【学術活動報告】

高気圧医学に関連した論文の年間レビュー：2006 UHMS 年次大会の講演から

合志清隆

2006年6月に米国OrlandoでUHMS（Undersea & Hyperbaric Medical Society）の年次総会が開催されましたが，plenary sessionとして1年間の高気圧医学に関連した論文レビューの紹介がありました。その分野で著名な2名の研究者の講演であったことからも，本総会で最も重要な企画であったことが推察されます。潜水医学領域ではRichard Vann博士が，高気圧酸素治療の領域からはDick Clarke博士が代表的な論文を紹介していました。蛇足ですが，お二人とも同じニックネームで，抄録集にはニックネームのDickで記載されておりました。

講演を聴いておりまして，その内容は高気圧医学に携わる研究者と医療者にとって極めて重要と感じられましたので，この講演後に「日本の学会員に紹介したいので，発表のスライドを頂けないか」と話してみました。一人は面識のなかったVann博士でしたが，彼は眞野理事長とよき友人関係にあることから，Clarke博士ともに突然の申し出にもかかわらず快く承諾していただきました。

そこで本総会の終了早々に，掲載の方式などを含めて池田知純編集委員長と何度か相談しました。発表のスライドだけでは理解しにくいものですから，お二人には本学会員あての要旨ないしメッセージを改めてお願いしました。これには多少の時間を要しましたが，お二人からは講演内容をわかりやすく論文のエッセンスのみをまとめていただきました。ここに紹介されている代表的な論文の概要は，高気圧医学での最新の研究報告が凝縮されたものになっていますので，すべての本学会員の方々に極めて有用ではないかと自負しております。

多忙なスケジュールのなかで，本学会員のために貴重な資料とメッセージを送っていただいたお二人に感謝を申し上げる次第です。

高気圧医学の最新の文献情報「米国からご挨拶!」

Dick Clark

講演の概要は，この1年間に英文医学雑誌に掲載された高気圧医学関連のいくつかの論文要旨の紹介です。それはFloridaのOrlandoで2006年6月開催のUndersea and Hyperbaric Medical Society年次総会で発表したものです。

最初にCochrane Libraryのレビューでの要旨を紹介しました（No.4～10）。Cochrane Library（www.cochrane.org）は様々な診断法や治療法の妥当性を支持するエビデンスを集積しています。Cochrane Libraryでは，報告されている臨床経験のエビデンスレベルを検討し，その全体から診断法や治療法の妥当性にグレードをつけます。驚くことではありませんが，レビューされている高気圧医学関連の文献のほとんどが明らかなエビデンス（レベル1と定義－ランダム化比較試験からの結果）を欠いています（No.7）。これは医療全般でいえることですが，むしろレベル1のエビデンスが得られていることは例外的です。

次いで，急性，亜急性と慢性の脳卒中での高気圧酸素（HBO）治療のメタ解析です（No.11～5）。この著者らは有用性を評価するには未だ十分なエビデンスが得られていないとしています。多くの研究では手法に問題があると判断されているのです。従って，脳卒中におけるHBO治療の有効性は解決されていないのです。しかし，Cochrane Libraryのレビューでもそうですが，注意を要する重要な点はエビデンスがないからといって有効性を否定するものではないことです。2

つ目のメタ解析結果は，輸血設備の整った医療施設での急性大量失血性貧血です（No.16～9）。しかし，この最良のように思われる治療法を，すべての患者が受けられるものではありません。クロスマッチが難しいこともあるでしょうし，血液型の確認が遅れることもあります。あるいは，宗教上の理由で患者や家族が輸血を拒否することもあるでしょう。この著者は，現在までのエビデンスをうまく整理して，どのような場合にHBO治療を考慮すべきかを示しています。

2件の論文は癌におけるHBO治療について述べたものです。最初の研究は乳癌の同一患者から得られた正常細胞，原発巣と転移巣の腫瘍細胞に関するものです（No.20～8）。これらの細胞を2.4 ATA（1,800 mmHg）のHBO曝露と，いくつかの対照環境とで比較しています。HBOは細胞の増殖やコロニー形成を抑えて細胞増殖を阻害しました。さらにHBOは，一般によく使用されている3種類の化学療法剤と比べても，細胞増殖を抑制することがわかりました。その結果は明瞭なものですが，慎重な評価も必要です。このような高い酸素負荷をヒトでは安全に行えないからです。HBO治療装置では1,800 mmHgの酸素吸入が標準ですが，このように高い酸素分圧でも組織レベルでは300-500 mmHgになっています。この論文に記載されている腫瘍細胞への影響は，臨床的に耐えられる程度の高酸素状態で検討する必要があります。

次いで，乳癌患者での前向き臨床試験の報告です（No.29～32）。化学療法の前に，連日10日間のHBO曝露あるいはプラセボとで無作為に分けています。この臨床試験の目的は，高い酸素状態が腫瘍血管の新生を誘発し，HBOが化学療法剤への反応性を改善しないかを検討したことです。曝露群とプラセボ群では予後に有意差はありませんでしたが，この研究から得られたものがいくつかあります。その一つですが，HBOで血管新生が誘発されなかったことは，晩発性組織損傷を受けている癌患者にHBO治療を行っている医療者には朗報になります。もう一つは，HBO治療直後の化学療法でも，合併症は認められなかったことです。さらに，これまでの動物やヒトでの研究（最近のいくつかは日本から出されている）からは，HBO治療と化学療法を同時に行う治療法が，併用法として最も適しているものと考えられます（No.33）。

非常に興味深い2件の論文は，慢性の低酸素性創傷の治癒に対してHBOの有効性の機序を検討したものです（No.34～9）。'深層'の生体医学ないしサブ細胞の領域まで検討した点では，これまでにない画期的なものです。HBOがシグナル伝達系を介して創傷修復を刺激するという機序が示され，エビデンスが次第に蓄積されてきています。そのシグナル伝達系のほとんどはNOを介したものです。

下顎骨の感染と壊死に着眼して，その根本に低酸素状態が存在することを示したドイツからの報告があります（No.43～8）。酸素電極を慎重に深く埋め込んで測定された結果は，従来の経皮的（非侵襲的）測定結果を確認したものになっています。骨髄炎や放射線照射を受けた骨では酸素分圧は異常に低値であり，それが治癒障害やその後の壊死の原因となることを確認しています。この測定法を用いて，骨切除を任意に行うために辺縁設定が可能になっています。

次いで，放射線骨壊死の予防に批判的な3つの報告です（No.49～53）。その一つはHBOですが，著者らは報告文献の検討から抜歯後の放射線骨壊死の発生率に周術期のHBO付加で改善はないとしています。その発表から分かるかもしれませんが，引用された参考文献をより詳しく調べると，まったく異なった結論にもなります。さらに高い水準のエビデンスは必要ですが，現在のエビデンスの重要度からしますとHBOは効果的であると考えています。

高圧下の'前処置'は心臓や脳の手術領域で関心が高まりつつあります（No.54～8）。術後の脳卒中の頻度と認知能力の低下を抑制する試みが実験的になされていますが，HBOと実験での標準的な低酸素状態とで改善度は同じでした。これに否定的な意見もあるでしょうが，私は別の捉えかたをしています。低酸素の前処置はハイリスクの手術の治療予後を改善する手段として実験的には明らかですが，これを実際の臨床に応用できるでしょうか?心臓手術を受ける患者に対して，

術前に８％の酸素を曝露させますか?耐えられるのはHBOであることは明らかで，しかも同程度の結果です。CABG手術前の１回のHBOで（‘偽’高気圧処置と比較して），認知機能の有意な改善がランダム化比較試験で示されています（No.59～61）。この結果は全身の炎症反応の抑制状態から生じたものと考えられます。

最後に２つの論文を再検討しましたが，歯科インプラント手術におけるHBOの役割の議論です（No.62,3）。インプラントと骨の癒合の改善にHBOが有用であることに‘賛成’と‘反対’の意見です。この論争は，そのうちに激しくなってきました。いくつかの相違点から生じたものでしょうが，それらを適切に議論していないからだと思います。HBOの有用性を詳細に検討するには，全照射線量，放射線の照射部位にインプラントを行ったかどうか，放射線治療からインプラント手術までの期間，インプラントの素材（長さ，表面の粗さ，コンソール台）を明らかにする必要があるのではないでしょうか?このような情報を検討してはじめて，HBOの補助療法としての役割を文献から正確に評価できます。

日本の皆様に高気圧医学の関連論文を紹介する機会を与えてくださり，ありがとうございました。皆様からのご質問やご意見をお待ちしております。

敬具

Dick Clarke, Director
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（和訳文責：合志清隆）

HYPERBARIC MEDICINE LITERATURE UPDATE

"Greetings from the United States of America!"

The following lecture outline represents a summary of some of the literature on hyperbaric medicine that has entered English language medical journals over the past year. It was presented as a plenary session during the June, 2006, annual meeting of the Undersea and Hyperbaric Medical Society, in Orlando, Florida, USA.

The presentation began with a summary of several Cochrane Library reviews. This library (www.cochrane.org) serves as a repository of evidence supporting a wide range of diagnostic and therapeutic interventions. The library grades these interventions based upon the sum of their reported clinical experience, using the medical evidence hierarchy. Perhaps not surprisingly, the hyperbaric uses that were reviewed lacked for the most part, convincing evidence (defined as Level 1 - that resulting from randomized controlled trails). Of course, the same is true for the practice of medicine in general, where Level 1 evidence is the exception rather than the rule.

