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DIFFERENCES IN TRANSIENT AND STEADY STATE ISOBARIC COUNTERDIFFUSION

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Final Report: ONR
Contract N00014-78-C-0749

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I. Abstract

In order to develop an experimentally supportable and predictive theory of gas elimination and bubble formation which is needed both for avoiding and treating decompression sickness (1,3,4,27,28,63), we need further understanding of both the physical and physiological factors involved in bubble formation and growth. Recent studies in this laboratory (12-14) have demonstrated not only the interpretive difficulty associated with decompression experiments - whether or not they use doppler bubble detection - but also the advantages associated with isobaric experiments involving either transient or steady-state counter-diffusion (15-20). In order to exploit this experimental advantage to the fullest we needed to first investigate and determine the potential advantages and/or hazards associated with sequential breathing of inert gas/oxygen mixtures using helium and nitrogen as the inert gases. Because of the previous discovery of steady state isobaric counterdiffusion by Lambertsen's group in Philadelphia (31,47-50,61,61), it was deemed most important first to clarify the differences between steady state isobaric counterdiffusion (SSIC) and transient isobaric counterdiffusion (TIC) (2,17,34,68,69) in terms of the amount of gas bubbles they would produce. This was best accomplished by temporal measurements of the production of bubbles following an isobaric gas switch using the ultrasonic doppler bubble detectors in the form of perivascular cuffs at the central venous location and the Applied Physics Laboratory (University of Washington) bubble counter, developed in that laboratory under subcontract from a previous Navy contract (N00014-69-C-0402) with VMRC.

To properly distinguish between the effects of steady state isobaric counterdiffusion (SSIC) and transient isobaric counterdiffusion (TIC) it was first necessary to determine the minimum depth where TIC would produce bubbles. It has been found that for awake goats equipped with central venous dopplers, saturation on nitrogen (.3 bar of O_2) at 100-132 f.s.w. appears to be the threshold at which significant numbers of bubbles are produced by an abrupt gas switch to He (See Table 1). In view of the known variability, however, it was decided to carry on most of the studies at 165-198 f.s.w.

Testing of the differences between SSIC and TIC required setting up an independent mask breathing system for the animal, so that a choice between chamber gas and an external gas could be made remotely. Although two gas switches applied through tracheostomy had been performed (20), it was desired to avoid this type of invasive procedure. A mask system was therefore developed by Roland White and Dick Dunford of the Department (Fig. 12) to apply the breathing gas to the animal remotely from the exterior of the chamber.

In order to be sure that breathing by a mask itself was not attended by any differences in bubble counts or formation, a number of TIC experiments were performed using the breathing system rather than a chamber flush. This procedure revealed no statistically significant differences in the numbers of bubbles produced between either changing the entire chamber gas or just changing the breathing gas. In both cases the bubble counts were transient and appeared to go through a maximum and then decrease slowly.

The final phase of the project studied the effects of SSIC applied by saturating the animal on gas 1 (breathing it through the mask) and 17 hours later adding the second gas, helium, to the chamber by a layering technique. These experiments produced bubble counts which were too high to be

accurately counted because of signal processing limitations of the equipment, and demonstrated the extreme differences in TIC vs. SSIC. This confirmed earlier work of Lambertsen et al. (42,47) in Philadelphia. What has not been shown previously, however, is the quantitative relationships and temporal differences which we have demonstrated between the two alternative isobaric counterdiffusing techniques carried out on the same animal (Fig. 23).

In conclusion, we have demonstrated: (1) a very marked difference in the numbers of bubbles produced in a given time from a TIC gas sequencing experiment as compared to a steady state, standing gradient experiment; (2) an extremely large variability which probably reveals the real nature of vascular and other factors which influence the number of bubbles collected and delivered to the central venous detector; (3) strong evidence for the importance of bubble growth and clearance kinetics in the type of results produced by either kind of experiment; (4) reasonable estimates of critical supersaturations which fit with several current estimates arrived at by quite different experimental techniques (11); (5) a very pronounced periodicity in numbers of bubbles with time following a gas switch which is as yet unexplained but may be most easily accounted for on the basis of periodic blood flow changes linked with other natural cycles. Periods appear to range in time from 40-90 minutes, and may be due to simple factors such as bubbles building up and sticking in areas of sluggish venous flow and then being released over a period of several minutes.

Finally, perspectives for future work in this area are very encouraging in that our results confirmed and extended our previous work and have suggested that combined experiments where a given area of skin is masked (with an ability to pass helium over it) and combined with breathing a more soluble gas (such as nitrous oxide) to produce central venous bubbles, would then allow an approximate calculation of actual numbers of bubble sites in the skin! This has never before been possible; however, the advantage of this hypothesis is that it can be tested and is no longer subject to the uncertainties inherent in post-decompression studies.

II. Original Objectives and Background

The overall objective of the hyperbaric program at Virginia Mason Research Center as it relates to decompression sickness has been to describe and clarify the complete etiology and pathogenesis of decompression sickness. The last 20 years have seen a vigorous increase in manned deep diving research (9,36,37,38,39,43,64). Although this has led to some important new insights in medical treatment of decompression sickness such as the need for fluid resuscitation (27,28), anti-platelet and antithrombotic therapy (1,51,56,58), factors affecting the recruitment, growth and clearance of gas emboli from a tissue to the lungs are far from clearly understood. In order to obtain a clear picture of the etiology and pathogenesis of decompression sickness, it is necessary to distinguish the physical from the physiological factors. The former include the concepts predicting gas exchange (10,36-41,44,45,46,52,62) and ascent criterion (7,8) while the latter include the body's response to decompression. In the past, studies attempting to clarify these relationships have almost invariably used decompression as the experimental modality causing gas separation. We have demonstrated in this laboratory the experimental and theoretical limitations of this approach in two previous studies (12-14) and have further demonstrated extreme day-to-day variability in numbers of vascular emboli (ultrasonically detected) as a result of similar hyperbaric exposures (24). For these reasons the demonstration ten years ago that bubbles could be produced in vivo without changing pressure (31,42,47) appeared to provide a promising experimental alternative for understanding bubble formation and growth in vivo. In the ten years since the initial communication of the consequences of breathing an inert gas more soluble than the surrounding gas (known as steady state isobaric counterdiffusion - SSIC) (42,47), few quantitative insights have resulted from attempts to exploit this technique except the

knowledge that with sufficient time, the condition can be made potentially lethal, and that the volume of separated gas was proportional to surface area and solubility of the respired gas (47). On the other hand, the occupationally more relevant situation of gas sequencing known as transient isobaric counter-diffusion (43) in which an entire environmental gas is suddenly changed has provided qualitative insights on hazards (17-19), experimental evidence of possible decompression advantages (24,43), critical levels of supersaturation (24) and (very crudely) major time constants of the body.

A critical part of our goal has been to clarify the factors allowing bubble formation and its sequelae in vivo. The relationship of this project to the overall program at WMRC was therefore to examine the use of the two alternative forms of isobaric counterdiffusion to experimentally produce supersaturation in an awake animal where all the confusing results associated with decompression itself were absent (15,16). The primary objective of the program, therefore, was to determine quantitative and qualitative differences in bubble formation, growth and collection associated with steady state isobaric counterdiffusion (SSIC) vs. transient isobaric counterdiffusion (TIC); the latter represents both a research tool and a potential operational hazard or advantage, depending on how it is used whereas SSIC represents only an experimental tool. Therefore it is essential to understand the quantitative and qualitative differences resulting from these two isobaric techniques.

III. Summary of Major Accomplishment to Date

Work in the first year of this project has allowed us to titrate the approximate minimum depth and presumably therefore the average minimum supersaturations which are required to cause bubbles to form under conditions of TIC. It appears at this point that an excess tissue gas pressure (ΔP) less than approximately 17 f.s.w. usually produces no significant bubbles (see Table 1). This is supported by other recent work (11). We have also made considerable progress in demonstrating the remarkable degree of physiological variability in animals which we can now conclude is not related to decompression. This variability represents perhaps the most important key to really understanding decompression sickness, since it has been known for many years that bubble thresholds, response to decompression and adaptation are all aspects of this problem and are very poorly understood (11,29,32,33,74-77). Having removed one of the reasons previously held to account for variability, i.e., decompression itself (13,14), we have now a means of studying first hand the physical and physiological factors affecting the numbers of bubble counts at any given threshold which can now be computed with more accuracy. As the progress report will show, it is often possible to get quite different responses from transient isobaric gas switches in the same animal on two successive experiments two weeks apart.

The major accomplishment of the work remains the demonstration of the relative differences in SSIC and TIC experiments performed on the same animal at different times (Figs. 22-26). These profound differences allow the following conclusion: Transient isobaric counterdiffusion represents a much less serious hazard than the steady state situation. This is fortunate because the steady state situation is not one likely to be encountered in operational diving. As stated above, it remains a research tool with great promise for sorting out major factors affecting bubble growth, clearance, embolic effects, and numbers of bubble sites in any one tissue.

IV. Detailed Progress Report

1. Methods:

(a) Doppler Bubble Detection. The experimental methods used in this project are as described in previous publications (17,19,63) and the first progress report for this project submitted in 1980. We are now using doppler cuffs produced by L&M Enterprises, Daley City, Ca.

(b) Animal Restraint. Figure 1 shows the original Doppler cuffs designed and built in the Applied Physics Laboratory (University of Washington), and Figure 2 shows the strain-relieved exit pack and leads which can be connected when needed. Surgical implanting is as previously described (19). Figure 3 shows restraining arrangements for two goats subject to transient isobaric counterdiffusion. They are free to move vertically but have less freedom of motion to the side, so that doppler leads remain intact. Animals tolerate this restraint well for periods of one week.

(c) General Experimental Protocol. The general experimental protocol is, briefly:

(1) The doppler leads are attached to the animal outside the chamber by means of the connections shown in Figures 1 and 2.

(2) The animal is walked into the chamber and attached to the stanchion via the head harness and caribiners which slide on vertical pipes. The latter are protected against static production by being covered by plastic tubes to act as insulators.

(3) Food and water are provided and can be locked in with a gravity feed system during an experiment.

(4) Animals are saturated overnight on gas 1 (nitrogen with .3 bar O_2) for 17 hours.

(5) Doppler recordings are begun 15 minutes prior to the gas switch. All methods of ultrasonic doppler counting are described in a previous publication (5,6,17,19,35) and in final report #N000-14-69-C-0402.

(6) The gas switch is carried out after 17 hours of saturation (unless otherwise indicated) by layering the light gas (He) on top of the heavy gas (N_2) and allowing the latter to escape through the bottom of the chamber. This provides a rather clean and rapid switch; in fact, light diffraction can be noticed at the interfaces of the gas layers during the change; the densities are so different that they provide this clear discontinuity.

(7) Records are taken for 12 hours or for a shorter period depending on the outcome of the experiment, as shown in the results, but in no case for less than two hours.

(8) Decompression is begun according to an initial ascent to 105 f.s.w; thereafter decompression is at the rate of 6 ft/hr to 50 f.s.w., at which point an air flush is carried out and the decompression rate is reduced to 5 ft/hr to 20 f.s.w. at which point the rate is further reduced to 4 ft/hr to the surface.

(d) Mask Breathing System. In order to develop a means of having the animal breath one gas while surrounded by another and still maintain the animal unanesthetized and awake so that experiments could be free of the constraints of anesthesia, three alternative methods were contemplated. The first involved a tracheostomy which could be made chronic by sewing the externalized sides of the trachea and its supporting cartilaginous rings to the outside skin layer. This approach, which was tried on two occasions was considered unsatisfactory because of its invasive nature, stress on the animal, and difficulties in

maintaining the trachea patent, as well as (and most important) severe ventilatory restrictions which any swelling occasioned by the surgery might produce. Such restrictions are compounded at 7 atm and in our view this eliminated this approach as an option.

The second approach considered involved constructing a hood which could be sealed around the neck and fastened to the horns of the goat for strain relief. This approach involved considerable engineering and also involved a certain amount of dead space without which adequate gas sampling techniques would be unknown. It also limited goat subjects to those with horns. Although feasible, the contract did not provide the financial resources for such development, and this approach is being developed elsewhere (Lambertsen, personal communication).

The final approach settled upon was to construct a mask molded to the contours of the foward part of the face of the animal and sealed by rubber dental dam material in the internal edge. Such a set-up was constructed and is shown in Fig. 12. The input and output of the mask which allowed minimal dead space were connected to large wire-wound hoses, each of which went into a T on the lower side of which breathing bags were fastened (see arrows in Figure 12), and which, on its output was fastened to a pneumatically operated large diameter ball valve. This arrangement was strain-relieved to the same frame/stanchion set-up which restrained the animal (see arrows in Fig. 12). It was necessary to hobble the front legs of the animal to avoid its catching its feet in the hose. However, this still provided vertical movement to the animal, which tolerated the mask fairly well for two days. The two tubes shown coming out of the top of the mask provided (1) a drain for saliva, (2) a monitor of mask pressure during exhalation and inhalation. This was recorded with two sensitive "Magnehelic" gauges shown on the lower left of the figure which could be observed from the

exterior through the outside port above. A flow of gas to the breathing bags and out of the breathing bags could be controlled from external restrictor valves so that their volume could be maintained constant.

Animals adapted to this arrangement reasonably well. Breathing rate often increased as a reflection of the animal's state of anxiety or dislike for the confines of the mask. However, with several hours of adaptation the breathing rate usually subsided to normal levels. The breathing restrictions shown by the "Magnehelic" gauges by pressure changes which were measured in the mask was usually less than one inch of water at 200 f.s.w. Thus, there was no serious ventilatory restrictions or extra work involved in breathing through the mask. Any problems with the mask would have been psychomotor and related to a state of anxiety produced by the feeling of the mask around the muzzle of the animal. We found that different animals behave differently to the mask but all eventually tolerated it and adapted over time. Initial experiments often showed high minute volumes during a switch to helium, which may have had something to do with the sensation and "feel" of the gas to the animal rather than any airway restriction. Both the heat capacity and the density of the gas would cause detectably different breathing sensations which, combined with the mask might have had a number of unknown effects. We are convinced, however, that the mask system was the preferable one and was most easily implemented into the experimental protocol required.

2. RESULTS

(a) Transient Isobaric Counterdiffusion -- Relation of Depth to Bubble Counts

The following results (Figs. 4-10) present the records of bubble counts plotted against time after gas switches from nitrogen to helium at different

depths. These have provided some very interesting and useful results, which are presented and discussed in terms of the relationship of minimum ΔP's (see Table 1), the variability in bubble counts of any one animal at different times, and between different animals at any one time, and the interesting periodicity in bubble counts - sometimes of greater degree than others. These experimental results are summarized in Figures 4-10. The ordinates are average bubble counts/min and time is the abcissa. The ordinates on different figures are set at appropriate linear scale for comparisons.

Figure 4 summarizes the results of bubble counts with time following a gas switch at 66 f.s.w. after a 17-hour saturation. It can be seen that very few counts were heard - less than 10/minute. This level is at the limit of detection sensitivity and depends upon the signal, involves considerable variability, error and uncertainty. However, the levels plotted are maximums and indicate virtually no bubbles at the central venous location at this depth. Notice that this gas switch is associated with a calculated ΔP of 2.6 f.s.w. as shown in Table 1 and a pressure ratio of 1.030. Thus, we can assume that this degree of supersaturation was inadequate in the time available to cause vascular bubbles, assuming our calculations are approximately correct. Other work (22, 73) has shown that if one assumes the detected bubbles originate in the vasculature, a perfusion dependent supersaturation results which cannot exceed a supersaturation ratio greater than 1.2; when oxygen is considered this further reduces the possible ΔP (see Table 1).

Figure 5 shows similar results for a 99 f.s.w. switch after an identical saturation period. This treatment also appears essentially free of bubbles, with a calculated ΔP (Table 1) of 7.2 f.s.w. and pressure ratio (π/P) of 1.073.

Figures 6 and 7 indicate the same information at 132 f.s.w. after 17 hours of saturation (ΔP = 11.8 f.s.w., π/P = 1.068). It can be seen that considerable variability between animals is evident.

In an earlier paper (17) we indicated considerable numbers of bubbles following gas switches at 132 f.s.w. The methods used to switch gases in this experiment in 1976 involved high volume flushing rates which produced much noise and probably much more anxiety on the part of the animals than was produced in these experiments, which used the lower flow layering technique. It is therefore possible that the reduced bubble counting rates resulting from these experiments in Figures 6 and 7 were related to a lower degree of anxiety in the animals since the gases were introduced more quietly by density stratification. This raises the possibility that levels of anxiety, stress, and a number of other variables which at present must remain invisible to us actually affect the bubble counts. Whether this is an effect on the number of bubbles formed or their clearance is not clear. This suggests the need to examine indeces of stress such as cardiac output, vascular tone, levels of catecholamines and other vasoactive agents, as well as blood rheology during such experiments.

Figures 8 and 9 show results of a gas switch at a depth of 165 f.s.w. It can be seen that there is easily a factor of 2 between the average bubble counts in the two animals. This may be related to the volume of animal allowing a greater number of bubble sites, and therefore more bubbles (but not in the same way that decompression would imply sensitivity according to time constants related to size). In this case there is simply more tissue to collect bubbles from. Notice that Table 1 gives ΔP values of 16.4 and π/P of 1.083. Finally, Figure 10 indicates results of a gas switch carried out at 198 f.s.w. Notice the increasing periodicity (bubble showers) in bubble counts shown in Figures 9 and 10. The ΔP and π/P values shown in Table 1 for these experiments are 21.0

and 1.092 respectively. These levels are compared with those currently used in recent decompression tables.

