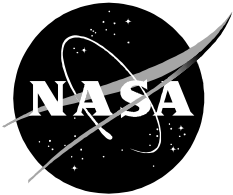


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Gender and Decompression Sickness: A Critical Review and Analysis

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ACRONYMS AND NOMENCLATURE

AFB	Air Force Base
ATM	atmosphere
BCP	birth control pill
DCS	decompression sickness
EVA	extravehicular activity
JSC	Johnson Space Center
kg	kilogram
M-H	Mantel-Haenszel
ml	milliliter
N ₂	nitrogen
O ₂	oxygen
PB	prebreathe
PFO	patent foramen ovale
PMS	premenstrual syndrome
psia	pounds per square inch absolute
SD	standard deviation
T-W	Tarone-Ware
VGE	venous gas emboli

ABSTRACT

The statement “we are a slave to our hormones” captures a central theme in this review and discussion about gender and the risk of decompression sickness (DCS). Hormones are potent compounds that effect and integrate every system of the body. Hormones profoundly shape the body, and ultimately our response to any stress. If there is a gender-effect on the risk of DCS and venous gas emboli (VGE), then it is ultimately linked to how we respond to the decompression stress or more formally, the decompression dose.

I addressed the following questions: are women at greater risk of DCS and VGE at certain times in their reproductive cycle, is risk modified by the use of birth control pills (BCP), and is there a difference in overall risk between men and women under the same decompression dose? Most cases of DCS present as symptoms of pain, and few as signs. Since volunteering a symptom is biased by many factors, the presence of VGE in controlled experiments provides an alternative and unbiased indicator of the effective decompression dose. There may be no real practical difference in the risk of DCS between men and women, but a “macho” factor in men and a hypersensitivity to pain during part of the reproductive cycle in some women could produce an artificial difference that is incorrectly attributed to a real physiological difference.

There was generally no rigorous control over or accounting for the decompression dose from SCUBA diving activities. There were only a few cases of DCS, so there were inadequate response data in divers to evaluate. Both of these deficiencies were also present in most, but not all, of the results from research in altitude chambers. All except one report described retrospective analyses, several analyses were underpowered from a statistical perspective, or the investigator used statistics inappropriately to make a point. Some of the best gender data were from research on unrelated topics in hypobaric altitude chambers. The gender results became part of a research effort, and more experimental control was exerted compared to results from divers or aviators “in training”, or from sport diving activities.

My summary comments consider information from both the few abstracts and few reports that were available. Except for the observation of more Type II DCS in women, particularly in

women who fly after diving, there was no compelling evidence of a difference in DCS risk between men and women SCUBA divers. Many women that presented with DCS symptoms seemed to be in or near menses, with statistically fewer cases reported as time increased from menses. There was no compelling evidence that the use of BCP in SCUBA divers increases the risk of DCS. There were insufficient data about VGE from SCUBA diving to make any conclusion about the incidence of VGE and gender. In contrast, there were ample data about VGE from research in altitude chambers. Women produced less VGE and less Grade IV VGE compared to men under the same decompression dose, certainly when resting oxygen prebreathe (PB) was performed prior to ascent to altitude. Dual-cycle ergometry exercise during PB tends to reduce the differences in VGE between men and women for reasons not completely understood. There was no compelling evidence that the risk of altitude DCS was different between men and women. However, a large number of DCS cases were associated with menses, and the use of BCP did seem to put women at a slightly greater risk than those that did not use BCP. There were substantial observations that women comprised a larger number of difficult cases that required complicated medical management. It is certainly evident that information about the menstrual cycle and the use of BCP needs to be routinely collected in future research about DCS in altitude chambers. It is in this research environment that conclusive evidence might be found.

INTRODUCTION

Observation precedes detailed investigation. It has been observed that women seem to be at greater risk of decompression sickness (DCS) compared to men after returning from dives, either open-water or in hyperbaric chambers, after ascending to altitude after diving, after ascending to high altitude in airplanes, and even after ascending to high altitude in hypobaric chambers. In addition to a greater risk of DCS, there is also the assertion that there may be different signs and symptoms of DCS that are related to gender, and that women comprised a larger number of difficult cases that required complicated medical management (5,7,15,16,23,33,35,39,45).

The question of gender and risk of DCS is constantly raised in various settings, and those raising the questions must make decisions to move forward based on some objective criteria. For example, provided with only a few reports from the Air Force from 1973 to 1983 (5,7,35) NASA took a conservative approach and proposed additional oxygen (O₂) prebreathe (PB) time for female shuttle astronauts (personnel communication with Mr. James M. Waligora) that would perform space walks (extravehicular activity [EVA]). Women were also encouraged to participate in testing of PB procedures at the Johnson Space Center (JSC). Subsequent reviews of the scant data, favorable results from female subjects in subsequent testing, and the operational desire to standardize the PB options for both men and women resulted in conservative PB options to cover both men and women. The Air Force after a similar review of limited and equivocal data by 1989 was not convinced to change the way women performed PB prior to flying the U-2 / TR-1 aircraft (48).

There are at least three factors to consider about gender and the risk of DCS: 1) change in DCS risk within the normal reproductive cycle, 2) change in DCS risk with the use of hormone contraceptives, and 3) overall difference in DCS risk between men and women. It is more complicated to assess the above when age is superimposed on the reproductive cycle, or if there has been a hysterectomy. So it is not surprising that there is no consensus of opinion on how each of these factors alone or in combination affect the risk of DCS, even after 30 years of observation. I will not cover in detail the limited published information about the assertion that

women present with difficult DCS cases that required complicated medical management, but will note this if the report provides more than a passing comment on the subject.

There has been limited systematic effort to understand if gender modifies the DCS and venous gas emboli (VGE) outcomes. Most insight today comes from retrospective multivariable statistical analyses. The results are tied to the conditions of the experiment, so are not generalizable. As a result, the literature abounds with results that seem to contradict. A complicating reality is that factors associated with gender may only influence DCS or VGE outcome when the decompression dose is high, and not even the most significant factor matters if there is no decompression dose. In other words, the degree a physiological variable modifies the DCS or VGE outcome is conditional on the decompression dose, and there was no systematic effort to prospectively evaluate these complex interactions.

PURPOSE OF REPORT

Enough data has been reported over 30 years to attempt a formal review and synthesis of opinion about gender and the risk of DCS. Unfortunately, prospective, well controlled, and statistically relevant studies are lacking. As a minimum, this report documents and summarizes data, and identifies trends in those data. I take the opportunity to briefly summarize the DCS and VGE data related to gender collected over 20 years at JSC, which are available in the NASA DCS Database located at the JSC. Finally, I summarize unpublished nitrogen (N₂) washout data from men and women also collected at JSC.

BACKGROUND

The Normal Reproductive Cycle

Any current textbook on human physiology or endocrinology has a chapter devoted to the female reproductive system. I briefly summarize the key events and vocabulary about the normal menstrual cycle where fertilization of the egg does not occur. This background is necessary to understand and integrate the technical information to follow. The focus here is on healthy, physically active, non-pregnant adult women who are engaged in activities that could lead to DCS. I briefly discuss the use of hormone contraceptives [birth control pills (BCP)] and

reproductive physiology in women nearing menopause, but do not include information about abnormal reproductive physiology.

By common usage, the days of the menstrual cycle are identified by numbers, starting with the first day of menstruation, which is vaginal bleeding that occurs with the shedding of the uterine mucosa. Although variable, the average length of the cycle is 28 days, with a range of periodicity from 20 to 45 days (21). The cycle is described in two phases: the follicular (preovulatory) and the luteal (postovulatory) phases. Ovulation at about day 14 is defined as the day of peak luteinizing hormone that triggers the release of the ovum from the developing ovarian follicle. Figure 1 shows the major cyclical hormone changes during the normal reproductive cycle (21).

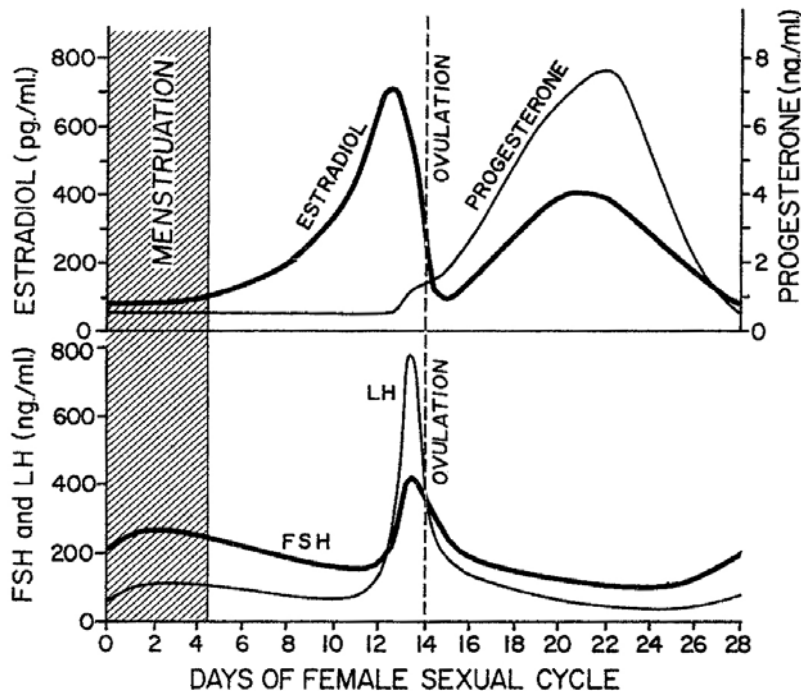


Figure 1. Plasma concentrations of the gonadotropins and ovarian hormones during the normal female sexual cycle.

Figure 1. Taken from Guyton (21) and shows the major hormone changes during the normal reproductive cycle.

Two gonadotropic hormones called the luteinizing and follicular stimulating hormones are cyclically released from the anterior pituitary gland in response to the secretion of releasing

factors by the hypothalamus. These hormones in turn regulate the secretion from the ovary of two classes of female steroid hormones called estrogens and progesterones. There are three forms of estrogen released, but in the human the 17- β estradiol is the most biologically active. Preovulatory estrogen is produced primarily by the developing ovum. During the follicular phase in the first two weeks postmenses, all three estrogen levels are low, but peak one to two days before ovulation. This peak in estrogen(s) is associated with a transient decrease in body temperature. After ovulation, the estrogen levels rapidly return to preovulatory levels and then gradually increase and plateau during the middle of the luteal phase, about three weeks postmenses, and then suddenly decline three to five days before the start of the next menses. Postovulatory estrogen is produced primarily by the corpus luteum. In contrast, progesterone levels remain low during the follicular and early luteal phases of the cycle. There is a gradual rise and peak in the middle of the luteal phase. The observed rise in body core temperature (about 0.5 c) during the luteal phase is a direct effect of progesterone to increase the setpoint temperature. Resting metabolic rate is about 10% greater in the luteal phase than in the follicular phase (44). Approximately five days before menses, progesterone and estrogen levels rapidly fall to preovulatory levels as the corpus luteum degenerates. Progesterone, like postovulatory estrogen, is secreted from the corpus luteum. Menstruation follows, and then a new ovarian cycle begins.