Next came a meta-analysis of hyperbaric oxygen in the treatment of acute, sub-acute and chronic stroke. It was the opinion of the authors of this analysis that insufficient evidence exists at this time to allow physicians to determine the value of this treatment option. Most of the research was considered of poor methodological quality, so the question as to what role hyperbaric oxygen plays in stroke remains open. As with the Cochrane reports, it is important to appreciate that lack of evidence does not mean lack of efficacy, of course. A second met analysis addressed acute exceptional blood loss anemia. Appropriate management centers on blood replacement. However, this best practice standard is not always available to a patient. There may be cross-matching difficulties, delays in obtaining the correct blood type, or the patient or family member may refuse blood on religious grounds. The author of this paper does an excellent job of summarizing all available evidence, then provides a well considered approach to when

hyperbaric oxygen should be considered.

Two papers investigate hyperbaric oxygen in cancer. The first was a study of normal, primary tumor and metastatic breast cancer cells from the same patient. These cells were exposed to 2.4 ATA (1,800 mmHg) oxygen, and compared to several control environments. Hyperbaric oxygen suppressed cell proliferation and cell colony formation, and inhibited cell growth. Hyperbaric oxygen also inhibited cell growth, when compared to three common chemotherapy agents. While the results were impressive, they should be viewed with caution. This degree of oxygenation cannot be safely achieved in humans. While a patient routinely breaths 1,800 mmHg oxygen in a hyperbaric chamber, this will only translate to 300-500 mmHg at the tissue level. More work is necessary to see if clinically tolerable hyperoxia can still influence cancer cells in the manner noted in this paper.

The second paper reported a prospective clinical trial, again involving breast cancer patients. Prior to beginning chemotherapy patients were randomized to undergo 10 daily hyperbaric oxygen exposures, or placebo, prior to commencing chemotherapy. The idea was to see if hyperbaric oxygen could improve chemotherapeutic response through hyperoxia induced tumor angiogenesis. There was no difference in outcome between the groups. There were some positives to take from the work, however. First, failure to induce angiogenesis is certainly good news for those who use hyperbaric oxygen to treat cancer patients who suffer late radiation tissue injury. Next, no complications were reported as a function of hyperbaric oxygen closely followed by chemotherapy. Finally, and based upon previous animal human experience (some recently from Japan), it may well be that *simultaneous* hyperbaric oxygen and chemotherapy represents the most favorable sequencing.

Two very impressive papers investigated the mechanistic basis of hyperbaric oxygen in the healing of chronic and hypoxic wounds. These two reports went further than any before then, in that they investigated 'deep' biomedical and sub-cellular territories. It is becoming increasingly evidence that hyperbaric oxygen stimulates wound repair processes via signal transduction pathways, and in large part mediated by nitric oxide.

A report from Germany shed some light on mandibular infection and necrosis and the underlying presence of hypoxia. Carefully implanted oxygen electrodes confirmed earlier transcutaneous (non-invasive) oxygen data, in that oxygen levels are abnormally in osteomyelitic and irradiated bone and form the basis for healing compromise and resultant necrosis. Using this measuring tool, the authors have been able to map out margins in order to undertake optional bony resection.

Next was a paper critical of three common osteoradionecrosis prevention measures. One was hyperbaric oxygen. The author reviewed the literature and determined that peri-operative hyperbaric oxygen offered no advantage regarding the incidence of osteoradionecrosis resulting from dental extractions. As you will see from the handout, an entirely different conclusion can be reached if the references cited by the author of this paper are looked at more comprehensively. It is my opinion that the weight of present evidence supports the role of hyperbaric oxygen, although more high quality evidence is needed.

Hyperbaric 'pre-conditioning' is an area of growing interest in cardiac and brain surgery, as efforts take place to try and reduce the incidence of post-operative stroke and cognitive decline in animals, both hyperbaric oxygen and a laboratory standard

model of hypoxia produced almost identical degree of improvement over controls. While some may determine this to be a negative study I would suggest otherwise. While hypoxic preconditioning is a well appreciated laboratory model for improving outcomes in high risk procedures, how clinically practical is it? Do we really want to exposure a patient scheduled for heart surgery to 8% oxygen preoperatively? Clearly, hyperbaric oxygen is infinitely more tolerable and produces the same outcome advantage. A randomized clinical trial determined that a single hyperbaric oxygen exposure prior to coronary artery by-pass grafting (compared to a 'sham' hyperbaric treatment) generated a statistically significant improvement in cognitive function. It appeared that this result was secondary to a downregulation of the systemic inflammatory response.

One final review actually involved two papers. They represented a debate on the role of hyperbaric oxygen in dental implant surgery. These papers provided 'pro'(for)and 'con'(against)opinions on the need for hyperbaric oxygen as a method of improving osseointegration of dental implants. This debate has raged for some time. It is my opinion that the issue really evolves around several distinctions, distinctions not always addressed in publications arguing this issue. In order to fully consider the value of hyperbaric oxygen therapy one must be able to determine the total delivered radiation dose, were the implants introduced into the irradiated portal or not, how long out from radiotherapy prior to dental implant surgery and what was the composition of the implant (length, coarse or smooth surface, and console abutment types)? Only with this information can one accurately assess the literature with regard to the adjunctive role of hyperbaric oxygen.

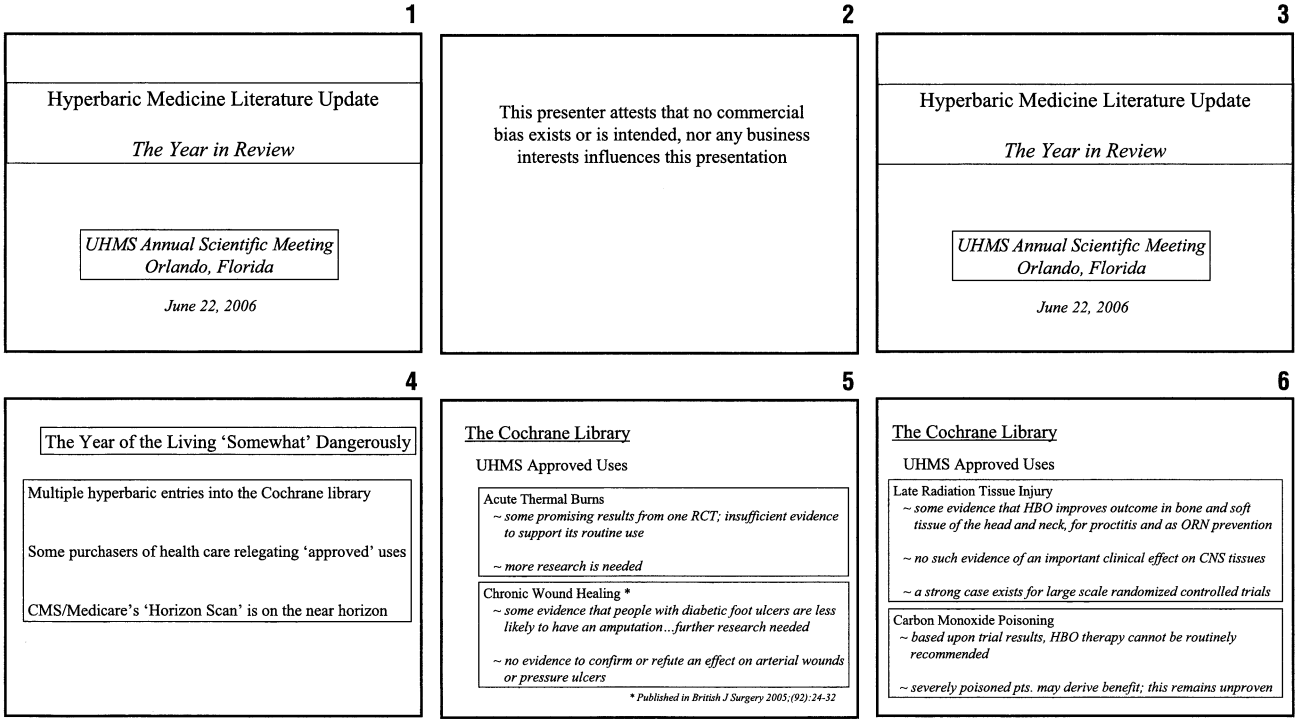
Thank you for the opportunity to present this material to my Japanese colleagues in hyperbaric medicine. I welcome any questions or comments you may have.

Respectfully,

Dick Clarke, Director

The Baromedical Research Foundation

www.baromedicalresearch.org



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Evidence-based Medicine

Two key concepts frequently overlooked...

