Albuterol metered dose inhaler performance under hyperbaric pressures.

G. A. JOHNSON[1], V. R. GUTTI[2], S. K. LOYALKA[2], K. A. O'BEIRNE II[1], S. K. COCHRAN[1], H. M. DALE[1], G. R. KRACKE[1]

[1]Department of Anesthesiology and Perioperative Medicine and Jefferson C. Davis Hyperbaric Medicine Center, University of Missouri School of Medicine, Columbia, MO 65212; [2]Nuclear Science and Engineering Institute and Particulate Systems Research Center, University of Missouri, Columbia. MO 65211.

Johnson GA, Gutti VR, Loyalka SK, O'Beirne, II, KA, Cochran SK, Dale HM, Kracke GR. Albuterol metered dose inhaler performance under hyperbaric pressures. Undersea Hyperb Med 2009; 36(1):55-63. The weight change per actuation and aerosol particle size and number delivered by albuterol metered dose inhalers (MDIs) were measured in a multiplace hyperbaric chamber at pressures ranging from one atmosphere absolute (1 ATA, 0 feet of seawater, fsw, 101 kPa) to three ATA (66 fsw, 304 kPa). Weight change per actuation by CFC (chlorofluorocarbon) and long canister HFA (hydrofluoroalkane) powered MDIs was 13±1% and 12±1% less, respectively, at 3 ATA compared to 1 ATA. However, weight change per actuation by short canister HFA MDIs was not significantly changed with pressure. The geometric mean diameters of nano particles from the CFC and short canister HFA MDIs decreased from 50 nm at 0 fsw to 32 nm at 66 fsw whereas the long canister HFA aerosol diameters were not affected. The numbers of nanometer size particles delivered at 66 fsw were only 4-7% of those delivered at 0 fsw for the CFC and long canister HFA MDIs whereas for the short canister MDIs it was 26%. We conclude that the weight change per actuation of albuterol and the sizes and numbers of aerosol particles emitted from albuterol MDIs actuated in a hyperbaric environment vary by canister type.

INTRODUCTION

Aerosol delivery by pressurized metered dose inhalers (MDIs) is an effective method for introducing therapeutic agents into the respiratory tract and lungs. A number of drugs including corticosteroids, anticholinergics, mast cell stabilizers, and beta agonists have been formulated and used successfully in MDIs. The mass of the canister contents of a typical MDI is composed of about 1% drug, 80% liquid propellant, with the remainder of the mass accounted for by the non-pharmacologic excipients such as co-solvents, surfactants, or dispersal agents (1). The drug is released from the MDI as an aerosol with particle diameters ranging from nanometers to microns (2). Its release is powered by the high vapor pressure of the propellant or propellant mixture delivered by a fixed volume metering chamber. The propellants used in MDIs are highly volatile liquids with boiling points well below ambient temperatures. Propellants in MDIs have historically been chlorofluorocarbons (CFCs). However, these are currently being phased out because of their ozone-depleting properties and replaced by the environmentally friendly hydrofluoroalkanes (HFAs) (3).

In the present study, we measured MDI weight change per actuation and aerosol particle size and number emitted from albuterol MDIs at increased atmospheric pressures in a multiplace chamber. Our study was prompted by an observation we had of an asthmatic patient being treated emergently

with hyperbaric oxygen for upper limb wounds who suffered an acute bronchospasm. It was our impression from this incident that the MDI used on this patient delivered diminished doses of albuterol at increased pressure. Therefore the purpose of this study is to test the hypothesis that the weight change per actuation of albuterol MDIs and the aerosol particle size and number released by MDIs are reduced at pressures encountered by patients undergoing typical hyperbaric treatments in multiplace chambers. We report that some inhalers show a diminished weight change per actuation and decreased aerosol particle diameter and number at increased pressure, whereas others show no decreases at all in weight change per actuation. Factors contributing to possible changes in drug delivery to asthmatic patients by MDIs at increased ambient pressures are discussed.

METHODS

Materials

We tested a total of 39 MDIs from 5 different pharmaceutical companies (Table 2). The MDIs were divided into three groups based on obvious characteristics: CFC inhalers, all with the same size canister, HFA inhalers with short, 5.6 to 6.0 cm in length (including valve), canisters, and HFA inhalers with long, 7.8 cm in length (including valve), canisters.