Fluid and Electrolyte Balance and the Reproductive Cycle

Fluid and electrolyte balance is exquisitely regulated in humans through an integrated neural, endocrine, and kidney physiology. Water is the single largest component of the body, representing about 50 – 70% of body weight for adult males and about 40 – 60% for adult females. It comprises about 72% of the lean body mass in both males and females. The wide range of values for the proportion of total body water to body weight is primarily due to the amount of body fat. Fat is a major contributor to an increase in body weight without a corresponding increase in total body water. Fat and water content and distribution in males and females are important considerations in any discussion about DCS and VGE. A 60 kg woman with 25% body fat has more N_2 in fat compared to a 75 kg man with 18% body fat, but this woman has less total N_2 in fat and lean tissues compared to the man.

Fluid and electrolyte intake, absorption, and excretion are balanced such that we maintain homeostasis under a wide range of conditions. In women, these same neural and hormonal mechanisms are present but due to the cyclic fluctuations in female reproductive hormones, it is better to describe their “baseline homeostatic level” as cyclical, not constant. Both men and women undergo cyclical changes ultimately regulated by hormones. We all have a 24-hr circadian cycle, biorhythm cycles that mark periods of physical, emotional, and intellectual peak (28), and of course a single long cycle from birth to death. However, unique to women is the reproductive cycle. No other mammalian species is capable of fertilization on a monthly basis.

Estrogen and progesterone mentioned above have multiple biological actions that include direct and indirect effects on fluid and electrolyte balance. Other hormones that modify fluid and electrolyte balance also vary during the reproductive cycle. Hormones like prolactin, aldosterone, arginine vasopressin, cortisol, and testosterone are elevated just prior to ovulation and on into the luteal phase. So the integrated control of fluid and electrolyte balance is complicated in women.

Water retention and body weight gain to various degrees are outcomes of the reproductive cycle. Premenstrual water retention is severe in about 25% of women and about 50% experience weight gain prior to ovulation and menstruation (2,29). An impaired ability to vasoconstrict leg blood vessels upon standing and increased capillary permeability are observed during the luteal phase. This may contribute to a greater pooling of blood or a greater fluid filtration to the interstitium. Therefore, much of the weight gain associated with the late luteal phase may be caused by fluid retention in the interstitial compartment (23).

Premenstrual Syndrome (PMS) has recently received a great deal of attention. Symptoms are only associated with the luteal phase, and are absent during menstruation. PMS does not occur before menarche, after menopause, or in women that do not ovulate. It is necessary to briefly review some of these observations since it is certainly conceivable that physical and psychological changes caused by PMS could confound, reinforce, or exacerbate symptoms of DCS related to diving and flying activities. One consistent finding with PMS is that there is an

increase in the capillary filtration coefficient. The capillary filtration coefficient increased 30% in those with PMS in the luteal phase and was accompanied by a mean 3.6 mmHg reduction in interstitial colloid osmotic pressure without a significant change in body weight. The conclusion was that PMS was related to an altered fluid distribution rather than fluid retention *per se* (38). Although the exact mechanism for PMS is not known, there are observations of excess estrogen, reduced progesterone, or abnormally high estrogen to progesterone ratio in those that suffer from PMS. Symptoms such as irritability, headache, and anxiety may result from the over stimulation of the limbic system by excess estrogen (1). These are also symptoms that if reported after aviation and diving activities could be incorrectly classified as Type II DCS.

Exogenous estrogen administration causes fluid and sodium retention leading to increases in body weight and expanded plasma volume, possibly by altering the pituitary secretion of vasopressin and by a direct effect of estrogen on receptors in the renal tubules. The whole body systemic response to estrogen is to increase vascular compliance, lower blood pressure, and increase skin and muscle blood flow. So blood pressure is lowest near ovulation and during the midluteal phase when estrogen levels are highest, and blood pressure is highest during menses when estrogen levels are lowest. There is also an enhanced vasoconstrictor response in the luteal phase when compared to the follicular phase.

Contraceptives and the Reproductive Cycle

Contraception is a term that includes many methods to prevent pregnancy. The perspective here is on the use of hormone therapy to prevent ovulation, and otherwise modify the normal ovarian cycle. The basic strategy is to provide excess estrogen or progesterone, or both, to inhibit ovulation through a negative feedback to the hypothalamus and anterior pituitary to prevent the secretion of gonadotropic hormones. But there are significant side effects to hormone therapy that modify the normal menstrual cycle. If either estrogen or progesterone, or both, are present then the hypothalamus fails to secrete the normal surge of luteinizing hormone releasing factor, which in turn fails to stimulate the production of luteinizing hormone, which in turn does not trigger ovulation (21). The effects of estrogen and progesterone on body fluids and vascular responses are potentially more pronounced in women who use oral or subcutaneous contraceptives. Even with the use of low-dose (< 50 µg of ethinyl estradiol) estrogen pills in

some women is associated with enhanced fluid and sodium retention (9), decreased glomerular filtration rate (30), body weight gain, increased plasma volume, and increased cardiac output (41). There is a well-known hypertensive effect of oral contraceptives that may be due to the effects of estrogen that increase renin production from the kidney and, therefore, angiotensin II vasoconstrictor activity, even with doses as low as 35 µg. The timing and dosing of the contraceptive provides the negative feedback to the hypothalamus and anterior pituitary to prevent ovulation but to otherwise allow for a near-normal menstrual cycle.

Age and the Reproductive Cycle

Women have and will continue to be active in sports and careers past their peak fertility. At about 45 to 50 years the reproductive cycle usually becomes irregular, and ovulation fails to occur during many of the cycles (21). There is a point defined as menopause when there are no primordial follicles in the ovary to be stimulated by follicle stimulating hormone and luteinizing hormone. As a result, the production of estrogens by the ovary decreases. There is no negative feedback to inhibit the production of follicle stimulating hormone and luteinizing hormone from the anterior pituitary gland, so there is an increase in these hormones. The loss of estrogen often causes marked physiological changes in the function of the body, and cause symptoms that could confound, reinforce, or exacerbate symptoms of DCS related to diving and flying activities. Low-dose estrogen therapy is used to reverse or blunt symptoms associated with menopause.

SUMMARY REVIEW OF ABSTRACTS

Since there are few reports about gender and the risk of DCS, information documented in abstracts is first summarized. An abstract documents work in progress with the implication that a complete report will soon follow. The preliminary data and conclusions in an abstract often change as the report matures, so I just identify major trends in the summary. There are several intriguing abstracts that were not followed with complete reports. An initial interesting observation is made and documented in an abstract, but a full report is not pursued. So caution is certainly warranted to not “over interpret” the few abstracts about gender and DCS.

Table I identifies 13 abstracts: seven based on research in hypobaric altitude chambers, five from sport diving activities, and one recent abstract (27) not directly related to gender and

DCS risk but about the likelihood of a right-to-left shunt through a Patent Foramen Ovale (PFO) depending where you are in the reproductive cycle. The **bold** entries are abstracts that pertain to divers (hyperbaric exposure returning to surface), and the others pertain to aviators (from surface to hypobaric exposure). The distinction between DCS from “non-saturation” diving and “saturation” flying is important to maintain since diver DCS and aviator DCS have differences that may or may not be important when gender and DCS risk are evaluated (47).

TABLE I: Summary Abstracts on Gender and DCS

investigator	menstrual cycle	hormone contraceptive	male versus female	brief note
Waligora 1986	0	0	1	no DCS or VGE incidence difference with gender
Dixon 1986	0	0	1	more DCS and delayed symptoms
Baumgartner 1989	0	0	1	greater DCS treatment rate in women
Eckenhoff 1990	0	0	1	no DCS or VGE difference with gender
Dunford 1992	1	0	1	greater risk of DCS during menses
Doyle 1997	1	1	0	BCP during menses associated with DCS
Krause 1998	1	0	0	DCS during menses with high DCS dose
Lee 1998	1	0	0	DCS during menses
Webb 1999	0	0	1	no DCS difference but women with less VGE
Conkin 2000(a)	0	0	1	risk of Grade IV VGE less in women
Conkin 2000(b)	0	0	1	no DCS or VGE incidence difference but older males more Grade IV VGE
Mutzbauer 2004	1	0	0	right-to-left shunt and reproductive cycle

The earliest abstract from Waligora (40) showed there was no difference in the incidence of DCS or VGE after combining results from two altitude tests with a total of 67 exposures: 33 females and 34 males. The DCS incidence of 6% for males was not different than the 9% for

females, and the VGE incidence of 23% for males was not different than the 18% for females in this small sample. Dixon (17) concluded in 30 women that repeated exposures to 7.8 psia over three days that females appeared to suffer more delayed DCS symptoms necessitating more hyperbaric O₂ treatment than males, and that females had less VGE compared to males under identical experimental conditions. In a larger sample of similar research data, Webb (43) in 183 exposures and Conkin (10) in 549 exposures also found no difference in DCS risk with gender. However, women had a lower incidence of VGE (43,17) and less risk of Grade IV VGE (10,11) compared to male counterparts. Baumgartner (8) reviewed 282 treatment records from the Air Force covering from 1985 to 1987 and found a 2.3 fold increase (relative risk) in DCS rate for women across nine hypobaric chamber training profiles. Eckenhoff (20) showed in 30 women divers that there was no DCS after direct ascent from 16 feet seawater gauge after a 48-hour saturation exposure, and this compared to no DCS in 54 men. He also monitored for VGE and found no difference in the VGE incidence, the duration of the VGE signal, the latency time for the first detected VGE, or the time to peak VGE score between men and women. None of these results were detailed in his abstract, and I could not locate a published report for these details.

The remaining abstracts addressed the risk of altitude and diving DCS during the reproductive cycle, and the risk of diver DCS related to the use of BCP. Dunford (19) observed that both male and female inside attendants had the same low incidence of DCS in the performance of their hyperbaric treatment duties, but a larger number of women (5 / 9) with information about their menstrual cycle had DCS associated with menses. This is in agreement with Lee (25) for other reported cases of diver DCS, and with results from altitude chamber flights (24). Lee noted in 26 cases of DCS, that nine (35%) were associated early in menses with fewer cases in subsequent intervals of time past menses. Krause (24) made a similar observation based on 62 cases of DCS in 152 subject-exposures in an altitude chamber. DCS correlated with menses, with the highest probability of DCS on the second day of menses. Krause made an important observation that the risk of DCS associated with menses was also dependent on the decompression dose. There was no correlation between the few cases of DCS and menses when the decompression dose was low. There was a correlation between a greater number of DCS cases and menses when the decompression dose was high.

Finally, what mechanism(s) could explain a greater risk of DCS during menstruation, no increased risk between men and women overall, and lower VGE incidence in women compared to men who perform the same decompression? There are no answers at the moment, but Mutzbauer (27) suggests that it is not an enhanced right-to-left shunt during menstruation. Ten of 40 women (25%) all had right-to-left shunt via a PFO. This is about the prevalence of PFO in the normal population. But the 10 women were found to have this right-to-left shunt on day 15 (ovulation) of their menstrual cycle, while only four of these 10 had the shunt detected on the first day of menses. The estrogen peak near ovulation has a vasodilator action, and this may explain the observation. The supposed increase in risk of DCS during menses is not supported by an increase in right-to-left shunt as a mechanism since the increase comes at the wrong time in the menstrual cycle. He does suggest that measuring for PFO in women near the time of ovulation will improve the chance of finding a PFO.