Lack of high level evidence does not mean lack of efficacy

If no Level 1 evidence exists for a given condition one follows the trail to the next best level and work from there

Sackett DL, *et al. 1996* BMJ; 312: 71-72

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The Cochrane Library

Other Potential 'Unapproved' Uses

Acute Ischemic Stroke
- *~ there is currently little evidence to support the use of HBO*
- *~ with regard to long term outcomes, no relevant data exists*

Traumatic Brain Injury
- *~ limited evidence that HBO reduces risk of dying*
- *~ little evidence that survivors have a good outcome*
- *~ routine use of HBO cannot be justified*
- *~ further research needed*

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The Cochrane Library

Other Potential 'Unapproved' Uses

Dental Implant Surgery
- *~ lack of reliable evidence for and against the use of HBO*
- *~ definite need for controlled trials*

Sports Injury/Delayed Onset Muscle Soreness
- *~ HBO cannot be justified in DOMS*
- *~ some evidence that HBO increases pain*
- *~ routine use of HBO cannot be justified in ankle sprain or acute knee ligament injury*

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The Cochrane Library

Other Potential 'Unapproved' Uses

Fracture Healing
- *~ insufficient evidence to support or refute use of HBO*

Multiple Sclerosis
- *~ no consistent evidence of a beneficial effect*
- *~ routine use of HBO cannot be justified*
- *~ further research needed*

Tinnitus/Hearing Loss
- *~ the value of HBO is unclear; further research is needed*

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Hyperbaric Medicine and Stroke: A Systematic Review of the Evidence

US DHHS/Agency for Healthcare Research and Quality

Inclusion Criteria: *Human, English language; original data; controlled and uncontrolled studies; in and outpatient settings*

Data Analyzed: *~ 157 potentially relevant citations *...4 RCT's; one controlled trial; 17 observational studies*

~ of the 5 trials, quality was assessed as fair in 3 and poor in 2

* databases, libraries, textbooks

Carson S, *et al.* 2005 Clinical Rehab;19;819-833

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Hyperbaric Medicine and Stroke: A Systematic Review of the Evidence

Acute Stroke: *Treated within 24 hours after stroke*

Benefits	Harms
No effect on mortality or neurological outcomes	Treatment groups: 12% ear pain or claustrophobia; 6% withdrew due to worsening neuro status; 6% MI Sham Groups: 19% claustrophobia 24% withdrew, worsening status

Carson S, *et al.* 2005 Clinical Rehab;19;819-833

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Hyperbaric Medicine and Stroke: A Systematic Review of the Evidence

Subacute Stroke: *Treated within two weeks after stroke*

Benefits	Harms
No effect on neurological outcomes	28% withdrew before completing the study, reasons and group (HBO or sham) not reported

Carson S, *et al.* 2005 Clinical Rehab;19;819-833

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Hyperbaric Medicine and Stroke: A Systematic Review of the Evidence

Chronic Stroke: *Treated at least two months after stroke*

Benefits	Harms
No benefit on communication and cognitive outcomes (1fair trial) Benefit on neurological outcomes (1 poor trial)	Adverse effects not reported

Carson S, *et al.* 2005 Clinical Rehab;19;819-833

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Hyperbaric Medicine and Stroke: A Systematic Review of the Evidence

- 'The overall evidence is insufficient to determine the effectiveness of HBO in any subgroup'... 'no good quality study has been done'
- 'The present literature is not cohesive enough to guide clinicians or patients looking for answers'
- Physicians and patients cannot feel confident about the risk file

Carson S, *et al.* 2005 Clinical Rehab;19;819-833

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A Systematic and Evidence-based Review of Hyperbaric Oxygen in the Treatment of Severe Anemia

Comprehensive analysis, using evidence-based grading schemes
~ AHA, NCI and BMJ

'An established and effective option when blood products may not be used'
~ especially when the alternative is severe organ injury or death

'Useful bridging therapy'

Overly optimistic, perhaps, regarding the future availability of critical care HBO

Serves as an excellent source document; > 120 years of animal and human data

Van Meter KW, 2005 UHM;32(1):61-83

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Evolution of Evidence-based Medicine

Initial Version

The initial model's limitation was its great reliance on RCT's

...which de-emphasized traditional determinants of clinical decision-making, including physiologic rational and individual experience

Current Version

Research evidence alone is not an adequate guide to action

...physicians must apply their expertise to assess a patient's problem, incorporate research evidence, and consider the pt's preferences and values

Hayes, RB *et al. 2002 APC Journal Club; 136*

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Evolution of Evidence-based Medicine

~ integration of clinical state, patient preferences and actions and research evidence with clinical expertise Sackett DL, 2000

Clinical State: Remote areas vs. tertiary settings

Patient Preferences and Actions: Personal values, aversion to risk, degree of compliance, health insurance and resources

Research Evidence: No longer limited to RCT's; but includes other systematic observations from laboratory and pathophysiologic studies

Clinical Expertise: Basic practice skills as well as individual practioner experience, while carefully balancing the above factors

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A Systematic and Evidence-based Review of Hyperbaric Oxygen in the Treatment of Severe Anemia

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HBO Inhibits Mammary Benign and Malignant Epithelial Cell Proliferation

In - vitro work stimulated by:

- *~ breast cancer's resistance to standard care; mortality*
- *~ recurrence resection difficulties, chemo resistance, XRT*
- *~ HBO's synergism with XRT*
- *~ animal findings of chemo's enhanced tumoricidal effects when HBO added*

Granowitz EV, *et al.* 2005 Anticancer Research;25

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HBO Inhibits Mammary Benign and Malignant Epithelial Cell Proliferation

HBO's effects were investigated on proliferation of:

- *~ normal mammary epithelia*
- *~ primary tumor cells*
- *~ metastatic cells, and*
- *~ MCF7 human mammary adenocarcinoma cell line*

Granowitz EV, *et al.* 2005 Anticancer Research;25

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HBO Inhibits Mammary Benign and Malignant Epithelial Cell Proliferation

These immortalized cells were cultured for 20 hours at:

- *~ 1.0 ATA air*
- *~ 1.0 ATA oxygen*
- *~ 2.4 ATA normoxia*
- *~ 2.4 ATA oxygen*

Assayed for cell proliferation, cell inhibition, cell colony formation and effects of several anti-cancer agents

Granowitz EV, *et al.* 2005
Anticancer Research;25

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HBO Inhibits Mammary Benign and Malignant Epithelial Cell Proliferation

HBO suppresses mammary cell proliferation, by cell counting

Cell Type	Control * (cells x 10^5)	HBO * (cells x 10^5)	
Normal	5.07	3.30	(35%)
Primary tumor	2.66	2.17	(18%)
Metastatic tumor	4.90	3.70	(25%)
MCF7	2.85	1.82	(36%)

** After 20-h incubation*

Granowitz EV, *et al.* 2005
Anticancer Research;25

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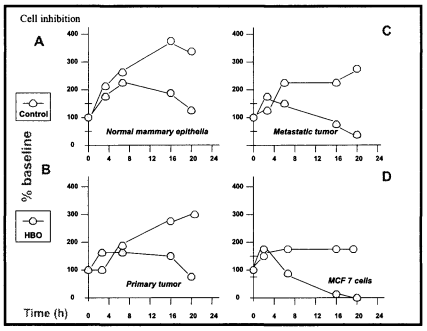

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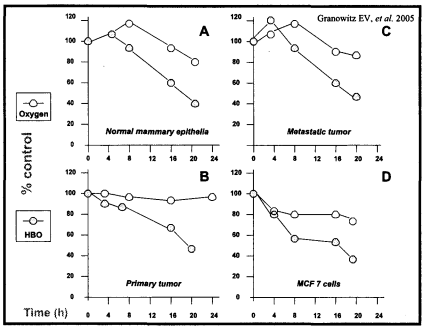

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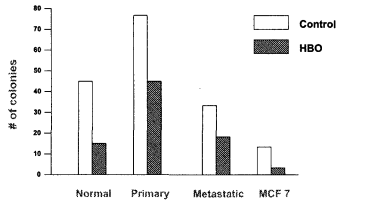

Granowitz EV, *et al.* 2005

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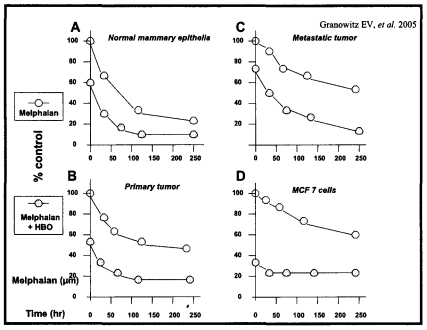

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What to make of this?

Well designed study, validated cell immortalization process

Encouraging results, a clear HBO, not HBA, effect

Hyperbaric dosing not clinically transferable

Animal model necessary

Mechanism?

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Combination HBO and Chemotherapy in Locally Advanced Breast Cancer

~ randomized pilot trial with long-term follow up

32 pts. randomized to receive either:

Six IV pulses of cyclophosphamide, doxorubicin and vincristine alone, or preceded by ten daily HBO treatments (2.4 or 2.0 ATA)

- *11/15 tolerated the chemo-HBO arm*
- *All 17 tolerated the chemo only arm*

Heys SD, *et al.* 2006
UHM;33(1):33-43

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Combination HBO and Chemotherapy in Locally Advanced Breast Cancer

Primary Assessments

- Tumor cell volume
  - *~ mammography and ultrasound*
- Pathologic Response
  - *~ surgical resection specimens*
- Tumor blood flow and permeability
  - *~ contrast MRI*
- Neovascularization
  - *~ biopsy histology and immunohistochemical (anti-CD34)*

Heys SD, *et al.* 2006
UHM;33(1):33-43

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Combination HBO and Chemotherapy in Locally Advanced Breast Cancer

Clinical Response

Clinical Response to Treatment	Chemo Only	Chemo and HBO
Disease Progression	1	
Stasis of Disease	6	2
Partial Response	7	9
Complete Response	3	

Heys SD, *et al.* 2006
UHM;33(1):33-43

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Tumor Blood Flow/Vascular Permeability

	K trans			Ve (%)		
	First	Second	Difference (F-S)	First	Second	Difference (F-S)
Control	0.06	0.70	0.11	18.72	21.48	-2.76
HBO	0.58	0.52	0.06	21.31	18.79	2.76*

* 0.013

Neovascularization (Antibodies against CD34)

	No. Comp. Tx.	No. Comp. Assessments	Pre-Tx.	At Resection
Control	17	12	30.0	29.5
HBO	11	8	21.9	25.9

Heys SD, *et al.* 2006
UHM;33(1):33-43

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What can we take from this?

