DUKE UNIVERSITY MEDICAL CENTER

Center for Hyperbaric Medicine and Environmental Physiology • Dept of Anesthesiology

Durham, North Carolina

Pulmonary hemodynamics during cold-water exercise in subjects who have experienced immersion pulmonary edema and the effect of sildenafil

Dionne F Peacher, MD

JAV Fraser MD, C Otteni BS, JJ Freiberger MD, MPH, MJ Natoli BS, EA Schinazi, PO Doar, AE Boso BS, AJ Walker, RE Moon MD.

DAN

NAVSEA

NAVAL SEA SYSTEMS COMMAND

Immersion Pulmonary Edema (IPE)

- First described by Wilmshurst *et al.* in 1981 [1]
  - Syndrome of dyspnea, expectoration of blood-tinged frothy sputum, palpitations in scuba divers in cold waters
  - Attributed to exaggerated vascular response to cold
  - Also termed swimming-induced pulmonary edema
- Observed in divers and surface swimmers
- Pathophysiology incompletely understood
  - Risk factors: cold water, heavy exertion, hypertension, long duration of swim/dive, overhydration [2, 3]
  - Prevailing theory: high intravascular pressures in pulmonary vessels result in stress failure of pulmonary capillaries [2, 4]

1. Wilmshurst P, et al. Br Heart J 45: 349, 1981.
2. Adir Y, et al. Chest 126:394-399, 2004.
3. Miller CC, et al. Am J Emerg Med 28: 941-946, 2010.
4. Koehle MS, et al. Sports Med 35(3):183-190, 2005.

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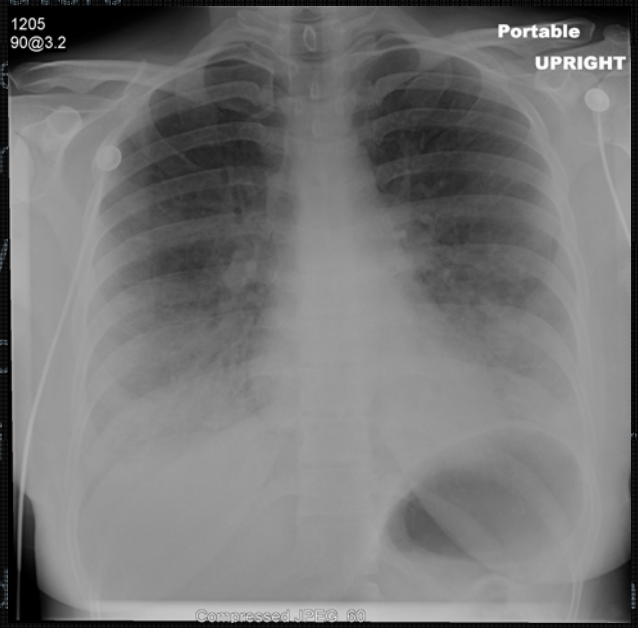

Normal chest radiograph

Chest radiograph in IPE

33 year old female triathlete

1. Wilmshurst P, et al. Br Heart J 45: 349, 1981.
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Immersion Pulmonary Edema

Numerous reported cases

- Scuba and commercial divers [3, 4]
- Combat swimmers [1, 5, 6, 7]
- Endurance swimmers [2, 8]

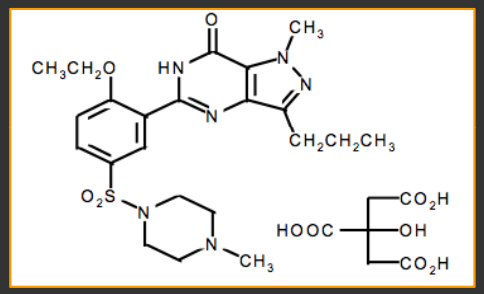
Generally an absence of identifiable cardiac or pulmonary dysfunction upon subsequent evaluation

1. Adir Y, et al. Chest 126:394-399, 2004.
2. Koehle MS, et al. Sports Med 35(3):183-190, 2005.
3. Hampson NB and Dunford RG. Undersea Hyperb Med 24(1):29-33, 1997.
4. Slade JB, et al. Chest 120:1686-1694, 2001.
5. Lund KL, et al. Ann Emerg Med 41: 251-256, 2003.
6. Mahon RT, et al. Chest 122:383-384, 2002.
7. Shupak A, et al. Respir Physiol 121:25-31, 2000.
8. Miller CC, et al. Am J Emerg Med 28: 941-946, 2010.

