HYPOXIA SYMPOSIUM 1999

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Introduction

The 11th Hypoxia Symposium was held at the Jasper Park Lodge in the Canadian Rockies from Feb 27th to March 5th. The change of venue from Lake Louise was dictated mainly by the rising cost of the Chateau. Jasper is rather more challenging to reach as one of the British members demonstrated. When driving on his own, he spun off the snowy road between Lake Louise and Jasper in the early hours of Monday morning desperately trying to get posters and slides to his colleagues for presentation later that day! The views may not be quite so dramatic but the conference facilities are better, the skiing was great and the record number of registrants endorses the decision of the organizers to change the venue. It was also the first symposium organized by Rob Roach and Peter Hackett after taking over from Charlie Houston, Geoff Coates and the late John Sutton. They, with help from Bengt Kayser, and Toshio Kobayashi, are to be congratulated on running a very successful symposium. Sharon Studd did a great job in backroom support. I particularly welcomed the format of the proceedings and the splendid name badges which were in large enough type for even the most presbyopic to read at a safe distance. She even had the conference time table on the back of the label, a great idea.

There were 232 registrants from 24 countries. USA were by far the largest contingent (104) followed by UK (26), Germany (17), and Japan (16) and it was good to see many from less developed countries such as Bolivia, Kyrgystan, and Poland. In some cases delegates were enabled to come through financial support from Medical Expeditions Ltd., UK and the U.S. Army Medical research and Materiel Command.

Scientific Program, Day 1

The first day opened with a talk from Drummond Rennie who reminisced through his own climbing and research career and that of Herbert Hultgren. Herb, known to many for his early work on high altitude pulmonary edema (HAPE), died in 1997 just after completing his book, “High Altitude Medicine”. This Hypoxia Symposium was dedicated to him.

The rest of the day was devoted to “A day in Mountain Medicine”. Brownie Schoene discussed the pulmonary patient at altitude; apart from asthmatics who usually do well, they do badly. Susan Niermeyer talked about the pregnant altitude visitor; AMS may be less common but danger of pre-term labour and danger of trauma late in pregnancy suggests cautious advice in this area. John West discussed the problems posed by the requirement to staff new mines at altitudes around 5000 m in Chile with labour from the coast. Men have to commute to altitude for perhaps a week and then have a week at sea level. He advocated oxygen enrichment of the air in sleeping quarters as being beneficial and practical. Peter Hackett gave a talk based partly on his recent paper in JAMA on MRI scans in high altitude cerebral edema (HACE).

This together with talks in the session on Monday on Frontiers in Neuroscience gave us a lot to think about in this area. There seems to be a growing consensus that HACE is a development or a more severe form of AMS, the mechanism being one of cerebral edema. It is suggested that hypoxia causes an increase in permeability of the blood brain barrier with its “tight endothelial junctions”. There was also discussion of why some are susceptible. Perhaps they have little room for expansion of brain within the skull - tight brains. But while CSF was shown to decrease in volume at altitude (a paper on Tuesday by Milton Icenogle) and the brain to swell (a poster by Steve Muza on Wednesday both using MRI), there was no correlation of these changes with AMS scores.

After the ski break we had a number of papers on HAPE and possible mechanisms. Simon Gibbs gave us evidence of high tone in the pulmonary arteries of subjects susceptible to HAPE, rather than the suggestion that they might have small lungs, and that this, with patchy vasoconstriction (as originally proposed by Hultgren), might be the mechanism of edema formation, though inflammation might add to the problem at a later stage. Marco Maggiorini also concluded, from a study of HAPE susceptible subjects, that there was an initial increase in pulmonary capillary pressure before any increase in permeability (measured by labeled transferin) or in various cytokines. Urs Scherrer, using a rat model where peri-natal exposure to hypoxia induced an exaggerated pulmonary pressor response, showed that such a response by itself was insufficient to produce HAPE. He suggested that it needed also a defect in transepithelial sodium transport such as he had found in HAPE susceptible subjects. This is thought to be due to a defect in the amiloride sensitive Na channel. His group had two posters on this subject one using transgenic mice, the other looking at the nasal PD in HAPE susceptible subjects and controls. The HAPE susceptible subjects had 30% lower PD and smaller decreases in PD with amiloride than controls suggesting a defect in amiloride sensitive Na channels in their epithelium. Another poster from Peter Bartsch’s group also found altered ion transport in the mononuclear leukocytes of HAPE susceptible subjects. A study of incidence of HAPE in a cohort of 262 unselected subjects climbing to the Margarita Hut (4559 m) was reported by George Cremona. Using rather subtle changes in the chest X-ray as the criterion of HAPE they found an incidence of 15%. Many of these cases would be sub-clinical but does confirm, what many of us have thought likely, that shortly after arrival at altitude, especially after exercise, sub-clinical HAPE is not uncommon.

