

## ROLE OF INFLAMMATORY RESPONSE IN EXPERIMENTAL DECOMPRESSION SICKNESS

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### INTRODUCTION

Decompression to altitude can result in gas bubble formation both in tissues and in the systemic veins. The venous gas emboli (VGE) are often monitored during decompression exposures to assess risk for decompression sickness (DCS). Astronauts are at risk for DCS during extravehicular activities (EVA), where decompression occurs from the Space Shuttle or Space Station atmospheric pressure of 14.7 pounds per square inch (PSI) to that of the space suit pressure of 4.3 PSI.

DCS symptoms include diffuse pain, especially around joints, inflammation and edema. Pathophysiological effects include interstitial inflammatory responses and recurring injury to the vascular endothelium. Such responses can result in vasoconstriction and associated hemodynamic changes. The granulocyte cell activation and chemotaxin release results in the formation of vasoactive and microvascular permeability altering mediators, especially from the lungs which are the principal target organ for the venous bubbles, and from activated cells (neutrophils, platelets, macrophages). Such mediators include free arachidonic acid and the byproducts of its metabolism via the cyclooxygenase and lipoxygenase pathways (see figure). The cyclooxygenase pathway results in formation of prostacyclin and other prostaglandins and thromboxanes that cause vasoconstriction, bronchoconstriction and platelet aggregation. Leukotrienes produced by the alternate pathway cause pulmonary and bronchial smooth muscle contraction and edema. Substances directly affecting vascular tone such as nitric oxide may also play a role in the response to DCS.

We are studying the role and consequent effects of the release inflammatory bioactive mediators as a result of DCS and VGE. More recent efforts are focused on identifying the effects of the body's circadian rhythm on these physiological consequences to decompression stress.

### METHODS

The studies are divided into five categories using several animal models. Hyperbaric and hypobaric decompression and direct venous air embolization were evaluated in a dog model simulating the bubble load observed in ground-based EVA decompression studies. Rodent models involve decompression from hyperbaric exposures to determine the effectiveness of mediator inhibition on DCS symptoms and inflammatory response as well as the role of the circadian time structure.

In the canine studies, hemodynamic assessment was carried out before, during and following decompression or VGE infusion. DCS evaluation included VGE characterization using echo ultrasound; gross symptoms; pulmonary edema (gravimetric analysis); collection of arterial blood, urine, pleural fluid and bronchial alveolar lavage (BAL) for protein analysis; differential

cell counts and eicosanoid (thromboxane B2 [TxB2], 11-dehydro TxB2 [11dhTxB2] and leukotriene E4 [LKE4]) analysis using ELISA techniques. Changes in plasma nitric oxide levels were determined in both canine and rodent samples using chemoluminescence.

Protocols:

- 1) Hyperbaric DCS: Anesthetized dogs were decompressed from 184 kPa after 120 mins.
- 2) Hypobaric DCS: Anesthetized dogs were decompressed to 40,000 ft (4.3PSI) for 180 mins.
- 3) VGE: Venous air infusions of 0.15, 0.25 and 0.35 ml/kg/min for 180 mins.
- 4) Rodent DCS / Eicosanoid Inhibition Studies: Sprague-Dawley rats pretreated with drug (Dibutyl cAMP[DBcAMP], ziluton or accolate) were decompressed from 616 or 683 kPa after 60 mins.
- 5) Circadian Rhythm influences on DCS risk and response in a rodent model using 6 time points in a 24 hr. cycle.

## RESULTS

- 1) The canine **hyperbaric decompression exposures** resulted in VGE formation at a level of Spencer Grade 4 using a 0-4 scoring method as well as moderate increases in pulmonary artery pressure and systemic vascular resistance. These increases paralleled a decrease in plasma nitric oxide levels. Similarly, increases occurred with pulmonary edema and BAL protein levels as well as arterial and BAL white blood cell (WBC) and neutrophil counts. Increases in eicosanoid levels included; arterial, lung tissue and BAL LKE4, and urinary TxB2 and 11dhTxB2 levels.
- 2) **Hypobaric decompression exposures** resulted in VgE formation (Spencer Grade 1-4), increases in pulmonary edema, arterial and BAL WBC's and neutrophils. Urinary TxB2 and 11-dhTxB2 levels were increased.
- 3) **VGE TxB2 and LKE4 levels** were increased with the larger air dose in both urine and BAL, as were WBC counts and myeloperoxidase levels. Hemodynamic and pulmonary edema changes were increased over baseline in all groups, with no difference between groups. Plasma nitric oxide levels were decreased in the 0.15 and 0.35 ml/kg/min groups immediately after VGE and remained depressed following recovery in all three groups.
- 4) In the **rodent hyperbaric decompression exposures** urine and arterial levels of TxB2, 11-dhTxB2 and LKE4 increased in the 683 kPa group over controls as did BAL 11-dhTxB2 and LKE4 levels. With DBcAMP treatment the increases in arterial, BAL and urinary 11-dhTxB2 and LKE4 were attenuated. DBcAMP also attenuated the increases ( $p < 0.05$ ) over controls in; pulmonary edema formation, BAL and pleural protein levels and BAL WBC counts (683 kPa group). Pretreatment with the leukotriene antagonist accolate or the 5-lipoxygenase inhibitor ziluton, failed to show any significant change in DCS outcome in two additional studies.
- 5) With the **circadian rhythm studies** preliminary results indicated circadian rhythm dependencies ( $p < 0.05$ ) in pleural protein and neutrophils, BAL WBC, and arterial and BAL LKE4 using a 24 hour cosine fit. A 12 hour pattern showed significance with BAL neutrophils, urinary TxB2 and BAL 11-dhTxB2. Pulmonary edema and DCS symptoms had greatest effects at 14 and 18 hours after lights on.