Facilities

Studies were performed in a Perry Baromedical Services Sigma II dual place hyperbaric chamber equipped with a medical transfer lock. MDIs were weighed to the nearest 0.1 mg on a Sartorius model B120S analytical laboratory balance located outside the chamber.

Measurements

The MDI canisters were weighed and transferred into the chamber via the medical transfer lock. The MDIs were then inserted into their appropriate plastic mouthpieces and actuated five times in succession with a one second delay between actuations by a technician wearing gloves in the chamber. The MDIs were shaken between each actuation according to manufacturers' instructions. One actuation is equivalent to one puff or one "shot" of the MDI. The canisters were then removed from the mouthpieces, transferred out of the chamber, and re-weighed. MDIs were tested at 1, 2, 2.4, 2.8, and 3 atmospheres absolute (ATA). These pressures correspond to diving pressures of 0, 33, 45, 60, and 66 feet of seawater (fsw) and 101, 203, 243, 284, and 304 kPa, respectively. These increased pressures represent those commonly used in hyperbaric centers. The MDIs were actuated in a random order at the different pressures and the order of pressures was increasing, decreasing, or mixed in three separate experiments. The temperature outside the chamber was 21.2^{o}C and the temperatures inside the chamber at the pressures were 22.8 ^{o}C at 33 fsw, 23.4^{o}C at 45 fsw, 26.0^{o}C at 60 fsw, and 26.8^{o}C at 66 fsw.

Particle size analysis.

Aerosol particle diameters in the nanometer range were measured with a TSI Model 3080L electrostatic classifier, with aerosol inflow rate = 1.5 l/min and sheath flow rate = 15 l/min., in tandem with a TSI Model 3776 ultrafine condensation particle counter (TSI Inc., Shoreview, MN). The response of the classifier and counter was verified by measuring the particle size distribution of 21, 50, and 99 nm diameter polystyrene standards suspended in a buffer solution (Bangs Laboratories, Inc., Fishers, IN). For the MDI experiments, the instruments were placed adjacent to the hyperbaric chamber and connected by plastic tubing to a ball valve and penetrator plate port of the medical lock on the chamber. In the chamber the MDIs were

actuated 12 times over a two minute period into a 1 l glass funnel connected by plastic tubing to the penetrator plate port. MDIs were shaken between actuations and samples measured at pressures of 0, 33, and 66 fsw. Nanometer particle size and number data from the 102 size bins were fitted to log Gaussian functions using Graphpad, San Diego, CA, to estimate particle diameters and numbers of particles at different pressures.

Statistics

The statistical significance of differences between mean MDI weight losses at different pressures compared to 0 fsw was calculated using Friedman's repeated measures one way analysis of variance (ANOVA) followed by Dunn's multiple comparison test. Mean MDI weight losses per actuation at different pressures were fitted by linear regression (GraphPad, San Diego, CA). The mean fractional weight loss of each group of MDIs at 66 compared to 0 fsw was calculated from this regression line. Differences among these means were tested for statistical significance using one way ANOVA followed by Bonferroni's multiple comparison test. Differences between these means and zero were tested with a one sample t test. Data are presented as mean ± SEM and p values less than 0.05 were considered significant.

RESULTS

Albuterol MDIs were tested for the weight change per actuation and nano particle size distribution at atmospheric pressures ranging from ambient to 66 fsw. The weight change per actuation was measured by weighing the MDI canister before and after actuation. According to the manufacturers, all of the MDIs tested delivered a 90 microgram metered dose of albuterol of per actuation. The albuterol is a microcrystalline suspension with excipients in a liquid propellant. Therefore the change in canister weight loss per actuation is a relative measure of dose delivered with each actuation. The weight losses per actuation for the 24 CFC MDIs measured at five pressures are shown in Fig. 1. The line is a linear least squares fit of the means at each pressure.