Possible role of pulmonary vascular pressures in IPE

- Pulmonary venoconstriction
- Diving/swimming (immersion + exercise)
  - Immersion → central redistribution of blood (↑ preload), vasoconstriction in cold water (↑ afterload) [1, 2]
  - Exercise → increased cardiac output
- Cold water and pulmonary artery pressure
  - Cold water immersion increases mean pulmonary artery pressure (MPAP) in healthy subjects [3]
  - Individual response in MPAP during exercise vary widely (range 16-39.6 mmHg in thermoneutral immersed exercise at the surface) in healthy subjects [4]

1. Adir Y, et al. Chest 126:394-399, 2004.
2. Koehle MS, et al. Sports Med 35(3):183-190, 2005.
3. Wester TE, et al. J Apply Physiol 106:691-700, 2009.
4. Peacher DF, et al. J Appl Physiol 109:68-78, 2010



Sildenafil and pulmonary vascular pressures

- Mechanism of action
  - selective phosphodiesterase 5 inhibitor → reduces breakdown of cGMP → smooth muscle relaxation
- Pulmonary vasodilatation
  - Clinical indication in treatment of pulmonary hypertension (WHO class I)
- Systemic venodilatation
- Maximal plasma concentrations 30-120 minutes after oral administration (median 60 minutes)
- No negative effect on inotropy

Gold Standard, Inc. Sildenafil monograph. Clinical Pharmacology [database online]. Available at: http://www.clinicalpharmacology.com. Accessed: May 22, 2011.

Hypotheses

1. Subjects who have had IPE have an exaggerated increase in pulmonary artery pressures in response to cold water exercise
2. Sildenafil attenuates this response

Methods

Subjects:

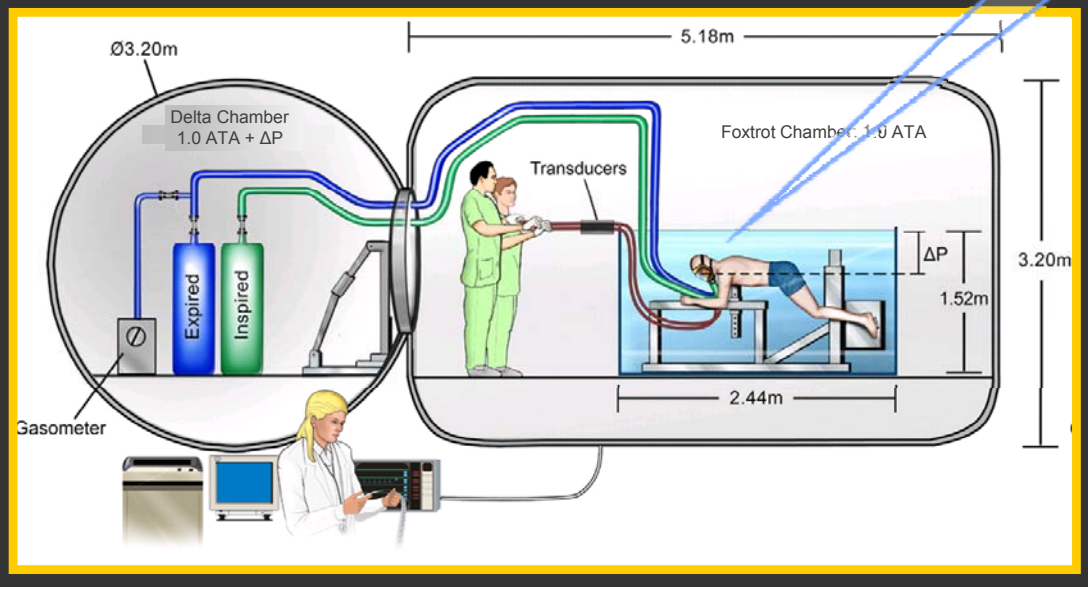
- IRB approval and informed consent
- 4 subjects (2 male, 2 female), age 33-47 years