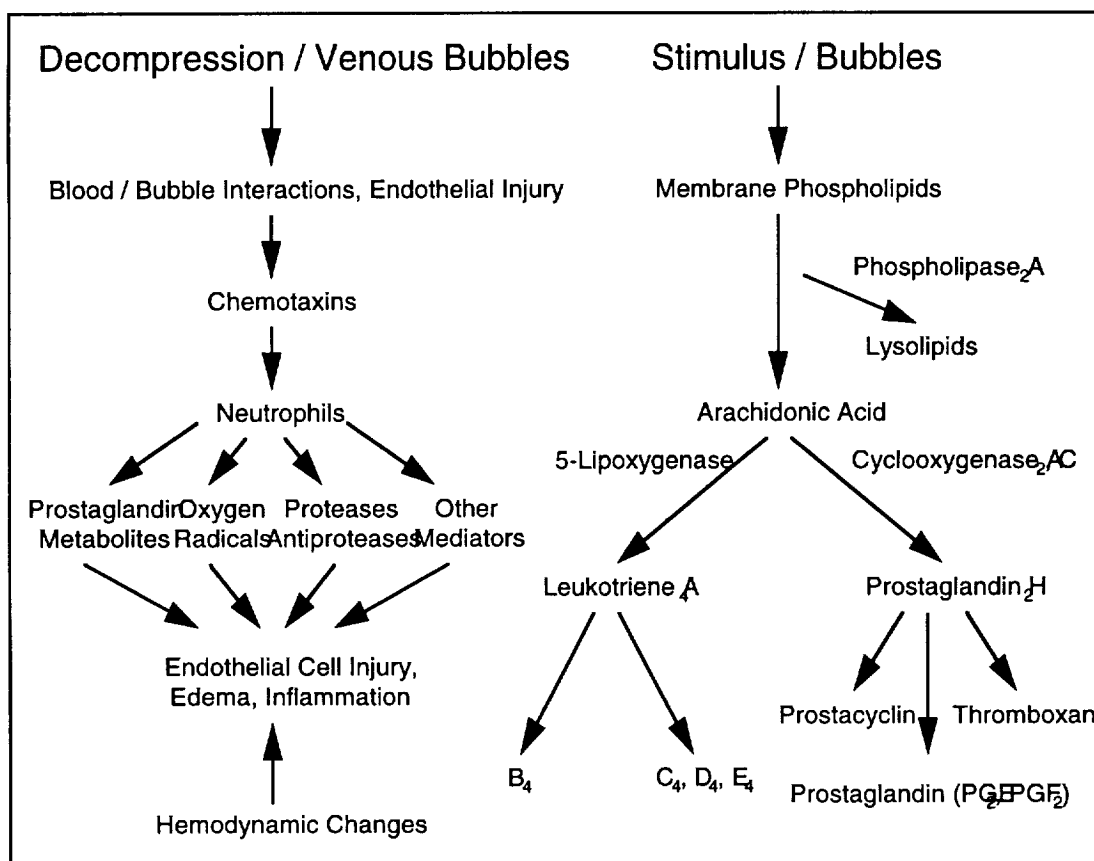
## CONCLUSIONS

These studies demonstrate an inflammatory-type of response to DCS-induced venous bubble formation and elucidate some of the underlying mechanisms of DCS symptoms. Microvascular endothelial injury and subsequent changes in vessel wall tone and permeability can account for

some of the localized edema formation and the concomitant release of bioactive mediators that may be involved with pain sensation and associated cellular activation. Increased numbers and activation of neutrophils likely play an additional role in the production and release of arachidonic acid and its byproducts of metabolism including the eicosanoids. Plasma nitric oxide levels were consistent with observed changes in vascular resistance. Increased microvascular permeability manifesting as edema was further verified by the elevated protein levels in the BAL and pleural fluids. The protective effects of exogenous DbcAMP (increases intracellular AMP) are attributable to such factors as; positive inotropic and chronotropic effects, pulmonary vasodilation, reduction in intracellular calcium and therefore reduced phospholipase A2 and eicosanoid production, and inhibition of intercellular gap formation or endothelial cell contraction. The more recent data demonstrate that there is likely a circadian-rhythm dependent outcome to DCS and should therefore also be considered with regards to operational concerns where DCS is a risk factor.

**FUTURE STUDIES**

Future studies will concentrate on further defining the circadian rhythm dependency of DCS outcome, as well as the use of inflammatory inhibitors and their role in symptom attenuation, especially with regards to dose variation and time dependencies.



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