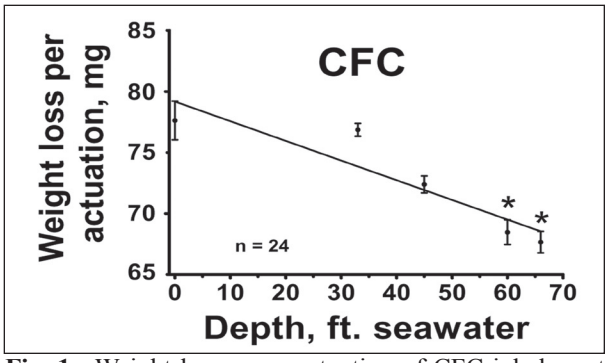

Fig. 1. Weight losses per actuation of CFC inhalers at different increased pressures. MDI identities are in Table 2. Asterisks represent means significantly different from 0 fsw. Slope = -0.161 ± 0.040 mg/fsw, intercept = 79.2 ± 1.9 mg, $r^2 = 0.84$.

CFC MDIs lost a mean of 79.2 ± 1.9 mg per actuation at 0 fsw. The mean weight loss from the canister at 66 fsw was 68.5 ± 0.7 mg, a decrease of 13 ± 1% compared to 0 fsw.

Weight loss at different pressures by the 15 HFA MDIs is shown in Fig. 2.

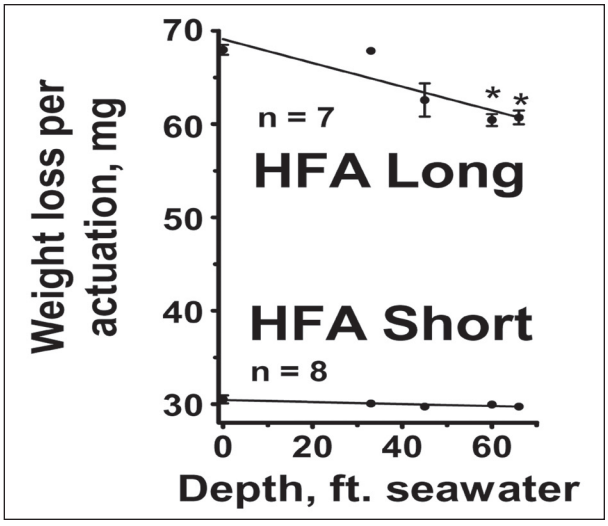

Fig. 2. Weight losses per actuation of HFA inhalers at different increased pressures. MDI identities are in Table 2. Asterisks used as in Fig. 1. Slopes = -0.127±0.038 and -0.011±0.003 mg/fsw, intercepts = 69.1±1.8 and 30.4±0.1mg, r^2s = 0.79 and 0.80, respectively.

The lines are least squares fits of the means at each pressure.

The HFA long group delivered a mean weight loss of 69.1± 1.8 mg per actuation at 0 fsw and 61.1±0.4 mg at 66 fsw, a decrease of 12 ± 1%. The HFA short group lost a mean weight of 30.4 ± 0.4 mg per actuation at 0 fsw and 29.7 ± 0.2 mg at 66 fsw. This 2±1% decrease is not significantly different from zero ($p>0.05$). Therefore hyperbaric pressures in the range studied have no significant effect on weight change per actuation by HFA short MDIs. The percent decreases in MDI weight change per actuation at 66 fsw compared to 0 fsw are summarized in Fig. 3.

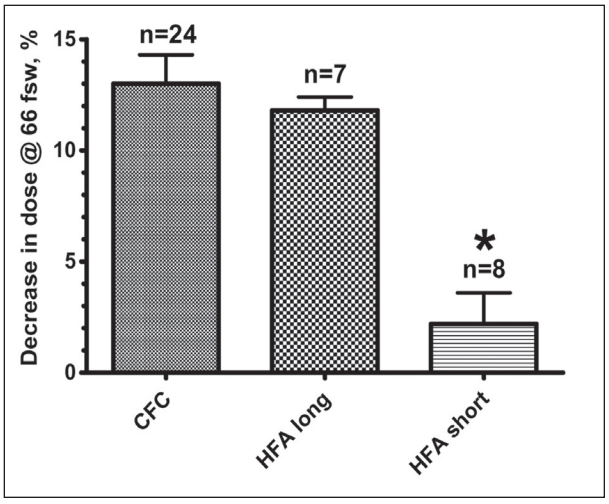

Fig. 3. Summary of percent decreases in delivered doses for the three groups of MDIs at 66 fsw compared to 0 fsw. Data are from Figs. 1 and 2. Asterisk indicates the mean is not significantly different from zero ($p>0.05$).