— Time of Saturation. Having established in this project that a consistent depth for producing bubbles was 165 f.s.w., we proceeded in another study (HL 22406, "Isobaric Vascular Bubbles and the Etiology of Decompresion Sickness") to "titrate" the minimum critical times of initial saturation required for bubble production following a gas switch. These results (shown in Figures 11 a-f) are included in this report because of their relevance to the saturation times. They show results of gas switches at 165 f.s.w. with progressively increasing saturation times from 2, through 4, to 8 hours. Comparing these count levels to the previous experiments at 165 f.s.w. (Figures 8 and 9) allowing 17 hours of saturation reveals significant differences in bubble counts when the saturation time was 2 hours (note the different scales on the ordinate) when the obvious variability between animals is considered. Compare, for example, Figures 11a and 11 b, which involve a saturation time on gas 1 (N_2) of only two hours and gave virtually no bubbles. The actual traces shown in the figures are actually very conservative; lower bubble counts accrued than shown because of the problem of sensitivity (5,6).

If we can believe the ΔP values shown in Table 1 calculated from two simple exponentials (17) the experiments shown in Figures 11 establish that the minimum time of N_2 saturation of the tissues from which we are "collecting" bubbles is well over two hours. Thus, since the last saturation interval tested was 4 hours (Figures 11c and 11d), we have assumed - for the present at least - that a 30-40 minute tissue half time is involved (8 x 30 or 6 x 40 minutes = 240 minutes = 4 hours). A 30-minute tissue would therefore be saturated to 99.6% and a 40-minute tissue would be saturated to 98.4% within 4 hours. This line of reasoning gives us an approximation of the (N_2) tissue time constants most likely involved in the bubbles we are detecting.

These depth and time "titrations" are at best very crude at the present time, but nevertheless provide stronger evidence than can be produced by decompression experiments (3,4,7-10), and indicate the reality of definite physilogical supersaturation "limits" and their accompanying critical bulk time constants.

As our counting procedures become more accurate (we are very near to incorporating a computer algorithm developed by Belcher (6) which will allow much more reliable counting of bubbles using this same Applied Physics Lab bubble counter), more accurate determinations of both low and high counting rates, and therefore more sensitive titrations of critical limits, will be provided.

(b) Transient Isobaric Counterdiffusion Applied by Mask. In order to assure ourselves that there were no serious problems in switching breathing gases via the mask we carried out several transient isobaric counterdiffusion experiments (Figs. 13-20) by suddenly switching only the gas breathed. For this treatment the protocol was as follows: (1) the animal was placed in the chamber and prior to the dive the mask was fastened in the manner shown in Figure 12. Compression then occurred on nitrogen with .3 bar of oxygen. This gas was breathed by the animal through the ball valves which opened to the chamber so that the animal breathed chamber gas through the mask system. After a saturation period of 17 hours, the breathing mask system would be connected through the ball valves actuated from the exterior to helium, with .3 bar oxygen while the surrounding chamber gas remained the same. This is effectively the same sudden change that was imposed by flushing the chamber to helium in the previous study of TIC (Figs. 4-10) but imposes a much more abrupt change. However, in this case there is also a subtle difference in that the chamber gas remains nitrogen and oxygen whereas the breathing gas is composed of helium and the same percentage of oxygen.

This arrangement will produce an undersaturation at the skin but apart from this difference the transient isobaric counterdiffusion exposure in all the other tissues would be similar to switching the entire chamber gas, since the animal was previously saturated on nitrogen and is now suddenly breathing helium. There is a slight gradient in transport of nitrogen from the skin to the alveoli but this probably represents a very small addition to any bubble growth in the vasculature, and cannot contribute in the skin because of an undersaturation. The results of these control TIC switches are shown in Figs. 13-21.

In many cases a 4-hour saturation period was used since we had found in other studies funded by NIH (see Fig. 11) that a minimum saturation time of 4 hours would apparently produce the same transient bubble count similar to that produced by a 17 hour saturation. These results are shown in Figs. 11 a-f. This conclusion must remain tentative in view of the extreme variability seen from animal to animal and in any one animal at different times. However, both the bubble counts and their ranges have been similar whether a 4-hour or a 17-hour saturation time is used. This is shown by comparing Figs. 13 and 14 respectively, carried out on the same animal two weeks apart. The results of these two gas switches on the same animal two weeks apart, but one with a 4-hour saturation time and the other with a 17-hour saturation time are similar. As can be seen, both the magnitude and duration of bubbles for the same animal were approximately the same and the overall average bubble count rate does appear as a transient which presumably parallels but lags slightly the transient peak in average full body supersaturation as a result of the gas switch (17).

If one assumed that saturation was complete in 4 hours, this would imply that the longest time constant of significance for saturation was approximately 40 minutes. This assumption allows estimation of an optimum time of delay after

an undersaturating gas switch in order to facilitate more rapid decompression by allowing a greater initial jump (ΔP) to the most shallow depth consistent with safe compression. This is also shown in Figures 13 and 14 where after an isobaric period of approximately 4 hours and 40 minutes, a switch back to air (gas switch 2) was imposed and 45 minutes later (the time that computation indicated maximum undersaturation was achieved) a decompression directly to 116 f.s.w. was imposed. As can be seen from the figures, this did not cause a large burst of bubbles, and the remaining decompressions were routine. Such a decompression would normally be associated with a large production of bubbles as can be seen in Figure 15, which shows the results of a direct decompression from saturation on nitrogen at 198 f.s.w. to 116 f.s.w. but with no previous undersaturating gas switch. As can be seen, a very large number of bubbles were produced with, interestingly enough, a much lower variability rate relative to the average bubble *counts* than in the transient situation as shown for example in Figure 16.

The significance of these observations will be discussed later. For the present time it is sufficient to note that this is good evidence, particularly since the same animal was used within a two-week period, that the undersaturating switch provides very definite decompression advantages and that this modality needs to be further explored for its operational, tactical and emergency applications (24).

A further example of a consistent response in one animal at different times is shown in Figures 17 and 18 which show results of a transient gas switch applied by mask using 4-hour saturation time on the same animal two weeks apart. Here, however, the bubble count was less than that shown in Figures 13 and 14. In fact, almost a 10-fold difference in the numbers of bubbles is observed.

It has been suggested that repetitive dives (and therefore by implication repetitive TIC or SSIC exposures) cause cumulatively larger responses in bubble formation. Although that might apply to these experiments, we have observed both extremes in other studies; as often as not the larger number of bubbles appear on the first experiments and a smaller number later.

In a long series of decompression experiments which were part of another study using 25 minutes bottom time and immediate ascent to the surface (manuscript in preparation), very large differences in bubble counts during successive experiments were observed, and this seemed to bear no relation to whether the experiments were two weeks apart, one week apart, or one day apart! Therefore at least in the awake goat prepared as they were in these experiments, it can be surmised that we are observing rather subtle factors at work and that the same factors conspire to produce the variable response to both decompression exposures and isobaric gas switches.

An example of an animal with low bubbling response or "potential" is shown in Figures 19, 20, and 21. These illustrate similar responses to a 4-hour saturation and a TIC experiment applied by mask. In all three experiments very few bubbles were observed, and the experiments were two weeks apart. Such a response would justify the assumption that this animal is one with a consistently low response. In fact even decompression without an undersaturating gas switch (cf. Fig. 15) failed to produce more bubbles! Decompression resistance may be among other things simply a low probability of bubble formation as shown in Figures 19-21. this has been observed in human decompression studies (53,65-67), in animal decompression studies (13), and animal isobaric studies (23,24). However, it is also known that succeptibilities to bubble formation change abruptly. This is shown in the experiment summarized in Figure 22 which was a TIC experiment using a 17-hour saturation time on the same animal as

Figures 19-21, but several months later. A very high initial bubbling rate was observed, with a high mean to standard deviation ratio.

This response could have been related to the longer saturation time - which by reference to Figure 11 seems unlikely - or the presence, through some sort of "regeneration" process, of a larger number of microgas nuclei than in previous experiments. This remains one of the perplexing problems in this field (70-77).

Another expected phenomenon of TIC experiments is shown by Figures 17 and 18 where a pulse of bubbles - which may be due to the soluble gas effect - is observed shortly after the point of switching back to air. This might be due to the known enhancement of bubble volume which will result when a bubble filled with a gas of low solubility is suddenly perfused by blood containing gas of high solubility (54,73). The resulting gas exchange due to the gradient from blood to bubble of the higher solubility gas results in an increase in volume and may have resulted in a sufficient degree of bubble growth to produce the brief higher count rates observed. Interestingly, in most of these experiments the switch back to air protected against the expected decompression bubbles as shown in Figure 15, and allowed only a minor increase in bubble count rate following a jump of 81 f.s.w.

The variability shown in the above results is strong support for the hypothesis that there are biophysical, biochemical and physiological processes involved in causing an animal to be prone to form bubbles. Many of these factors are as yet unknown but must have something to do with microgas nuclei dynamics (29,33,70,71,74-77), blood lipid chemistry surfactant levels, microcirculation health (51,56,58), integrity and control, and probably many other factors yet unsuspected (1).

What is certain is that these sorts of experiments provide a far more subtle view of the physical stability of subjects than decompression studies which tend to obscure many important physiological responses to bubble formation and its effects (cf., Figure 15 where a much less variable and transient response occurs).

(c) Steady State Isobaric Counterdiffusion in the Awake Goat

The main objective of this contracted project was to compare the effects of transient versus steady state counterdiffusion of different inert gases in the same kind of animal under the same depth and gas mixtures. It was felt that although much had been learned about the production of bubbles under steady state conditions (47-50,59,69) and that the effect was potentially lethal (47), the potentially useful information available from this technique had not yet been realized. It was clear that only by comparing the two techniques with respect to both bubble thresholds and numbers in the same animal species, and the same individuals, would we gain some insight into the real processes going on. Although we stated earlier (17) that the transient approach had many experimental advantages in that it was transient and therefore one could study the processes responsible for bubble dissipation, we also appreciated the merit of an experimental technique which localized the site of bubble production to one single tissue, the skin.

Before discussing these results it is necessary to explain some of the difficulties in these latter series of experiments. As has been shown by Lambertsen et al. (47) steady state isobaric counterdiffusion produces large volumes of gas in a relatively short time of a few hours. In fact, sufficient gas is produced to be lethal even at 1 atm of pressure provided the right gas pairs are chosen (24). By adjusting either the surface area exposed or by

choosing the appropriate gas for breathing it should be possible to produce a certain number of bubbles in a given time at any pressure.

Our initial studies were based on the experience gained from TIC experiments (17-20,22-26) where a transient switch which therefore includes the entire body is imposed at 198 f.s.w. (7 atm) produced bubbles for a period of as much as 48 hours (20) in the pig, but in most cases shows no signs of problems for the animals and in any case dissipated within 6 to 12 hours in the goat. For this reason it was felt that steady state isobaric counterdiffusion of the same pair of gases, nitrogen being breathed by mask and helium suddenly surrounding the animal in the chamber, would produce similar results. In fact, our first experiment carried out at 7 atm produced, within two hours, so many bubbles that the doppler signal was essentially a roar and automatic electronic counting (5,6) was not possible. This degree of response, shown in Figure 23, can be best likened to the signal received if an animal is saturated on nitrogen at 198 f.s.w. and decompressed directly to the surface. This actually was necessary in one case several years ago when a medical emergency necessitated aborting a dive! Under such conditions - a 7 atm decompression from saturation - so many bubbles were produced that an unreadable signal resulted. The same kind of response was heard in the experiment but of course a longer time was required for maximal response (2 hrs.). This is shown in Figure 23 by the solid line; by two hours the bubbles had reached apparently saturating levels. Note that the apparent plateau in the solid line curve does not mean that this was the extent of the bubbles numbers. In fact it is probable that they were at the level of many thousands per minute. Figure 23 also shows this experiment contrasted with that shown in Figure 22 (dotted line) according to the same scale which represents the effects of a transient switch also carried out with a mask (shown by the solid line) at 198 f.s.w. The supersaturation was sufficient to cause a large number of bubbles which nevertheless subsided after several hours.

Two comparisons here are important. One is that the time course of increase in bubbles was similar in both experiments. The other of course is the very great difference in number of bubbles produced in any given time. The animal used in this experiment (solid line) appeared by the second hour to be in some distress. Accordingly, the pressure was raised by half an atmosphere as is shown in Figure 23. This did not audibly affect the bubble signal in any way. A further hour was allowed to elapse during which time the animal appeared in further distress causing concern for its survival. Accordingly, another full atm of pressure was added as shown in the top solid line (right hand ordinate). Again, no changes in the bubbles signal resulted. This is not surprising since it is known that the gradient and the supersaturations are imposed at the skin and increasing the pressure will increase the ΔP (23,42,73). For this reason at the time shown by the second vertical arrow (approximately 5 hours) the chamber external gas (gas 2) was changed back to air. This resulted in a relatively rapid return of the bubble signal to countable levels and eventual dissipation of all bubbles within an hour and a half. As can be seen, a couple of small peaks remained which presumably were due to previously occluded areas of the circulation opening up again following the dissipation of excess gas.

In order to remove the mask, a rapid decompression was then imposed (as shown in the top (solid line) pressure trace) allowing a technician to lock down, remove the mask, feed the animal, and return to the surface. This produced some increase in bubble counts but not an alarming one, and once the technician locked out was immediately followed by recompression to 198 f.s.w. at which point a saturation decompression at 6 feet/hour was resumed. The remarkably high bubble counts and the animal's response constrained future experiments to a shallowed depth where the ΔP produced by the counterdiffusion gradients would be lower and presumably therefore fewer bubbles would be produced.

Figure 24 shows the results of a similar SSIC experiment at 132 f.s.w. imposed in the same way as that shown for Figure 23. The same transient gas switch shown in Figure 23 is also superimposed (dotted line) in order to compare the time course of development of maximum bubble counts in the transient versus the steady state experiment. In this situation, presumably because of the lower ΔP imposed and the resultant slower bubble growth, the bubble counts took longer to rise, did not rise quite as rapidly nor apparently to as high a level, but nonetheless reached levels which saturated the counter and prevented continual monitoring. It is clear nevertheless it is clear that fewer bubbles were produced since the oscillations in bubble count which are known to occur under these conditions pushed the bubble count frequently down to reliable levels of 1000-1500 per minute several times during the course of recording. After six hours the chamber gas (gas 2, helium) was again changed back to air, resulting in a rapid return to countable levels of bubbles and eventual dissipation of the bubble signal entirely. This happened within an hour in this experiment which was a shorter time than in the previous experiment; again probably consistent with the smaller amount of excess gas involved. This animal also exhibited discomfort during the high bubble count phase of the experiment, but was later in good condition, maintained an appetite, and was decompressed with no further incident.

In order to produce bubble counts amenable to analysis and not sufficiently high to saturate the counter and to further study the time course of development, a still lower pressure was obviously needed. This raised the question of the actual lower limit and so it was decided to carry out an SSIC experiment at 1½ ATA (16.5 f.s.w.) in order to explore the minimum supersaturation levels (ΔP) which would produce bubbles. Accordingly, a similar experiment as shown in the previous figures was carried out at 16.5 f.s.w.

using 17 hours of pre-saturation and applying gas 2 suddenly by simply switching the chamber gas from air to helium.

The results of this experiment were extremely clear and completely negative and for this reason no figure is included. No bubbles were detected in the entire isobaric period following the gas switch. This places one reliable lower limit on depth (and therefore ΔP) where bubbles will be produced, cleared, and detected at the central venous location as a result of the steady state gradient applied between nitrogen as gas 1 and helium as gas 2.

The possibility remains of course that some gas phase separation occurred in this experiment (15). However, it was not sufficient to allow bubbles to grow and be cleared to the central venous location. This raised the possibility of further titrating the numbers of bubbles produced by a given gas pair by performing similar experiments at steadily increasing depths. Sufficient insight had been gained in previous experiments in this laboratory (24,73) and was available from the literature (48) to suggest that the substitution of argon for nitrogen as gas 1 and keeping helium as gas 2 would also produce a larger number of bubbles at any one depth than nitrogen and helium. In view of the variability of results of TIC experiments and the known range of critical thresholds shown in Table 1 and described in the literature (22,71,74-77), this approach seemed admirable. Accordingly, Figure 25 shows results of a gas switch carried out at 132 f.s.w. using argon as gas 1 and helium as gas 2. This also resulted in bubble counts ranging from 1200 to saturating levels and the time required for their development was approximately 3 hours. In characteristic fashion, switching back to air at 6 hours rapidly reduced the counts to zero.

Finally, in order to attempt to reduce the bubble count still further, a similar experiment was carried out at 99 f.s.w. after a 19-hour saturation (Figure 26). In this experiment, as in the previous experiment, approximately

the same time was required for the bubbles to begin to be detected following the imposition of the gradient. Apparently fewer bubbles were experienced, however, since at 4 hours an obvious drop in counts reduced the number to 1000/minute, consistent with the possibility that the average numbers of bubbles produced were lower than in the 132 foot experiment. A switch back to air at 5 hours rapidly reduced the counts to zero within approximately 30 minutes, significantly faster than in Figure 25.

This difference in "bubble decay" times undoubtedly is related to the actual depth and therefore ΔP at which the counterdiffusion is occurring. For example, in the first experiment where the initial depth of the experiment was 198 f.s.w. it required approximately an hour and a half before the bubbles returned to zero, whereas in the present experiment carried out at only 99 f.s.w. it required only 30 minutes. Because the gradient occurs in the skin it is plausible that it is produced very rapidly and the delay time involved in imposition of the gradient and detection of bubbles at the central venous location which can be as much as 3 hours, involves factors affecting bubble growth rates, location of the bubbles, proximity to or location in the blood capillaries, rheological factors which have to do with the ease with which bubbles are cleared or become "unstuck" from capillary walls, or, if they are extravascular, the probability that they can penetrate through pores in the microcirculation so that a new gas phase is "budded" into a vessel (15).

