Sildenafil for Prevention of Swimming-Induced Pulmonary Edema (SIPE)

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Purpose of the Study

Problem to be Addressed. The problem addressed in this proposal is occurrence of immersion pulmonary edema (SIPE) during heavy exertion while swimming or diving in cold water.
Hypothesis and Specific Aim. We hypothesize that a 50 mg dose of sildenafil will reduce or eliminate SIPE in susceptible individuals. The specific aim will be to perform a randomized placebo-controlled study of 20 SIPE-susceptible volunteers. The aim of this proposal is to test the effectiveness of a standard dose of sildenafil for prevention of SIPE in healthy SIPE-susceptible individuals. The objective is to perform a placebo controlled trial of a single 50 mg dose of sildenafil one hour before a 40-minute exercise during head-out immersion in 20°C water.
Deliverable. The aim is verify a pharmacological method to prevent SIPE in susceptible individuals.

Background & Significance

Immersion pulmonary edema (IPE, also known as swimming-induced pulmonary edema, SIPE) is a condition in which cough, hemoptysis, dyspnea and hypoxemia develop after surface swimming or diving, often in young, healthy individuals (1-11). It has been reported predominantly in males, including naval trainees during strenuous swimming (6,7,10,12,13). The condition generally spontaneously resolves within 24 hours or with β2 adrenergic agonist or diuretic therapy, but it can be fatal (5,14). SIPE-susceptible individuals have higher pulmonary artery (PA) and PA wedge pressures during exercise in cold water (15). Thus it is believed that SIPE represents a form of hemodynamic pulmonary edema due to excessive pulmonary vascular pressures in response to cold water exercise.

There are some risk factors for SIPE, which include swimming or diving in cold water (1,3,11), negative static lung load (16), heavy exertion (3,4,6-8,10-12), fluid loading (12) and low vital capacity (7). Other predisposing factors are hypertension, left ventricular hypertrophy (LVH) and other cardiac abnormalities (17). It also tends to recur in susceptible individuals (1,3,7,11,13,17). Pulmonary hemorrhage can also occur in certain breath-hold divers due to pressure-related engorgement of the pulmonary vasculature induced by descent when lung volume is at or below residual volume. In those susceptible to hemorrhage certain genotypes (related to eNOS and angiotensin converting enzyme) have been observed to be more frequent (18), providing plausible rationale that genotyping may also be predictive of SIPE-susceptibility.

Approximately 30-40 cases per year are observed at the Naval Special Warfare Center (8,10,19). Cases of SIPE are also seen at the Naval Diving and Salvage Training Center. Its prevalence in 2.4-3.6 km open sea swimming trials has been reported to be from 1.8-60%, depending upon the severity (7,13). Prevalence during SEAL training is 1-3% of trainees during spring, summer and fall, and 5% in the winter (20). Pulmonary edema in a normal lung occurs when pulmonary artery (PA) wedge pressure acutely exceeds a critical value of 18-25 mmHg (21-23). Both PA and PA wedge pressures increase during immersion, primarily due to central redistribution of blood from the extremities (24,25), which engorges the central veins, heart and pulmonary vessels (24,26-28). This peripheral to central redistribution of blood is augmented by cold water immersion (28,29) and attenuated by a concurrent reduction in venous tone (26). Studies from our lab have demonstrated significant pulmonary arterial and venous hypertension (and systemic hypertension) during submersion, particularly in cold water (28). We have demonstrated that in SIPE-susceptible volunteers the peripheral-to-central blood redistribution leads to excessively high PA and PA wedge pressures at levels sufficient to precipitate pulmonary edema.

With a technique developed in our lab we have the ability to examine susceptibility to SIPE and test medications that might prevent it. Identification of a medication to prevent SIPE would be applicable not only to Navy divers and swimmers, but civilians known to be at risk for SIPE (e.g. triathletes) and individuals with heart failure, for whom swimming exercise may be beneficial for aerobic fitness but dangerous because of a risk of inducing pulmonary edema (30).

RELEVANCE

SIPE remains a problem during training for SEALs and Special Warfare Combatant-Craft Crewmen. Nevertheless, SEAL candidates who experience SIPE have graduation rates similar to those who have not experienced it (31). Therefore, there must be a significant number of SIPE-susceptible operational SEALs and Special Warfare Combatant-Craft Crewmen who are at risk for SIPE during an operation. A medication with few side effects such as sildenafil that could prevent SIPE in susceptible individuals would be a valuable tool for use in mission-critical tasks where the individual best-suited for the task is SIPE-susceptible. An effective prophylactic drug would also be useful for civilians, particularly the increasing number of recreational triathletes in whom SIPE-susceptibility is around 1.5% (32). Deaths among amateur divers and triathletes due to SIPE have been reported (14,33,34).