Ideally, MDIs are designed to deliver drug in an aerosolized form with an appropriate particle size distribution to maximize mass deposition in the respiratory tract. In addition, MDIs are designed to deliver uniform drug doses when they are used in a variety of changing environmental conditions such as temperature, humidity, agitation, or pressure (4). Therefore, in order to investigate the effects of hyperbaric pressure on aerosol particle size and numbers, we measured MDI aerosol sizes in the nanometer size range at 0, 33, and 66 fsw (Fig. 4).

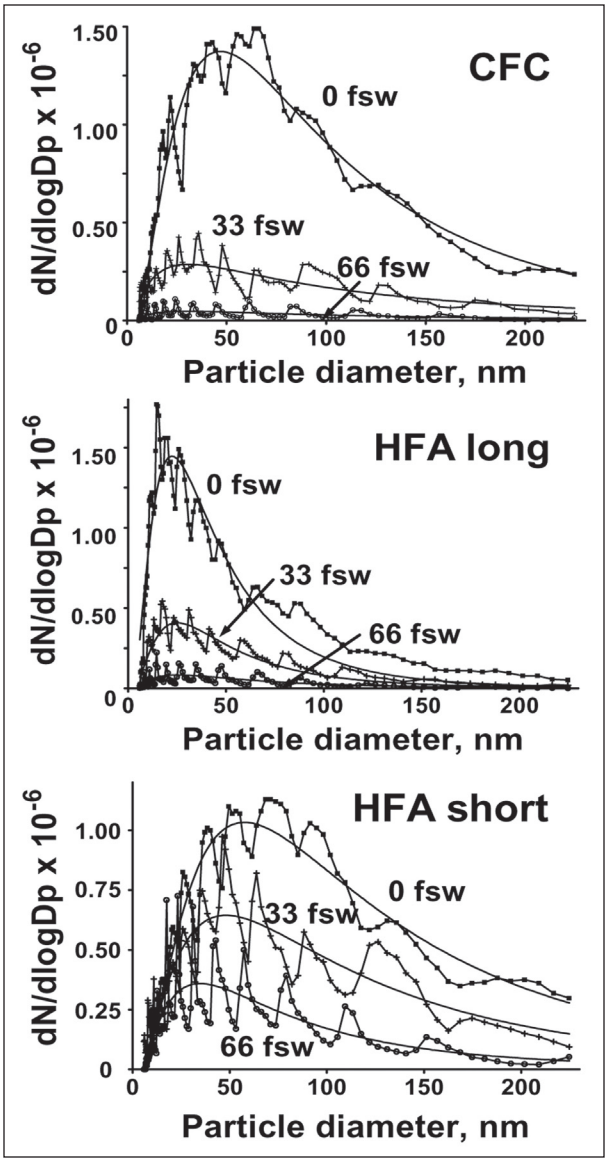

Fig. 4. Nanometer size analysis of MDI aerosols. The size distributions of aerosols of representative MDIs from the three groups were measured at 0, 33, and 66 fsw. Lines are non-linear regression fits. Fit parameters are presented in Table 1.

The ordinate, dN/dlogDp, represents the normalized number concentration of particles. The number concentration, dN, measured by the SMPS spectrometer is the concentration of particles in a given size channel or bin. The normalized number concentration, dN/dlogDp, is calculated by dividing dN by the geometric

width of the size channel. The abscissa represents the 102 particle diameter bins determined by the nanoparticle classifier and counter instruments as described in Methods. The fluctuations in numbers of particles across the size range represent the 12 actuations used to generate each MDI distribution. Aerosol particles ranged in diameter from 5 nm to 225 nm with the majority of particles having diameters at the lower half of the range, 10-100 nm. The number of nano particles decreased with increasing pressure for all MDIs. Interestingly, we found that at 66 fsw the CFC and HFA long groups delivered only about 4 to 7% of the number of particles they delivered at 0 fsw, whereas the HFA short group delivered about 26 % of the number delivered at 0 fsw (Table 1).

Aerosol particle sizes were calculated from log Gaussian curve fits of the data (5) and are presented in Table 1.