SUMMARY REVIEW OF REPORTS

The review of abstracts above now leads to a critical review of reports that followed the abstracts in only a few cases. Most of the reports did not have prior abstracts. In general, the conclusions from the abstracts are supported in the full reports. A disturbing observation is that at least one report or abstract supports each particular view of male versus female DCS risk, DCS risk during the reproductive cycle, and DCS risk associated with the use of BCP. Table II identifies 19 reports: 14 based on research in hypobaric altitude chambers, five from sport diving activities, and one at the bottom that shows an analysis of male and female DCS and VGE response from NASA-sponsored research published only in this report. What are missing from this list are significant contributions from the Navy, either from Navy aviation training, research, or operational activities or from Navy diver training, research, or operational activities. The presence of women in the Navy will increase, so these data should soon be available to either support or refute the current data.

TABLE II: Summary Reports on Gender and DCS

Investigator	menstrual cycle	hormone contraceptive	male versus female	brief note
Bassett 1973	0	0	1	first report about gender and DCS risk
Bassett 1978	0	0	1	1966 – 1977 review of Air Force DCS Treatment records
Bangasser 1978	1	1	1	
Bassett 1980	0	0	1	also summary of 1973 report
Skinner 1983	0	0	1	more Type II, and less effective treatment outcome
Zwingelberg 1987	0	0	1	Navy training dives
Bangasser 1987	1	1	1	also summary of 1978 report
Dixon 1986 (males)	n/a	n/a	male results only	results compared to 1988 results
Dixon 1988 (females)	1	0	1	
Rudge 1990	1	1	0	
Weien 1990	0	0	1	
Conkin 1990	0	0	1	no DCS difference but women with less VGE
Schirmer 1992	1	1	0	about distribution within reproductive cycle and use of BCP in chamber exposures
Vann 1993	0	0	1	Type II DCS in women
Thompson 2002	0	0	1	Grade IV VGE
St. Leger 2002	0	0	1	
Webb 2003	1	1	1	metaanalysis
Lee 2003	1	1	0	evaluates only DCS cases
Conkin 2003	0	0	1	
Conkin 2004 (unpublished)	0	0	1	DCS and VGE results in this report

Except for the reports by Dixon (15,16), all others are based on retrospective analysis from assembled database information, or from survey and questionnaire results. There are serious limitations to retrospective analysis, especially from survey and questionnaire results. In

a few reports (26,31,34,35,39), only the numerator data (cases of DCS) are available, with denominator data (no cases of DCS) also estimated or clearly available in the remaining reports. Often the samples of data are too small to warrant anything but a cautious conclusion.

Diver DCS and Gender

Diver experience about gender is separated from aviator experience to better assess if there are trends about DCS not only based on gender but also on the type of decompression profile. Divers return from a dive with “fast tissue compartments” controlling the decompression schedule, or the no-decompression time and depth limits. Aviators often PB 100% O₂, so “long tissue compartments” limit the maximum altitude or time at altitude. The differences between diver and aviator DCS are not documented here to limit the scope of this report. Any good medical textbook on diving (Bennett and Elliott, *Physiology and Medicine of Diving* (5th ed.), 2003) or aviation (DeHart, *Fundamentals of Aerospace Medicine* (2nd ed.), 1996) would cover the details about the distribution of Type I and Type II DCS symptoms in divers and aviators, so that information is not reproduced here. Diver DCS and then aviator DCS is reviewed as it relates to gender, and then similarities or differences are summarized at the end of this report.

DCS Risk within the Reproductive Cycle

Four reports (3,4,26,36) were available about the risk of DCS in SCUBA divers within the reproductive cycle. All results were from retrospective analysis of survey information. The 1987 report by Bangasser (4) essentially reproduced the same information from her 1978 (3) report. Unfortunately, the report by St. Leger Dowse (36) contained limited information about DCS risk within the reproductive cycle even though 2,250 (53% male and 47% female) responses to a questionnaire were analyzed. Twenty-two percent of 58 DCS cases reported from 1990 to 1994 occurred in women who were menstruating, so 78% of the cases occurred when women were not menstruating, or could not remember where in their cycle they were at the time of DCS. By chance alone, 25% of all DCS would appear in the first week of a monthly cycle, so there is nothing significant in these results, which is her main conclusion. Bangasser (4) found no difference in her subset of survey data from female dive instructors in the DCS incidence between menstruating women (3.9%), women on BCP (3.7%), and women not on BCP (3.9%)

that engaged in decompression diving. There was also no difference in the DCS incidence between menstruating women (1.2%), women on BCP (1.3%), and women not on BCP (2.2%) that engaged in no-decompression diving. Except for the results from Lee (26), there is nothing conclusive in these reports about increased risk of DCS in SCUBA divers that dove during menses. One confounder discussed by St. Leger Dowse (36) is that some women change their dive patterns because of the concern about DCS during menstruation, and because of the additional discomfort. Unless these biased conditions are controlled, it is unlikely that definitive information will come from retrospective survey methods.

The report by Lee (26) is the best on the subject of DCS risk in SCUBA divers within the reproductive cycle. She collected information from female divers who presented for DCS treatment. The information from 150 women was detailed enough to make conclusions about DCS risk during the reproductive cycle and DCS risk associated with the use of BCP. Of the 150 women with DCS, 87 did not use BCP and 63 did use BCP. In women with DCS, there were more cases associated with the first half (first two weeks from start of menses) of their cycle regardless if BCP was used. Sixty percent (90 / 150) of all DCS cases were associated with the first half of the cycle leaving 40% (60 / 150) associated with the last half of the cycle. The 87 cases that did not use BCP had a non-uniform distribution of cases across the reproductive cycle with 64% (56 / 87) of cases during the first half of the cycle compared to 36% (31 / 87) for the last half of the cycle. It was unclear if the decompression dose was comparable in the 150 reports of DCS. On balance, a conservative conclusion from these data is that there is not enough information collected under controlled conditions to say that the incidence of DCS in female SCUBA divers is increased during menstruation. More women that present with DCS (only numerator data) after SCUBA diving have done so during menstruation, with fewer and fewer cases after menstruation.

DCS Risk and the use of Contraceptives

The same four reports above (3,4,26,36) also included information about the risk of DCS in female SCUBA divers that used BCP. Some duplication of information is inevitable because of the way I organize the topics. St. Leger Dowse (36) writes, “There was no statistical difference between those women who suffered DCS and were taking the oral contraceptive pill,

and those who were not. Given the overall unreliability of some women (both on and off the oral contraceptive pill) to record their menstrual records at the time of the incident, these data should be regarded only as an interest factor". As mentioned above, Bangasser (4) found no difference in her subset of survey data from female dive instructors in the DCS incidence between menstruating women (3.9%), women on BCP (3.7%), and women not on BCP (3.9%) that engaged in decompression diving. There was also no difference in the DCS incidence between menstruating women (1.2%), women on BCP (1.3%), and women not on BCP (2.2%) that engaged in no-decompression diving. Lee (26) provides the best information. The use of BCP in 42% (63 / 150) of women SCUBA divers presenting with DCS was not associated with a higher risk of DCS compared to 58% (87 / 150) of those with DCS that did not use BCP. It was unclear if the decompression dose was comparable in the 150 reports of DCS. The 63 cases of DCS in those that did use BCP had a uniform distribution of cases across the reproductive cycle; 54% (34 / 63) in the first half of the cycle compared to 46% (29 / 63) in the last half of the cycle. On balance, a conservative conclusion is that it does not appear the use of BCP in female SCUBA divers modifies the risk of DCS.

DCS Risk between Men and Women

Even if it is true that women SCUBA divers have a greater risk of DCS during menses than at other times in their cycle, or greater risk of DCS while on BCP, the overall risk of DCS may be the same for male and female SCUBA divers. This section ignores the confounding variables of location within the reproductive cycle and use of BCP and just evaluates if male and female SCUBA divers have a similar DCS response after a similar dive profile. All results in this section come from retrospective analysis of Navy diver training records (47), from a flying after SCUBA diving survey (39), and SCUBA diver surveys already introduced above (3,4,36). Zwingelberg (47) compared the DCS reported in 28 female Navy divers to 487 male Navy divers after 878 air and helium-oxygen training dives. No females reported DCS while there were eight cases in males. He presents a convincing case that males and females were represented in the 10 types of training dives, so we can assume there was comparable but very low decompression dose between genders. He concludes that there was no difference in DCS incidence between males and females. But this conclusion was challenged in a *Letter to the Editor* (32) when it was

noted that you would need 266 females with no report of DCS to conclude that there was no statistical difference between men and women in training dives with low decompression dose.

In yet another *Letter to the Editor* (33) what seems to be an important conclusion about Type II DCS in women divers was not followed by a full report. Robertson (33) says in an analysis of 111 cases of DCS treated in Australia that a 4.3 fold greater risk of Type II DCS was evident in women compared to men. Vann (39) evaluated 1,159 DCS treatment records for SCUBA divers that flew after various surface intervals when DCS symptoms were or were not present before the flight. There were 293 cases classified as Type I DCS and 866 cases classified as Type II DCS. He computed the probability of Type II DCS as opposed to Type I DCS using logistic regression with several explanatory variables, including gender. It was clear that you should not fly with prior symptoms of DCS regardless of gender. Women reported and were treated for more Type II DCS, there were more residual symptoms after treatment, and less relief of symptoms during treatment compared to men. He conservatively concluded that there could be two explanations for the results: a reporting bias related to gender (the “macho male” versus “wimp female” factor), or that female divers who fly after diving have a greater susceptibility to Type II DCS. You can also suppose that women are more truthful about reporting symptoms, which has nothing to do with a possible physiological difference to account for these observations.

St. Leger Dowse (36) showed in an analysis of 2,250 returned questionnaires (53% male and 47% female) by SCUBA divers a 1.67 fold greater DCS incidence (0.262 / 0.157 confirmed DCS rate per 1,000 dives) in females before other diving pattern factors were taken into account. After accounting for these diving pattern factors, there was a 2.57 fold greater DCS incidence in males. Bangasser (3,4) reported from her survey that 10 cases of DCS in women instructors out of 44,154 dives (0.023%) was a 3.3 fold increase in risk for women compared to 3 cases out of 43,126 dives (0.007%) for male instructors.

At best, there are indications that female SCUBA divers under increased decompression dose are more susceptible to Type II (33,39), and less likely to respond as well to treatment when compared to males (38). The decompression dose is very low in the remaining reports

(3,4,36,47) so few cases of DCS are actually reported. It is conservative to conclude from these data that there is no difference in DCS risk between male and female SCUBA divers under low decompression dose. There may be statistical significance in some of these results, but no real clinical difference. What is needed is a way to increase the number of DCS cases (numerator data) without a concomitant increase in Type II DCS so that adequate response data is available for analysis. This is available in the next section with a review of gender and DCS results from research in altitude chambers.