It is clear from Figures 23-26 that the decay of the bubble count signal following removal of the standing gradient is far more rapid than is the appearance of bubbles at the central venous location. This indicates some physical/physiological processes involved in the development of bubbles are not involved in any way once the gradient has been eliminated. These observations tend to support a general picture of this process consistent with current ideas

on critical conditions for bubble formation, and the importance of gas solubility in bubble growth and resolution rates.

It is unfortunate that further experiments could not be carried out within the financial limits of the contract; when this is possible, the obvious approach will be to more accurately titrate the minimum depth where consistent bubble count rates occur with a given gas pain and to then determine the physiological, pharmacological, biochemical factors related to bubble formation, bubble numbers, and bubble counts at the central venous location.

(3) DISCUSSION:

(a) Variability Between Animals. The results indicate considerable differences in bubble counting rate both following a gas switch in TIC and SSIC. Table 1 indicates that at 132 f.s.w. the computed supersaturation expresed in feet of sea water is 11.8 f.s.w. at a pressure ratio of 1.030. Notice also in Table 2 that in order to get a ΔP value approaching those currently used as limits at the surface for both nitrogen and helium diving (Tables 3 and 4) one would have to accomplish the same gas switch from nitrogen to helium at depths well beyond those used here. We know from experience that gas switches well beyond 231 f.s.w. would produce a very high bubble count. The conclusion must be that the time during which the supersaturation exists is an important factor for any given ΔP.

Many examples of individual variability between animals occur such as those from the experiments shown in Figures 8 and 9 where subjects Kernal and Diablo show variations of at least 50% following the same gas switch. In view of their similarity in weight (34 and 28.1 kg, respectively), this appears to be related to factors other than weight, and consequently on factors other than their "average time constants."

(b) Periodic Variability in Bubble Counts. Figures 4-11 and 13-26 show that frequently there are periodically large fluctuations in bubble count. For example, Figures 9 and 10 which are gas switches carried out at 165 f.s.w. show several strong modes of high bubble counts in each animal (but particularly in the goat Kernal) which last for 30 to 40 minutes and occur at approximately 2-hour intervals. Other good examples of such periodicity are in Figures 13-20. These variations are statistically significant and suggest that changes in blood flow to certain regions (perhaps the skin) in general may be involved in producing these lasting changes in bubble count. Whether this is a local change in perfusion or a general change in cardiac output is not clear at this time, but we feel it is important to understand. It may also be simply a matter of bubble accumulation through adherence at areas of sluggish flow until a critical volume or a change in flow triggers their release.

These findings now provide additional support for the current understanding of the etiology of decompression sickness as a combination of 1) a physical insult and 2) a physiological response. The discrepancies between the low ΔP values shown by this work to cause bubbles and the high calculated values used as limiting in a 40-minute tissue for both He and N_2 provide a rationale for the following very general sequence of events.

When these supersaturations are applied by decompression, bubbles form rapidly and probably grow sufficiently to either physically or physiologically block further blood flow at that area. This not only affects further gas and bubble elimination (12-14) but also may potentiate further blood shunting responses so as to prevent further flow to that area. The scale of these changes is not certain but probably depends on the severity of the insult. Further study similar to the above is therefore required to more accurately delineate the actual range of critical ΔP values (74-77) allowing vascular

capillary bubbles to form, as well as the minimum times required for such bubbles to be transported to the heart.

(c) Calculation of Actual Supersaturation Levels. We must still admit the lack of a predictive theory of decompression; obviously no theory can possibly be completely predictive because the body is under a constant dynamic control system which continually insures temporal fluctuations in blood flow, metabolism, and hemostatic function. It is of course naive to hold the scientific goal of complete predictability of gas uptake and elimination as well as critical thresholds. On the other hand, we have now shown and it is now agreed by many investigators (7,8,63,74-77) that improvements are possible in the decompression models in use. Depending upon whether one is trying to avoid bubbles or avoid bends, a quite different level of understanding as well as physiological model is required. Since the demonstration by ultrasonic doppler of the production of bubbles by decompression (Spencer, 1968) the relationship between bubbles and bends has been less uncertain, but the quantitative relationship is still debatable (8,15,65-67). It has been our assumption here that there is at present no clear way to decide this issue until we understand more clearly the biophysical and physiological factors affecting bubble formation, growth, collection and resolution. We have also pointed out here the descrepancy between the calculated ΔP values known to produce bubbles in isobaric experiments (17,21,24) and those used in decompression tables.

It is clear that much of the reason for the discrepancy is related to time; the time for bubble growth and clearance and establishing the degree of supersaturation (30) required to "trigger" incipient bubble growth. Future studies should reveal the relationship of permissible ΔP, pressure ratio and the actual probabilities for bubble formation associated with different combinations of ΔP and π/P.

(4) CONCLUSION

We have demonstrated that SSIC will produce many more bubbles in the same period of time than TIC, probably due to the permanence of the gradient and the fact that it is quickly established. The relationships of P and time need further examination.

We have also demonstrated that gas switches (TIC) at depths as shallow as 132 f.s.w. with .3 atm of oxygen always cause bubbles, and that this is related to a computed P value of a minimum of 12 f.s.w. at a minimum pressure ratio of 1.068. The validity of these estimates depends obviously on the validity of the calculations on which they are based. However, we feel that our estimates of P are reliable for the following reasons (73).

In the first place, much evidence supports a perfusion limited system and with such a system, it is not possible to produce supersaturations higher than these levels (40,73). The alternative calculation based on a diffusion dependency requires very, very fast blood flows to produce the supersaturations higher than these levels (73). This would seem to suggest that we should initially see many more bubbles than we do just after a transient switch. In fact the maximum in bubbles is usually encountered well after the gas switch in TIC or SSIC (from one to two hours and sometimes more) and often appears in several modes as discussed above. Finally, in other experiments (24) a transient gas switch from neon to helium failed to produce bubbles and our analysis (24,73) predicted <u>undersaturation</u> according to a perfusion dependent model. For these reasons, we believe that these estimates are not only reliable but also close to actual physiological limits of micronuclei existing in the vascular system. They are certainly consistent with past experience, but more than that, they also indicate that <u>low levels of supersaturations can produce</u>

bubbles which eventually appear in the vasculature and are collected and transported back to the heart. Thus, the as yet unknown relationship of such bubbles to the pathophysiology of bends symptoms and decompression sickness can now be tested, and further explored with a sensitivity previously not possible (4).

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TABLE 1

Inert Gas Supersaturations ($\Delta P = \pi - P$) and Pressure Ratios π/P calculated by the equation $\pi = (P - pO_2)\ (1 - e^{-k_1 t} + e^{-k_2 t})$ where π = total inert gas pressure; P = ambient pressure; k_1 = time constant of saturating gas; k_2 = time constant of desaturating gas; t = time after gas switch. Values for k_1 and k_2 were derived from another study (24). This is calculated for total gas switches from saturation on N_2/O_2 (.3 Atm O_2) to He/O_2 (.3 Atm O_2) at depths from 66 f.s.w. to 264 f.s.w. using a Na half time of 40 minutes. Gas switches below the dotted line consistently give bubbles. On the right of the vertical dotted line are the empirically derived values of ΔP and π/P for N_2 and He diving used in the U.S.N. tables for a 40-minute tissue. These computed values are only estimates of ΔP and therefore subject to controversy. However, they are undoubtedly within 50% of actual limits, and this justifies the comparisons with the current limits shown on the right half of the table.

ISOBARIC SUPERSATURATION					CURRENT USN DECOMPRESSION LIMITS			
					N_2		He	
Depth	pO_2 (Atm)	$\%O_2$	ΔP	π/P	ΔP	π/P	ΔP	π/P
66	.3	11.1	2.57	1.030	49	1.499	40	1.407
99	.3	8.1	7.19	1.073	64	1.485	47	1.354
132	.3	6.4	11.8	1.068	76	1.461	53	1.323
165	.3	5.0	16.43	1.083	89	1.449	59	1.302
198	.3	4.3	21	1.09	102	1.442	66	1.288
231	.3	3.8	25.6	1.092	115	1.436	73	1.277
264	.3	3.3	30.2	1.102	127	1.433	80	1.369

FIGURE LEGENDS

Fig. 1 Original design of doppler cuff used initial studies. Top left - cuff with crystal-holding insert terminating in perf-board strain-relief which is then epoxy-potted into a dacron-felt envelope (bottom left). This allows attachment of long leads (top right) as shown on bottom right.

Fig. 2 Close up (left) view of doppler crystal-containing insert attached to dacron-felt subdermal pack which contains the "sub minimam" BCD connectors.

Fig. 3 Double goat restraints used in TIC experiments where entire chamber gas is switched. Food can be locked in through a gravity system and two external double ball valves holding approximately 1 liter, and guided to each animal's tray through the diagonal PVC pipes.

Fig. 4 Record of bubble counts plotted against time following a gas switch carried out at 66 f.s.w. (3 Atm). After 17 hours of saturation on nitrogen, the chamber gas was switched to helium. The bubble counts are extremely low and although levels appear to reach something like 3 bubbles/minute sometimes during the switch, in fact they are probably lower than this value most of the time. Such a response is viewed as negative based on our experience with this experimental technique. Four animal dives were carried out at this depth and all had the same result.

Fig. 5 Bubble count plotted against time following a gas switch carried out at 99 f.s.w. with gases and experimental conditions otherwise similar to those shown for Fig. 4. A brief low bubble count following the gas switch may have been due to vasoactive responses triggered by different sensations of breathing helium. In any case, at the level of two hours where both maximum counts are usually perceived, the level of counts is no different than those shown for 66 f.s.w.

Fig. 6: Record of bubble count plotted against time for a switch from nitrogen saturation (17 hours) to helium. A slightly greater bubble count is seen than occurred in previous experiments at 66 and 99 f.s.w.

Fig. 7: Another gas switch carried out on a different animal at 132 f.s.w. (5 Atm) following a 17-hour saturation period. Significantly more bubbles are evident in this experiment and maximum count rates are around 22/minute at 5 hours. The periodicity in bubble showers which last several minutes is evident in this experiment, suggesting that a considerable number of bubble sites were triggered by this technique.

Fig. 8: Response time following a gas switch carried out at 6 Atm following a 17-hour saturation period. In this case the maximum bubble counts appeared early following the gas switch, as presumably shorter time constant tissues became supersaturated, and had enough bubble sites to allow formation, growth and clearance of bubbles back to the central venous location. Notice however that bubbles continued for a period of 12 hours at very low rates. This obviously unsymmetrical transient is a common response to transient isobaric supersaturation.

Fig. 9: Results of another experiment carried out at 6 Atm following a 17-hour saturation period on nitrogen. In this case an apparently constant average bubble count is seen with prolonged periodic showers of over 50/minute. These showers sometimes last over an hour and suggest differences in vascular programming as a cause.

Fig. 10: Results of an experiment carried out at 198 f.s.w. (7 atm) following a 17-hour saturation on nitrogen. In this case the maximal bubble count appears at about 4 hrs with the same degree of change in periodic bubble showers, which however are not evident for as long a time. The initially large spike in bubble counts is presumably the result of a tissue with a short time constant having a large number of bubble sites, as compared to other tissues.

Fig. 11: a-f This figure summarizes some experiments carried out as part of another project funded by the National Institutes of Health (HL 22406). (a) and (b) show the results of a gas switch carried out at 165 f.s.w. which, as shown in Figs. 8 and 9, often produce counts of 100 bubbles/minute. The difference in this experiment is that only a 2-hour saturation time on nitrogen was allowed. This prevented sufficient gas being dissolved in the major tissues of the body to allow enough supersaturation to occur following the gas switch. (c) and (d) both plot results of two gas switches following a 4-hr saturation, which produced up to 50 counts/minute reliably. (e) and (f) show results of a gas switch carried out at the same depth as in (a)-(d) following an 8-hr saturation. A similar number of bubbles was observed in Fig. 11e and approximately twice the number of bubbles were observed in 11f, suggesting that saturation is complete somewhere after 4-8 hours. Further discussion appears in the text.

Fig. 12: This shows the goat fitted with the mask developed for imposing SSIC. The mask was fashioned from a nalgene beaker re-shaped with heat to conform more approximately to the animal's muzzle. Dental dam material was stretched around the opening and held with an O-ring (white arrow, center) to keep it in position and provide a gas-tight seal. The mask was held on by fasteners hooked to a head harness, which held the mask and seal against the animal's muzzle. Intake and exit hoses are provided at the forward part of the mask, each of which connects through a T (white arrows, upper right) to (a) a regulator and (b) a ball valve opening to either the gas supply or the overboard dump. The front of the mask is also fitted with two small hoses (black arrows, center) which (a) serve as a drain and (b) serve as an indication of pressure in the mask during the input and exit breathing cycles. This pressure was shown on two "Magnahelic" gagues located in the lower left (black arrows) of the chamber. The animals were prevented from turning by means of caribeeners (black arrow, middle right) connected to the head harness and fastened around vertical plastic insulated pipes to prevent vertical mobility. To prevent the animal from disconnecting the hose or otherwise damaging the mask with its forelegs, hobbles (white arrow, lower center) were placed around its forelegs at the ankle. This still allowed the animal to stand or lie down as it desired and the entire arrangement was tolerated well for several days.

Fig. 13: This shows the results of a TIC experiment imposed through the mask system shown in Fig. 12. A 4-hour saturation time was used, which as Fig. 11 shows, appears to be sufficient. The first gas switch to helium was imposed where shown on the left of the figure near 0-time and the second gas switch which was back to air was imposed at 4 hours. Forty minutes following this gas switch, which produced undersaturation, direct decompression to 116 f.s.w. was imposed. In spite of the large pressure ratio, which as shown in Fig. 15 causes a large number of bubbles, no large pulse bubbles were encountered following this decompression. This is very strong support for the presence of undersaturation which can be used to decompression advantage.

Fig. 14: This summarizes the results of another experiment, the same as that shown in Fig. 13 but with a 17-hour saturation time on nitrogen. As can be seen, a similar level of bubbles was encountered, with a similar time course and again an undersaturating gas switch at 5 hours followed by decompression 40 minutes later produced no significant bubble formation.

Fig. 15: This experiment shows what can be expected in terms of bubble production following a direct decompression from saturation on nitrogen at 198 f.s.w. (7 Atm) to 116 f.s.w., which is the same first stop depth used in the experiment summarized in Figures 13 and 14. Here, however, because there was no undersaturating gas switch, large numbers of bubbles were expected and observed on reaching 116 f.s.w. Notice the bubbles required approximately 2 hours to reach a peak, and then subsided over a further 3-hour period to 0 with a small pulse at 7 hours. Decompression was resumed when no further bubbles were observed. Another striking observation of this experiment is the ratio of the mean bubble count to the variability observed. Here, there is a much smoother curve as a result of the decompression, presumably because a larger number of bubbles was produced, and the supersaturation was transient.

Fig. 16: This shows results of a further mask switch carried at 132 f.s.w. (5 Atm) following a 17-hour saturation on nitrogen. In this animal a lower bubble count was observed with the usual observation of periodic showers of bubbles lasting several minutes or more. Again, an undersaturating gas switch, this time at 8 hours, prevented further bubbles upon decompression.

Fig. 17: This shows results of a further experiment using a 4-hour saturation time applied at 198 f.s.w. (7 Atm) switching from nitrogen to helium at 0 time and from helium back to nitrogen at 4 hours. A brief pulse of bubbles follows this switch back to air, which could be due to the soluble gas effect, where any existing bubbles would be further expanded by being perfused with blood containing a more soluble gas than helium. In any case, following this shower of bubbles decompression after 40 minutes caused a larger pulse of bubbles but never exceeding more than 150/minute.

Fig. 18: This shows results of a similar experiment which produced a similar response following gas switch 1 on a much more brief pulse of bubbles following gas switch 2. Decompression to 116 f.s.w. 40 minutes after gas switch 2 again produced very few bubbles, which is further support for the undersaturating effects of the second gas switch.

Fig. 19: This shows results of a gas switch on an animal which showed a particularly low response to what in previous experiments caused bubble counts of 100-300/minute. Following a gas switch back to air and a 40-minute period of decompression to 116 f.s.w. the animal failed to produce any further bubbles. Compare this result with that shown for Figs. 20 and 21 where no undersaturating gas switch was imposed.

Fig. 20: Results of an experiment carried out identically to that shown in Fig. 19 but with no undersaturating gas switch applied prior to decompression. Decompression immediately after this gas switch failed to produce bubbles; this indicates that the animal must have been free of potential bubble sites to a much greater degree than most others examined in this project.

Fig. 21: This shows a further similar experiment two weeks later with the same animal again apparently free of bubble-forming sites. Even decompression to 116 f.s.w. with no undersaturating gas switch failed to trigger bubble formation.

Fig. 22: As an indication that this animal was not permanently free of bubble sites, this figure shows results of a gas switch following 17 hours on nitrogen applied by mask which resulted in a very high bubble count. The differences in bubble count produced in this experiment versus that shown in Figs. 19-21 could be due to saturation time but in view of the fact that very few bubbles were produced by decompression alone this explanation does not seem able to explain the differences in this experiment as compared to those shown in Figs. 19-21. Further, in this case after the second gas switch decompression 40 minutes later to 116 f.s.w. did produce bubbles which suggest strongly that the differences were due to the animal having regenerated its population of microgas nuclei prior to this experiment. Obviously differences in saturation time cannot explain the lack of decompression induced bubbles in Fig. 19 as compared to this experiment.

