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Running head: Sildenafil: SIPE Prevention

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Abstract

Swimming-induced pulmonary edema (SIPE) occurs during swimming and scuba diving, usually in cold water, in susceptible healthy individuals, especially military recruits and triathletes. We have previously demonstrated that pulmonary artery pressure (PAP) and pulmonary artery wedge pressure (PAWP) are higher during immersed exercise in SIPE-susceptible individuals vs. controls, confirming that SIPE is a form of hemodynamic pulmonary edema. Oral sildenafil 50 mg 1 hour before immersed exercise reduced PAP and PAWP, suggesting that sildenafil may prevent SIPE. We present a case of a 46-year old, female ultra-triathlete with a history of at least five SIPE episodes. During a study during exercise submerged in 20°C water, physiological parameters before and after sildenafil 50 mg orally were: O2 consumption 1.75 , 1.76 L.min-1; heart rate 129, 135 bpm; arterial pressure 189/88 (mean 121.5), 172/85 (mean 114.3) mmHg; mean pulmonary artery (PA) pressure 35.3, 28.8 mmHg; PA wedge pressure 25.3, 19.7 mmHg. She has had no recurrences during 20 subsequent triathlons while taking 50 mg sildenafil before each swim. This case supports sildenafil as an effective prophylactic agent against SIPE during competitive surface swimming.

Key Words: **Swimming, Immersion, Swimming-Induced Pulmonary Edema, Phosphodiesterase-5 Inhibitors, Pulmonary Hemodynamics**

Introduction

Swimming-induced pulmonary edema (SIPE), also known as immersion pulmonary edema (IPE), presents with dyspnea, hemoptysis, cough, hypoxemia and usually bilateral pulmonary edema in susceptible individuals during immersed exercise (1).The condition was first described in 1989 by Wilmshurst et al, who proposed hypertension and cold water as predisposing factors (15). Since then nearly 300 cases have been reported in swimmers and divers, including triathletes and military combat swimmers (1, 2, 7-9, 11, 12, 14). Among civilian cases, approximately 44.9% of reported cases have an underlying cardiopulmonary conditions or risk factors that may have contributed (11). These include hypertension (1, 2, 5, 13, 14), asthma (11, 13) and cardiac disease (4, 11). In military trainees underlying conditions have not been reported. One survey reported that 1.4% of triathletes experienced consistent symptoms consistent with SIPE (9), although the prevalence of SIPE is most likely underestimated. Among military combat swimmer trainees, its prevalence in 2.4-3.6 km open sea swimming trials has been reported as high as 60% (12). Direct hemodynamic measurements in humans during cold water exercise supports the pathophysiology of SIPE as excessively high pulmonary artery and capillary pressures during exercise in cold water in susceptible individuals. The study also showed that sildenafil reduced the pressures and therefore may prevent SIPE (10). This case report provides evidence that it does: an elite triathlete with a history of multiple SIPE episodes who has experienced no recurrences when taking sildenafil 50 mg orally prior to each swim.

Case report

A 46-year-old, female, elite ultra-triathlete with a history of multiple SIPE episodes was recruited for an IRB-approved physiological study (Duke IRB Protocol # Pro00003158). From May 2005 to August 2010, the patient participated in 32 triathlon events, ranging from sprint to full Ironman distances (0.5-3.8 km swim, 22.2- 180 km bike, 5-42.2 km run). During this period she had experienced symptoms of SIPE, such as dyspnea, hemoptysis, and lung congestion, during at least five triathlon or swimming events. On one such occasion, the patient was hospitalized with a blood oxygen saturation of 73% on room air measured by pulse oximetry. Chest radiograph confirmed pulmonary edema.

The patient had a history of hypertension controlled on candesartan 16 mg per day and was otherwise healthy and extremely fit. Previous stress echocardiography revealed normal systolic and diastolic function with no wall abnormalities and a maximum heart rate of 190 bpm at 26.1 METs. At the time of screening on the day before the study, height, weight, BMI and vital signs were as follows: 1.44 m, 58.9 kg, 28.4 kg/m^2; blood pressure 124/80 mmHg, heart rate 60/min.