Table 1. Mean Diameter and Number of Nanometer Particles

Parameter	CFC	HFA Long	HFA Short
Diameter			
0 fsw	46.9±0.7	22.3±0.5	57.5±1.0
33 fsw	30.8±1.5	25.1±0.8	48.0±1.5
66 fsw	31.4±3.8	26.0±2.1	34.8±1.9
Number of particles			
0 fsw	$1.59x10^8$	$9.34x10^7$	$1.38x10^8$
33 fsw	$3.46x10^7$	$2.87x10^7$	$8.20x10^7$
66 fsw	$5.84 x10^6$	$6.60x10^6$	$3.54x10^7$

Diameters are geometric mean diameters in nm ± SE and were calculated from best fits to log Gaussian functions of data in Fig. 4. The number of particles is represented as the area under the curves in Fig. 4 and has units of dN/dlogDp x nm.

For the CFC group, the geometric mean diameter of aerosols emitted at 0 fsw was about 47 nm but decreased to about 31 nm at 33 and 66 fsw. The geometric mean aerosol diameter for the HFA long group was about 22 nm at 0 fsw and this increased slightly at the two pressures. The HFA short group had a geometric mean diameter of about 58 nm at 0 fsw, but diameters decreased at 33 and 66 fsw to about 48 and 35 nm, respectively.

DISCUSSION

Rationale

From our clinical experience using a CFC MDI in a patient requiring bronchodilator therapy at increased pressure and knowing that CFC MDIs were being withdrawn from clinical use, we wondered what doses of albuterol we were delivering to our patient under hyperbaric conditions and how the CFC MDIs might compare to the replacement HFA MDIs under these conditions. Therefore we tested a group of currently available CFC and HFA albuterol MDIs for weight change per actuation at the increased atmospheric pressures encountered by patients undergoing hyperbaric therapies in a multiplace chamber. We found that the weight change per actuation by these inhalers at different pressures varied with the MDI design, with some MDIs showing decreased weight change per actuation at increased pressure whereas other MDIs showing no decrease at all. To the best of our knowledge this is the first report of albuterol MDI weight change per actuation measured under hyperbaric conditions and the first report of nanometer sizing of particles from albuterol MDIs at any pressure.

MDI design

An explanation of the principle behind dose delivery by MDIs is helpful to explain our data. In albuterol MDIs, the drug is a microcrystalline suspension in a volatile liquid propellant, either CFC or HFA, along with a minor amount of excipients. The drug

and propellant are contained in a pressurized metal canister which is fitted at one end with a spring-loaded metering valve. The pressure in the canister is a consequence of the high vapor pressure of the liquid propellant which is in equilibrium with its gas phase. The pressure in the canisters at room temperature is about 80 psia whereas ambient atmospheric pressure is about 14.7 psia. Although the pressure difference across the canister wall is substantial, this pressure difference is not used to deliver the dose of drug in MDIs. Instead, a metering chamber located in a spring-loaded rod is exposed to either the pressurized compartment or the ambient pressure, but not to both at the same time. Since the inhaler is inverted by the user before use, the drug-propellant suspension is at the bottom of the canister and a portion of this liquid suspension enters the metering chamber. Upon actuation of the MDI, the metering chamber is exposed to the external environment. The highly volatile propellant in the metering chamber boils explosively and forces itself and the suspended drug through an orifice in the plastic mouthpiece thus making a fine aerosol cloud that is inhaled by the user. Thus, in essence, the MDI is a liquid volume dispenser that dispenses a metered volume of a highly volatile liquid suspension. The CFC propellant is typically a mixture dichlorodifluoromethane (also called CFC 12) with a vapor pressure (V.P.) of 82.3 lbs/in^2 absolute (psia) at 20^o C and a boiling point at one atmosphere (B.P.) of -29.8^o C and trichlo romonofluoromethane (CFC 11) which has a V.P. of 12.9 psia at 20^{o}C and a B.P. of 23.9^o C. The hydrofluoroalkane propellant is 1,1,1,2-tetrafluoroethane (HFA-134a) which has a V.P. of 83 psia at 20^{o}C and a B.P. of -26.5^o C.

Technical considerations

The observed weight change per actuation of the inhalers at increased atmospheric pressure can be compared to two hypothetical situations in Table 2, see below.

