompressible. They relate the deformation of the shell to the stored energy of strain. Gent and Lindley (1958) tried several forms of the stored energy function which are applicable to rubberlike materials and found that they gave substantially the same results. In the derivation of the bubble growth equation, they selected the simplest form which is derived from the kinetic theory of elasticity for a so-called *neo-Hookean* material.

Figure 1 shows that a nucleus in tissue which is negatively supersaturated can be stable. At the time of formation, $(r/r_0 = 1)$, the pressure within the bubble is equal to the hydrostatic pressure ($\Delta P = 0$). Since tissue is negatively supersaturated, the sum of the dissolved gases is less than ΔP, ($\Sigma P_i < P_{Inf}$). Gas diffuses out of the nucleus, decreasing its radius ($r/r_0 < 1$) until the internal pressure equals the dissolved gas pressure ($\Delta P = \Delta P_g < 0$). Thus the nucleus is stabilized when the collapsing force of negative supersaturation is balanced by the elastic resistance of the tissue.

DECOMPRESSION SICKNESS AND FAILURE THEORY: A THEORETICAL TISSUE MODEL

Consider a stable nucleus at sea level in an isotropic tissue having a shear modulus (G). If the tissue is subjected to increased hydrostatic pressure during a dive, the nucleus radius decreases, but is larger than predicted by Boyle's law because of the resistance of tissue to deformation. During the bottom time of the dive, gas is transported through the blood into the tissue and the nucleus tends toward a volume defined by the local negative supersaturation at depth and Gent's relationship (Fig. 1). During decompression, if any supersaturation (ΔP) is incurred, the cavity expands to a radius predicted from Fig. 1 when the pressure is given by

$$\Delta P = \Delta P_g + \Delta P_m < 0.$$

(Equation 1) and the shear modulus of the tissue is used. The size towards which the cavity

expands depends upon the sum of the gaseous and mechanical supersaturations. If this sum should approach 2.5 G, the radius becomes unbounded and the tissue will tear, relieving the internal pressure. If a capillary is ruptured during this process, gas will enter the blood. The Young's modulus (E) in muscle tissue has a range of about 3 to 412 psi (p. 95, Yamada 1970). For isotropic materials $G \simeq E/3$; thus G may be estimated to be from 1 to 134 psi.

In modern applications of the Haldane technique for computing decompression tables (Hamilton, Kenyon, Freitag, and Schreiner 1973), positive gaseous supersaturations (ΔP_g) are reported to range from 0.5 atm in the 240-min half-time tissue at a depth of 10 fsw, to 4.8 atm in the 5-min tissue at 100 fsw. Recalling Gent's relationship for unbounded growth, $\Delta P = 2.5$ G, and taking G to be 1 psi, it can be found that a supersaturation as low as 0.2 atm can produce unbounded bubble growth. Alternatively, if $\Delta P = 4.8$ atm, unbounded bubble growth occurs in tissues having shear moduli less than 28 psi.

Although many Haldane-type tables are satisfactory when judged on the presence or absence of pain (e.g. the U.S. Navy Tables), intravascular gas has often been detected during or after the decompression period of dives in which no pain occurred (Spencer and Clark 1972). This asymptomatic intravascular gas may originate from unbounded bubbles which form in tissues having low shear moduli (e.g. muscle).

Nims (1951) suggests that pain occurs because trapped gas deforms tissue, distorting pain-producing nerve endings. The pain of decompression sickness occurs most often in the joints which are well endowed with cartilage. Since cartilage has a shear modulus of about 1000 psi (calculated from data on p. 80, Yamada 1970), unbounded bubbles would not be expected to form, and the gas would remain constrained. Deformation might progress until the threshold of pain was reached. Nims quotes Inman and Saunders, who found a pressure of 35 cm H_2O was required to produce pain when fluid was injected into "tight" tissues. This would indicate that very little volume change can be tolerated before pain occurs.

Unbounded bubble growth in the model is a function of mechanical failure of the tissue surrounding the nucleus. Tissue cannot discriminate between force produced by gas within the nucleus and forces with the same vector quantities arising from mechanical stress. Gent and Lindley (1958) have demonstrated that dilatant pressure produced by tensile forces on short wide cylinders of rubber cause mechanical failure through bubble growth when the threshold of 2.5 G is exceeded, even though gas pressures are 1 atm. It thus seems reasonable that gaseous pressure and mechanical stress are additive in producing failure and, whenever $\Delta P_g + \Delta P_m = 2.5$ G, tissue lesions will be produced.

Calculation of ΔP_m is beyond the scope of this paper, although values are known for simple geometries in isotropic materials.

The proposed theoretical tissue model provides insight into the nature of the interaction of exercise, supersaturation, and tissue properties in producing decompression sickness and suggests experiments for quantifying the relationship. Furthermore, the model suggests that the high levels of supersaturation generally employed in the calculation of decompression tables may cause inert gas to be trapped within nuclei and bubbles to be released into the blood as a result of unbounded expansion. If this is so, it would appear advisable to decompress men in a manner which subjects them to less supersaturation.

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Vann, R. D., and H. G. Clark. 1975. La croissance de bulles et les propriétés mécaniques des tissus lors des recherches sur la décompression. Undersea Biomed. Res. 2(3):185-194.–L'étude de la littérature sur la décompression nous amène à conclure que quand un tissu subit une sursaturation gazeuse, des micronoyaux gazeux pré-existants deviennent les bulles de gaz observées si fréquemment lors des recherches sur la décompression. Ces micronoyaux peuvent naître d'une *tribonucléation* ou cavitation d'origine mécanique à l'intérieure des articulations. Un nouveau modèle du tissu dans la maladie de décompression, basé sur la théorie des défaillances dans le caoutchouc, est donc propose. Le modèle démontre d'une façon théorique que les noyaux existants au niveau de la mer peuvent être stabilisés aux profondeurs par des forces élastiques dans le tissu. Ces mêmes forces élastiques inhibent la croissance des noyaux quand survient la sursaturation. Le stress mécanique reduira la sursaturation gazeuse necessaire pour la croissance des noyaux. La sursaturation gazeuse, le stress mécanique, et les propriétés élastiques des tissus divers réagissent réciproquement l'un sur l'autre pour produire une croissance des bulles de laquelle peut resulter des lesions tissulaires quand les sursaturations gazeuse et mécanique excèdent une valeur liminaire. La réduction des valeurs très élevées de sursaturation utilisées pour la décompression humaine est donc à recommander.

sursaturation	tribonucléation	croissance de bulles
micronoyaux gazeux	stress mécanique	module d'effort de cisaillement
bulles de gaz	décompression	théorie de défaillances

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