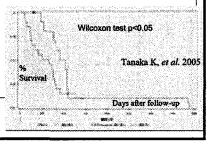
Were ten treatments sufficient? BID HBO? Was it the best approach?

Clear evidence that HBO did not stimulate tumor growth
~ small number of patients, relatively few treatments (vs. wound referrals)

Would HBO during the course of chemotherapy be of benefit?
~ this has recently been reported in malignant gliomas, involving carboplatin

Six year follow-up!

No HBO-chemo related complications reported



34

Two papers further investigate the underlying mechanisms of hyperbaric oxygen-induced wound repair

Stem Cell Mobilization by Hyperbaric Oxygen

Thom SR, *et al.* 2006
Am J Physiol Heart Circ;290C

Induction of VEGF expression through ERK, JNK and c-Jun/AP1 activiation

Lee *CC, et al.* 2006
J Biomed Science;13(1)

35

Hyperbaric Oxygen-Induced Angiogenesis

- HBO observed to induce angiogenesis; enhanced VEGF expression
- VEGF critical to new vessel formation
  - *~ its activity only initiates formation of immature vessels*
  - *~ for mature functioning vessels, VEGF must work in concert with angiopoietins*

HBO selectively enhanced Ang2 gene expression; eNOS pathway
~ inhibition of eNOS blocked this process

Lin S, *et al.* 2002
Biochem Biophys Res Comm; 296

36

Stem Cell Mobilization by Hyperbaric Oxygen

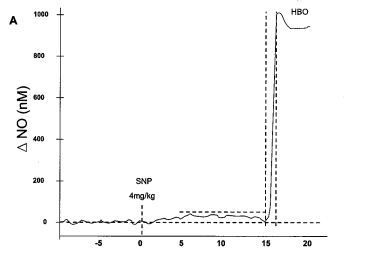
Stem cells (SPC's) mobilized by peripheral ischemia, vigorous exercise, chemotherapeutic agents and hematopoietic growth factors
~as well as by harvesting and ex-vivo manipulations

Nitric oxide plays a key role in triggering SPC mobilization
~ can HBO also activate this process?

An analysis of hyperbaric patients, air breathing chamber attendants, healthy HBO exposed volunteers and then on to mouse models!

Thom SR, *et al.* 2006
Am J Physiol Heart Circ;290C

37



Thom SR, *et al.* 2006
Am J Physiol Heart Circ;290C

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Take home messages

These observations may have been missed if the work began with mice

HBO increased circulating stem cells by a factor of 50%

HBO-induced elevation in bone marrow NO not replicated by SNP

Stem cell mobilization did not occur in mice lacking genes for eNOS

Nor in wild mice treated with a NO synthase inhibitor

So NO was the mechanism where by HBO mobilized stem cells

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Further investigation into the VEGF angiogenic regulator pathway, considered to induce hyperbaric-wound healing

~using human umbilical vein endothelial cells

The authors demonstrate that HBO-induced VEGF expression occurs through several complimentary pathways:

c-Jun/AP-1 activation and simultaneous activation of:

ERK, one of the first cell signaling pathways discovered

JNK, a pathway necessary for normal development

Lee CC, *et al.* 2006
J Biomed Science;13(1)

40

Fournier's Gangrene

Retrospective review of 41 patients from a single institution (20 yrs)
~ all received aggressive medical and surgical care, 18 (43.9%) also received HBO

Mortality: 9/41 (21.9%) … 9/23 (39.1%) non-HBO and 0/18 HBO

Ayan F, *et al.* 2005
ANZ J Surgery;75:1055-1058

Retrospective review of 42 patients from a single institution (10 yrs)
~ same standard medical and surgical care, and 26 (61.9%) HBO

Mortality: 9/42 (21.4%) ... 2/16 (12.5%) non-HBO and 7/26 (26.9%) HBO

Mindrup SR, *et al.* 2005
J Urology;173:1975-1077

41

What if there are three variants of necrotizing infections?

One very aggressive; universally fatal

One quite indolent; all survive with reasonable care

One intermediate - care determines outcome

~ but how can we distinguish one type from the other?

42

Messages

More conflicting case experience

Low evidence level; retrospective, small number of patients

Standardized medical and surgical practice patterns

Few patients per center, multi-center controlled trial necessary

43

Mandibular Bone Oxygen Measurements

~ values in mmHg

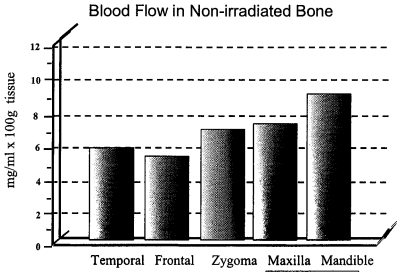
Polarographic fine needle probe-based cancellous bone oxygen tension mapping in patients and subjects

Feasibility/concept testing; normal and diseased bone

Maurer P, *et al.* 2005
Int J Oral Maxillofac Surg;35

44

Blood Flow in Non-irradiated Bone



Granstrom G *et al.* 1993
XIXth Annual Meeting EUBS

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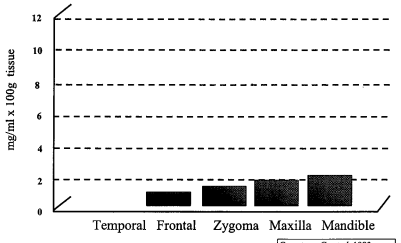
Blood Flow in Irradiated Bone



Granstrom G, *et al.* 1993
XIXth Annual Meeting EUBS

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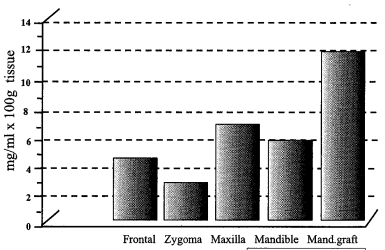
Blood Flow in Irradiated Bone after HBO and Bone Grafting



Granstrom G, *et al.* 1993
XIXth Annual Meeting EUBS

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Mandibular Bone Oxygen Measurements

~ values in mmHg

	Measurements	Mean	SD	Min	Max
Control (12)	863	71.4	9.7	47.0	97.1
Osteoradionecrosis (17)	1,721	32.3	12.5	1.4	59.4
Osteomyelitis (13)	1,125	28.4	15.3	0.9	59.5

Maurer P, *et al.* 2005
Int J Oral Maxillofac Surg;35

48

Findings consistent with the Marx (1987) observations of a clear reduction in capillaries, and tcPO2 within XRT portal

Impressive distinction between healthy and pathologically altered bone regions

A definition of the oxygen threshold value…transition from healthy to diseased bone… proposed as 55mmHg.

Authors report (in press, *same journal*) a case of mandible resection guided by tissue oxygen 'mapping'

Maurer P, *et al.* 2005
Int J Oral Maxillofac Surg;35

49

Osteoradionecrosis Prevention Myths

Myth 1
Extraction of healthy or restorable teeth before irradiation is a reasonable method of preventing ORN

Myth 2
Prophylactic hyperbaric oxygen for post-radiation extractions is a safe, simple, and effective prevention of ORN

Myth 3
Prophylactic antibiotic therapy is a safe, simple, and effective preventive for ORN

Wahl MJ, 2005
Int J Radiation Oncol Biol Phys;64(3) C

50

The Hyperbaric Myth

Argues the importance of the Annane paper

Argues that HBO is costly and not simple

Points out serious risks involved, with decompression mortality

Minimal clinical science quality

Pooled data since 1986 shows a 3.5% incidence without HBO and 4.0% when it is employed

Lack of sufficient geographical availability

Wahl MJ, 2005
Int J Radiation Oncol Biol Phys;64(3) C

51

Sulaiman F, *et al.* 2003

In all pts. only 4% developed ORN…but, of the pts. who underwent pre-extraction HBO (mean 6,300 cGy) none developed ORN. Two-five year follow-up

Chavez JA Adkinson CD, 2001

A 1.5% incidence in those receiving peri-operative HBO, no controls

David LA, *et al.* 2001

True, a 4.2% incidence…this was one patient with a dry socket, went on to complete healing, not ORN by any reasonable definition

Lambert PM, *et al. 1997*

75pts. received HBO, no (0%) ORN in 47 (62.7%) pts. available for follow-up, this paper referenced a 4.54% incidence (not using HBO)

52

Vudiniabola S, *et al.* 1999

HBO group: 4%, true, but author neglected to report the non-HBO Group with 15% incidence

Serious side effects?...none reported in the above publications

5 deaths ...*rapid decompression of patients breathing air not oxygen in a hyperbaric chamber*

53

Take home message

Careful analysis of referenced material

Where was the radiation portal vs. extracted teeth?

What was the radiation dose?

Was the HBO protocol followed appropriately?

Statement that most established ORN cases heal with time or stabilize not supported, inconsistent with the published literature, bad medicine (QoL)

54

Cerebral Arterial Gas Embolism?

"Perhaps the optimal approach to minimizing morbidity is to find effective neuro-protective agents"

~ rather than identifying any surgical shortcomings

Mark DB Newman MF 2002 JAMA : 287 (11)

In CABG surgery, most MEE's are probably gaseous

Stygall J, *et al.* 2000 Stroke; 31

A pre-operative operative hyperbaric medicine ?