Aviator DCS and Gender

As mentioned earlier, differences between diver and aviator DCS are not documented. One distinction, however, must be clear. A person ascending from sea level to altitude has about one liter (STPD) of N₂ dissolved in the tissues and blood, a bit more if they are obese, and a bit less if they have minimum body fat. Most ascents to altitude are made after some period of 100% O₂ PB, so the risk of serious DCS is very low even with as little as 30 min of PB. So the incidence of Type I DCS can be high even when Type II DCS is low. There is an advantage here in data analysis that is not available from SCUBA diving. A diver can take on substantial N₂ depending on the dive profile. A diver who surfaces with the same high risk of Type I DCS as the aviator also has a very high risk of Type II DCS. As a result, dive profiles are designed to produce very low risk of any DCS, and still the risk of Type II is greater for the diver compared to the aviator. As a result, there are significant DCS and VGE outcomes from altitude decompressions that are available for analysis that are just not available from SCUBA divers. So the best information about gender and risk of DCS and VGE will likely come from research studies in altitude chambers. Unfortunately, during the time between 1940 and 1950 when the value of prebreathing was being quantified there were very few women exposed to high altitude. Women are now routinely included in altitude chamber flights, but everyone receives some protection through PB. As a result, the response of women to higher altitude decompression dose is not available to evaluate.

DCS Risk within the Reproductive Cycle

Dixon (15,16) provided the only prospective study to evaluate the incidence of DCS and VGE by gender, and makes a compelling observation about females (15). Thirty women in groups of two or three depressurized to 7.8 psia on three consecutive days. There was no PB, and they breathed 50% N₂ and 50% O₂ while at 7.8 psia while performing light exercise. Two had delayed symptoms reported on the fourth day. Three reported a total of four additional cases of DCS during the exposure to 7.8 psia. All five women reported their six cases of DCS while in or near menses. Only 32% of women who did not report DCS were in menses. Webb (42) evaluated records from 269 women-exposures, but it was unclear how many times and which of the 70 women had repeated exposures. There were 149 women-exposures without BCP and 120 women-exposures with BCP. He reported there was no difference in the 45% incidence of DCS in the first half of the reproductive cycle in those on BCP (n = 68 exposures) and those without BCP (n = 88 exposures). In the last half of the cycle, women on BCP had 59.6% DCS (n = 52 exposures) compared to 31.1% DCS (n = 61 exposures) that did not use BCP. This was a two-fold increase in DCS risk in the last half of the cycle in women on BCP. It was unclear if the decompression dose was comparable between the first (n = 156 exposures) and last half (n = 113 exposures) of the cycle. There was no mention of BCP in the Dixon report (15), but his observations do not support the observations from Webb (42) about no increase in DCS incidence in the first half of the reproductive cycle. In contrast, Rudge (31) shows results from 81 records of DCS in women collected over 11 years that indicate the number of Type I and Type II DCS is greater at 35% (28 / 81) at the beginning of menstruation than the 6% (5 / 81) at the end of the cycle. He showed that the number of cases decreased as the time from menses increased. These observations do support the conclusion from Dixon (15).

Finally, Schirmer (34) makes a contribution by collecting descriptive data of the reproductive cycle and use of BCP from 508 women that completed altitude chamber training. The decompression dose was low, and she concluded that the absence of any DCS indicated that it was irrelevant what stage of menses the women were in, or if they were on BCP. You can also conclude that when there is low decompression dose that no factor linked to DCS can be properly evaluated. The dominant training profile for 42% of the records was a Type V chamber flight. The average age was 30.3 ± 6.8 standard deviation (SD) years with a range from 18 to 52

years. In 508 women, 33.3% of women reported using BCP. She noted that menses lasted about five days, and that women who completed training without DCS were equally distributed across their reproductive cycle during the altitude flights. Those on BCP were also equally distributed across their reproductive cycle during the altitude flights. On balance, there does appear to be enough evidence to conclude an increased risk of DCS during the early stage of menses in women exposed to significant altitude decompression dose.

DCS Risk and the use of Contraceptives

The use of BCP was associated with twice the risk of DCS in the last half of the reproductive cycle (59.6%, n = 52 exposures with BCP compared to 31.1%, n = 61 exposures without BCP) as mentioned earlier in the report by Webb (42). He also found a statistically higher risk of DCS when he combined information from the first half of the cycle (52.5%, n = 120 exposures with BCP compared to 40.3%, n = 149 exposures without BCP). But there was no difference in the DCS incidence of 45% when only the information in the first half of the cycle was evaluated. Rudge (31) notes that about 26% of the Type I DCS cases (17 / 62) and Type II DCS cases (5 / 19) included the use of BCP. So it seems the use of BCP does not favor one symptom category over the other. As mentioned earlier, Schirmer (34) reported that 33.3% of 508 respondents used BCP during altitude training flights. There were no DCS cases reported during these training flights and those that used BCP were equally distributed across their reproductive cycle during the altitude flights. The data from Webb (42) are the most compelling to address the issue of increased risk of altitude DCS with the use of BCP. There may be a small increased risk of DCS with the use of BCP.

DCS Risk between Men and Women

Webb (42) notes that the 59.4% incidence of DCS for women on BCP in the last half of the cycle is the same as the 49.5% incidence for men. However, the 31.1% incidence of DCS for women not on BCP in the last half of the cycle was statistically less than the 49.5% incidence for men. It was unclear that the decompression dose was comparable between men and women in these comparisons. Weien (45) reviewed 528 cases of DCS, with 77.3% of the cases from Air Force students. There were hundreds (n = 403 cases) of cases of late symptoms and only 123 cases that occurred at altitude. The results came mostly from training flights, and it is unclear if

the decompression dose was comparable across all training flights. In those that reported symptoms, the relative risk was 4.3 fold greater in females than males ($334 / 694,583 = 48.08$ per 100,000 for male and $95 / 45,922 = 206.87$ per 100,000 for female to yield $206.87 / 48.08 = 4.3$ relative risk). There seems to be an unexplained bias to report symptoms after a training flight, especially in women.

Bassett (5,7) in the first report that associated females with an increased risk of altitude DCS (5) reviewed treatment records from 1968 to 1972. He found a small number of women ($n = 8$) and men ($n = 9$) who were treated. The incidence of DCS for women was 0.219% and 0.022% for men, and he concluded that women had a ten fold greater risk of DCS compared to men ($0.219 / 0.022 = 10$). He later reviewed cases from 1973 to 1977 where 14 females and 15 males required treatment for DCS (7). During this interval of time, the incidence for women was 0.54% and 0.15% for men, so the relative risk of DCS for women was 3.6 fold greater than for men ($0.54 / 0.15 = 3.6$). He mentions an analysis of 104 cases of DCS reported by students from 1966 to 1977. And his notes (not published) for a conference presentation showed 7 / 72 (10%) cases of cutaneous DCS in men with DCS compared to 8 / 32 (25%) cases of cutaneous DCS in women with DCS. This difference was statistically significant, but he was not specific on what qualified as cutaneous DCS, i.e., skin mottling, itching, urticaria, etc. He provides additional details in an unpublished Air Force report (6) that covers a period from 1966 through 1977. In summary, he reported the incidence of serious Grade IV DCS (not defined) was 2.5 fold greater for inside observers compared to students in training (0.10% versus 0.04%). Grade IV consisted of both Type I and Type II DCS, and the severity of the symptoms determined the Grade of DCS. Air Force Academy cadets training at Paterson Air Force Base (AFB) had a high DCS incidence (0.73%), with female cadets at 1.94% compared to male cadets at 0.60%. Bassett offered no explanation for the “outbreak” of DCS among Air Force Academy cadets. Another source (46) reported that cadet altitude training at Paterson AFB ended at a site pressure of 4,500 feet, but the students would travel within 12 hrs back to the Air Force Academy located at 7,000 feet altitude. The second ascent to altitude in a short span of time may have contributed to the higher DCS incidence in this group. Female students and pararescue students (mostly male) training at the School of Aerospace Medicine at Brooks AFB had a DCS incidence of about 0.52% compared to 0.12% for the remaining males. A concluding paragraph from Bassett (6) is

reproduced here because the report is difficult to obtain, and because it provides his best explanation for the increased number of reported symptoms from 1966 to 1977, and possibly an explanation for the higher DCS rate for women in training. He says, “The early diagnosis and conservative management of DCS cases in USAF personnel received, and continues to receive, a great deal of emphasis in 1974, due in large measure to the establishment of the full-time hyperbaric therapy unit at the USAF School of Aerospace Medicine. The influence of these efforts appears particularly in the increase in reported Grade IV cases of Type I (Bends-pain only) DCS and the increase in the number of such cases treated in hyperbaric chambers”.

Skinner (35) evaluated 283 cases of DCS to see how long symptom resolution would take regardless of the treatment option. Since women were included in the cases, a comparison between genders was made. However, no statistics were applied, just a comparison of incidence about Type I and Type II DCS, and subsets of how symptoms responded to treatment. The investigator states, “Examination of cases by sex shows a higher incidence of Type II DCS, of vasomotor symptoms, and of recurrence of symptoms following initial resolution in women”. The incidence to support these conclusions are: of all men with DCS, 25% had Type II and 36% for women, only 4% of Type II were vasomotor symptoms, but 67% of these were in women, and 73% of recurrent Type I DCS were in women with 71% of recurrent Type II DCS also in women.

The two reports by Dixon (15,16) provide the best comparison between men ($n=30$, 29.8 ± 4.7 SD years with 20 to 41 years range) and women ($n=30$, 27.0 ± 4.7 SD years with 21 to 39 years range) because it is clear that the decompression dose was comparable, and VGE were recorded and provide an unbiased measure of the effective decompression dose. Both males and females were exposed for six hrs to 7.8 psia on three consecutive days. As mentioned earlier, there were six cases of DCS reported by five women, with two cases of delayed symptoms reported after the last test. There was only one case of DCS on the first day in the males. There was less incidence of VGE in women ($13 / 30 = 0.43$) compared to men ($22 / 30 = 0.73$). Males who experienced Grade III and IV VGE were significantly older (31.4 years) than females who experienced Grade III and IV VGE (26.9 years) even though the mean age overall for males and females was the same.

Finally, Conkin (12,13) and Thompson (37) used multivariable logistic and survival analysis to describe DCS and VGE results from large samples of data collected at JSC. Previous data had only come from the Air Force, so there is the issue of “institutional bias” in the data. An independent analysis of additional data collected from another laboratory is therefore important. Conkin (13) compared the incidence of Type I DCS and VGE between 174 male-exposures and 147 female-exposures obtained from seven different tests of resting PB procedures. There was comparable representation of males and females in each test, so the results could be combined for a valid comparison of gender. There was a 2.8% incidence (5 / 174) of Type I DCS in males compared to 6.1% incidence (9 / 147) in females, with $p = 0.07$ for Fisher’s Exact χ^2 . There was 38.0% incidence (67 / 174) of VGE in males compared to 25.1% incidence (37 / 147) in females, with $p < 0.01$. In these 321 exposures, females tended to report more DCS and produced less VGE compared to males. In contrast, Conkin (12) found no difference in DCS or VGE incidence attributed to gender when he combined results from both resting and exercise PB. Exercise during PB has recently been used by the Air Force and NASA to accelerate N_2 washout and reduce the incidence of DCS and VGE. Seven tests with 188 male-exposures and 50 female-exposures were evaluated in statistical models. Three of the seven tests used resting PB procedures while the remaining four used exercise PB procedures. Older ambulatory subjects had an increased risk of VGE and Grade IV VGE than younger adynamic subjects. As shown later in this report, the use of exercise PB procedures eliminates the difference in VGE incidence between men and women. Thompson (37) performed a detailed survival analysis on the time to Grade IV VGE from 549 altitude exposure records from JSC. These data were collected from tests on resting PB procedures, and tests without PB. There were 453 records from males and 96 records from females. The model accepted gender, age, decompression dose, and adynamia as significant explanatory variables for Grade IV VGE failure time. The probability of Grade IV VGE is greater in males than females irrespective of age, and the probability of Grade IV VGE increases through time in males and females as decompression dose increases, and if either are ambulatory rather than adynamic before and during the altitude exposure.