Written informed consent was obtained prior to testing. Methods have been described elsewhere (10). Briefly, the subject was instrumented with pulmonary and radial artery catheters. Submerged exercise (125 Watts external work, approximately 175 Watts total, including water resistance) in the prone position submerged in 19.3°C water was performed for 6 minutes. This was repeated one hour after oral administration of 50 mg sildenafil (approximately two hours after initial exercise). The following measurements were taken during supine, dry rest (prior to exercise) and during submersed exercise: oxygen consumption (VO_2), heart rate (HR), arterial

blood pressure, mean pulmonary artery pressure (MPAP), mean pulmonary artery wedge pressure (MPAWP), Fick cardiac output (CO), and central venous pressure (CVP). Measurements are reported in Table 1.

Following the controlled study, the subject's physician prescribed 50 mg sildenafil to be taken one hour prior to swimming competition. Since then, from May 2011 to November 2015, she has successfully completed 20 triathlons, of which 5 were Ultraman distances (10 km swim, 420.6 km bike, 84.4 km run), which she had never before attempted. She has been free of SIPE symptoms in all competitions.

Discussion

We previously reported that sildenafil reduces the higher than normal PAP and PAWP during immersed exercise in susceptible individuals, providing a rationale for its use as prophylaxis against recurrent SIPE (10). This case provides anecdotal evidence in a SIPE-susceptible triathlete that sildenafil may reduce the likelihood of experiencing SIPE without impairing exercise performance. Indeed, there is evidence that exercise performance is unimpaired even after 100 mg sildenafil, double the dose used by this triathlete (6). We are not aware of evidence that sildenafil improves exercise performance, other than possibly during competitive swimming by preventing SIPE. Sildenafil is not on the prohibited list of the World Anti-Doping Code (16).

It should be pointed out that use of sildenafil in this context for SIPE-susceptible scuba divers could be dangerous, as there is evidence that PDE-5 inhibitors may increase susceptibility to seizures as a result of central nervous system oxygen toxicity (3), especially if breathing gas PO_2

exceeds 1 atmosphere. Moreover, it must be pointed out that use of sildenafil for SIPE-prevention should not replace investigation of susceptible individuals for inadequately controlled hypertension, systolic and diastolic ventricular dysfunction, valve disease and silent coronary disease: conditions that had been specifically excluded in the study by Moon et al (10).

Notwithstanding the plausible rationale for sildenafil as prophylaxis against SIPE (10) and this case report, we feel that much stronger evidence for the effectiveness of this drug would be provided by a sufficiently powered controlled study.

Conflict of Interest and Funding Sources

The results of this study do not constitute endorsement by ACSM. The results are presented clearly, honestly and without fabrication, falsification or inappropriate data manipulation.

Conflict of interest: none declared.

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Table 1: Hemodynamic Measurements.

Condition	**Sildenafil**	**VO_2** (L.min^{-1} BTPS)	**VO_2** (mL.kg.min^{-1} BTPS)	**HR** (beats.min^{-1})	**BP (mean)** (mmHg)	**MPAP** (mmHg)	**PAWP** (mmHg)	**CO** (L.min^{-1})	**CVP** (mmHg)
Dry, supine, rest	Pre-	0.26	4.5	74	148/80 (102.1)	19.0	15.5	6.6	9.9
Immersed exercise	Pre-	1.75	30	129	189/88 (121.5)	35.3	25.3	13.6	13.1
Dry, supine, rest	Post-	0.37	6.4	64	134/74 (95.4)	18.8	15.2	7.5	9.9
Immersed exercise	Post-	1.76	30	135	172/85 (114.3)	28.8	19.7	15.0	7.6

Abbreviations: BTPS: body temperature and pressure saturated; VO2: oxygen consumption rate; HR: heart rate; BP: arterial pressure; MPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; CO: cardiac output; CVP: central venous pressure.