55

Hyperbaric Oxygen vs. Hypoxic Cerebral Preconditioning

Hypoxic stress induces significant neuro-protection in certain experimental etiologic settings; clinically risky, impractical

Novel alternatives sough for high risk clinical conditions...cerebral and cardiovascular surgery

Freiberger JJ, *et al.* 2006 Brain Research;1075:213-222

56

Hyperbaric Oxygen vs. Hypoxic Cerebral Preconditioning

~ rat pup model

Outcomes measures:
~mortality and brain weight

HBO...high dose = 1 x 2.5 ATA for 150 mins. 24 hrs. pre-insult
low dose = 2 x 2.0 ATA for 60 mins. 48 hrs. pre-insult
or 3 x 2.0 ATA for 60 mins. 24 hrs. pre-insult

Hypoxic Preconditioning ...8% oxygen x up to 150 mins.

Insult: unilateral carotid cauterization and 90 mins. 8% O2 postnatal day 7

Freiberger JJ, *et al.* 2006 Brain Research;1075:213-222

57

Findings

Essentially identical brain weight improvement and survival between the preconditioned groups, compared to controls

Mortality:	Controls	14.7%
	H-PC	5.9%
	H-HBO	5.7%
Brain Weight Decrease:	Controls	42%
	H-PC	25%
	H-HBO	26%

Freiberger JJ, *et al.* 2006 Brain Research;1075:213-222

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Thoughts

Good science

Hypoxic preconditioning effective but impractical, particularly in likely target populations

Single hyperbaric treatment within 24 hours of insult has an largely identical protective effect to hypoxic, imminently more feasible and safer

Mechanisms of protection very different

Outcomes great temperature sensitive

Will hopefully stimulate further research

Are there other markers of injury/recovery?

59

Hyperbaric Pre-conditioning Effect on Neuropsychometric Dysfunction Systemic Inflammatory Response after CABG

~ a randomized controlled double-blind trial

64 patients randomized to HBO (2.4 ATA) or HBA (1.5 ATA) before on-pump CABG

~ 24, 12 and 4 hours pre-operatively

Both groups well matched to demographic and peri-operative factors

Alex J, *et al.* 2005 J Thoracic Cardiovasc Surg;130(6)

60

Hyperbaric Pre-conditioning Effects on Neuropsychometric Dysfunction and Systemic Inflammatory Response after CABG

Comprehensive screening battery:

16/31 (51%) of controls had a significant dysfunction, vs. 9/33 (27%) HBO

Eight inflammatory markers assessed:

ANOVA found significant post-op increases in three (sE-selectin, CD18, HSP-70) of eight markers in controls in contrast to the HBO group

Alex J, *et al.* 2005 J Thoracic Cardiovasc Surg;130(6)

61

What to take home from this one?

Encouraging recruitment percentage (84%)

Controls received 30% O2

None of the tested variables predictive of neuropsych. decline

HBO reduced inflammatory response amplitude

Mechanism? An area of research need

62

Dental Implant Surgery in Irradiated Bone

The case for hyperbaric oxygen...
Gosta Granstrom; J Oral Maxiollofac Surg 2006;64;812-818

The case against hyperbaric oxygen...
R Bruce Donoff; J Oral Maxillofac Surg 2006;64;819-822

63

Hyperbaric oxygen in support of osseointegration implant surgery

	No (lower failure risk)	Yes (higher failure risk)
XRT pre/post tumor surgery?	no	yes
XRT pre O.I. surgery?	no	yes
Time(months) from surgery?	< 3	> 3
XRT dose (Gy), per implant site?	< 40	> 50
Adjuvant chemotherapy (at OI)?	no	yes
Implants into grafted bone?	yes	no
Implant length?	long	short(3-7mm)
Console® abutments?	no	yes
Coarse implant surfaces?	yes	no

年間レビュー:2005年の潜水関連文献の一覧

Richard Vann

2005年に発表された潜水に関係した論文は100件以上にのぼっていました。Orlandでの2006 UHMS総会で報告のために，この中から16件の論文を選択して，その概要を以下に紹介します。

Koehleらは，スクーバ潜水，水泳と息こらえ潜水により生じた浸出性肺浮腫の60例についてレビューしています。低温での血管収縮と運動による灌流量の増加は毛細血管血内圧を高めることから肺浮腫を招きますが，通常は

酸素投与や補助療法で24時間以内に改善すると述べています。(No.3)

Cochardらは，低水温スクーバ潜水における6例の肺水腫をレビューしています。症状は，深いところでの呼吸困難，潜水後の咳，喀血や低酸素血症でした。再発の1例は心停止から死亡していますが，CTで胸水と浸潤影が認められました。著者らは，救急医療者の教育が必要であるとしています。(No.4)

Shykoffは浸水と140 kPaでの酸素吸入とで肺に与える影響を調べています。水中の呼吸だけでも肺に障害が起きますが，空気よりも酸素呼吸のほうが大きく影響しました。8時間の酸素曝露は，数日で改善するような軽度ないし中等度の肺酸素中毒を引き起こしました。(No.5～8)

LindholmとGennserは，長時間の運動と炭水化物の少ない食事がCO_2産生を抑制して，息こらえ時間を延長させ，その後の酸素レベルが低下することを見出しましたが，そのことが低酸素性失神の危険性を高めるだろうとしています。(No.9～12)

Kohshiらは，海士で脳卒中様の症状(taravanaと同様のもの)を確認し，MRI画像で脳梗塞が生じていることを見出しています。静脈内ガスの動脈への移行によるガス塞栓症を機序として考えています。(No.13～7)

RiceとMooreは，米海軍チャンバーで治療された高度減圧症Type IIの半数はデルマトームに合わない感覚障害のみで，Type I DCSと同様に迅速に改善していることから，Type IIあるいは重症型に分類する必要はないとしています。DCS分類の改定は症候学的ではなく重篤度に重点を置いたものを推奨しています。(No.18～20)

Bryceらは，米空軍Davis高気圧研究所で治療された頭痛を伴う高度減圧症の23%が神経系DCSよりも関節痛に分類すべきではと述べています。このことはDCSを経験したという理由で航空機搭乗員の資格を失うという規則に，現実的な意義を唱えたものでしょう。(No.21～4)

Lundgrenらはフルオロカーボン乳剤を用いて血管内の微小気泡を作ったブタで窒素排出の増加を示しました。(No.25～9)

Blatteauらは，ヒトでディープストップ(中間停止)の有無で減圧スケジュールの3つを調査しています。彼らの調べた潜水プロファイルでは，ディープストップはVGEの抑制に効果がないことがわかりました。(No.30～5)

McInnesらはreverse dive profiles (RDP)のほうがforward dive profiles (FDP)よりもDCSが生じるリスクが高いことを見出しました。しかし，モルモット(0－60%)の潜水でDCSのリスクはヒト(0.01－1%)よりも高いようですが，2000件未満の潜水で統計学的な有意差は得られておりません。(No.36～41)

Bergeらは，ラットを用いて30分前に終わる潜水前の運動は血管気泡の発生率や生存率に影響しないことを見出しました(No.42～4)。Blatteauらは，ヒトで2時間前に終わる潜水前の運動が減圧後の血管気泡を減少させることを見出しています(No.45～9)。Bondiらは，ラットで減圧前のNO合成酵素の阻害は生存率を低下させることを見出しました (No.50～3)。減圧のリスクに運動が影響を及ぼす機序としてNOが提唱されてきましたが，灌流なのか気泡の核形成が作用しているのか明らかではありません。

Nelsonらは，ブタで血管拡張薬のisoproterenolを飽和潜水の減圧前に投与すると，死亡率と呼吸循環系DCSの発生が高くなることを見出しました。(No.54～9)

Smerzらは，大きな圧力のハワイ再圧治療表について20年間の経験を検討したところ，この治療法が有効であると述べています。(No.60～7)

Germonpreらは，PFOを有した40名のダイバーで6-8年後に再検討すると，より大きなPFOを有したダイバーが多くなっていることを見出しています。(No.68～9)

(和訳文責：合志清隆)

The Year in Review : A Synopsis of Diving Literature 2005

Richard Vann[1,2]

[1] Divers Alert Network, Department of Anesthesiology, Duke University Medical Center, Durham; [2] Center for Hyperbaric and Environmental Physiology, Department of Anesthesiology, Duke University Medical Center

A review of the diving literature for 2005 disclosed over 100 relevant publications. Sixteen were chosen for brief presentation at the 2006 UHMS Meeting in Orlando and are summarized below.

Koehle et al. reviewed 60 cases of pulmonary immersion edema resulting from scuba, surface swimming, and breath-hold diving. Cold vasoconstriction and increased perfusion due to exercise were cited as the likely causes of increased capillary pressure leading to pulmonary edema that usually resolved in 24 hrs with oxygen and supportive therapy.

Cochard et al. reviewed six cases of pulmonary edema in cold-water scuba divers. Symptoms included dyspnea at depth, post-dive cough, hemoptysis, and hypoxemia. One recurrent case led to cardiac arrest and death. CT findings were pleural effusion and opacities. The authors recommended education of emergency care providers.

Shykoff studied the pulmonary effects of immersion and oxygen breathing at 140 kPa. Breathing underwater alone was associated with some pulmonary insult but the effects were greater with oxygen than with air. An 8-hr oxygen exposure caused mild to moderate pulmonary toxicity that resolved after a few days.

Lindholm and Gennser found that prolonged exercise and a low carbohydrate diet reduced carbon dioxide production, extended breath-hold time, and decreased end breath-hold oxygen levels which might increase the risk for hypoxic syncope.

Kohshi et al. found stroke-like symptoms (similar to taravana) and cerebral infarcts by MRI imaging in Ama divers. Arterialized venous gas emboli were suggested as a possible mechanism.