On balance, the incidence of VGE and Grade IV VGE is less in females compared to males, but this difference can be reduced depending on how the PB is performed, i.e., a resting or exercise PB. The Air Force data in total does suggest that females are at greater risk of altitude DCS. But the latest report by Webb (42) clearly concluded that gender is not a factor for altitude decompression sickness risk. Analysis of data from JSC also consistently shows that any differences are not statistically significant.

ANALYSIS OF NASA DCS AND VGE DATA AND GENDER

What was lacking in the reviewed reports was a quantitative statement that the decompression dose was comparable between the male and female results on the DCS and VGE outcome. This is a critical consideration if the true difference associated with gender is small. You can make a good assumption in some reports that the decompression dose was comparable if men and women did the same decompression profile during diving and altitude training, or during the evaluation of a particular research protocol. Often, the outcomes from different trials (different doses) are combined, and the investigator first tries to show that both males and females are fairly represented in each trial, so are therefore fairly represented across all trials. An alternative is to perform a multivariable statistical analysis where the uniqueness of each trial becomes part of the reason, along with gender, for the outcome. In other words, a multivariable analysis such as logistic regression or survival analysis identifies and controls for confounding and interacting variables so that a better interpretation of the outcome is possible. A comprehensive multivariable analysis that evaluates gender is not provided here, but this has been done (12,37,39).

DCS and VGE Incidence and Gender

Table III shows data that supports the conclusion that after **resting** PB females produce less VGE than males. The statistical comparison between males and females is valid in that the computed decompression dose, about 1.57, is the same for each subset of data. We do not define how we compute decompression dose here, but just show that it is comparable when we compare male and female responses to the decompression dose. The 549 records summarized in Table III

were collected over 15 years of hypobaric research at JSC, and females participated in 17.5% of these altitude exposures.

TABLE III: Historical Research Data Summary about DCS, VGE and Gender During Resting Prebreathe

Variable	N = 96 females	N = 453 males	p-value
mean TR360 \pm SD	1.58 \pm 0.26	1.56 \pm 0.26	0.59
mean altitude \pm SD	5.83 \pm 1.42 psia	5.07 \pm 1.31 psia	<0.01
mean time \pm SD	4.12 \pm 1.41 hrs	4.02 \pm 1.33 hrs	0.48
% DCS (n)***	11.5 (11 / 96)	15.6 (71 / 453)	0.37
% VGE (n)	24.0 (23 / 96)	43.9 (199 / 453)	0.00045
% GIV VGE (n)*	10.4 (10 / 96)	25.1 (114 / 453)	0.0027
% GIV VGE (n)**	43.4 (10 / 23)	57.2 (114 / 199)	0.29

*proportion of Grade IV based on total exposures

**proportion of Grade IV based on those exposures with detected VGE

*** DCS reported or recollected to have occurred during the altitude exposure

Note: first three p-values from z-test, last four from χ^2

A conclusion from Table III is that there is no gender difference in DCS incidence, and that females have about half the incidence of VGE compared to males. Results about VGE after resting PB are certainly confounded by gender, but the reason is unclear. There was no systematic effort to collect information about menstrual cycle or the use of BCP in NASA-sponsored research. So only comparisons between DCS and VGE outcomes given information about gender are possible. Females produce less VGE compared to males under the same decompression dose. It is equally correct to say that males produce more VGE than females; it just depends how you phrase the result. This conclusion is supported by previous analysis of subsets of these data (13,37). The majority of published data are about results after resting PB.

For reasons not yet understood, gender does not confound VGE results when the PB includes exercise (12). Exercise PB is a technique to accelerate N₂ washout and shorten total PB time. The benefit of accelerated washout is balanced by the increased kinetic activity in the muscles that could potentiate the creation of micronuclei. These newly formed micronuclei could then easily transform into bubbles while at altitude. Table IV shows data that supports the conclusion that after **exercise** PB, gender is not a confounder of the DCS or VGE outcome. Our measure of decompression dose is similar in both subsets of data, 1.91 for women and 1.89 for men. This small difference due to a small standard deviation in the mean decompression doses is a statistically significant difference, the consequences of which are discussed later. The 217 records summarized in Table IV were collected in seven unique tests (Phase I, II, III, IV, V-1, V-

2, and V-3) over five years of recent NASA-sponsored hypobaric research, and females participated in 23.5% of these altitude exposures. Since about half of the total body store of N₂ is within a small amount of fat tissue relative to the total body mass, it is possible that N₂ in muscle tissue is removed with exercise PB, and the N₂ remaining in fat tissue is responsible for the similar VGE incidence between men and women.

TABLE IV: Recent Research Data Summary about DCS, VGE and Gender During Exercise Prebreathe

variable	N = 51 females*	N = 166 males*	p-value
mean ETR** \pm SD	1.91 \pm 0.04	1.89 \pm 0.04	<0.01
mean altitude \pm SD	4.30 \pm 0 psia	4.30 \pm 0 psia	1.0
mean time \pm SD	4.0 \pm 0 hrs	4.0 \pm 0 hrs	1.0
% DCS (n)	21.5 (11 / 51)***	11.4 (19 / 166)	0.10
% VGE (n)	39.2 (20 / 51)	44.5 (74 / 166)	0.60
% GIV VGE (n)!	7.8 (4 / 51)	10.8 (18 / 166)	0.72
% GIV VGE (n)!!	20.0 (4 / 20)	24.0 (18 / 74)	0.29

* Test of Hypothesis data covering from Phase I to V-3.

**ETR is computed Exercise Tissue Ratio using n = 159 NASA model!!!, and is a measure of decompression dose

*** Two females in Phase I test reported DCS hours after the altitude test

!proportion of Grade IV based on total exposures

!!proportion of Grade IV based on those exposures with detected VGE

!!! Conkin J, et al. A probability model of decompression sickness at 4.3 psia after exercise prebreathe. NASA Technical Publication (in review as of August 2004), Johnson Space Center.

Note: first three p-values from z-test, last four from χ^2

Given the information in Tables III and IV, what else can we statistically conclude? I addressed the question; “Does gender respond differently between two different PB procedures, i.e., resting versus exercise PB? Table V shows that for women, the difference in decompression dose is not providing a difference in DCS incidence, but a p-value of 0.08 suggests females have a greater incidence of VGE after exercise PB. In summary, women are responding the same across two different PBs in overall DCS incidence (p = 0.16) and VGE incidence (p = 0.08).

TABLE V: DCS and VGE Results Between Resting and Exercise Prebreathe in Females

Outcome	Resting Prebreathe	Exercise Prebreathe	χ^2 p-value
DCS incidence	11.5% (11/96)	21.5% (11/51)	0.16
VGE incidence	24.0% (23/96)	39.2% (20/51)	0.08
Grade IV VGE incidence	10.4% (10/96)	7.8% (4/51)	0.83
Grade IV VGE incidence in those with VGE	43.4% (10/23)	20.0% (4/20)	0.19

Table VI shows a different response in men who perform two different PB protocols. Men show less Grade IV VGE incidence. Men with VGE also show less Grade IV VGE incidence after exercise PB compared to resting PB. The men are responding the same across two different PBs in the overall DCS and VGE incidence; but, after performing exercise PB, men have less Grade IV VGE incidence. So men and women are responding differently across two different PB options.

TABLE VI: DCS and VGE Results Between Resting and Exercise Prebreathe in Males

outcome	Resting Prebreathe	Exercise Prebreathe	χ^2 p-value
DCS incidence	15.6% (71/453)	11.4% (19/166)	0.16
VGE incidence	43.9% (199/453)	44.5% (74/166)	0.96
Grade IV VGE incidence	25.1% (114/453)	10.8% (18/166)	0.00018
Grade IV VGE incidence in those with VGE	57.2% (114/199)	24.0% (18/74)	0.0000025

In the case of Tables III and IV, the question was if gender was associated with DCS and VGE outcomes within each decompression dose. In Tables V and VI, the question was does the decompression dose produce a different outcome related to gender. Each of these analyses considered only one variable, either gender or decompression dose in isolation of the other. A statistical analysis is provided where both gender and decompression dose are combined in one analysis, and we use the Mantel-Haenszel χ^2 test (M-H). The M-H test is equivalent to performing logistic regression. It is used to study the relationship between two variables, both

measured on a dichotomous categorical scale, but it provides the added capability of stratifying on (i.e. controlling for) any number of additional categorical variables in its analysis. By creating a separate 2-by-2 table for each level of the confounding variable, M-H provides a powerful statistic to analyze the relationship between two dichotomous variables of interest, like gender and DCS outcome, or gender and VGE outcome.

Gender is the factor that we wish to test, stratified by the two types of PB procedures. The M-H test evaluates a possible relationship between gender and DCS or VGE outcome after removing the confounding effect of different PB procedures. Table VII through X show the data matrix for the M-H test, and the resulting p-value for the comparisons.

TABLE VII: Comparison of DCS Outcome and Gender with Prebreathe Controlled

test	DCS Cases		Non-DCS Cases		p-value
	males	females	males	females	0.91
resting prebreathe	71	11	362	85	
exercise prebreathe	19	11	147	40	

TABLE VIII: Comparison of VGE Outcome and Gender with Prebreathe Controlled

test	VGE Cases		Non-VGE Cases		p-value
	males	females	males	females	0.0012
resting prebreathe	199	23	254	73	
exercise prebreathe	74	20	92	31	

TABLE IX: Comparison of Grade IV VGE Outcome and Gender with Prebreathe Controlled

test	Grade IV VGE Cases		Non-Grade IV VGE Cases		p-value
	males	females	males	females	0.0031
resting prebreathe	114	10	339	86	
exercise prebreathe	18	4	148	47	

TABLE X: Comparison of Grade IV VGE Outcome in Those with VGE and Gender with Prebreathe Controlled

test	Grade IV VGE Cases in those with VGE		Non-Grade IV VGE Cases in those with VGE		p-value
	males	females	Males	females	0.28
resting prebreathe	114	10	85	13	
exercise prebreathe	18	4	56	16	

Gender, after controlling for the effect of the PB procedure is not associated with different DCS incidence, but is associated with different VGE incidence and different Grade IV VGE incidence. When the PB procedure affect is removed as a confounder, then females show less VGE incidence and less Grade IV VGE incidence compared to males. There is no statistical difference between men and women in the incidence of Grade IV VGE in those with VGE. It is equally valid to phrase the result as males show a greater VGE incidence and a greater Grade IV VGE incidence than females. Since the M-H test combines two variables, gender and PB procedure, into one analysis, these results are a better reflection about the association of gender to DCS and VGE outcomes than the analysis of just gender (Tables III and IV) and the analysis of just decompression dose (Tables V and VI).