Fig. 23: This shows a comparison of steady state isobaric counterdiffusion (solid line) with the transient isobaric counterdiffusion applied by mask shown in Fig. 22 (dotted line). Both responses are plotted to the same scale of bubble counts versus time and it can be seen that both the SSIC experiment and the TIC experiment caused bubbles to form, grow, be collected, and detected at the central venous location in approximately the same time frame. Note the point shown in the figure where the bubble counter was saturated produces a wavy line which does not reflect the true bubble count, merely the fact that no bubble count is available. It is probable that bubbles at this stage were in the 3000-5000 level, but this cannot be confirmed with our counter. It is possible that a straight integrated signal energy approach might provide a rough estimate of this response. The top line is read against the right hand ordinate and reflects the depth of the experiment in f.s.w. At the point where the bubble counter saturated an increase in a half an atmosphere was applied. This caused no detectable change in the bubble count and therefore at 3½ hours was followed by a one atmosphere increase in pressure to 248 f.s.w. This also caused no detectable change in the bubble count, and at the right hand top arrow the chamber was switched back to air out of concern for the well being of the animal, which was by now showing severe signs of stress due probably to cardiopulmonary embolization. Within an hour and a half after the imposition of a near switch the bubble count had returned to less than 100/minute and a brief decompression to 132 f.s.w. to allow a technician to lock in and remove the mask also produced a relatively small number of bubbles. Following this treatment decompression was routine and the animal experienced no further stress.

Fig. 24: This shows results of an identical experiment but carried out at 132 f.s.w. In this case also the experiment with TIC shown in Fig. 22 is also plotted on the same time course following the gas switch (dotted line) or imposition of SSIC (solid line). In this case, in contrast to that shown in Figure 23, a longer time was required for the bubble count to build and grow, presumably because of the (a) fewer number of gas nuclei triggered because of the lower ΔP, and (b) a longer time required for bubble growth and clearance to the central venous location, also possible due to the lower gradient. In this case also the periodicity in bubble counts with time is evident where the bubble count decreases rapidly from the saturating level at over 2000 down to countable levels several times during the course of the experiment. In this case the bubble count returned to less than 100/minute within 40 minutes of gas switch 2.

Fig. 25: This shows results of a similar gas switch also carried out at 132 f.s.w. imposing SSIC on an animal but using argon as the breathing gas and helium again surrounding the animal at the point of time shown at the left. In this case a similarly long time was required for the appearance of bubbles at the central venous location (3 hours) but the bubble count increased very rapidly following this point, whereas in the previous figure which imposed SSIC with nitrogen, a slower development of bubble counts was evident. In this experiment too the counter was saturated, preventing estimates of the top number of bubbles per minute. However, within six hours sufficient discomfort was evident in the animal to require switching back to air. Again, the bubble counts returned to 0 within 40 minutes following this gas switch, suggesting that the lag period shown at the beginning of the experiment is due to bubble growth and not due to complicated factors of bubble clearance.

Fig. 26: This shows results of a SSIC experiment carried out at 99 f.s.w., this imposing a still lower ΔP on the animal again with argon and helium. In this situation the same delay in bubble count rate was observed with again a rather rapid increase to the saturating levels. This experiment was cut off at 5 hours exactly and the bubble count returned to 0 within less than 30 minutes while removing the SSIC gradient. Again, this is good evidence that the formation of bubbles and their growth to a "collectable" size is responsible for the delayed appearance since immediately removing the gradient also very rapidly removed the bubbles.

FIGURE 1

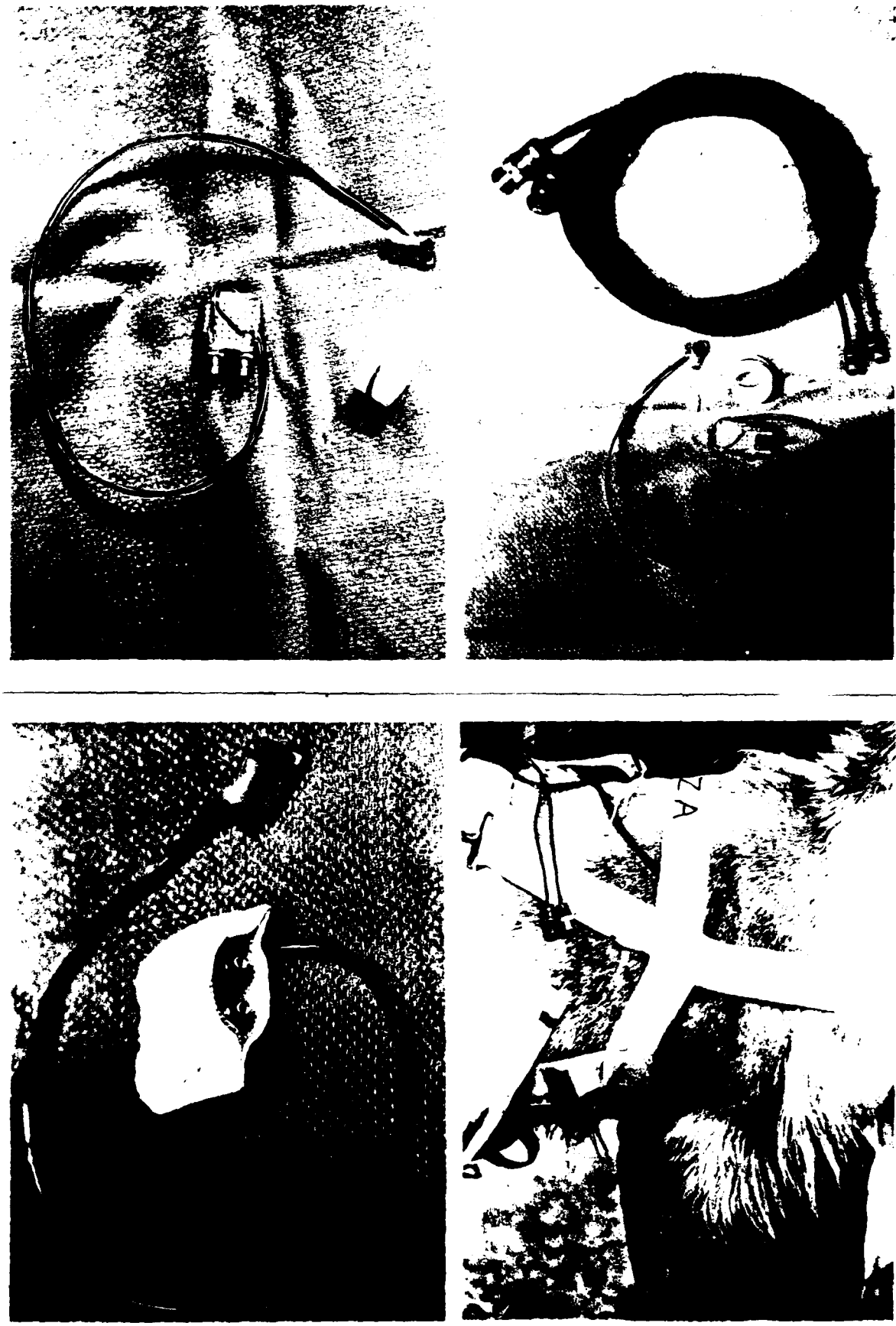


FIGURE 2

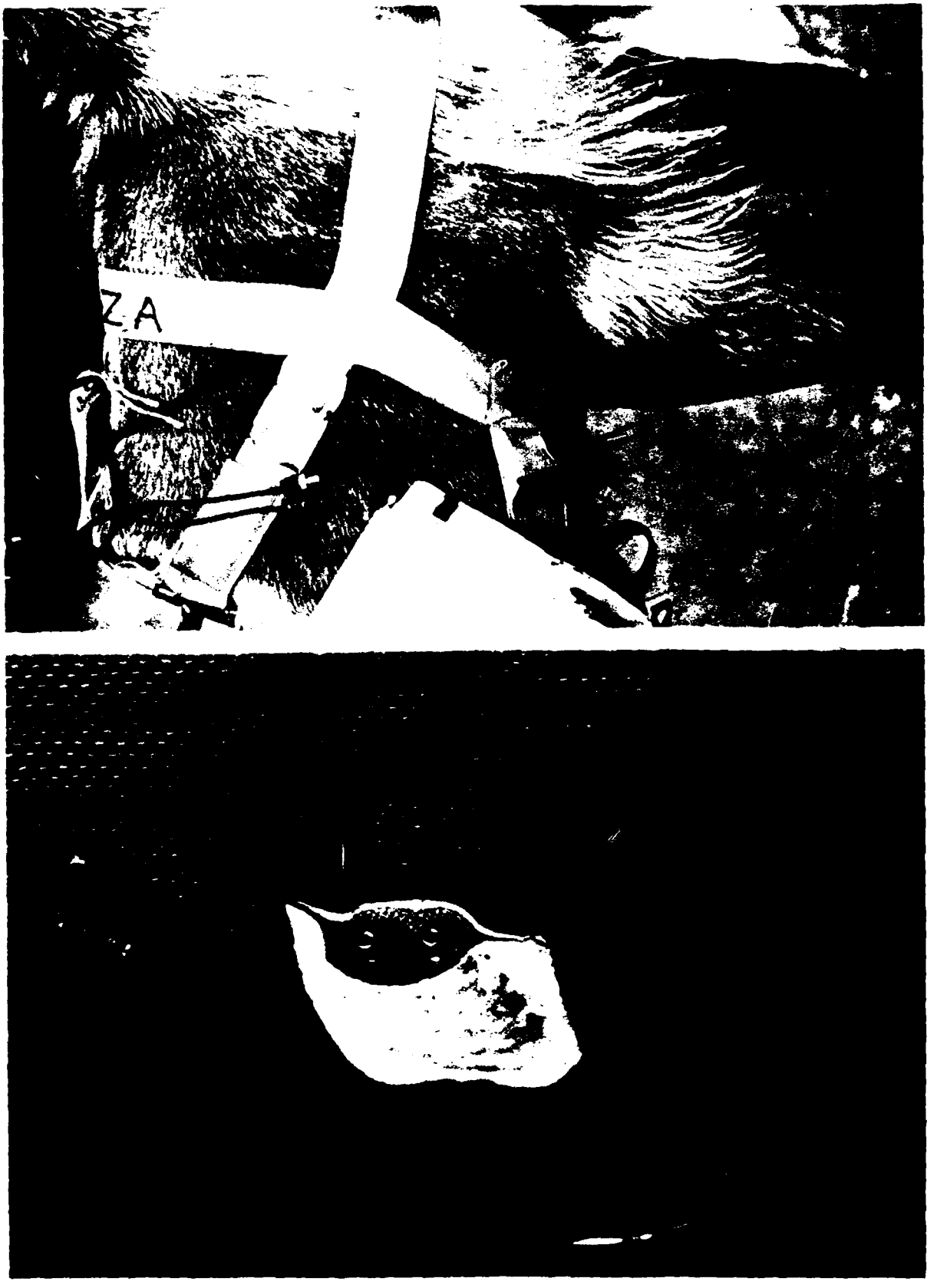
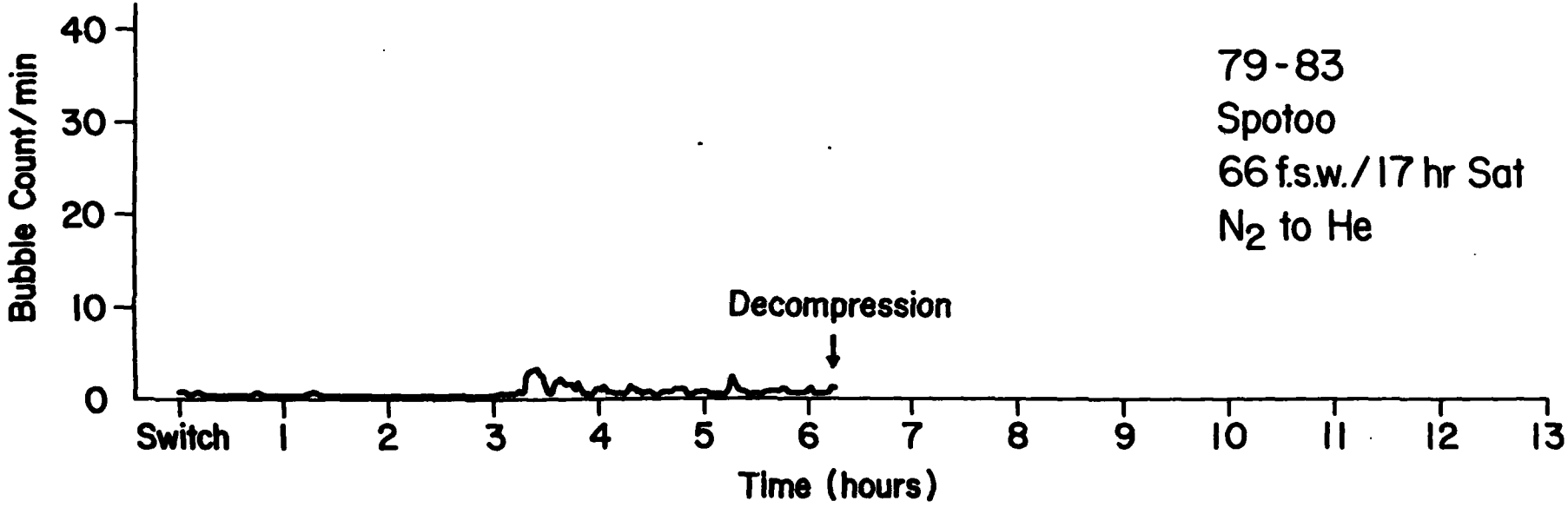


FIGURE 3

FIGURE 4



D'Aoust: 38

FIGURE 5

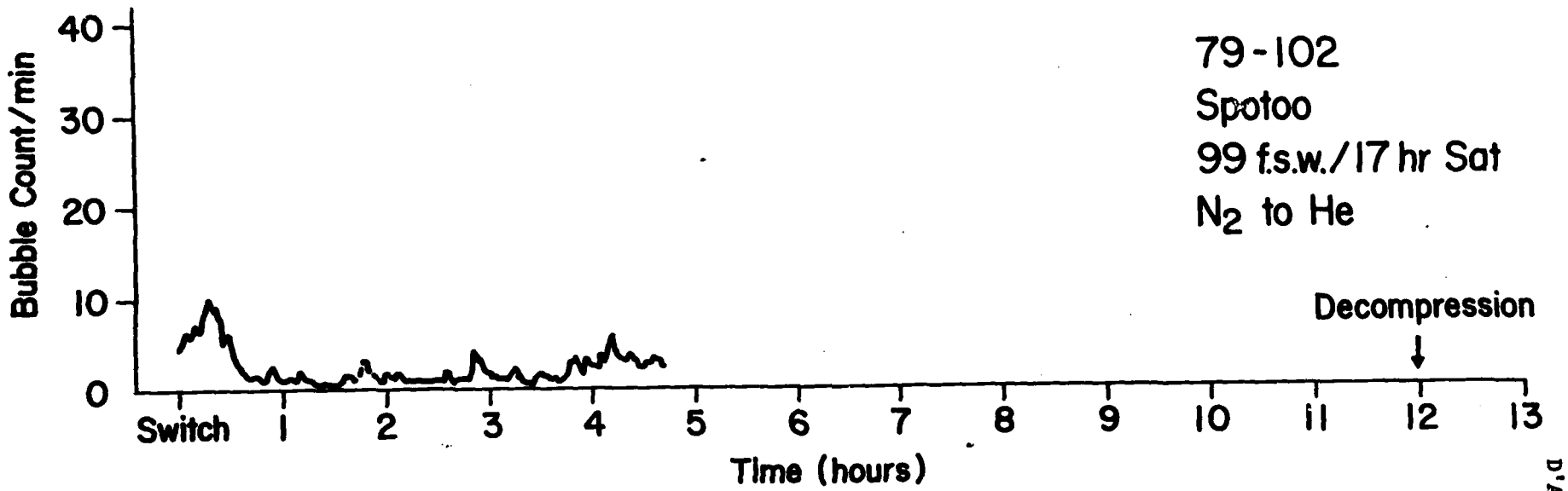

Bubble Count/min
40
30
20
10
0
Switch
1
2
3
4
5
6
7
8
9
10
11
12
13
Time (hours)
79-102
Spotoo
99 f.s.w./17 hr Sat
N_2 to He
Decompression