PRELIMINARY WORK

Previous studies in our laboratory supported by NAVSEA have demonstrated that pulmonary artery and pulmonary artery wedge pressures are higher in thermoneutral water compared to the dry, and even higher in cold water (28). When compared with individuals with no SIPE history, SIPE-susceptible individuals have higher PA and PA wedge pressures during exercise submerged in cold water. This study demonstrated the following (15):

SIPE-susceptible individuals have higher pulmonary artery and wedge pressures during exercise in cold water, thus demonstrating the mechanism for hemodynamic pulmonary edema in SIPE.

Sildenafil, a drug known to reduce pulmonary artery pressure in other settings, also does so in SIPE-susceptible individuals, suggesting that sildenafil may be an effective preventive medication.

Sildenafil is a phosphodiesterase-5 (PDE-5) inhibitor that is used clinically for treatment of erectile dysfunction and primary pulmonary hypertension. It has a peak plasma level approximately one hour after oral ingestion and a 4-hour half-life (35). In normal individuals the drug induces a slight decrease in blood pressure at rest and during exercise in the dry (36), but no significant change during submersed exercise (15). While it is plausible that PDE-5 inhibitors could improve exercise performance (37), the evidence is mixed. Some studies have shown that sildenafil tends to improve exercise performance at altitude but not at sea level (38). More importantly, exercise performance is not impaired by either sildenafil or the similar drug tadalafil. In a group of trained cyclists and triathletes aged 18-35 years, oral sildenafil 50 or 100 mg had no adverse effect on a 10 km time trial or hemodynamic parameters during cycle exercise at 55% peak work for 60 minutes (39). In another study of fit volunteers aged 24-56 years, oral sildenafil 50 mg did not decrease O2max (40). In a test of anaerobic performance on a cycle ergometer in 20 healthy male athletes, oral tadalafil 20 mg had no adverse effect on mean power, peak power or fatigue during an incremental test to exhaustion (41). The same dose also had no adverse effect on aerobic performance in a study of 14 healthy male athletes (42).

Sildenafil is the logical drug to test as a prophylactic against SIPE for the Navy because:

Its hemodynamic properties in humans have been measured during cold water immersion under a Duke IRB (Pro00003158), providing a plausible rationale for its use as prophylaxis against SIPE (15).

There is anecdotal evidence of its effectiveness in preventing SIPE (43).

Sildenafil does not impair exercise performance (39,42).

Overhydration was previously identified as contributing factor to SIPE: in one report each of 8 navy trainees who subsequently developed SIPE had consumed about 5 liters of water during two hours before exercise (12). This is confirmed by our most recent study (Pro00019996), in which oral pre-loading with a standard rehydration solution (Pedialyte®) followed by 40 minutes of head-out immersed exercise in 20°C water produced SIPE manifestations in 7 of 9 individuals with previous SIPE and 1 of 14 with no such history, thus providing a model for testing of an intervention to prevent SIPE.

Design & Procedures

The specific aim of this study will be addressed using a randomized, placebo controlled study of sildenafil in a group of individuals with proven susceptibility to SIPE. Volunteers between the ages of 18 and 45 years will be recruited who have experienced documented SIPE. The medical record of each individual will be screened carefully for underlying predisposing conditions including heart valve disease, cardiomyopathy, untreated hypertension and coronary artery disease and obstructive lung disease. Every effort will be made to ensure that these exclusions are met before they come to Duke. Volunteers who have not undergone resting and stress echocardiography will undergo these studies in our facility. Each subject will undergo VO2max testing on the day before the study. COVID testing will be performed prior to arrival at Duke.

On the day of the study each volunteer will be allowed to eat a light breakfast. Pre-exercise blood pressure, heart rate and SpO2 will be recorded. Spirometry will be measured according to recommendations of the American Thoracic Society (1) using best of three efforts. One hour before the study the subject will be administered oral sildenafil (50 mg) or placebo in a re-encapsulated unidentifiable pill. During the 30 minutes before the study the subject will drink 2 L Pedialyte® then, while immersed to the neck in 20°C water, perform exercise on a cycle ergometer (60 rpm, approximate VO2=70% VO2max). Subjects will be instrumented with EKG, pulse oximetry and noninvasive blood pressure measurement. VO2 will be measured 10 minutes after the start of exercise using a metabolic cart (ParvoMedics, East Sandy, UT). Subjects will be periodically asked about symptoms of shortness of breath, cough, chest tightness and whether they can continue. If symptoms occur the chest will be auscultated. The exercise will be stopped when any of the following occur:
Dyspnea
Cough
Audible wheezing
Hypoxemia
Unwillingness of the subject to continue

Immediately following exercise subjects will be removed from the water. Post-exercise assessment will include chest auscultation and measurement of vital signs and spirometry. Chest radiography (PA and lateral) will be performed if pulmonary edema is suspected. Symptomatic subjects will be treated as appropriate with oxygen and albuterol until they are asymptomatic.

Randomization will be performed by the Duke Pharmacy Investigational Drug Service such that half of the subjects will receive each drug first. Both subjects and investigators will remain blinded until the end of the study.