Absolute pressures are used for comparisons where one atmosphere of pressure is equivalent to 14.7 psia. The propellant V.P. at 20^{o}C is an approximation of a CFC inhaler with mostly CFC 12 as propellant and an HFA inhaler with HFA-134a. Hypothetically, if the measured dose of albuterol were expelled only by the pressure in the canister, then the increased chamber pressure at 66 fsw would decrease the pressure difference between the canister interior and the outside from 67 to 38 psia. Thus the weight change per actuation by the inhaler at 66 fsw would be 43% less than at 0 fsw (Expected Wt. Loss-Pressure). If, on the other hand, the inhaler were a perfectly

Table 2. Expected and Observed MDI Dose Weight Loss

Pressure		Propellant V.P	Δ	Expected Wt. Loss- Pressure	Expected Wt. Loss- MDI	Observed Wt. Loss, % MDI Group		
fsw	psia	psia	psia	%	%	CFC	HFA long	HFA short
0	14.7	82.0	67.3	0	0	0	0	0
66	44.1	82.6#	38.5	43	0	13±1	12±1	2±1*

fsw- feet seawater; psia- lbs/in^2 absolute; Wt.- weight; MDI- metered dose inhaler
V.P.- vapor pressures at 20^{o}C for CFC12 or HFC134a propellants
Observed dose weight losses of groups are means ± SEM.
#- Calculated from Gibb's equation, $\ln (P_1/P_2)=[V_l(P_{e1}-P_{e2})]/RT$ where P=V.P.s, V_l= molar vol., P_e=external pressures, R=gas constant, and T=K^o (Moore, 1962).
*- not significantly different from 0, p>0.05, n = 8.
MDI Group, manufacturer and (number of MDIs tested):
CFC- IVAX (5), Armstrong (5), Warrick (3), Key Proventil (11).
HFA long canister- GlaxoSmithKline Ventolin HFA (7).
HFA short canister- IVAX Pro-Air HFA (3), Key Proventil HFA (5).

metered dose inhaler, then the weight change per actuation would be nearly the same at both 0 and 66 fsw (Expected Wt. Loss-MDI) since atmospheric pressure has only a minor effect on vapor pressure as calculated from the Gibb's equation (6). The observed decreases in weight change per actuation at 66 fsw by groups CFC and HFA long (13 and 12%) fall in between the two hypothetical situations whereas those of the HFC short group approximate a perfectly metered dose inhaler with no decrease in weight change per actuation. This discrepancy is not due the nature of the propellant since HFA long inhalers showed a decreased weight change per actuation at 66 fsw whereas HFA short did not. Perhaps the metering valve mechanisms are different such that the inhalers affected by pressure have a seal that is sensitive to external pressure or a metering chamber that is in momentary contact with both the canister interior and the outside.

Other technical factors associated with pressurized MDIs may influence aerosolized drug delivery to the patient under hyperbaric conditions. For example, the aerosol particle size is a function of the vapor pressure of the propellant (7) and vapor pressure of a liquid is in turn affected by atmospheric pressure. Therefore aerosol particle size may change under increased atmospheric pressures. Respirable aerosol particles that deposit in the lower pulmonary system are reported to have a diameter size range of between 0.5 and 5 microns (7, 8). However, the smaller, nanometer diameter particles like the ones we measured here are also deposited in the lower pulmonary system. In fact, modeling studies show alveolar and interstitial deposition is highest for particles of 10-30 nm diameter range (2). Additionally, these nanometer sized particles may be particularly active, in spite of their low mass, because of their high surface to volume ratios (8, 9) and ability to penetrate rapidly to interstitial sites (10). Thus the changes in aerosol particle sizes with pressure we report here may affect drug pharmacodynamics and pharmacokinetics under hyperbaric conditions.

In our experiments we measured the weight loss per actuation of the MDIs as an indicator of the dose of drug delivered. Weight loss by MDIs is remarkably constant with successive actuations until the point where the propellant liquid is depleted, about 200 to 250 actuations depending on the propellant (3). Since albuterol is a microcrystalline suspension in the liquid propellant in the canister, and since the MDIs are shaken before actuations, measuring canister weight loss gives a relative measure of dose delivered with each actuation at different pressures since each metered volume contains the same amount of drug. In some MDI testing situations however, it is preferable to measure drug delivered per actuation by chemical rather than gravimetric analysis. An example of this type of testing would be a study of MDI tail off where MDIs have been actuated more than the recommended number of times and the canister contents approach exhaustion. Chemical analysis of the formulation delivered with actuations will ensure that drug is being measured as the MDI transitions from delivering complete doses to no delivery at all (3).