FIGURE 6

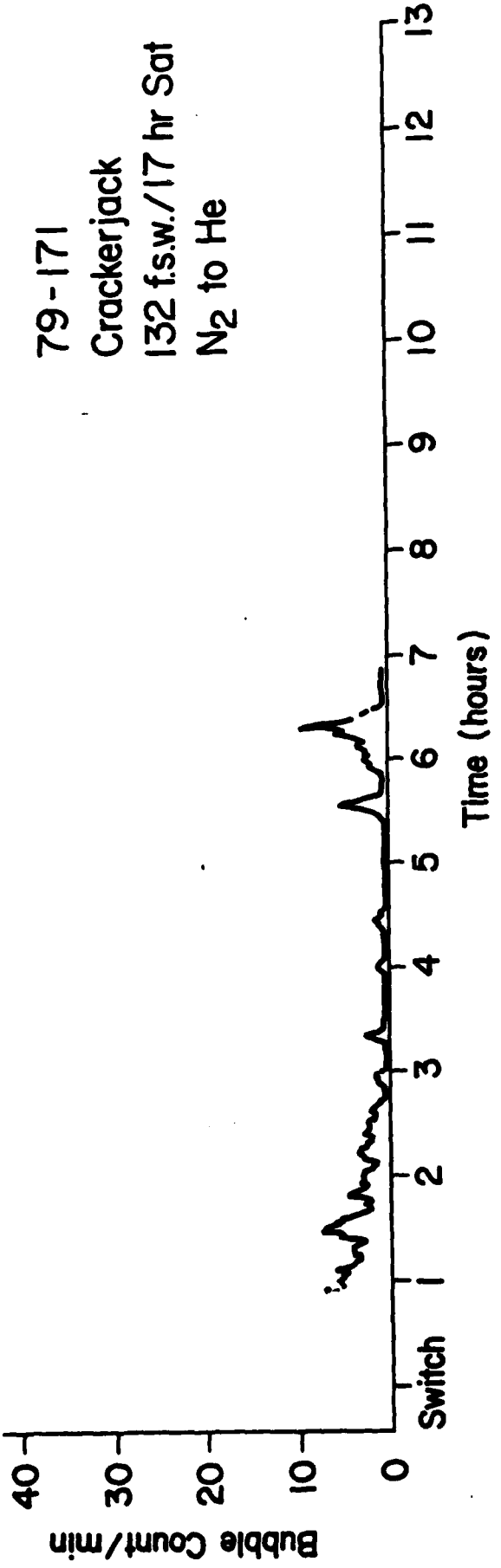
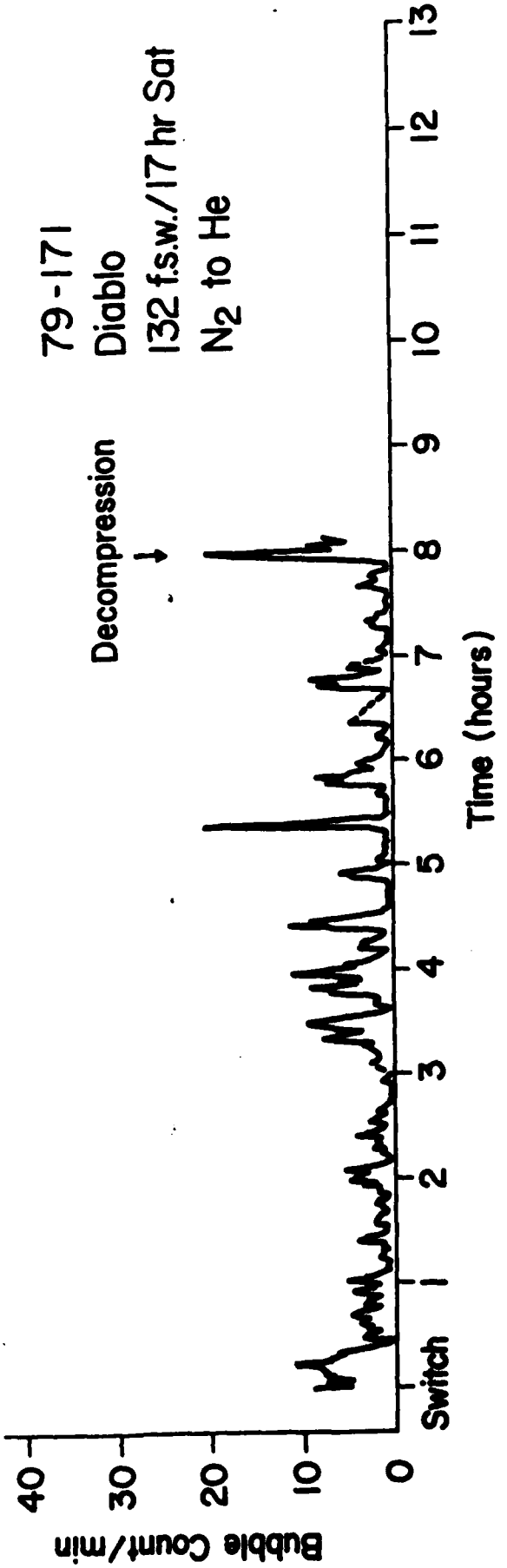

79-171
Crackerjack
132 f.s.w./17 hr Sat
N_2 to He
Bubble Count/min
0
10
20
30
40
Switch
1
2
3
4
5
6
7
8
9
10
11
12
13
Time (hours)

FIGURE 7


79-171
Diablo
132 f.s.w./17 hr Sat
N_2 to He
Decompression
Bubble Count/min
0
10
20
30
40
Switch
1
2
3
4
5
6
7
8
9
10
11
12
13
Time (hours)

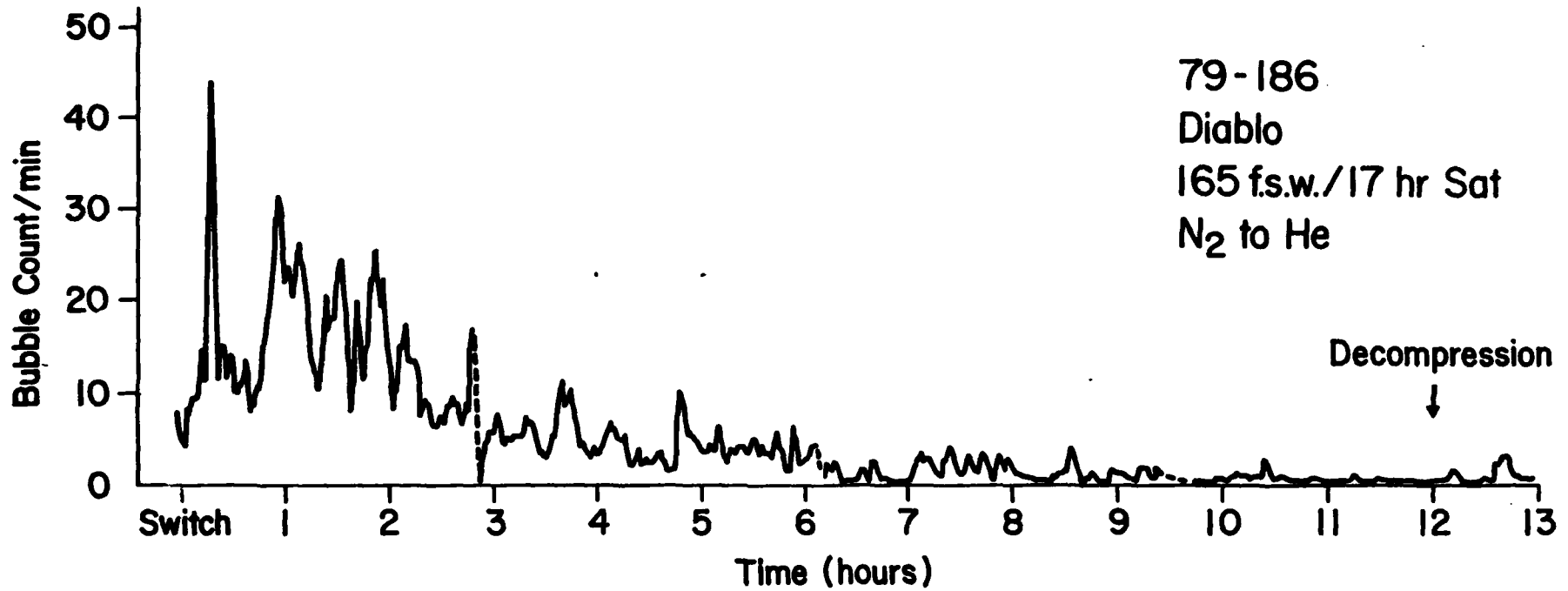
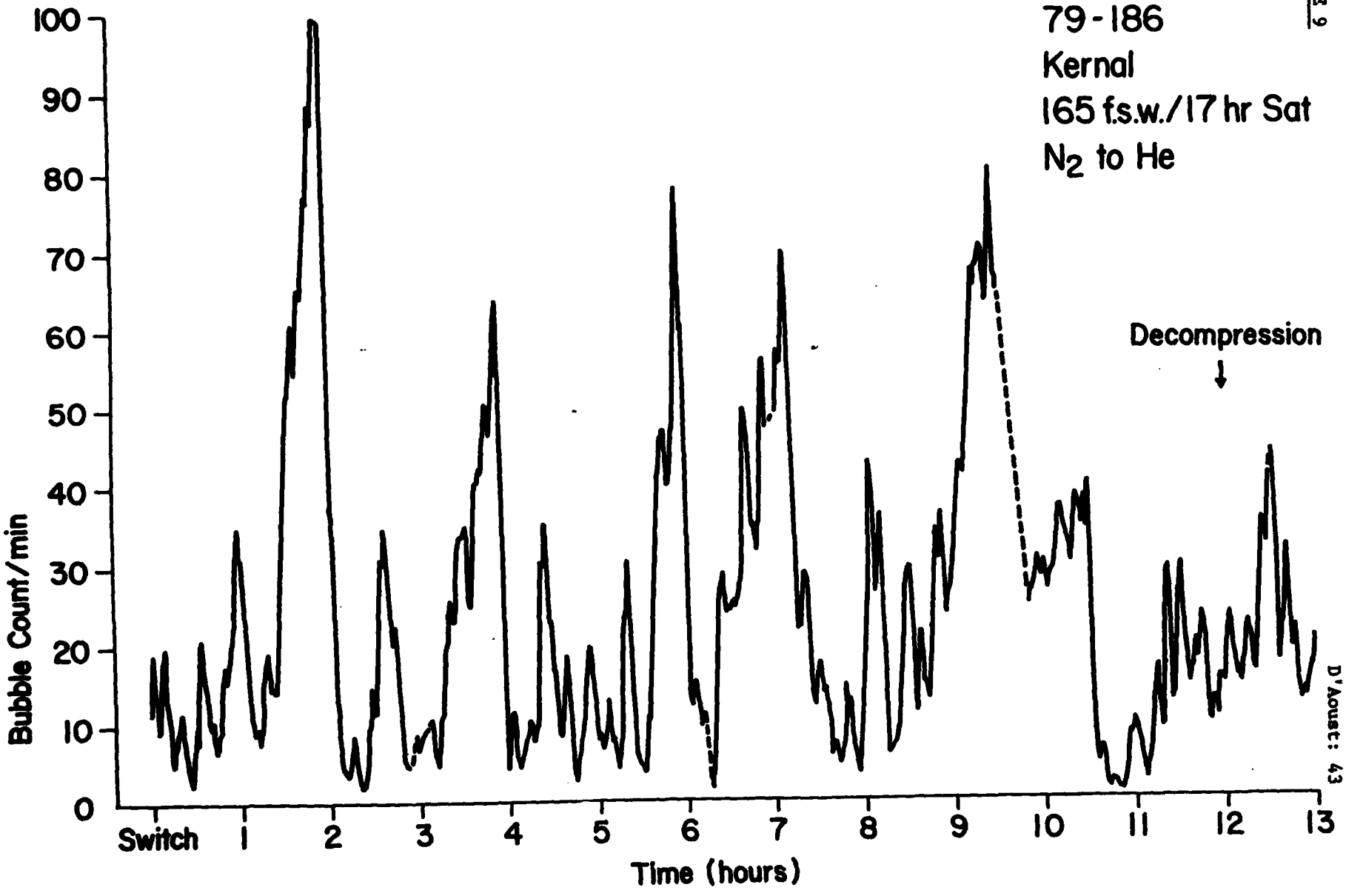

79-186
Diablo
165 f.s.w./17 hr Sat
N_2 to He
Decompression
Bubble Count/min
50
40
30
20
10
0
Switch
1
2
3
4
5
6
7
8
9
10
11
12
13
Time (hours)

FIGURE 8

FIGURE 9


79-186
Kernal
165 f.s.w./17 hr Sat
N_2 to He
Decompression
Bubble Count/min
100
90
80
70
60
50
40
30
20
10
0
Switch
1
2
3
4
5
6
7
8
9
10
11
12
13
Time (hours)
D'Aoust: 43

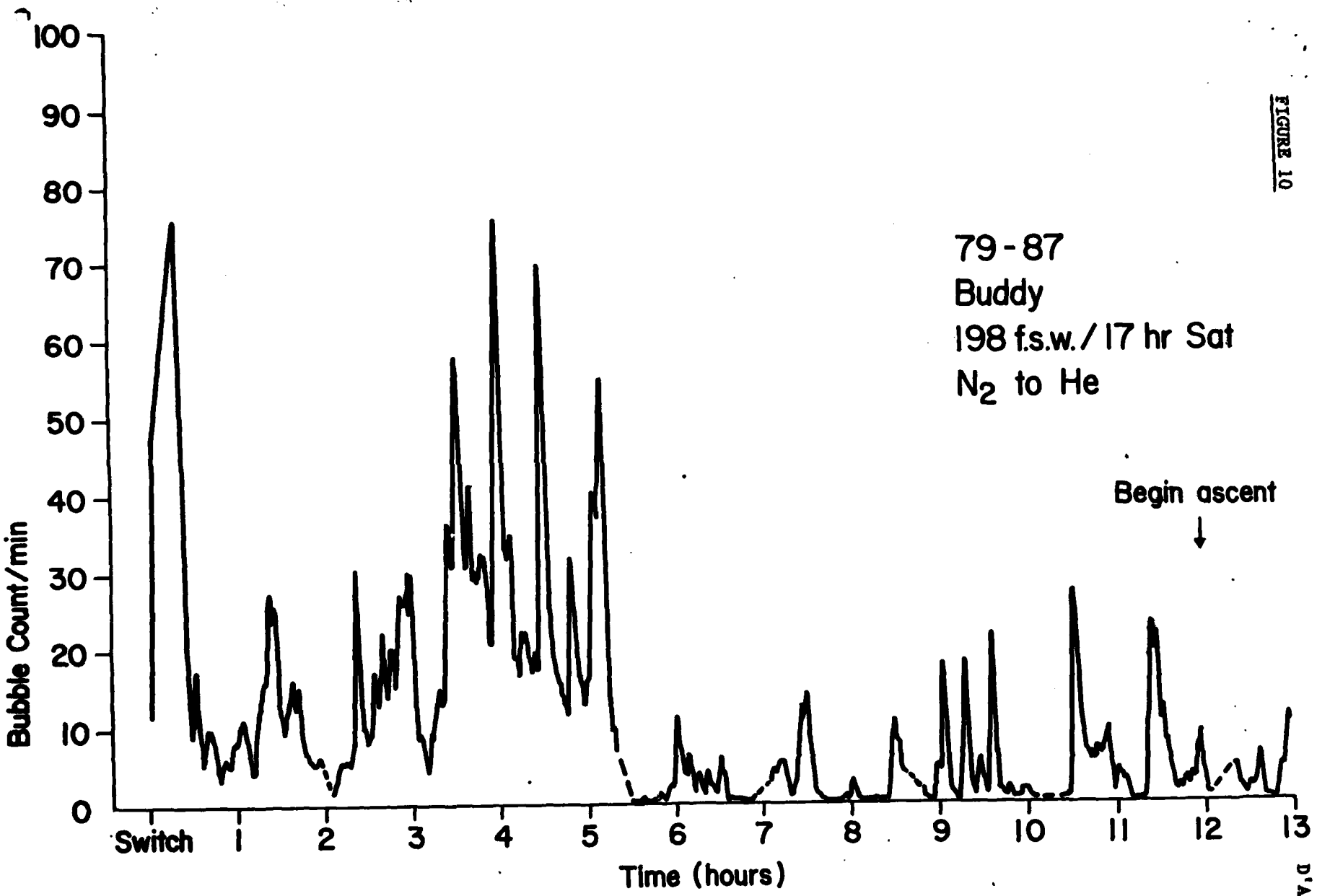


FIGURE 10

D'Aoust: 44

FIGURE 11 a-f

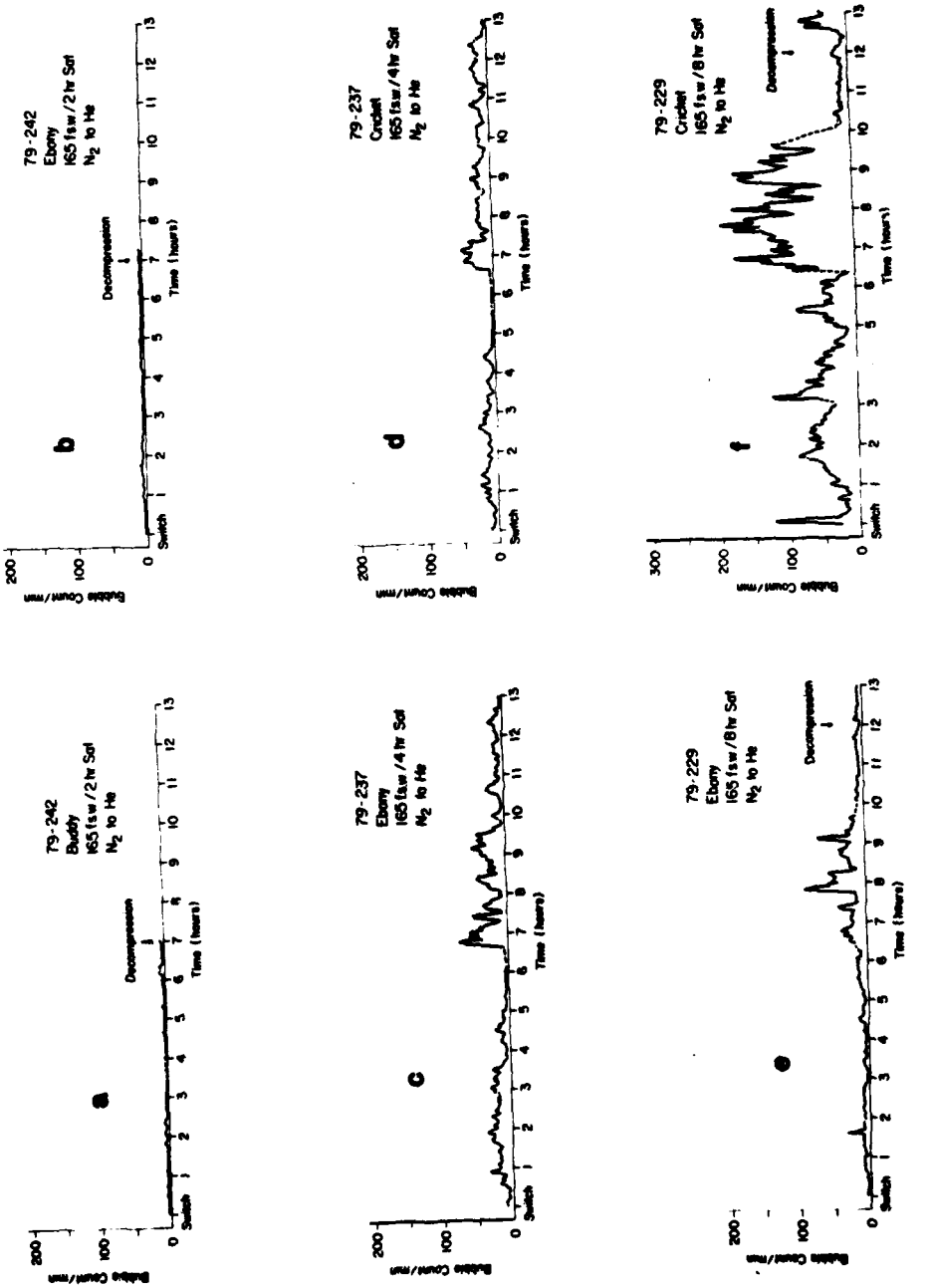

79-242
Buddy
165 fsw / 2 hr Sat
N_2 to He
a
79-242
Ebony
165 fsw / 2 hr Sat
N_2 to He
b
79-237
Ebony
165 fsw / 4 hr Sat
N_2 to He
c
79-237
Cricket
165 fsw / 4 hr Sat
N_2 to He
d
79-229
Ebony
165 fsw / 8 hr Sat
N_2 to He
e
79-229
Cricket
165 fsw / 8 hr Sat
N_2 to He
f
Decompression
Switch
Time (hours)
Bubble Count / min