The primary outcome will be pulmonary edema after exercise defined as one or more of the following:
Hypoxemia (SpO_2< 95% room air)
Productive cough
Pulmonary edema on chest radiograph
Wheezing on chest auscultation
Secondary outcomes will be:
Voluntary premature cessation of exercise due to shortness of breath
Post-exercise 10% decrease in forced vital capacity (FVC) or forced expiratory volume in one second (FEV1)
'Comet tails' seen on ultrasound of the lungs (2)
One blood sample will be obtained for extraction of DNA and storage in the Duke Biofluids Shared Resource for future analysis.

Selection of Subjects

Inclusion Criteria:
Healthy volunteers between 18 and 45 years
History of SIPE

Exclusion Criteria:
Pregnant women
Significant heart valve disease
Cardiomyopathy
Untreated hypertension
Coronary artery disease
Obstructive lung disease
VO_2max < 25 mL/kg as estimated by the University of Houston Non-Exercise Test (1)
Previous adverse reaction to sildenafil
Use of antihypertensives or other drugs that are known to interact adversely with sildenafil (e.g. nitrates, alpha adrenergic blockers)
Concomitant use of erythromycin or other potent cytochrome P450 3A4 inhibitors
History of non-arteritic anterior ischemic optic neuropathy (NAION)
COVID positive test
Subjects who are already taking sildenafil for another indication

The medical record of each individual will be screened carefully for underlying predisposing conditions. Every effort will be made to ensure that none of these exclusions are present before volunteers come to Duke. Volunteers who have not undergone resting and stress echocardiography as a result of previous workups will undergo these studies here.

Risk/Benefit Assessment

The main hazard in the proposed studies is the development of SIPE, although the risk is low. A physician will be monitoring the studies and will interrupt any exercise study in which signs of early SIPE develop.

The study will be conducted at the Center for Hyperbaric Medicine and Environmental Physiology within Duke Hospital, where diagnostic and therapeutic modalities including radiology, oxygen, bronchodilators, advanced monitoring and critical care facilities are immediately available. The investigative team has experience detecting and treating SIPE. Immersed exercise will be stopped immediately upon development of symptoms or signs suggestive of SIPE. Unlike development of SIPE in open water swimming, in the lab rapid removal from the water immediately reverses the hemodynamics that predispose to SIPE and allows appropriate support for resolution.

With sildenafil administration, the common adverse reactions include headache, flushing, dyspepsia, nasal congestion, urinary tract infection, diarrhea, dizziness, nosebleeds, insomnia, and rash. These effects are generally mild to moderate, transient, and more common at the maximum recommended dose (100 mg) and above (1). There is risk of visual disturbances, with alteration in color vision and excessive brightness, but these are also dose-dependent and reversible (1). Non-arteritic anterior ischemic optic neuropathy (NAION) has been reported rarely in temporal association with the use of sildenafil and other phosphodiesterase-V (PDE5) inhibitors. This effect is much less likely with only a single administration of sildenafil, and the annual incidence of NAION in sildenafil users is 2.8 cases per 100,000 men per year, similar to the estimated general incidence in the US (2.5-11.8/100,000/year) (2,3). It is difficult to determine if these events are related to PDE5 inhibitors or to other factors as those who experienced it already had autonomic or vascular risk factors for NAION (4). Single dose administrations of sildenafil in studies of high altitude pulmonary edema found no different secondary effects between sildenafil and placebo, and no erectile responses were reported in this setting as this effect would require sexual stimulus (5). No hemodynamic or other side effects were observed in an earlier study (6).

The main benefit to these SIPE-susceptible subjects will be to know whether their risk of SIPE can be reduced by oral sildenafil 50 mg.

Data Analysis & Statistical Considerations

Power analysis has been performed using previously obtained data from Pro00019996. Conservatively assuming that the study will result in SIPE in 70% of individuals with placebo and 5% with sildenafil, using a two-sided McNemar's test at alpha level 0.05 will achieve 96.7% power to detect a difference between sildenafil and placebo with N=20. There may be some washout of subjects due to screen failures or other reasons, however the same analysis reveals that a study of only 13 subjects will achieve 81% power to detect a difference between sildenafil and placebo. For the final analysis, comparison of the numbers of SIPE cases after sildenafil and placebo will be performed using McNemar's test (SAS software, SAS Institute, Cary, NC). N=40 subjects are planned for enrollment with the goal of 20 subjects participating and matched testing.

Data & Safety Monitoring

During the exercise portions of the study, subjects will be continuously monitored with EKG, SpO2, VO2 and intermittent noninvasive blood pressure, as wll as with a physician adjacent to the immersion pool. Data will be uiploaded to REDCap, where all observations will be stored. Dr. Claude Piantadosi, who is not part of the study, will act as the safety monitor. He will review the data on a regular basis and will be consulted for any adverse event.

All subjects will be monitored for safety while participating in the study and immediately (24 hours) post-participation, and the study investigators will be monitoring for adverse events throughout the course of the study. Dr. Claude Piantadosi will serve as the Independent Medical Monitor (also termed Research Monitor) for this study. He shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report. The Research Monitor shall have the responsibility to promptly report his observations and findings to the IRB or other designated official. The Navy Human Research Protection Program will be notified of any adverse events.