Equipment:

- Electronically braked cycle ergometer immersed in cold water (18.6-20.6°C) in hyperbaric chamber
- Adjacent hyperbaric chamber housed breathing gas (air), pressurized to match depth of subject

Monitoring:

- EKG, arterial catheter, pulmonary artery catheter



Measurements:
mean arterial pressure (MAP), central venous pressure (CVP), Mean pulmonary arterial pressure (MPAP), pulmonary artery wedge pressure (PAWP), Fick cardiac output (CO), heart rate (HR)

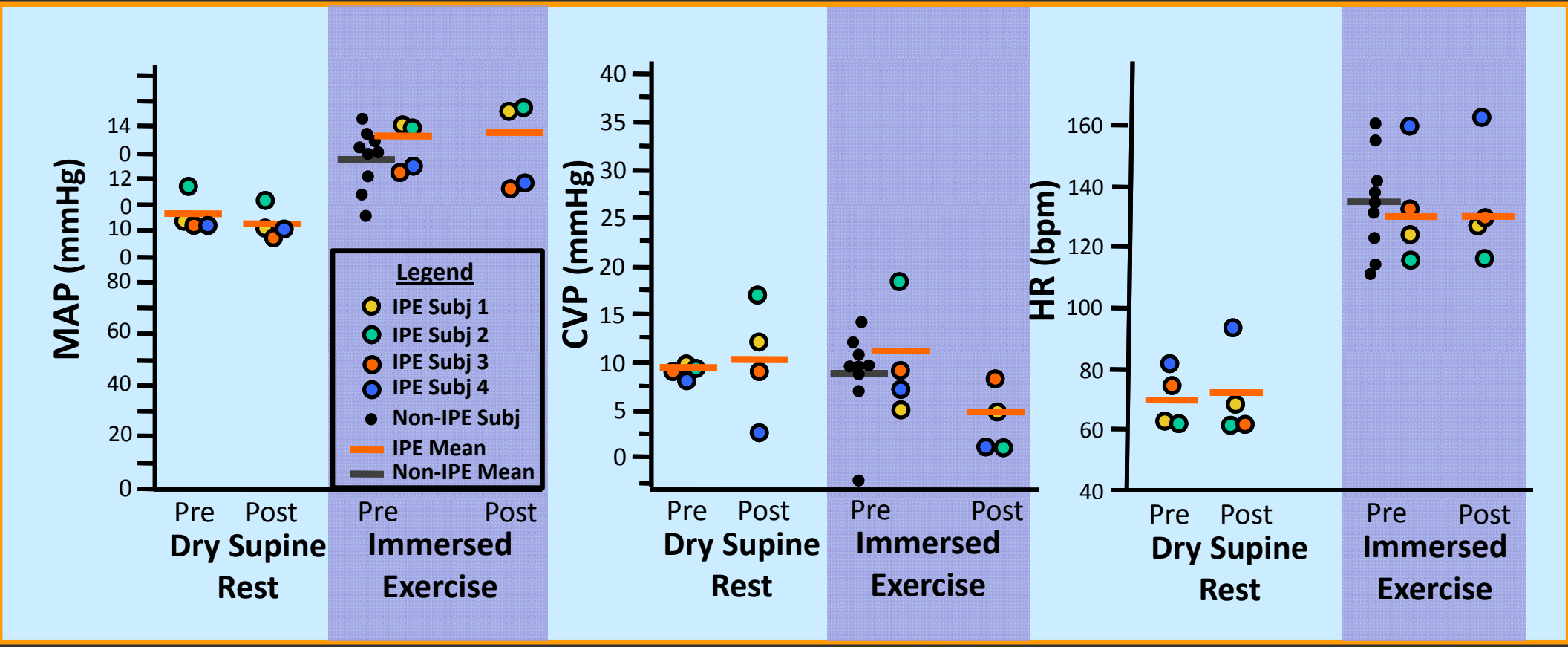
Protocol:

1. Dry supine rest
2. Immersed prone exercise
   6 min moderate intensity (O_2 consumption typically 1.4-2.2 $L \cdot min^{-1}$) in prone position
3. Administration of sildenafil 50 mg PO
4. Rest period (90 min)
5. Repeat rest and exercise protocol

Results: Subject Characteristics

Subject	Sex	Age (yr)	BMI (kg/m^2)	Activity	Number of episodes	Depth at onset	Significant past medical history	Cardiac studies
1	M	37	28.8	technical diving	1	140 fsw	none	cardiac biomarkers: negative stress echocardiogram: normal
2	M	45	29.4	technical diving	1	50 fsw	none	stress echocardiogram: normal
3	F	47	21.9	triathlon swimming	5	surface	Mild hypertension (normotensive on candesartan for latter 2 episodes)	stress echocardiogram: normal
4	F	33	25.2	triathlon swimming	2	surface	none	echocardiogram: hyperdynamic LV systolic function; no wall motion abnormalities; no ventricular hypertrophy; no significant valvular dysfunction

Results: Systemic Hemodynamics



Pre = before sildenafil; Post = after sildenafil.

Data for non-IPE subjects from previously published work by Wester TE, et al. J Appl Physiol 106:691, 2009

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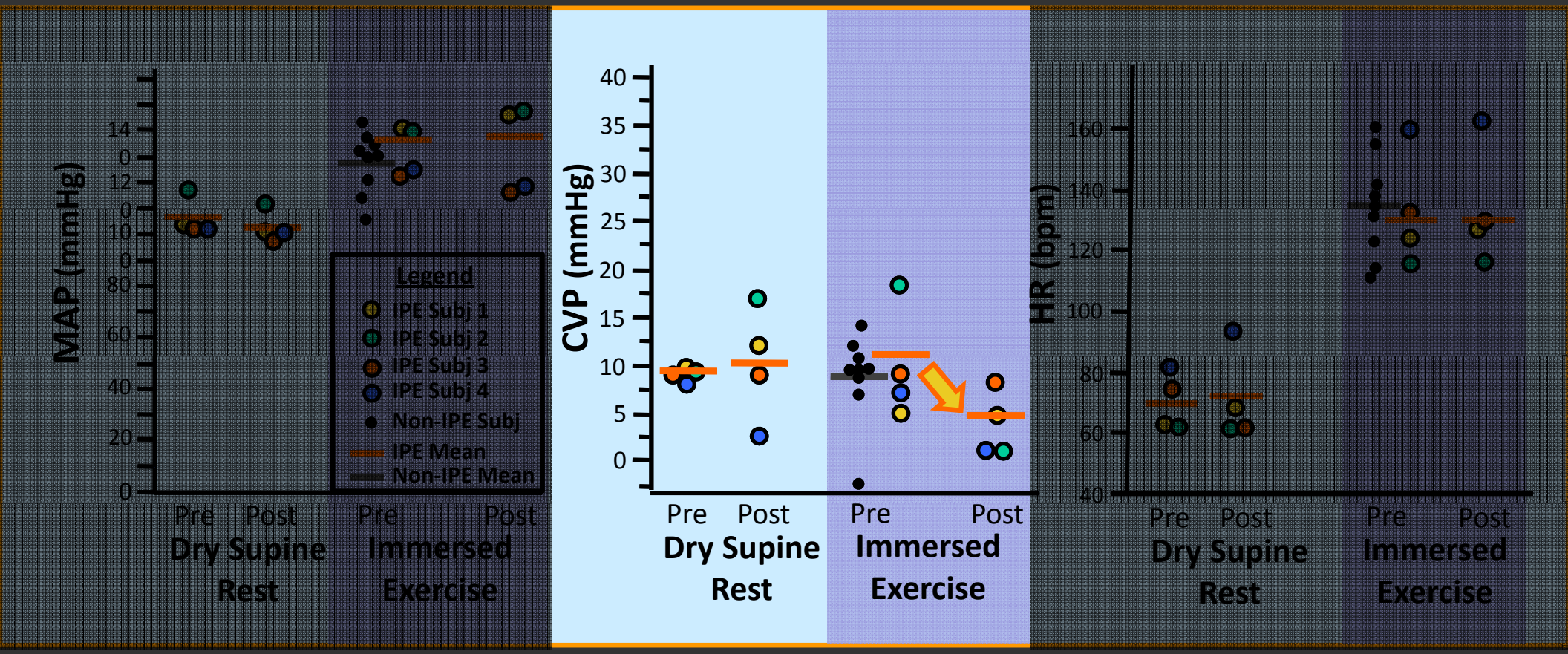