FIGURE 12

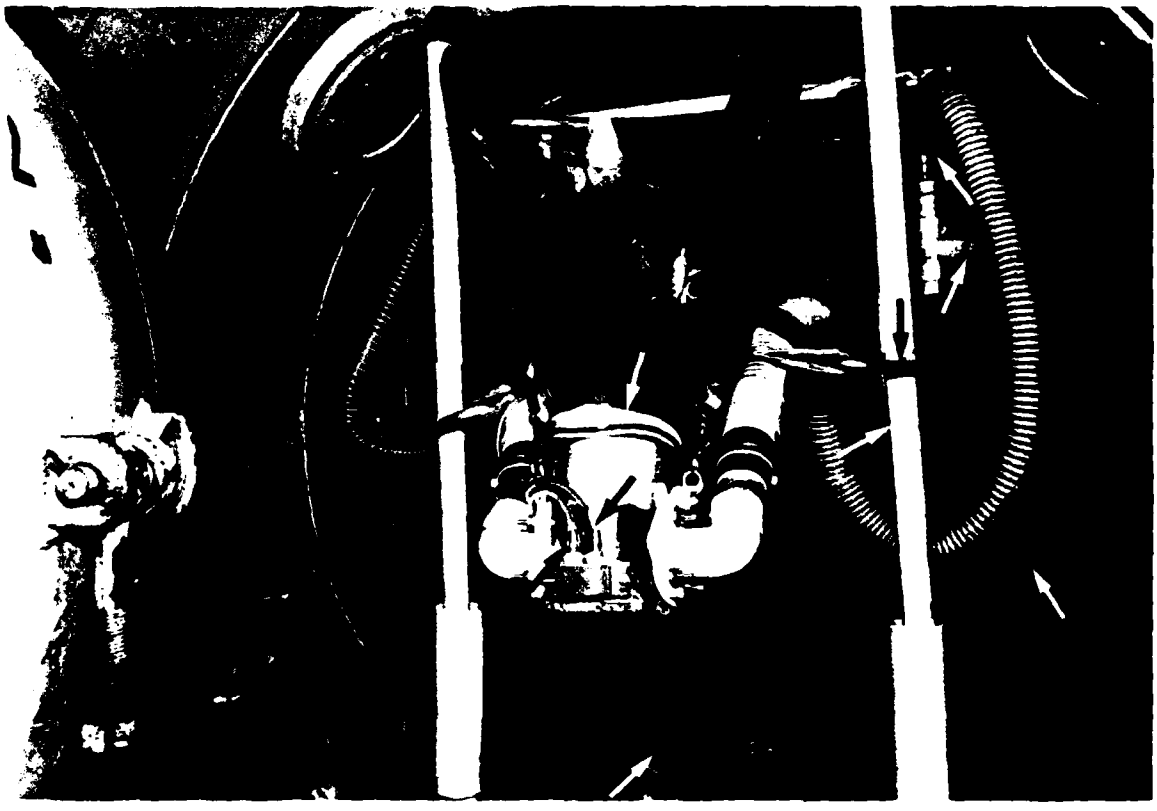


FIGURE 13

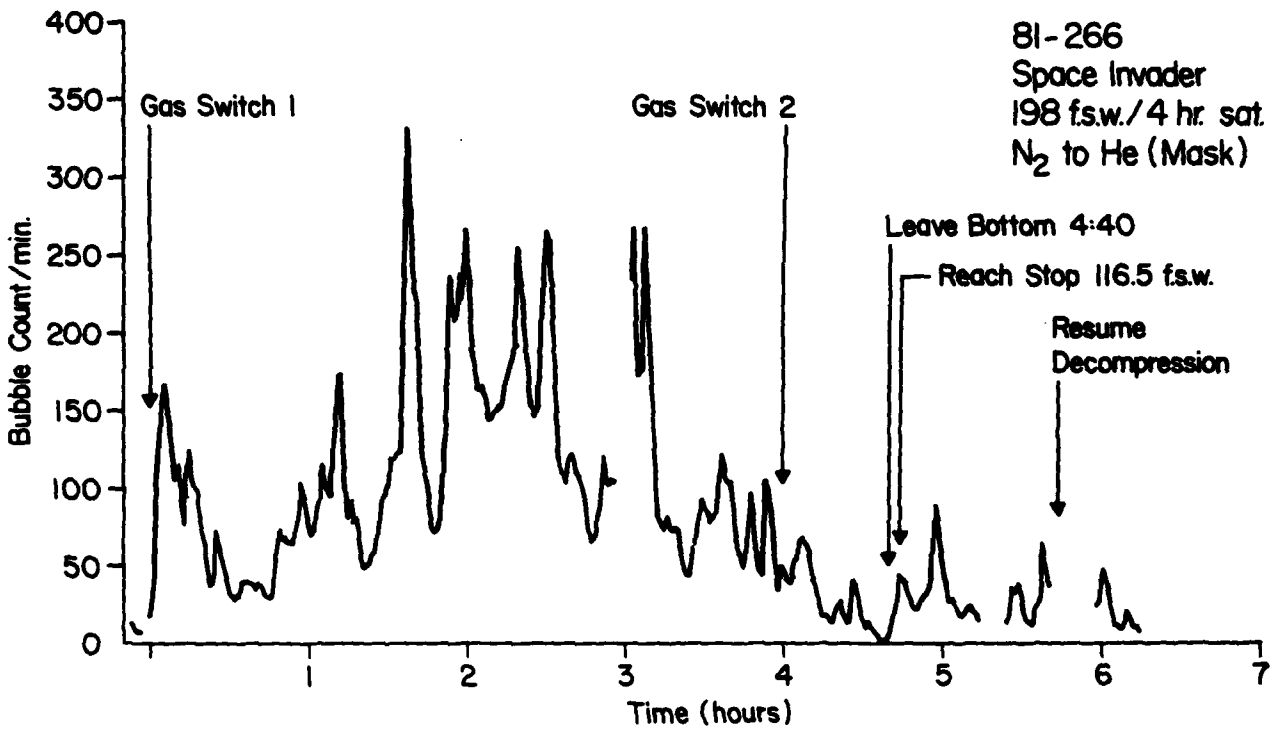


FIGURE 14

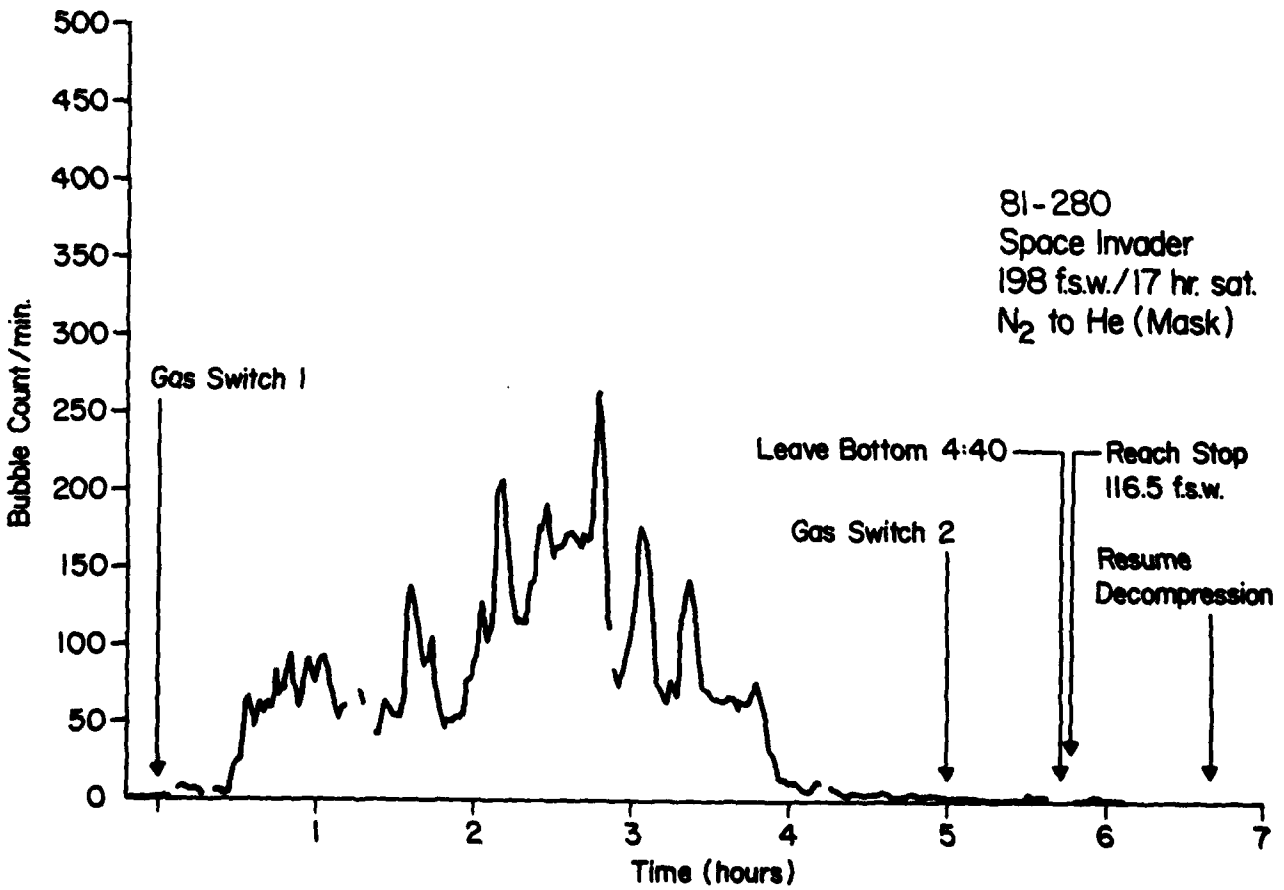


FIGURE 15

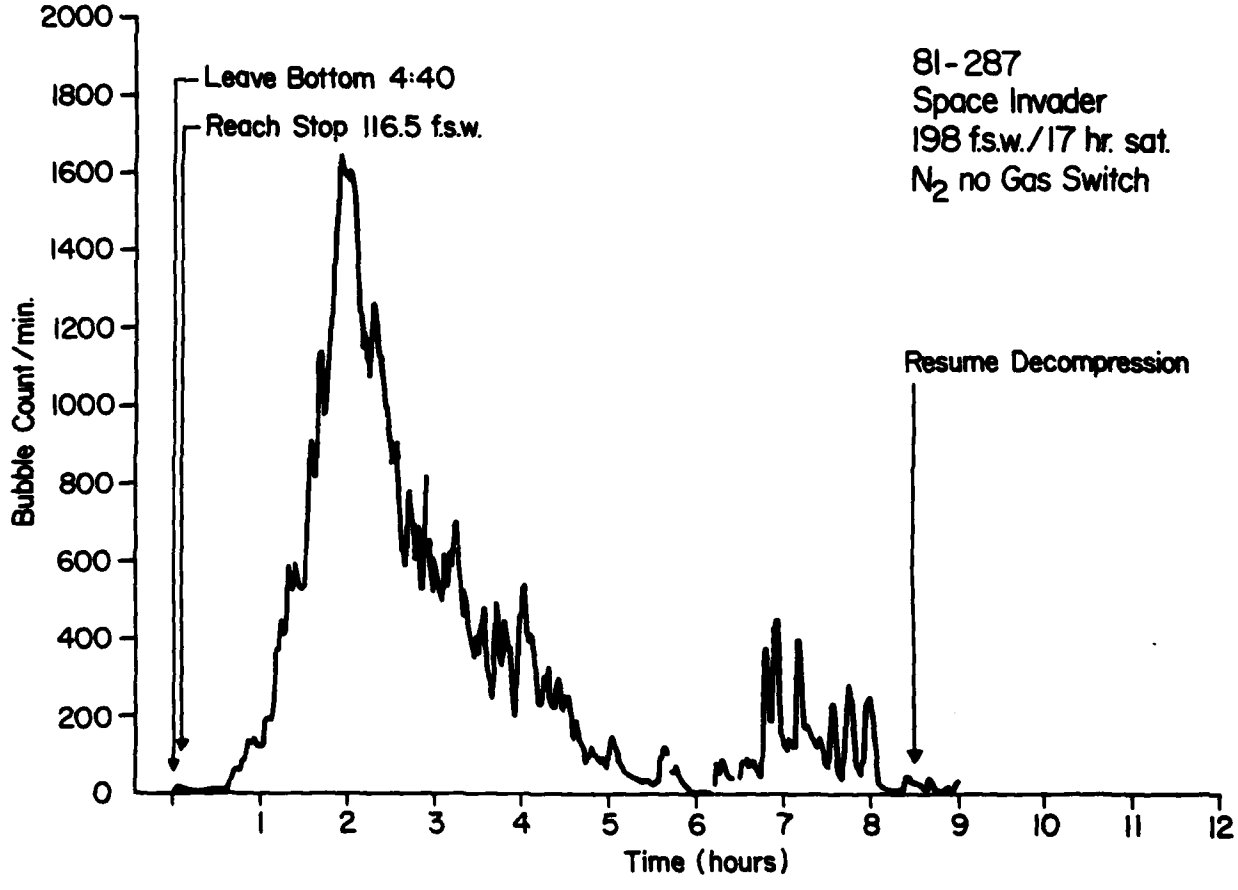

2000
1800
1600
1400
1200
1000
800
600
400
200
0
Bubble Count/min.
Leave Bottom 4:40
Reach Stop 116.5 f.s.w.
81-287
Space Invader
198 f.s.w./17 hr. sat.
N_2 no Gas Switch
Resume Decompression
1
2
3
4
5
6
7
8
9
10
11
12
Time (hours)

FIGURE 16

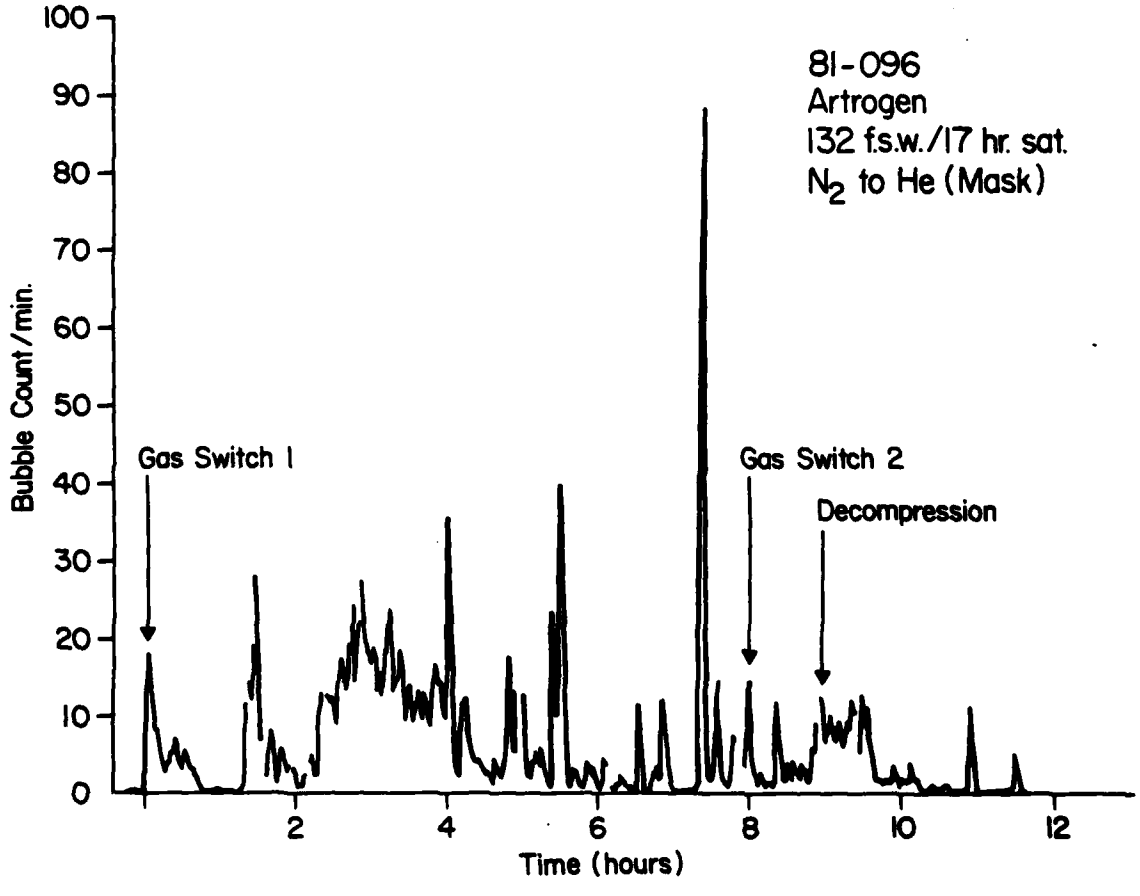

81-096
Artrogen
132 f.s.w./17 hr. sat.
N_2 to He (Mask)
Gas Switch 1
Gas Switch 2
Decompression
Bubble Count/min.
Time (hours)
0
10
20
30
40
50
60
70
80
90
100
2
4
6
8
10
12