DCS and VGE Latency Time and Gender

The above analysis was concerned if DCS or VGE were present, as they relate to gender. Since only the VGE results show a gender-effect, I continue with an analysis of VGE latency (failure) time. The analysis to follow is about when VGE were present, as it relates to gender. The latency time from the start of the test to the first detection of VGE is data available for analysis. Various Doppler ultrasound bubble-detecting devices have been used since the start of NASA-sponsored DCS research in 1980. At approximately 12-min intervals of time while at altitude the subject would rest from their EVA-simulation work and be monitored precordially for four min. A Doppler Technician and outside observers would listen for the presence of VGE returning to the lungs in the right pulmonary artery after each limb was flexed in a prescribed order. This cycle of light exercise and VGE monitoring would continue until the end of the test, or until the subject was removed from the altitude chamber, most often because of a DCS symptom. Because the Doppler bubble monitoring was not continuous, it is correct to describe the VGE latency time as interval censored time. Since the decompression dose between men and women are comparable within each of the two different PB procedures, it is valid to compare the VGE latency times between males and females within each PB procedure to look for a gender-effect.

Table XI shows the mean time in min for the first report or recollection of DCS and first detection of VGE between males and females for the resting and exercise PB procedures. The mean latency time for VGE is always shorter than the mean latency time for DCS symptoms since the onset of VGE often precedes the report of a symptom, but not everyone with VGE reports DCS. The mean latency time was about 120 min in 110 cases of DCS and 90 min in 316 cases of VGE.

TABLE XI: DCS and VGE Latency Time with Gender and Prebreathe Type

Prebreathe Type	DCS Dose \pm SD		mean DCS Latency		mean VGE Latency	
			\pm SD	n	\pm SD	n
resting male	1.66	0.17	120.1 min 70.7	71	81.8 min 61.6	199
resting female	1.64	0.24	130.3 min 69.3	11	100.6 min 73.3	23
exercising male	1.89	0.04	102.2 min 46.7	19	94.4 min 59.4	74
exercising female	1.92	0.05	118.2 min 29.3	9*	80.6 min 42.0	20

* two cases of DCS reported after test, so no DCS latency time during the test is available.

Since the decompression dose in the subset of total exposures with DCS and VGE are still comparable, it is possible to evaluate difference in VGE latency time as a function of gender and attribute any difference in latency time to gender and not decompression dose. Since the combined resting and exercise PB protocols are expected to have different overall DCS and VGE outcomes, the figures that follow only show gender and VGE latency time within each PB protocol.

Figure 2 shows the cumulative distribution of VGE latency time for males and females that underwent resting PB. The s-shaped curves represent the empirical cumulative distribution

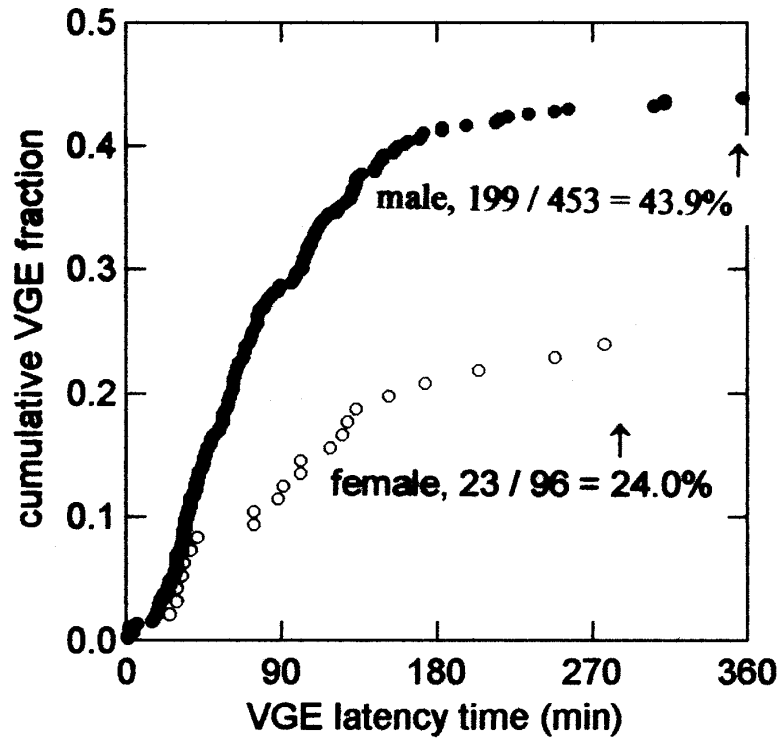


Figure 2. The cumulative VGE fraction for the first VGE detected in men and women who performed resting PB procedures increases to 43.9% for men and 24.0% for women. The difference in VGE incidence is statistically significant. Even though the cumulative VGE fraction looks different for men and women after resting PB, the incidence of DCS is not different in these data (15.6% for men versus 11.5% for women, $p = 0.37$)

function $[F(t)]$ for each sex, and the derivative of $F(t)$ $[dF(t)/dt]$ is the probability density function $[f(t)]$. The difference between men and women is striking due to the lower incidence of VGE in women. Based on Kaplan-Meier estimate of the survival function accounting for censored observation stratified by gender and using M-H log-rank test, the survival curves between men and women are statistically different ($\chi^2 = 12.67$ with 1 df, $p < 0.001$).

Additional insight is obtained by removing the difference in VGE incidence between men and women. This is done by normalizing the fraction of VGE by only accounting for those that

had VGE. Figure 3 shows the cumulative failure times conditional to those that had VGE. The figure shows that the overall pattern of normalized cumulative VGE is similar between men and women who perform resting PB procedures. Based on Kaplan-Meier estimate of the survival function based only on failure times stratified by gender and using M-H log-rank test, the survival curves between men and women are not different ($\chi^2 = 1.45$ with 1 df, $p = 0.23$).

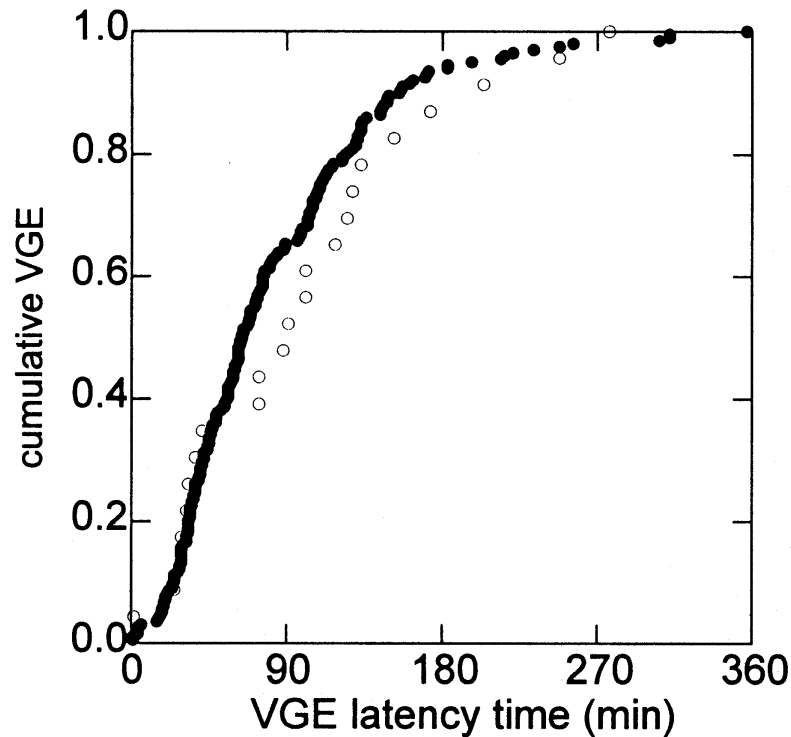


Figure 3. The normalized cumulative VGE in men and women after resting PB. Using only those with VGE eliminates the difference between genders so that the change in cumulative VGE can be evaluated. Both men and women that had VGE had comparable VGE latency time (failure time), but several cases had greater latency time for women (open circles) after about 80 min.

Figure 4 shows the cumulative VGE incidence after exercise PB in men and women. In addition to exercise PB, these subjects were not allowed to ambulate (walk) about 2.5 hrs before the test or during the 4-hr exposure to 4.3 psia. This same restriction was not present in most of the tests with resting PB, so the presence or absence of ambulation is a confounder that we do not address. Figure 4 shows there is no difference between men and women in the cumulative VGE fraction in contrast to Fig. 2. Based on Kaplan-Meier estimate of the survival function

accounting for censored observation stratified by gender and using M-H log-rank test, the survival curves are not statistically different ($\chi^2 = 0.33$ with 1 df, $p = 0.56$).

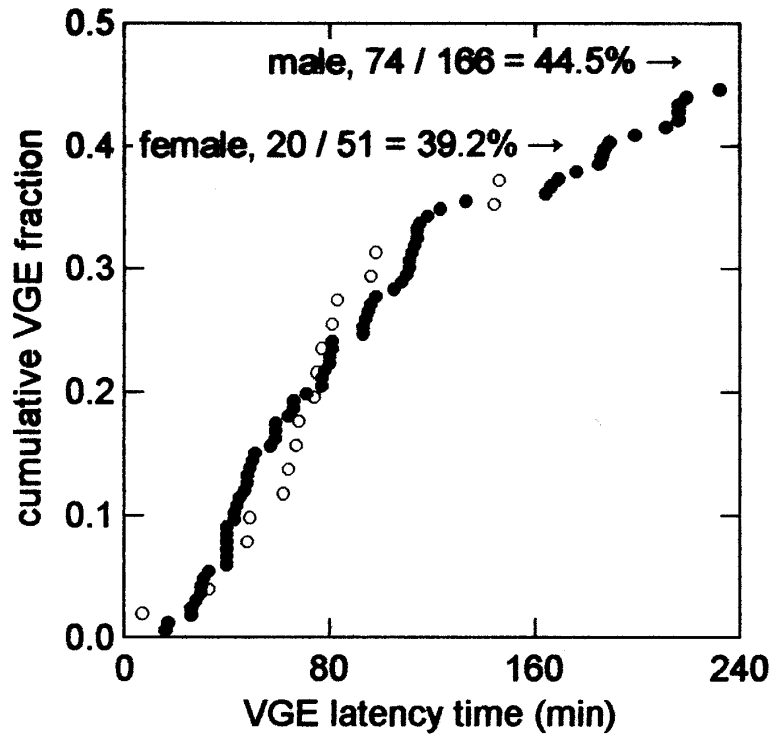


Figure 4. The cumulative VGE fraction for the first VGE detected in men and women who performed exercise PB procedures increases to 44.5% for men and 39.2% for women. The difference in VGE incidence is not statistically significant, $p=0.60$. The incidence of DCS is not different in these data (11.4% for men versus 21.5% for women, $p = 0.10$). The cumulative VGE fraction for men (filled circles) is about the same as in Fig. 2, regardless if resting or exercise PB procedures were performed. But the cumulative VGE fraction for women (open circles) looks very different than in Fig. 2. Women are responding more so than men with different incidence of VGE and different cumulative VGE fractions depending on the type of PB procedure.

Figure 5 shows the VGE data in Fig. 4 normalized. There were cases where both men and women had similar VGE onset time, but there were more cases of earlier failure time in women compared to men as seen past 80 min on Fig. 5. However, based on Kaplan-Meier estimate of the survival function based only on failure times stratified by gender and using M-H log-rank test, the survival curves between men and women are not different ($\chi^2 = 1.46$ with 1 df, $p = 0.22$).