Rice and Moore found that half the Type II altitude DCS treated in U.S. Navy chambers involved only non-dermatomal paresthesias that resolved as rapidly as Type I DCS and were unnecessarily classified as Type II or serious symptoms. Revision of the DCS classification system was recommended emphasizing severity not symptomatology.

Bryce et al. suggested that 23% of altitude DCS involving headache treated at the U.S. Air Force Davis Hyperbaric Lab might be classified as joint pain rather than neurological DCS. This would have practical implications regarding the disqualification rules for aircrew with DCS.

Lundgren et al. demonstrated increased nitrogen elimination in pigs having intravascular microbubbles derived from fluorocarbon emulsion.

Blatteau et al. tested three decompression schedules in humans with and without deep stops and found that deep stops provided no benefit for reducing VGE with the dive profiles they tested.

McInnes et al. found that reverse dive profiles (RDP) had a higher DCS risk than forward dive profiles (FDP). However, the guinea pig dives were of greater DCS risk (0-60%) than human dives (0.01-1%) making differences for humans statistically impossible to distinguish in less that 2000 dives.

Berge et al. found that exercise ending 30 min pre-dive had no effect on vascular bubbles or survival in the rat. Blatteau et al. found that exercise ending 2 h pre-dive decreased vascular bubbles after decompression in humans. Bondi et al. found that inhibition of nitric oxide synthase

before decompression decreased survival of rats. Nitric oxide has been proposed as a mechanism by which exercise affects decompression risk but whether perfusion or bubble nucleation is mode of action is uncertain.

Nelson et al. found that isoproterenol, which increases vasodilitation, increased death and cardiopulmonary DCS in pigs when given before decompression from saturation dives.

Smerz et al. described the deep Hawaiian recompression tables, reviewed 20 years of experience, and concluded that continued confidence in their effectiveness was warranted.

Germonpre et al. evaluated 40 divers for PFO at 6-8 years after a previous evaluation and found more divers with larger PFOs.

1

The Year in Review:
A Synopsis of Diving Literature 2005

Richard Vann
UHMS Scientific Meeting
June 22, 2005
Orlando

2

16 Papers

- Immersion edema
- O_2 diving & the lung
- Breath-hold diving
- DCS diagnosis, definition & disposition
- PFC enhanced N_2 washout
- Deep stops
- Reverse dives
- Pre-dive exercise & NO
- DCS & isoproterenol
- Hawaii deep treatments
- PFO & aging

3

Pulmonary Oedema of Immersion
Koehle, Lepawsky, McKenzie
Sports Med 2005; 35 (3): 183-190

- 60 published cases reviewed
  - endurance swimming; scuba & breath-hold diving
- Pathophysiology: pulmonary overperfusion
  - cold vasoconstriction & ↑ ambient pressure & ↑ blood flow due to exercise → ↑ capillary pressure → fluid extraversation
- Cases usually resolved in 24 hrs with O_2 & supportive therapy

4

Pulmonary edema in scuba divers: recurrence and fatal outcome
COCHARD, ARVIEUX, LACOUR, MADOUAS, MONGREDIEN, ARVIEUX
UHM, 2005, Vol. 32, No. 1

- 6 cases, 15 months, Brittany, cold water
- Symptoms: dsypnea at depth; post-dive cough, hemoptysis, hypoxemia
  - Cardiac arrest & death in one recurrent case
- CT findings: pleural effusion, opacities
- ***Author recommendation: educate emergency care providers***

5

Pulmonary effects of submerged oxygen breathing: 4-, 6-, and 8-hour dives at 140 kPa
SHYKOFF
UHM 2005, Vol. 32, No. 5

- Objectives:
  - separate the physical effects of breathing underwater from the chemical effects of high O_2 partial pressures
  - assess acceptable oxygen exposure times for shallow water submersion

6

SHYKOFF (2)

- Methods:
  - 24 resting subjects in freshwater pool
    - Paired dives at 3.6 mfw (chest level)
      - Air at P_{IO2} = 0.3 atm
      - 100% O_2 at P_{IO2} = 1.4 atm
  - 21 control subjects for 6 weeks
    - No-diving test for variability
  - Measure PFT changes & track symptoms
    - FVC, Peak Flow, FEV_1, D_LCO

7

SHYKOFF (3)

- Results:

Person-days	Changed PFT		* p<0.04 Symptoms	
Duration	AIR	O_2	AIR	O_2
8 hours	4	6	2 *	11 *
6 hours	2	4	2	5
4 hours	1	2	4	3

8

SHYKOFF (4)

- Conclusions:
  - Breathing underwater was associated with some pulmonary insult
    - Effects greater at P_{IO2} = 1.4 atm than with air
  - Symptom incidence increased with duration
    - A single 4-hour underwater exposure to P_{IO2} = 1.4 atm was no worse than to P_{IO2} = 0.3 atm.
    - 6-hr exposure to 1.4 atm warrants further study
    - 8-hour oxygen exposure causes mild to moderate pulmonary toxicity that resolves after a few days
- COMMENT:
  - Candidate for longitudinal data analysis?

9

Aggravated hypoxia during breath-holds after prolonged exercise
LINDHOLM & GENNSER
Eur J Appl Physiol (2005) 93: 701–707

- Background: breath-hold near-drownings after extended exercise without hyperventilation
  - prolonged exercise shifts metabolism from carbohydrates to lipids & lowers CO_2 production
- Hypothesis: lower CO_2 production during breath-hold diving after exercise exacerbates end-of-dive hypoxia

10

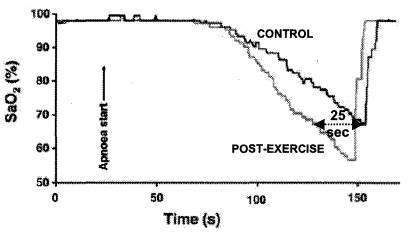
LINDHOLM & GENNSER (2)

- Methods: 8 subjects performed breath-holds under control & post-exercise conditions
  - Post-exercise: ~12 hrs on a carbohydrate-free diet followed by 2 hrs of sub-maximal exercise
  - Measured RER, $P_{et}O_2$, $P_{et}CO_2$, SaO_2
- Results:

	Duration (sec)	RER ---	$P_{et}O_2$ (mmHg)	$P_{et}CO_2$ (mmHg)
Control	96	0.83	52	59
Post-exercise	96	0.70	47	50

11

LINDHOLM & GENNSER (3)



12

LINDHOLM & GENNSER (4)

- Conclusions:
  - Lipid-rich diet and exercise-induced carbohydrate depletion increased the risk of end-breath-hold hypoxia
  - Potential for increased risk of hypoxic syncope

13

Neurological manifestations in Japanese Ama divers

KOHSHI, WONG, ABE, KATOH, OKUDERA, MANO

UHM 2005, Vol. 32, No. 1

- Background:
  - Taravana ("to fall crazily") is a condition observed in French Polynesian breath-hold divers
  - Affects the CNS and is believed to be DCI
  - Similar events common among Ama usually lasting only several hours with cerebral rather than spinal involvement

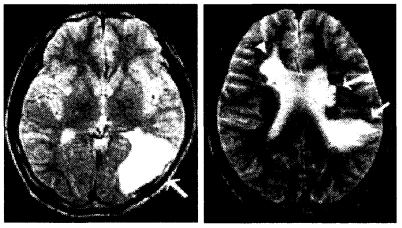
14

KOHSHI, WONG, ABE, KATOH, OKUDERA, MANO (2)

- Objective: review signs & symptoms of possible DCI in Ama divers
- Methods:
  - A survey of 16 Ama divers found 9 with stroke-like events (none spinal)
    - Transient hemiparesis or hemi-sensory disturbances
    - Euphoria, dizziness, nausea also common
  - MRI imaging of 4 Ama divers with histories of cerebral symptoms revealed cerebral infarcts in watershed areas

15

KOHSHI, WONG, ABE, KATOH, OKUDERA, MANO (3)



16

KOHSHI, WONG, ABE, KATOH, OKUDERA, MANO (4)

- Possible mechanisms
  - Autochthonous bubble formation in the brain
  - AGE from pulmonary barotrauma
  - VGE rarely detected in breath-hold divers
    - Bubbles <30-50 microns may not be detectable by Doppler
  - VGE shunting through PFO
  - Arterialization of VGE through pulmonary circulation
    - Bubble diameter threshold for transpulmonary passage is about 21 microns
  - COMMENT:
    - Smith observed bubbles in the lung were redistributed to arterial circulation by a repetitive dive after a short surface interval

17

KOHSHI, WONG, ABE, KATOH, OKUDERA, MANO (5)

- Prevention:
  - Limit bottom time
  - Fewer dives per day
  - Increase surface intervals
- Therapy:
  - Treat as for DCI

18

Type II decompression sickness in Naval hypobaric chambers: a case of mistaken identity?

RICE & MOORE

Aviat Space Environ Med 2005; 76:841– 6.

- Background:
  - USN altitude DCI classified & treated according to the USN Diving Manual
    - Mild paresthesias defined as Type II (severe) DCS
- Objective:
  - Review altitude DCS cases classified as Type II DCS at USN chambers

19

RICE & MOORE (2)

- Methods:
  - 50,355 training/operational exposures from NOMI records
- Results:
  - 97 DCS cases (0.19%)
  - 58 DCS-2 (60%)
    - 50% were paresthesias based on the presence of non-dermatomal paresthesias only
  - Paresthesia-only DCS-2 resolved as rapidly as DCS-1

20

RICE & MOORE (3)

- Discussion:
  - Differentiating "severe" (perhaps live-threatening) from mild neurological DCS such as paresthesias not possible with the USN Diving Manual
  - USAF & NASA considers non-dermatomal paresthesias-only to be mild DCS
- Conclusion:
  - Revise US Naval Aviation DCS classification system with emphasis on severity not symptomatology

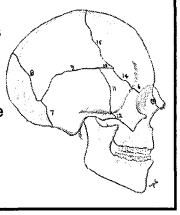
21

Headache and altitude decompression sickness: joint pain or neurological pain?