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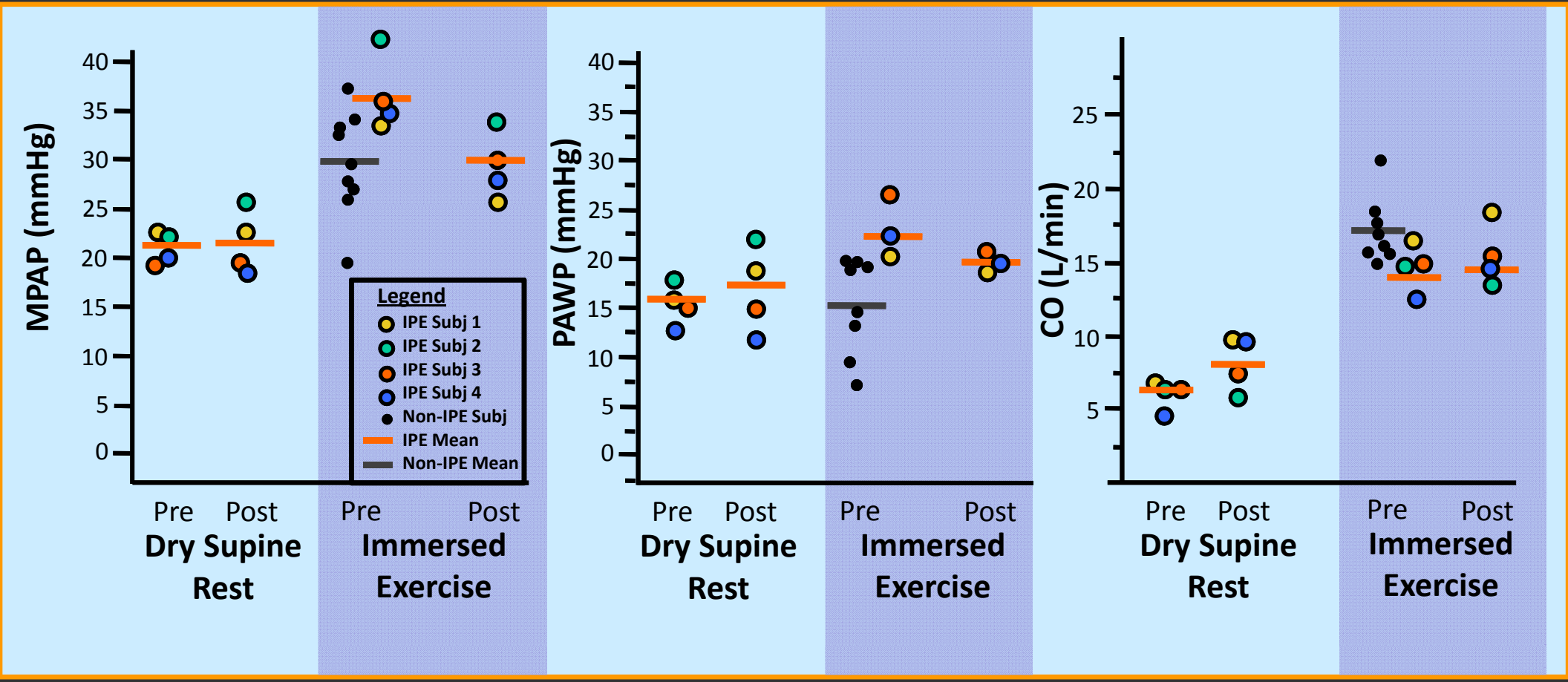