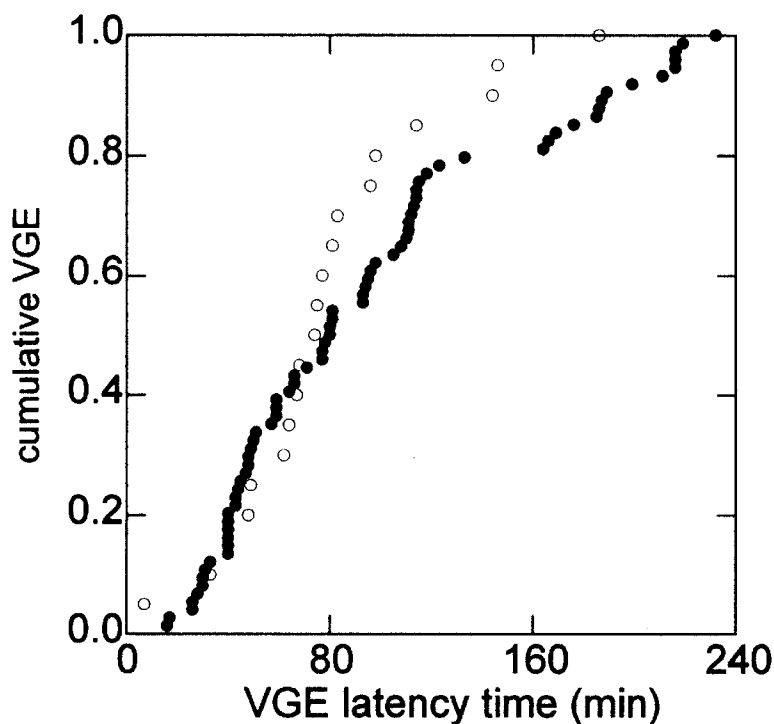


Figure 5. The normalized cumulative VGE in men and women after exercise PB. Using only those with VGE eliminates the difference between genders so that the change in cumulative VGE can be evaluated. Both men and women that had VGE had comparable VGE latency time (failure time), but some cases had earlier latency time for women (open circles) after about 80 min.

Gender was evaluated within each PB protocol in Figs. 2 through 5. But it is also helpful to summarize in Figure 6 differences in gender response to VGE latency time across each PB protocol. The pattern of cumulative VGE in men from Figs. 2 and 4 is more similar than the same comparison for women; the incidence for men was 43.9% after resting PB and 44.5% after exercise PB compared to 24.0% for women after resting PB and 39.2% after exercise PB. These proportions are seen in Fig. 6 as the last point on the survival curves after you subtract the indicated probability from one. Clearly, the men are responding about the same across both PB protocols, but the women are not, such that women have a lower VGE incidence (surviving longer) after resting PB than after exercise PB. What could account for this difference? It is difficult to offer one factor since several variables that influence VGE formation are present.

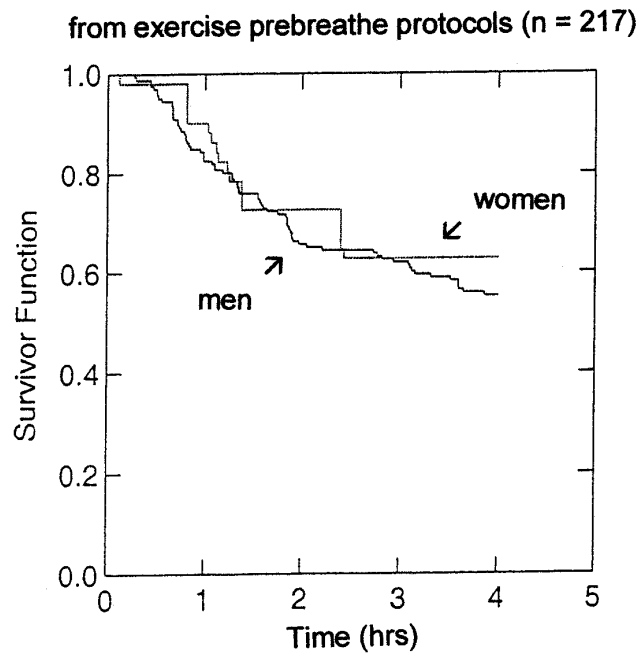
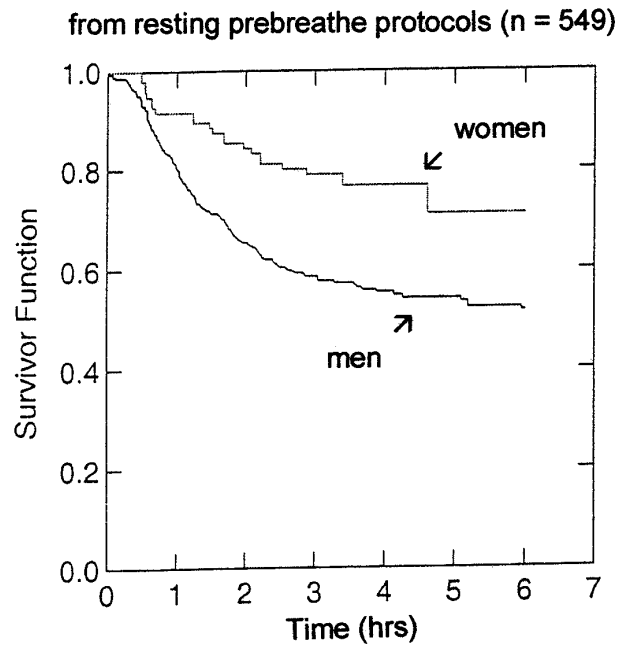


Figure 6. Comparison of Kaplan-Meier VGE survival curves in men and women after resting and exercise PB protocols.

I first evaluated if the VGE failure pattern, not just incidence, between men and women within resting or exercise PB protocols was modified depending on the computed decompression dose. The resting PB data was divided into low dose ($n = 222$, 1.30 ± 0.20 SD) and high dose ($n = 327$, 1.75 ± 0.06 SD) records, and the nonparametric Kaplan-Meier VGE survival curves for men and women statistically evaluated. In both the low and high dose records, women had significantly greater survival time than men ($p = 0.07$ for low dose comparisons, $p = 0.002$ for high dose comparisons from Tarone-Ware [T-W] log-rank test). The same approach was applied to the exercise PB records. But in this case there was no statistical difference between men and women in the low or high decompression dose records ($p = 0.35$ for low dose ($n = 117$) comparison, $p = 0.99$ for high dose ($n = 100$) comparison from T-W log-rank test). Since the exercise PB decompression dose is statistically higher for women than men in Table IV, I also compared VGE survival curves after first removing 51 records for men with decompression dose ≤ 1.875 as a means to increase the mean decompression dose for men. This left 115 records for males with a mean decompression dose of 1.91 ± 0.028 . The DCS incidence increased to 14.8% (17 / 115), the VGE incidence increased to 46.1% (53 / 115), the Grade IV VGE incidence increased to 12.1% (14 / 115), and the Grade IV VGE incidence in those with VGE increased to 26.4% (14 / 53). None of these increases were significantly different from the responses in the women. And there was still no statistical difference between men and women in the VGE survival curves after exercise PB ($p = 0.55$ from T-W log-rank test). So the difference in VGE pattern in the resting PB records associated with genders is evident under either low or high decompression dose. And no difference in the VGE pattern in the exercise PB records associated with gender is evident under either low or high decompression dose or when decompression dose is made equivalent between genders.

It could be argued that even with the same decompression dose of about 1.57 for men and women after resting PB (see Table III) that the slightly lower mean altitude of 5.83 psia (23,500 feet altitude) for women and 5.07 psia (26,500 feet altitude) for men could dramatically influence the VGE outcomes, particularly the latency time for VGE. This is reasonable since pressure-volume effects on growing bubbles at low absolute pressure can be significant. In the case of resting PB, a simple decompression dose was computed as the ratio of N_2 pressure in the 360 min half-time compartment after PB to the ambient pressure at altitude. Women in the above

case had a slightly shorter PB than men, but were exposed to a slightly lower mean altitude that resulted in a decompression dose that was still comparable. I never the less verified that the difference in VGE failure pattern between men and women was still evident after selecting from the 549 records the 348 records where the altitude exposure was to 4.3 psia. This was also the altitude in all of the 217 records from the exercise PB protocols. The mean decompression dose for 34 women was 1.54 ± 0.27 SD and 1.52 ± 0.26 SD for 314 men. The DCS incidence was 17.6% for women and 15.6% for men, with 26.5% VGE (9 cases) for women and 41.7% VGE (131 cases) for men. The VGE survival curves were still significantly different ($p = 0.05$ from T-M log-rank tests), so the small difference in the mean altitude exposure pressure between men and women is not the reason for the difference in VGE survival curves.

When 84 records that included adynamia were removed from the 549 records done under resting PB, the difference in VGE failure pattern between men and women was still evident. Including the adynamia data made the difference slightly greater. So by extrapolation, the presence of adynamia in all the exercise PB data is not the reason the VGE failure times are similar for men and women.

If ergometry exercise is reducing the difference in VGE failure pattern between men and women during exercise PB, then this could be tested if exercise during PB was done with and without dual-cycle ergometry. In fact, ergometry was used extensively in Phases I, II, V-2, and V-3 while it was not used extensively in Phases III, IV, and V-1. The VGE survival curves were not statistically different between men and women that used dual-cycle ergometry ($n = 143$, $p = 0.48$ from T-W log-rank test). But the VGE survival curves were different between men and women that did not use or did not extensively use dual-cycle ergometry ($n = 74$, $p = 0.03$ from T-W log-rank test). This is an important observation. The details about the seven exercise PB protocols are too numerous to document here, but are available (Conkin J, et al. A probability model of decompression sickness at 4.3 psia after exercise prebreathe. NASA Technical Publication (in review as of August 2004), Johnson Space Center).

It is suggested that the dual-cycle exercise may have a proportionally greater ability to generate micronuclei in women than men during the PB that later grow into detectable VGE

during the test at 4.3 psia. I also suppose that the enhanced perfusion of fat depots nearer the skin that are distributed in the limbs of women has “primed” these tissues to contribute VGE on subsequent decompression compared to resting PB where VGE may be trapped in these fat depots with limited opportunity to enter the venous return. Otherwise normal men do not have the same body fat content or distribution of fat as normal women. So it is reasonable to suggest that differences in blood perfusion through lipid tissues due to differences in anatomy (gender) occur when exercise is done. The old adage, “men perspire and women glow,” suggests an underlying true difference in how men and women achieve heat removal during exercise. We may be observing a manifestation of this gender difference to exercise response in the data on VGE latency time.

Nitrogen Washout between Men and Women

This report ends with a few observations about N₂ washout between men and women. Removing N₂ from the tissues prior to depressurization is the most common risk mitigation strategy for DCS. If there is no N₂ in the tissues, then there is no risk of DCS, regardless of gender. If there are differences in DCS and VGE outcomes between men and women, then it is logical to evaluate differences in the amount and distribution of N₂ taken to altitude after the same PB procedure. Table XII shows the estimated volume of N₂ dissolved in lean and fat tissues for a normal male and female. The total volume of N₂ is about the same for normal men and women given a N₂ solubility coefficient of 0.0146 ml N₂ / ml tissue * ATM N₂ in lean (aqueous) tissue and 0.0615 ml N₂ / ml tissue * ATM N₂ in fat (lipid) tissue, and the other information in the table. I did not reduce total body weight to compensate for the weight of inert bone.