BRYCE, BUTLER, PILMANIS, KING

Aviat Space Environ Med 2005; 76:1074–8.

- Background:
  - Headache at altitude occurs frequently and is often classified as neurological or serious DCS
  - Some headaches may have been joint pain associated with cranial sutures rather than neurological DCS



22

BRYCE, BUTLER, PILMANIS, KING (3)

- Objective:
  - Investigate the proposition that headache may be joint pain DCS & not always be neurological DCS
- Methods:
  - Record review of Davis Hyperbaric Lab
  - Criteria for headache as joint pain DCS:
    - Headache localized at a suture
    - Normal neurological examination
    - Resolution within 30 min of HBO

23

BRYCE, BUTLER, PILMANIS, KING (2)

- Results:
  - 480 altitude DCS cases
  - 70 with headache
  - 16 (23%) met criteria for joint pain
  - 54 were unclear or had focal neuro findings
- Discussion:
  - 23% of neuro (altitude) DCS might be reclassified as less serious joint pain
  - Disqualification rules for neuro DCS without residua: 72 h USAF, 1 month USA, 14-30 d USN

24

COMMENT

- Previous 3 papers suggested some discord concerning the definition, diagnosis, and disposition of DCS
- Would a workshop on the topic be of value?
- Oh no, not another DCS workshop!

25

Tissue nitrogen elimination in oxygen-breathing pigs is enhanced by fluorocarbon-derived intravascular micro-bubbles.

LUNDGREN, BERGOE, OLSZOWKA, TYSSEBOTN

Undersea Hyperb Med 2005; 32(4):215-226.

- Objective: determine the effect of a fluorocarbon emulsion (DDFP) on N_2 elimination during O_2 breathing at 1 ata in the pig

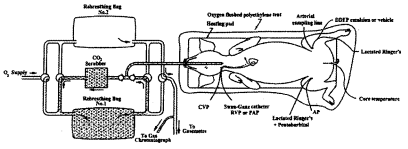
26

LUNDGREN, BERGOE, OLSZOWKA, TYSSEBOTN (2)

- Methods:
  - DDFP boils at 29°C & microbubbles form upon injection
  - 6 experimental animals received 0.08 ± 0.01 ml/kg of 2% DDFP emulsion i.v. over a 30 min
  - 5 control animals received vehicle only

27

LUNDGREN, BERGOE, OLSZOWKA, TYSSEBOTN (3)

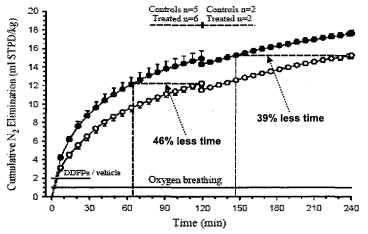


7 min rebreathing periods on each arm of the circuit

28

LUNDGREN, BERGOE, OLSZOWKA, TYSSEBOTN (4)

- Methods:



29

LUNDGREN, BERGOE, OLSZOWKA, TYSSEBOTN (5)

- Central venous O_2 tension higher in treated animals than in controls, probably due to enhanced O_2 transport by micro-bubbles
- Conclusions:
  - DCS treatment with DDFP-emulsion & O_2 breathing may enhance inert gas elimination & improve O_2 delivery to hypoxic tissues
  - Prior to testing this hypothesis, experiments must show that DDFP micro-bubbles do not increase the risk of gas embolism

30

Bubble incidence after staged decompression from 50 or 60 msw: effect *of adding deep stops.*

BLATTEAU, HUGON, GARDETTE, SAINTY, GALLAND

Aviat Space Environ Med 2005; 76:490–2.

- Objective: determine if deep decompression stops would reduce the incidence of Doppler-detected VGE

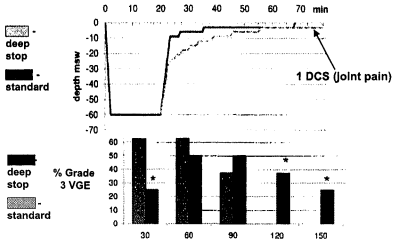
31

BLATTEAU, HUGON, GARDETTE, SAINTY, GALLAND (2)

- Methods:
  - 8 subjects
  - 2-60 msw single dive profiles with stops
  - 1 repetitive dive profile with stops
  - Moderate swimming at depth in wetpot with resting decompression

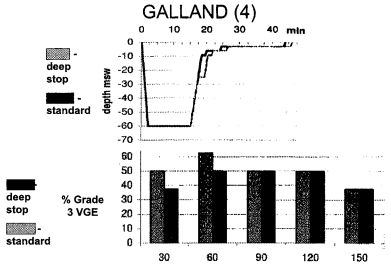
32

BLATTEAU, HUGON, GARDETTE, SAINTY, GALLAND (3)



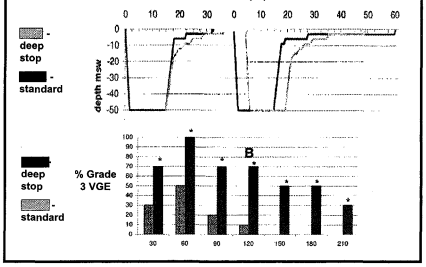
33

BLATTEAU, HUGON, GARDETTE, SAINTY, GALLAND (4)



34

BLATTEAU, HUGON, GARDETTE, SAINTY, GALLAND (5)



35

BLATTEAU, HUGON, GARDETTE, SAINTY, GALLAND (6)

- Conclusion:
  - Deep stops provided no benefit in reducing VGE
  - Use of deep stops requires careful consideration

36

The relative safety of forward and reverse diving profiles.

McINNES, EDMONDS, BENNETT

UHM 2005, Vol. 32, No. 6

- Objective:
  - Test the hypothesis that there is no difference in DCS risk between the RDP and FDP for multi-level and/or repetitive dives.
    - RDP – Reverse Dive Profile
    - FDP – Forward Dive Profile

37

McINNES, EDMONDS, BENNETT (2)

- Methods:
  - Multi-level
    - FDP: 36msw/30min-24/30-12/30
    - RDP: 12/30-24/30-36/30
  - Repetitive Profile # 1
    - FDP: 30/30-0/15-20/30-0/15-10/30
    - RDP: 10/30-0/15-20/30-0/15-30/30
  - Repetitive Profile # 2
    - FDP: 30/40-0/15-20/40-0/15-10/40
    - RDP: 10/40-0/15-20/40-0/15-30/40
  - 11 Guinea pigs in each group

38

McINNES, EDMONDS, BENNETT (3)

- Results:
  - Multi-level
    - FDP: 36/30-24/30-12/30 – 0% DCS
    - RDP: 12/30-24/30-36/30 – 55% fatal DCS
  - Repetitive Profile # 1
    - FDP: 30/30-0/15-20/30-0/15-10/30 – 0% DCS
    - RDP: 10/30-0/15-20/30-0/15-30/30 – 9% fatal DCS
  - Repetitive Profile # 2
    - FDP: 30/40-0/15-20/40-0/15-10/40 – 0% DCS
    - RDP: 10/40-0/15-20/40-0/15-30/40 – 60% DCS

39

McINNES, EDMONDS, BENNETT (4)

- Conclusions:
  - Multi-level and repetitive RDPs are not mirror images of FDPs & do not carry equal decompression obligations
  - We advise against advocating reverse profiles until the limitations are determined more factually & the decompression requirements are re-defined

40

COMMENT

- "...at least for the exposures we chose."
- Repetitive Profile # 1
  - FDP: 30/30-0/15-20/30-0/15-10/30 – 0% DCS
  - RDP: 10/30-0/15-20/30-0/15-30/30 – 9% DCS
- Repetitive Profile # 2
  - FDP: 30/40-0/15-20/40-0/15-10/40 – 0% DCS
  - RDP: 10/40-0/15-20/40-0/15-30/40 – 60% DCS
- The DCS incidence of diving is ~1.0-0.01%

41

COMMENT (2)

- Suppose RDP_{DCS} = 1.0% & FDP_{DCS} = 0.01%
  - 2 groups of 1,000 guinea pigs
- If RDP_{DCS} = 1.0% & FDP_{DCS} = 0.1%
  - 2 groups of 1,300 guinea pigs
- If RDP_{DCS} = 0.1% & FDP_{DCS} = 0.01%
  - 2 groups of 13,000 guinea pigs
- To be relevant to human diving, this is a difficult study

42

Exercise ending 30 min pre-dive has no effect on bubble formation in the rat.

BERGE, JØRGENSEN, LØSET, WISLØFF, BRUBAKK

Aviat Space Environ Med 2005; 76:326–8.