FIGURE 17

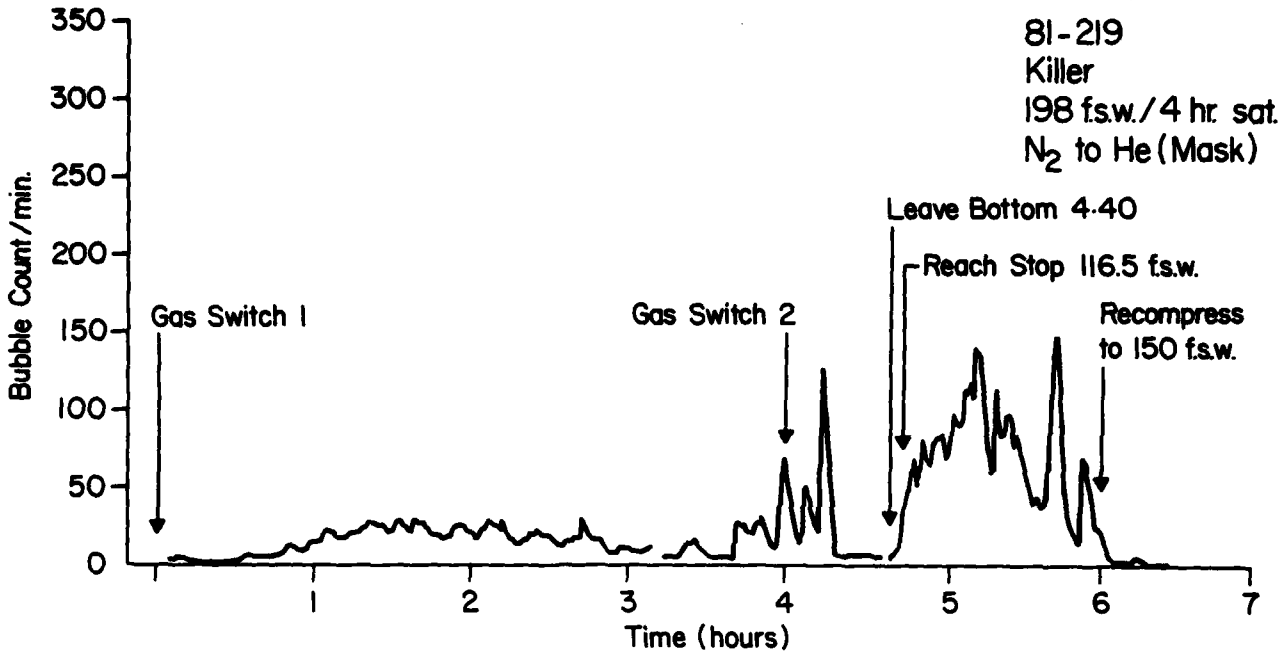
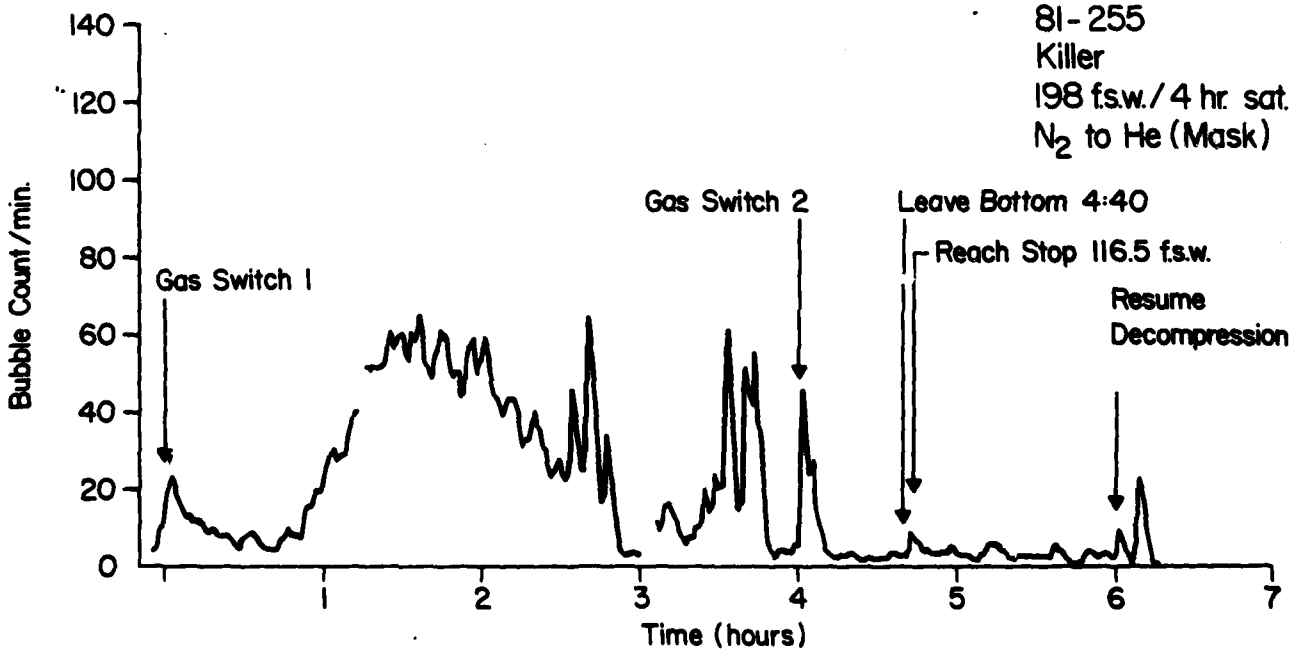