TABLE XII. Estimated N₂ Content in Normal Males and Females

gender	wt (kg)	body fat % (% total wt)	fat mass (kg)	N ₂ volume in fat (ml)*	lean mass (kg)	N ₂ volume in lean (ml)	total N ₂ volume (ml)
male	75	10	7.5	405	67.5	778	1183
female	60	25	15.0	809	35.0	403	1212

* used density of fat at 0.9 kg / liter, and 0.79 ATM N₂ in breathing air

What is apparent from this example is that twice as much N₂ is present in fat tissues of “normal” females compared to “normal” males and that about twice as much N₂ is present in lean tissues of males compared to females. Given enough PB time, the same total volume of N₂ would be removed from the male and female in the example. But PB time is always limited. So the discussion now turns to the kinetics of N₂ washout, and the relative contributions of N₂ from the fat and lean tissues during a limited resting PB.

During the early phase of a PB, a large amount of N₂ is removed from a well perfused and large lean tissue reservoir in men, with a lesser amount of N₂ compared to women coming from a poorly perfused and smaller fat depot. The poorly perfused fat contributes some N₂ throughout the PB, but is likely responsible for the long tail of a typical N₂ washout curve. Women also provide a large amount of N₂ initially removed from a well perfused but smaller lean tissue reservoir, with a greater amount of N₂ compared to men coming from a poorly perfused but larger fat depot. Poorly perfused fat tissue also has a five-fold affinity for N₂. As a result, a large amount of N₂ is available from fat tissue in women, and the N₂ slowly leaves the body during PB such that you would expect an even longer tail to a typical N₂ washout for women compared to men.

Figure 7 is from unpublished work on N₂ washout by Dr. Benjamin F. Edwards done at JSC around 1988. Each curve is a best-fit of data from a two-compartment exponential model. The dashed curve shows the average N₂ washout rate (ml / min) from 11 men in a 6-degree head down body position during the PB. The solid curve shows the average N₂ washout rate from eight women, also in a 6-degree head down body position. The curve for the females shows an initial rapid decrease compared to the males, but the curve crosses the curve for the men at about 200 min. The PB was only 210 min, but I extrapolate with the model to 360 min. The total expired N₂ was 659 ± 223 ml after 180 min for the 11 men and 335 ± 132 ml for the eight women.

Males are contributing substantial N_2 from a greater quantity of lean tissues early in the PB compared to women, but are doing so at a slightly slower rate. The rate constant (min^{-1}) for the first of two fitted compartments for the men was 0.1162 compared to 0.1388 for women. The women are rapidly clearing a compartment with a smaller fraction of the total N_2 compared to the men. The situation reverses for the rate constant in the second compartment. Now the rate constant for men is 0.0114 compared to 0.0078 for women. The rate of N_2 removal in the second compartment is slower for women than men, possibly indicating that the removal of a substantial reservoir of N_2 from poorly perfused fat in the female subjects is going to require a longer PB. This is seen more clearly when a natural log transformation of the y-axis is done as seen in Figure 8.

My conclusion is that after a short PB, either while at rest or during exercise, women likely start an altitude exposure with more N_2 in the body on a ml / kg basis compared to men because the additional N_2 is likely sequestered in a greater quantity of poorly perfused fat tissue. The additional N_2 might be responsible for differences in VGE outcomes between men and women. I have established that there is no difference in hypobaric DCS incidence related to gender after some PB, so the excess N_2 in fat has little impact on the mechanism of at least Type I DCS.

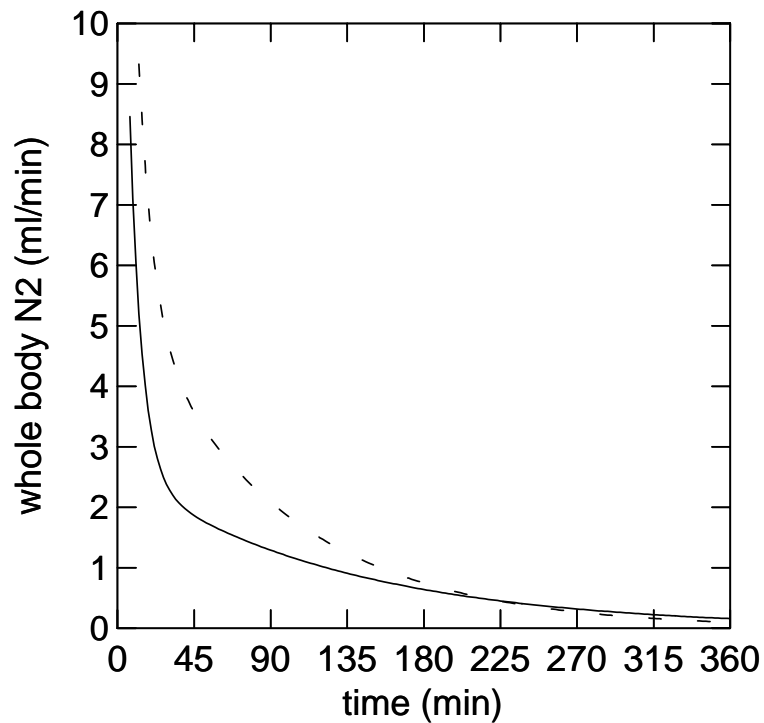


Figure 7. Average N₂ washout rate between 11 men and eight women. Dashed curve for men is from a two compartment exponential model optimized through least-squares regression. The equation for the dashed curve is: $N_2 \text{ ml / min} = 18.6 * \exp(-0.1162 * \text{time}) + 5.8 * \exp(-0.0114 * \text{time})$. The equation for the solid curve (women) is: $N_2 \text{ ml / min} = 16.3 * \exp(-0.1388 * \text{time}) + 2.6 * \exp(-0.0078 * \text{time})$.

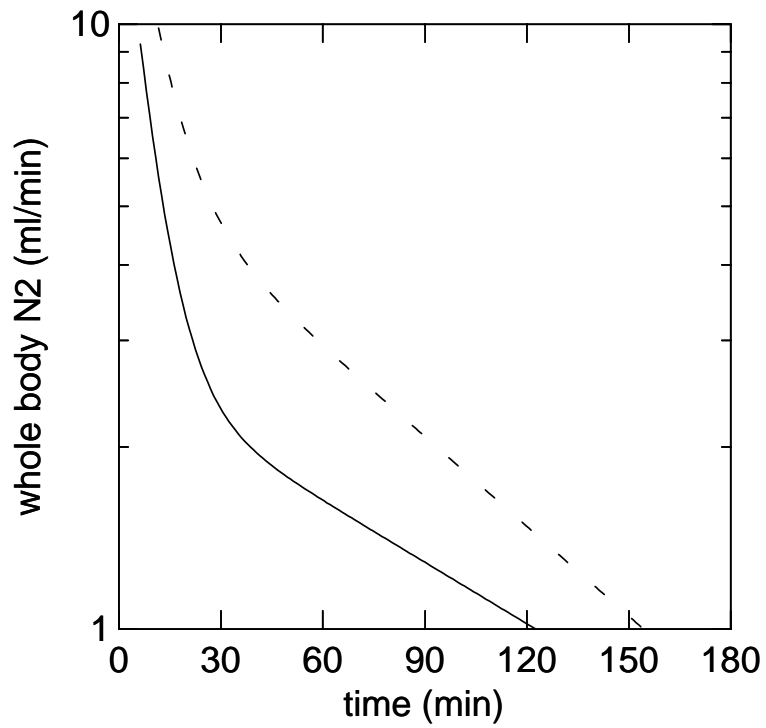


Figure 8. A natural log transformation of the curves from Fig. 7 to evaluate the kinetics of N₂ washout between men and women performing a 210 min PB from a 6-degree head down body position. Relative to the men, the women are quickly removing N₂ early in the washout but the rate slows later in the washout.

SUMMARY / CONCLUSIONS

There was generally no rigorous control over or accounting for the decompression dose from SCUBA diving activities. This is a critical deficiency in any comparison of DCS results between men and women. There were only a few cases of DCS, so there was inadequate response data in divers to evaluate. Both of these deficiencies were also present in most, but not all, of the results from research in altitude chambers. My summary comments consider information from both the few abstracts and few reports that were available. Except for the observation of more Type II DCS in women from a *Letter to the Editor* (33) and more Type II DCS in women who fly after diving (39), there was no compelling evidence of a difference in DCS risk between men and women SCUBA divers. Many women that presented with DCS symptoms seemed to be in or near menses (26), with fewer cases reported as time increased from menses. There was no compelling evidence that the use of BCP in SCUBA divers increased the risk of DCS. There were insufficient data about VGE from SCUBA diving to make any conclusion about the incidence of VGE and gender. In contrast, there were ample data about VGE from research in altitude chambers, mostly because you have a “captive” audience for the duration of the test. Women produced less VGE and less Grade IV VGE compared to men under the same decompression dose, especially when resting PB was performed prior to ascent to altitude. Dual-cycle ergometry exercise during PB tends to reduce the differences in VGE between men and women for reasons not completely understood. There was no compelling evidence that the risk of altitude DCS was different between men and women. However, a large number of DCS cases were associated with menses, and the use of BCP did seem to put women at a slightly greater risk than those that did not use BCP. There were substantial observations that women comprise a larger number of difficult cases that required complicated medical management. It is certainly evident that more information about the menstrual cycle and the use of BCP needs to be collected in future research about DCS in altitude chambers. As women make greater strides to expose themselves to hazardous environments, as part of their careers or just for recreation, it is clear that focused, well-controlled, prospective research is needed.

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13. ABSTRACT (Maximum 200 words) The author addressed the following questions: are women at greater risk of decompression sickness and venous gas emboli at certain times in their reproductive cycle, is risk modified by the use of birth control pills (BCP), and is there a difference in overall risk between men and women under the same decompression dose? The summary considers information from the few abstracts and reports that were available. Except for the observation of more Type II DCS in women, particularly in women who fly after diving, there was no compelling evidence of a difference in DCS risk between men and women SCUBA divers. Many women that presented with DCS symptoms seemed to be in or near menses, with statistically fewer cases reported as time increased from menses. There was no compelling evidence that the use of BCP in SCUBA divers increases the risk of DCS. There were insufficient data about VGE from SCUBA diving to make any conclusion about the incidence of VGE and gender. In contrast, there were ample data about VGE from research in altitude chambers. Women produced less VGE and less Grade IV VGE compared to men under the same decompression dose, certainly when resting oxygen prebreathe (PB) was performed prior to ascent to altitude. Dual-cycle ergometry exercise during PB tends to reduce the differences in VGE between men and women. There was no compelling evidence that the risk of altitude DCS was different between men and women. However, a large number of DCS cases were associated with menses, and the use of BCP did seem to put women at a slightly greater risk than those that did not use BCP. There were substantial observations that women comprised a larger number of difficult cases that required complicated medical management.				
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