Asthma and diving

The prevalence of asthma in the general population may be as high as four percent. While some expert diving sources cite an equal prevalence of asthmatics as divers (11), others heartily disagree (12). The nature of the drowning/near drowning phenomenon as associated with diving combined with the pathophysiology of asthma, that is, air trapping and airway hyper reactivity, has led asthma to be considered a contraindication to sub-aquatic activities. Divers surviving near-drowning associated with acute bronchospasm often self-select from further underwater sports. While several of the asthma triggers that are

associated with underwater activity (cold, dry inspired gases, inspiration of hypertonic saline, exercise, allergic sensitizers, and high-resistance gas regulator valves) are entirely absent or minimized in the hyperbaric oxygen therapy (HBOT) environment (12), some of the common triggers such as increased inspired CO2, high density inspired gas, fear, pain, and hyperventilation remain (13). This is in addition to the asthmatic's baseline tendency for chronic air trapping secondary to increased inspiratory reserve volumes, increased volume and tenacity of secretions with frequent plug formation, increased resistance to exhalation, and possible cystic changes (12).

Bronchodilators

Many feel that aerosolized bronchodilators are to be avoided for those participating in underwater diving (14). Bronchodilator medication may allow normal descent to desired pressure but not be as effective as time and triggers mount. The sympathomimetic side effects may also aggravate the stresses of diving, especially by increasing the incidence of cardiac dysrythmias and panic, and causing pulmonary vasodilatation. This latter condition decreases the efficacy of pulmonary vascular filtration of venous gas emboli, which in turn increases the risk of arterial bubbles and severe decompression sickness (12). Although there are reports of occupation-induced symptoms of asthma in a diver at increased pressure (15) and changes in pulmonary function in exercise-induced asthmatics at increased pressure after exercise (16), neither report employed the use of MDIs at increased pressure. It was recommended that exercise-induced asthmatics use medication before diving (16). We used MDIs in this study although, typically, bronchodilators are delivered by a nebulizer in multiplace chambers. However, we could not find any evidence in the literature supporting the use of or describing the performance of either device in hyperbaric chambers. Advantages of MDIs are that they are familiar with users and they can be quickly passed to the patient via the medical transfer lock in the multiplace chamber.

Our patient in this case was additionally hypermetabolic secondary to a life-threatening, high voltage electrical burn. Other patients can be hypermetabolic secondary to infection, especially victims of necrotizing fasciitis and gas gangrene. In these cases higher minute ventilations are necessitated. As bronchospasm by definition greatly increases airway resistance and thus total work of breathing, and profoundly limit expiratory and inspiratory flows at normobaric conditions, the combined challenges of increased gas densities of hyperbaric conditions and the increased needs of the hypermetabolic patient with an acute bronchospasm can represent a potentially overwhelming situation (17).

Asthma at increased pressure

Patient oxygenation in the event of an acute bronchospasm in HBOT may be in the normal range for a much longer period than would be the case at normobaric conditions. However, due to the increased work of breathing and rebreathing intrinsic to hyperbaric chambers and their oxygen hoods, the patient's pCO_2 would be expected to be mildly elevated prior to the bronchospasm but increase rapidly with the huge effort of breathing and as panic sets in (17). Ventilatory muscle exhaustion would also be expected to rapidly occur. This is a perfect set-up for a dry drowning scenario (18). Further, the chronically hyperexpanded lung of the asthmatic, and acute air-trapping occurring as part of the acute bronchospasm could increase the incidence of pulmonary barotrauma, and, secondarily, severe dysbaricism, if the patient would be rapidly brought to the surface (19). Thus, it would appear that the preferred action in the eventuality of an acute bronchospasm

occurring during HBOT would be to stay at the increased pressure at which the bronchospasm was diagnosed, and resolve the bronchospasm at that pressure with an MDI while breathing the highest Fi02 possible, then slowly returning from pressure.

SUMMARY

The present experiments provide evidence that HFA short MDIs showed no decrease in the mass of inhaler contents delivered with each actuation at commonly used hyperbaric pressures in a multiplace chamber and the decrease in the number of nanosized aerosol particles at 66 fsw was least compared to the other MDIs. The significance of our findings will be strengthened by clinical studies with albuterol MDIs in patients at increased pressures and by greater knowledge of the role of nanosize particles in drug delivery.

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