- Background: Previous work showed exercise 20 hrs before diving reduced VGE incidence, possibly by decreasing bubble formation in response to nitric oxide
  - However, no VGE reduction occurred with exercise at 48, 10, 5 hrs, or 30 min before diving
- Objective: determine if exercise 30 min before diving would increase VGE in rats

43

BERGE, JØRGENSEN, LØSET, WISLØFF, BRUBAKK (2)

- Methods:
  - 7 ata dive for 45 min with ascent at 0.5 ata/min
  - 29 control rats did no pre-dive exercise
  - 29 rats did 90 min exercise at 85-90% $\dot{V}_{O2max}$ at 30 min before diving
- Results:
  - No difference: in survival, >Grade 1 VGE, or median bubble grade

44

BERGE, JØRGENSEN, LØSET, WISLØFF, BRUBAKK (3)

- Conclusions:
  - The same type and intensity of exercise that reduced bubble formation when performed 20 hr prior to a dive neither promoted nor reduced bubble formation if performed 30 min before a dive

45

Aerobic exercise 2 hours before a dive to 30 msw decreases bubble formation after decompression.

BLATTEAU, GEMPP, GALLAND, PONTIER, SAINTY, ROBINET

Aviat Space Environ Med 2005; 76:666 –9.

- Question: what is the effect of exercise two hours before diving on Doppler VGE?

46

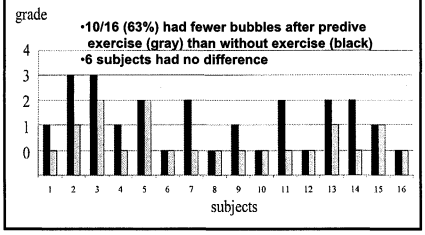
BLATTEAU, GEMPP, GALLAND, PONTIER, SAINTY, ROBINET (2)

- Methods
  - 16 military divers
  - Exercise 2 hrs before diving at 60-80% max heart rate for 45 min
  - 30 msw/30 min dry chamber dive with a 9 min stop at 3 msw

47

BLATTEAU, GEMPP, GALLAND, PONTIER, SAINTY, ROBINET (3)

- Results:



48

BLATTEAU, GEMPP, GALLAND, PONTIER, SAINTY, ROBINET (4)

- Discussion:
  - The mechanism by which pre-dive exercise reduces VGE is unknown
  - Rather than altering the nitrogen elimination rate, exercise may affect the population of gaseous nuclei from which bubbles form
    - Through their action on the endothelium, nitric oxide and heat shock proteins have been mentioned as possible mediators

49

COMMENT

- Blatteau found exercise 2 hr pre-dive reduced VGE in humans
- Berge (previous paper) found exercise 30 min pre-dive had no effect in rats

50

Delayed effect of nitric oxide synthase inhibition on the survival of rats after acute decompression

BONDÌ, CAVAGGIONI, MICHIELI, SCHIAVON, TRAVAIN

UHM 2005, Vol. 32, No. 2

- Background:
  - to gain insight into the vascular function of nitric oxide in acute decompression sickness, the effects of the nitric oxide synthase inhibition by L-NAME was studied in rats.

51

BONDÌ, CAVAGGIONI, MICHIELI, SCHIAVON, TRAVAIN (2)

- Objective:
  - Test whether the acute inhibition of NOS activity by L-NAME had a delayed effect on DCS and the survival of the rats.
- Methods:
  - anesthetized rats were exposed to hyperbaric conditions for two hours and decompressed approximately 2.5 hours after a single subcutaneous injection of L-NAME

52

BONDÌ, CAVAGGIONI, MICHIELI, SCHIAVON, TRAVAIN (3)

- Results:
  - A single L-NAME dose greater injected in rats approximately 2.5 hours before ascent increased the risk of death in acute DCS

53

BONDÌ, CAVAGGIONI, MICHIELI, SCHIAVON, TRAVAIN (4)

- Conclusion:
  - Although we have not excluded effects of nitric oxide synthase inhibition on distribution of perfusion and therefore inert gas elimination from tissue during decompression, this result highlights a delayed benefit of nitric oxide synthase activity in preventing death in acute decompression sickness

54

Isoproterenol accelerates decompression sickness and death after saturation dives in swine

NELSON, WERNER, BURGE

Aviat Space Environ Med 2005; 76:97–102.

- Background:
  - Personnel in a disabled submarine might be saturated at up to 5 ata
  - Rescue could require direct ascent to 1 ata
  - Isoproterenol was beneficial in rats for treating cardiopulmonary DCS and promoting normobaric N_2 washout

55

NELSON, WERNER, BURGE (2)

- Objective:
  - Determine if isoproterenol could prevent or delay Type II DCS & death in swine
- Methods:
  - 22 hr exposure to 4.33 ata with direct ascent to 1 ata
  - 18 swine given 0.002 mg/kg isoproterenol just before decompression
  - 34 (historical) control swine

56

NELSON, WERNER, BURGE (3)

- Results:

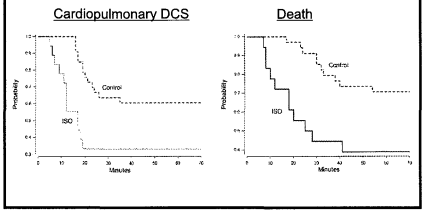
DCS	Experimental Group: Isoproterenol (n = 18)	Control (n = 34)
Any type	83%	77%
Cardiopulmonary	67%*	54%
Neurological	67%	71%
Death	61%*	29%
No Type II DCS	17%	23%

*p<0.01

57

NELSON, WERNER, BURGE (4)

- Kaplan-Meier survival plots



58

NELSON, WERNER, BURGE (5)

- Conclusions:
  - The deleterious effects of isoproterenol appear to outweigh the potential benefits in an emergency no-stop decompression from saturation conditions

59

COMMENT

- Would the swine-saturation/direct ascent model be helpful to identify the mechanism by which nitric oxide acts to protect against DCS?
- A beneficial effect with NO (unlike isoproterenol) might suggest that NO acts by decreasing bubble formation rather than, alternatively, by increasing perfusion

60

Hawaiian Deep Treatments: Efficacy and Outcomes, 1983-2003

SMERZ, OVERLOCK, NAKAYAMA

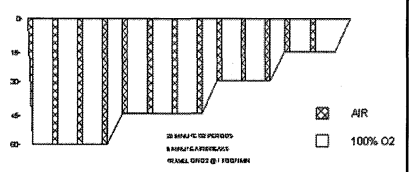
UHM 2005, Vol. 32, No. 5

- Background:
  - Reported high failure rate of Tables 5 & 6 in 1970-80s led Beckman, Yount & Kunkle to develop Tx tables with initial pressurization to 220 or 280 fsw
- Objective:
  - A 20-year review of experience with the Hawaiian deep tables

61

SMERZ, OVERLOCK, NAKAYAMA (2)

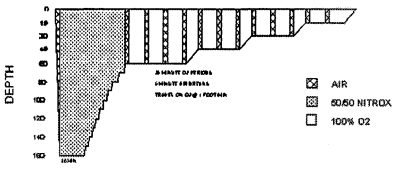
- **TT60**



62

SMERZ, OVERLOCK, NAKAYAMA (3)

- **TT160**

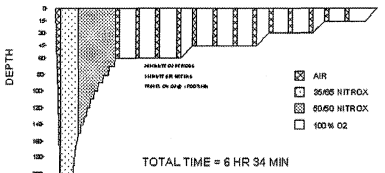


TOTAL TIME = 6 HR 18 MIN
UPTD = 887

63

SMERZ, OVERLOCK, NAKAYAMA (4)

- **TT220**

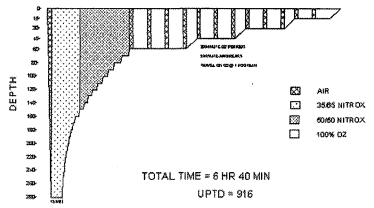


TOTAL TIME = 6 HR 34 MIN
UPTD = 904

64

SMERZ, OVERLOCK, NAKAYAMA (5)

- **TT280**



TOTAL TIME = 6 HR 40 MIN
UPTD = 916

65

SMERZ, OVERLOCK, NAKAYAMA (6)

- Methods:
  - 2004 chart review of 889 cases meeting definition
  - Outcome measure
    - Complete Functional Recovery (CFR): no deficits ***or only minor subjective symptoms*** at discharge
- Results as % CFR:
  - 93% overall
  - 92% AGE
  - 91% DCS-2 (only 73% for severe cases)
  - 99% DCS-1

66

SMERZ, OVERLOCK, NAKAYAMA (7)

- Mild cases
  - Table not important
  - 100% CFR
  - 22.3 hr mean delay
- Severe cases
  - Only deep tables used
  - 76.4% CFR
  - 16.7 hr delay
  - More severe injuries & less recovery for males than females

67

SMERZ, OVERLOCK, NAKAYAMA (8)

- Complications
  - 3 DCS in attendants
  - 7% O_2 toxicity
    - 0.6% seizures
- Conclusion:
  - Continued confidence in the deep Hawaiian treatment tables appears warranted

68

Evidence for Increasing Patency of the Foramen Ovale in Divers

GERMONPRE, HASTIR, DENDALE, MARRONI, NGUYEN, BALESTRA

Am J Cardiol 2005;95:912–915

- Objective:
  - Determine if PFO is subject to change with aging
- Methods:
  - 40 divers
  - Scanned 6-8 years earlier with contrast TEE
    - Grade 0: no bubble passage
    - Grade 1: <20 bubbles
    - Grade 2: >20 bubbles

69

GERMONPRE, HASTIR, DENDALE, MARRONI, NGUYEN, BALESTRA (2)

- Results:

Grade	Initial	Final
0	50%	47%
1	22%	10%
2	28%	43%

  - p=0.0354 by Wilcoxon signed rank test
- Conclusion:
  - Divers may develop increased susceptibility to neurological DCS over time