FIGURE 18



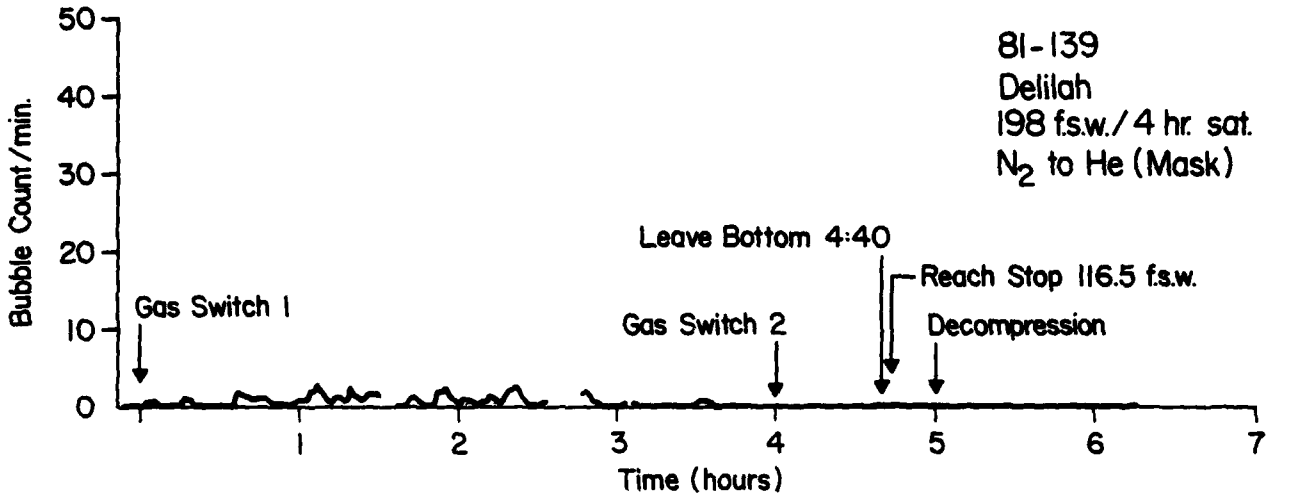


FIGURE 19

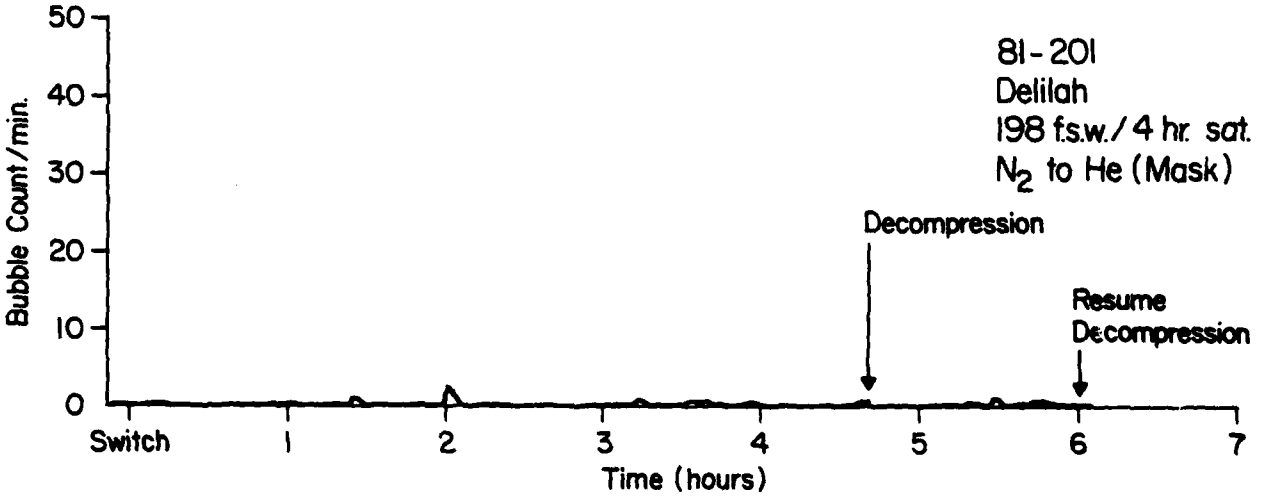


FIGURE 20

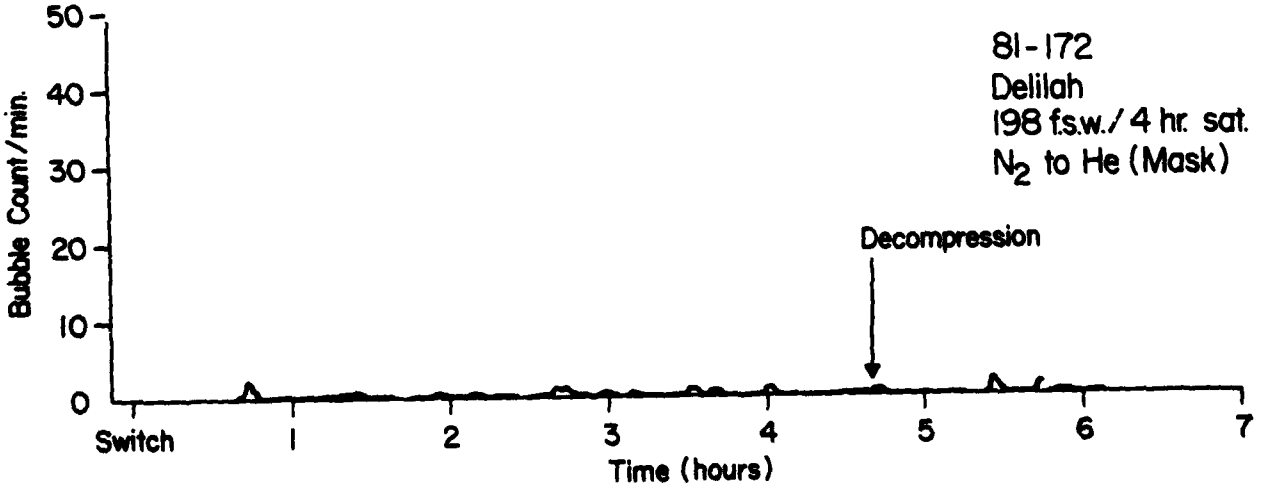


FIGURE 21

FIGURE 22

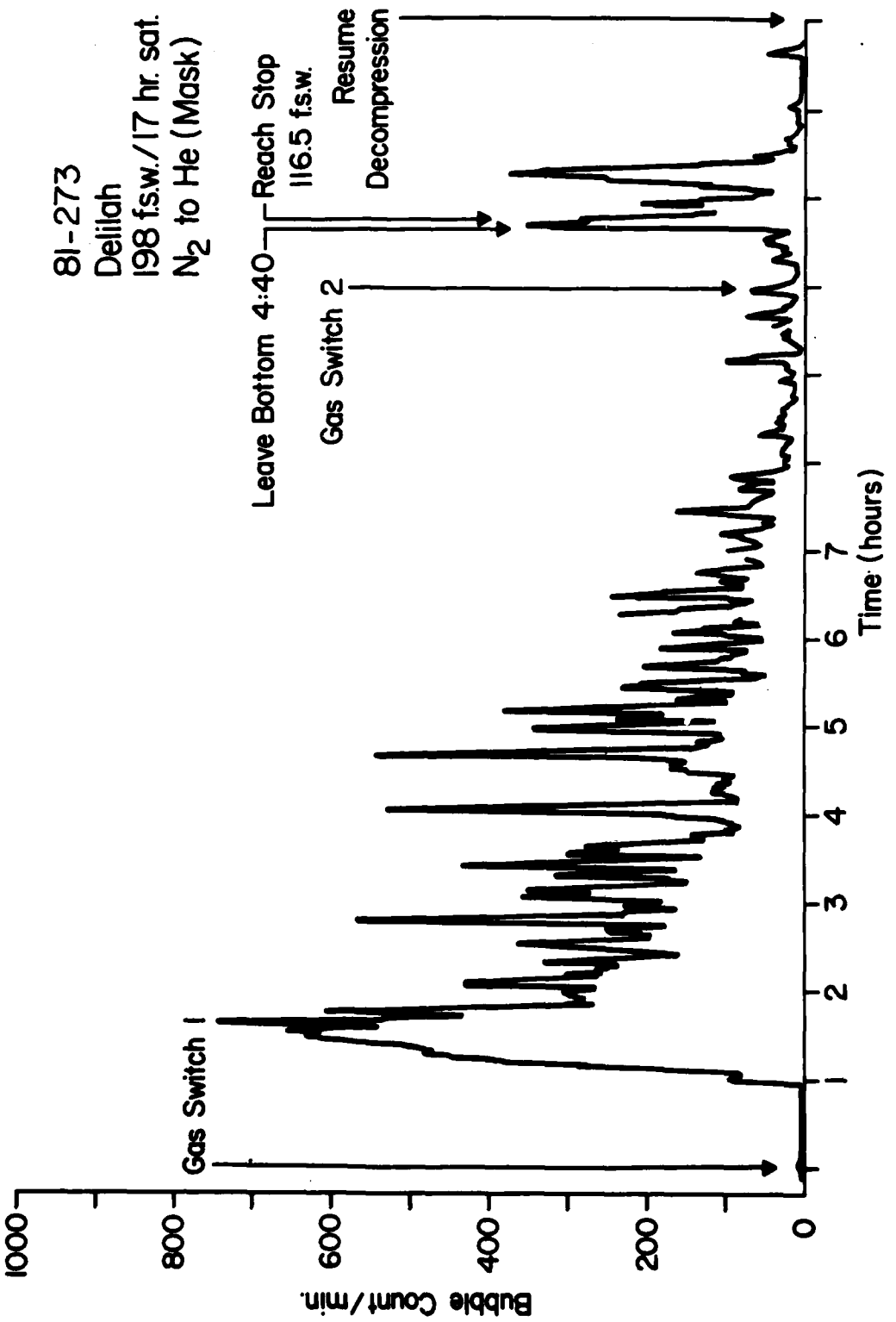
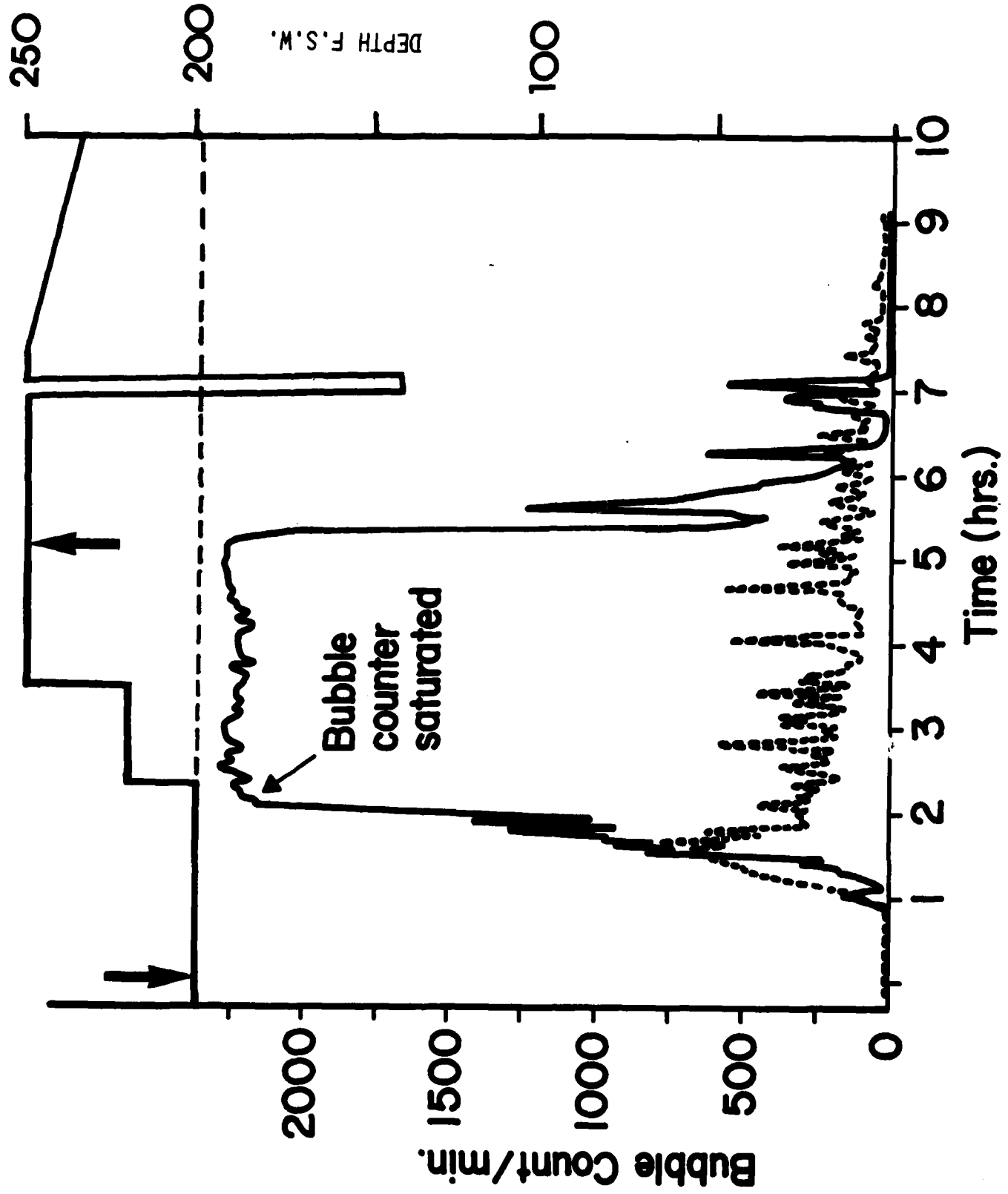
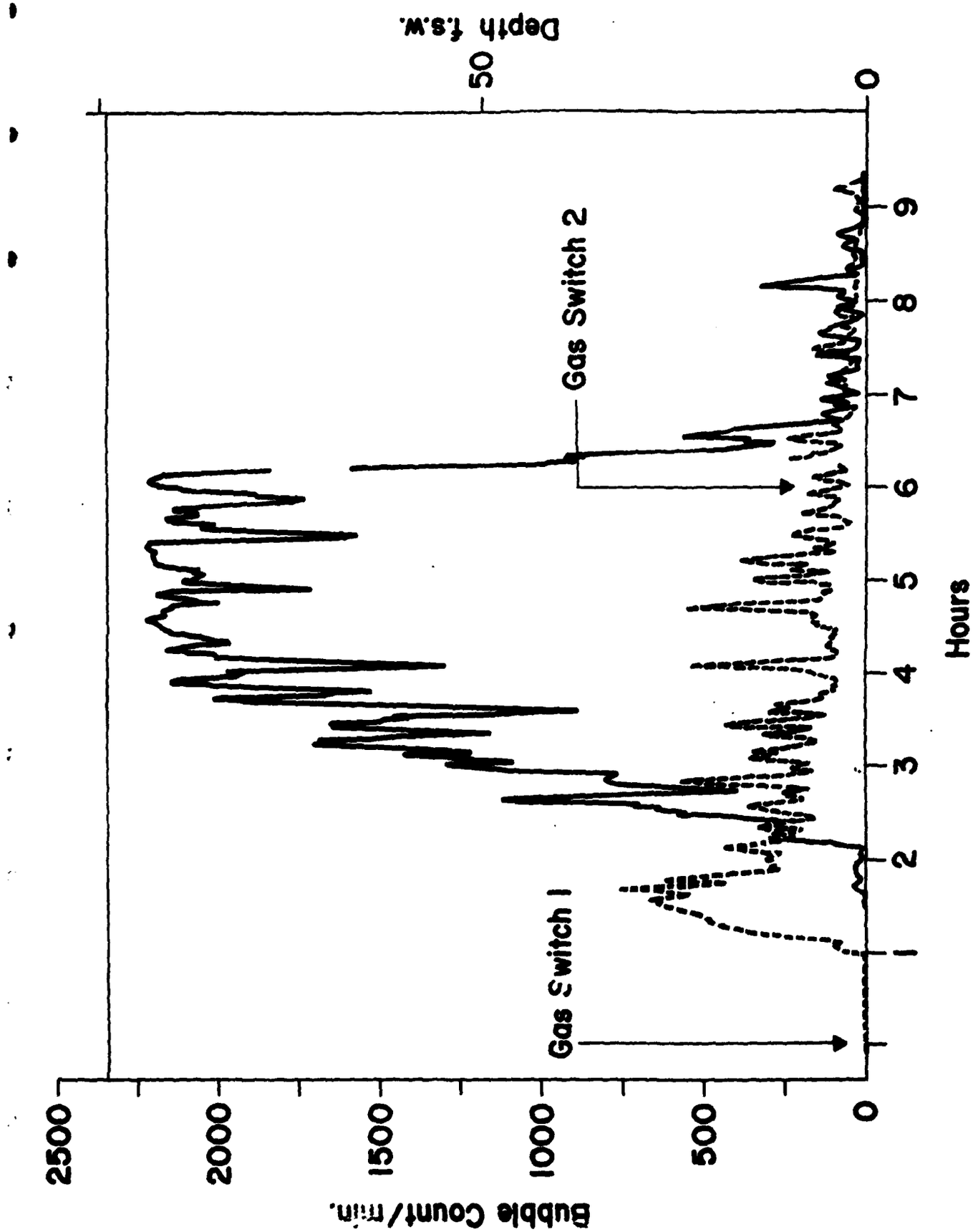

81-273
Delilah
198 f.s.w./17 hr. sat.
N_2 to He (Mask)
Leave Bottom 4:40
Reach Stop
116.5 f.s.w.
Resume
Decompression
Gas Switch 2
Gas Switch 1
Bubble Count/min.
0
200
400
600
800
1000
1
2
3
4
5
6
7
Time (hours)

FIGURE 23


DEPTH F.S.W.
250
200
100
Bubble counter saturated
Time (hrs.)
1
2
3
4
5
6
7
8
9
10
Bubble Count/min.
2000
1500
1000
500
0


Depth f.s.w.
50
0
Gas Switch 2
Gas Switch 1
1
2
3
4
5
6
7
8
9
Hours
2500
2000
1500
1000
500
0
Bubble Count/min.

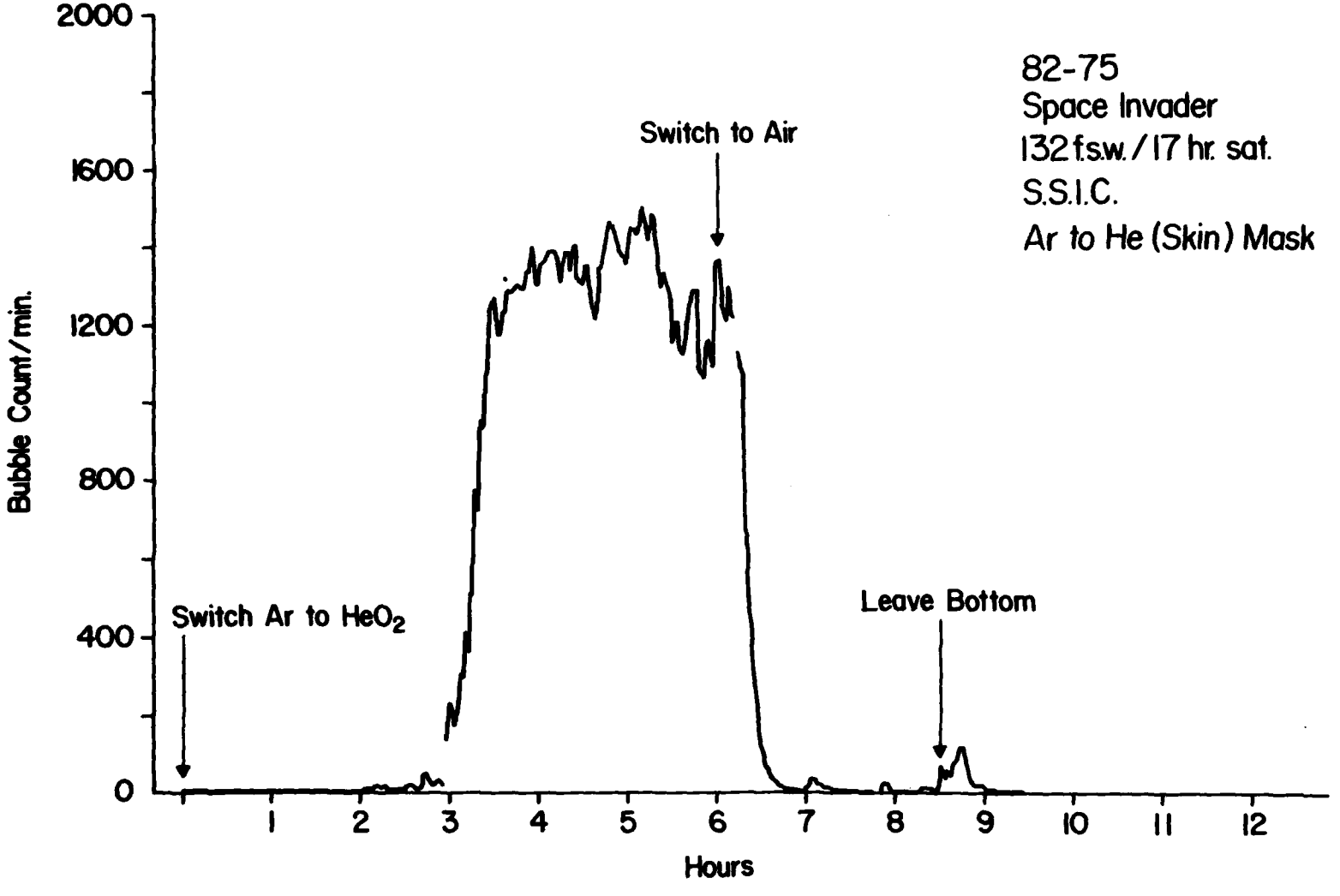

2000
1600
1200
800
400
0
Bubble Count/min.
Switch to Air
Switch Ar to HeO2
Leave Bottom
1
2
3
4
5
6
7
8
9
10
11
12
Hours
82-75
Space Invader
132 f.s.w. / 17 hr. sat.
S.S.I.C.
Ar to He (Skin) Mask

FIGURE 25

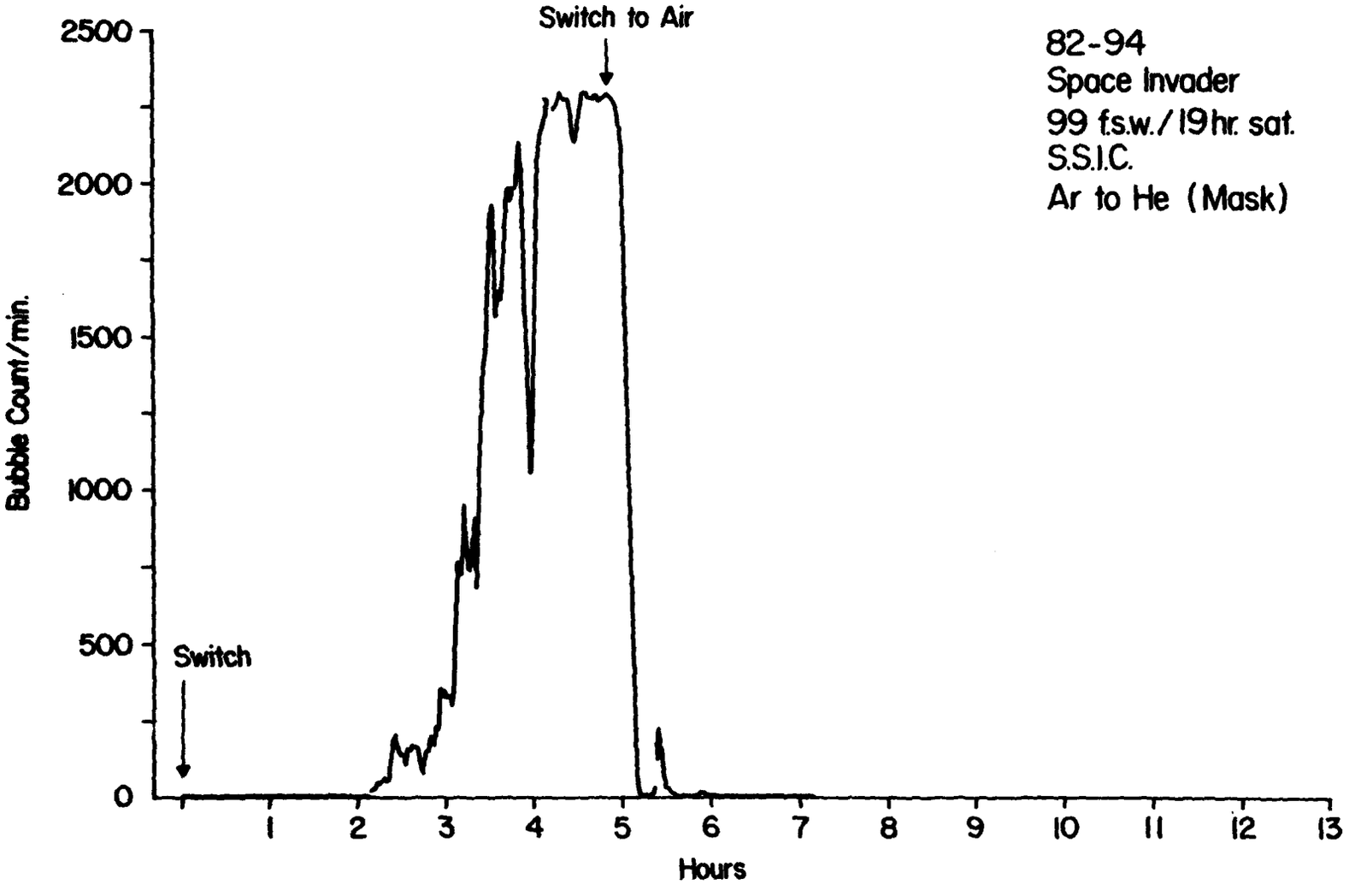

Switch to Air
82-94
Space Invader
99 f.s.w./19hr. sat.
S.S.I.C.
Ar to He (Mask)
Bubble Count/min.
2500
2000
1500
1000
500
0
Switch
1
2
3
4
5
6
7
8
9
10
11
12
13
Hours

FIGURE 26

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1. REPORT NUMBER: N00014-78-C-0749	2. GOVT ACCESSION NO. / 3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle)	5. TYPE OF REPORT & PERIOD COVERED: Final report 9/1/78 - 8/30/81
	6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s): Brian G. D'Aoust	8. CONTRACT OR GRANT NUMBER(s): N00014-78-C-0749
9. PERFORMING ORGANIZATION NAME AND ADDRESS: Virginia Mason Research Center, 1000 Seneca Street, Seattle, WA 98101	10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS
11. CONTROLLING OFFICE NAME AND ADDRESS	12. REPORT DATE: July 19, 1982
	13. NUMBER OF PAGES
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)	15. SECURITY CLASS. (of this report)
	15a. DECLASSIFICATION/DOWNGRADING SCHEDULE
16. DISTRIBUTION STATEMENT (of this Report): This document has been approved for public release and sale; its distribution is unlimited.	
17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)	
18. SUPPLEMENTARY NOTES: Prepared as final report for contract #N000-14-78-C-0749	
19. KEY WORDS (Continue on reverse side if necessary and identify by block number): TRANSIENT ISOBARIC COUNTERDIFFUSION, STEADY STATE ISOBARIC COUNTERDIFFUSION, DECOMPRESSION SICKNESS, DECOMPRESSION TABLES, ULTRASONIC BUBBLE DETECTION, BUBBLES.	

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

In order to develop an experimentally supportable and predictive theory of gas elimination and bubble formation which is needed both for avoiding and treating decompression sickness ~~(1,3,4,27,28,63)~~, we need further understanding of both the physical and physiological factors involved in bubble formation and growth. Recent studies in this laboratory ~~(12-14)~~ have demonstrated not only the interpretive difficulty associated with decompression experiments - whether or not they use doppler bubble detection - but also the advantages associated with isobaric experiments involving either transient or steady-state counter-

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SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

techniques (11); (5) a very pronounced periodicity in numbers of bubbles with time following a gas switch which is as yet unexplained but may be most easily accounted for on the basis of periodic blood flow changes linked with other natural cycles. Periods appear to range in time from 40-90 minutes, and may be due to simple factors such as bubbles building up and sticking in areas of sluggish venous flow and then being released over a period of several minutes.

Finally, perspectives for future work in this area are very encouraging in that our results confirmed and extended our previous work and have suggested that combined experiments where a given area of skin is masked (with an ability to pass helium over it) and combined with breathing a more soluble gas (such as nitrous oxide) to produce central venous bubbles, would then allow an approximate calculation of actual numbers of bubble sites in the skin! This has never before been possible; however, the advantage of this hypothesis is that it can be tested and is no longer subject to the uncertainties inherent in post-decompression studies.


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