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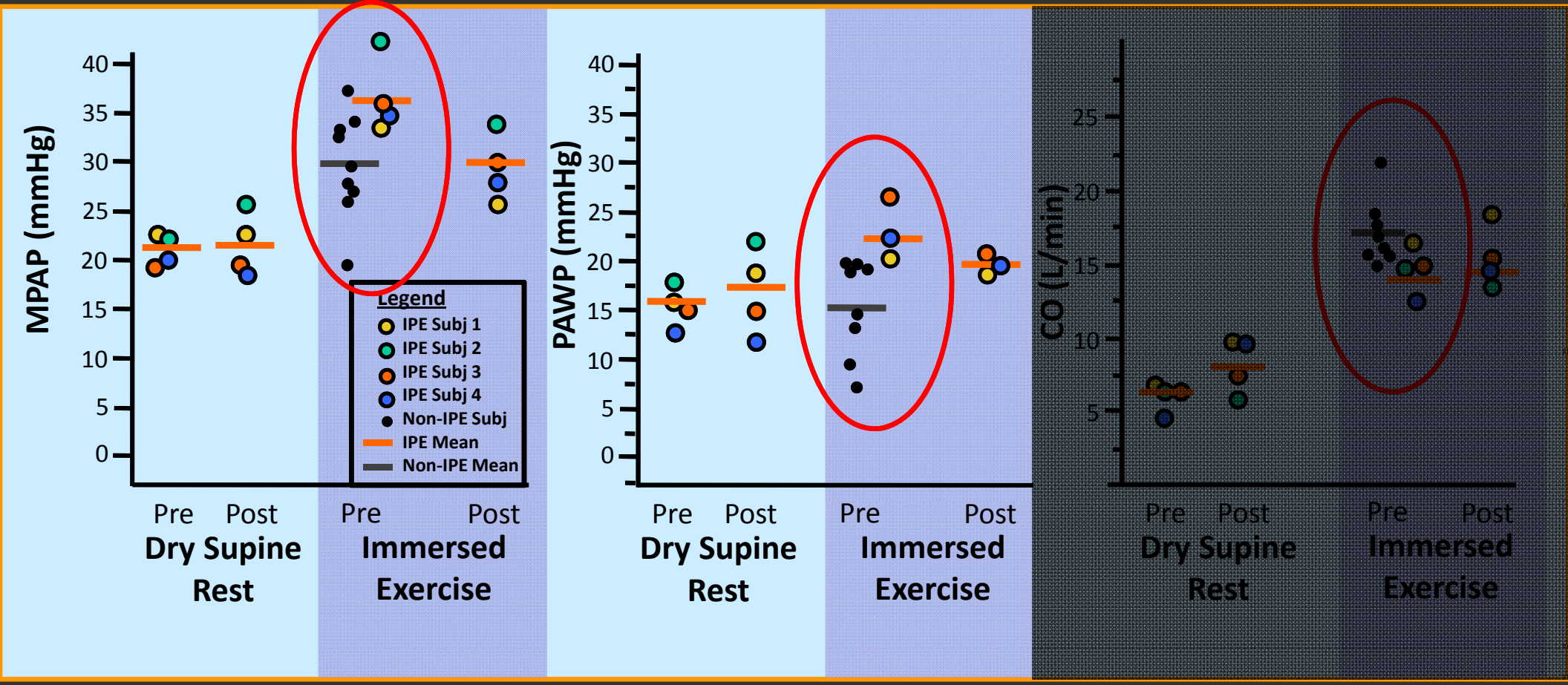

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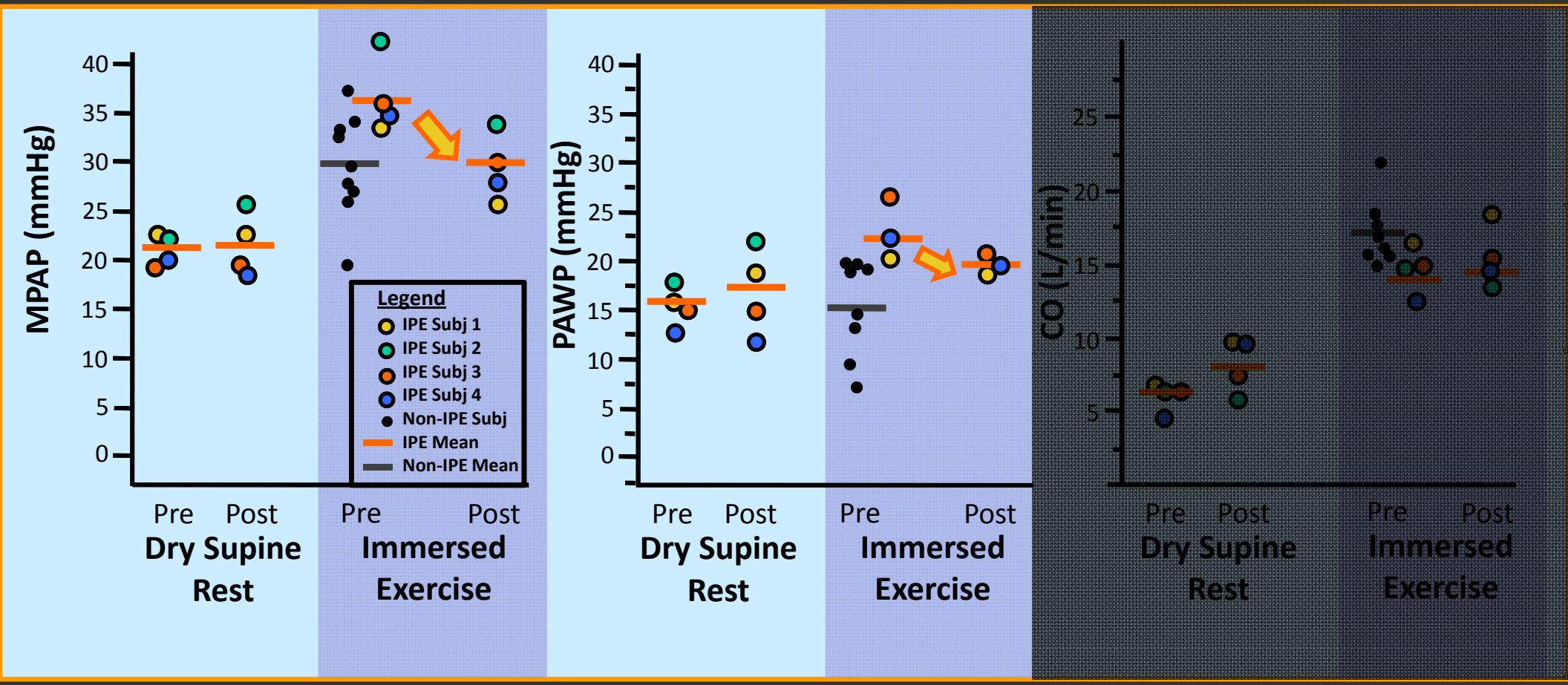

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Conclusions

- In this small series, individuals who have experienced IPE appear to have higher MPAP and PAWP during exercise in cold water compared to subjects without a past history of IPE
- In the IPE-susceptible, MPAP, PAWP, and CVP during exercise are decreased by sildenafil
  - Possible mechanisms: direct vasodilatation of pulmonary vessels, increased venous capacitance
- Sildenafil may be an effective prophylactic measure in individuals susceptible to IPE

Acknowledgments

- US Navy Sea Systems Command (NAVSEA)
- Divers Alert Network