There followed three papers in a session called, “Hot topics in Mountain Medicine”. Gerrit Van Hall told us that there was no Lactate Paradox in very healthy subjects fully acclimatized to 5200 m. They produced very respectable lactate levels after exercise. Why these results were at variance with most of the literature was not apparent. Thomas Kuepper reported a placebo controlled double blind trial of Theophylline (450 mg) in preventing AMS. There was a significant beneficial effect especially on sleep and there were no side effects. Finally Ian Clark made a case that the symptoms of AMS can be attributed to induction, by hypoxia, of inducible nitric oxide synthase analogous to the situation in cerebral malaria.

Science Day 2
Monday morning was devoted to neuroscience with contributions from scientists

coming to Hypoxia from a primary interest in neurology. John Krasney, who chaired this session, indicated that a consensus had now developed, that the symptoms of AMS as well as HACE were due to cerebral edema, as mentioned above. This in turn might be either vasogenic or cytotoxic. The two next speakers, Lester Drews and Lothar Schilling explored these possibilities. Lester gave us a splendid up-date on the blood-brain barrier and the characteristics of the tight junctions in this endothelium. Lothar reviewed the various mediators which might induce cerebral edema, including bradykinin, arachidonic acid, free radicals and, as Ian Clark had told us the day before, nitric oxide. Insights from research in migraine and in stroke were given by Michael Moskowitz and Konstantin Hossman. These were fascinating talks but their relevance to altitude and AMS was not as clear as it might have been. However it had been a good morning of cross fertilization; what “Hypoxia” is all about.

At four o’clock we had the first of two poster session, some 67 posters to get round and digest. A new innovation was the “3X3” presentations, three minutes, three slides and 3 minutes questions, of the best 10 posters. This seemed a good compromise between practice I have come across, presenting all posters with 2 minutes each or no presentation at all. I can only mention a few posters; apologies to the many who’s good work is left unsung. Katrina Riboni and colleagues address the long running question of AMS incidence and the menstrual cycle. They found no difference in AMS scores between the mid luteal and mid follicular phases of the cycle in subjects during 12 hour chamber exposures. The question was asked, “What about the pre-menstrual phase?”. Answer, “We don’t know”. This session had a further eleven posters on women or gender differences at altitude, many by Lorna Moore and friends. There have been anecdotal reports of the efficacy of garlic in all sorts of conditions including AMS. A poster by Sue Hopkins investigated its efficacy in subjects given capsules of pure garlic powder (30 mg/kg/day for two days) and then their pulmonary artery pressure estimated by Doppler echocardiography on air or 12.5% oxygen. The normoxic pressure was lower and the response to hypoxia less on garlic than control! The Birmingham group were present in force and had a number of posters including one showing that breathing 3% CO2 improved oxygenation at altitude in healthy subjects as did O2 . A mixture of the two was even more effective. Such a mixture might be useful in refractory cases of HAPE or HACE.

Science, Day 3

On Tuesday we had a session on Lactate and Hypoxia with the latest views of George Brooks, and George Heisgenhauser. Brooks pointed out some time ago that, just to measure the venous lactate and assume that exercising muscles turn over to anaerobic metabolism when exercise gets hard, is too simplistic. Lactate is produced elsewhere as well and is actually being used as a substrate by working muscles. Their use of lactate increases from 13% at rest to 40% on exercise. So exercising muscles are both using and releasing lactate. Having previously talked about lactate being shuttled from cell to cell, on this occasion he discussed an intracellular shuttle of lactate between cytosol and mitochondria. The second George focused our attention on the conversion of pyruvate to lactate by pyruvate dehydrogenase (PDH). The reason lactate goes up in hard exercise is not oxygen lack but because pyruvate production exceeds the catalytic activity of PDH and since the equilibrium constant

of lactate dehydrogenase markedly favours lactate, small increases in pyruvate result in large increases in lactate concentrations.

Peter Hochachka discussed the importance of intra cellular motion or streaming which promotes substrate-enzyme interaction thus increasing the flux of a metabolic pathway with very little change of chemical concentrations. There followed a very good session on Hypoxia and Regulation of vascular growth in which Kurt Stenmark, John Kingdom and Hans Hoppeler took us into the world of molecular cellular physiology where many new advances are taking place.

In the afternoon we had a session of fifteen minute papers called, “Hot topics in Hypoxia” amongst others we hear of a study from Operation Everest III (Comex ’97) by Paul Robach on the effect of replacing plasma volume, normally reduced on ascent to altitude. The effect was to improve, significantly, VO2max. Urs Scherrer presented a study on ten healthy young adults identified from neonatal intensive care unit records as having had hypoxic episodes in infancy. They were found to have normal pulmonary artery pressure at low altitude (by Doppler u/s) but had higher pressures than controls at altitude (4,559 m). Their response to NO was also greater. But despite such high pressures none of them had HAPE suggesting that HAPE susceptibility is more than just a brisk pressor response (see below).

Science, Day 4

On the last day there was a session on extreme altitude in which John West first reviewed results from the summit of Everest of both barometric pressure and physiological; the latter, from both actual Everest summit and simulated in chamber studies. Recent results appear to confirm the validity of the one reading of barometric pressure made in 1981 by Chris Pizzo, of 253 Torr. Long term chamber studies supported the proposition that the alveolar PO_2 is defended at about 35 Torr. This being the case the $PACO_2$ cannot be higher than about 8 Torr in the steady state if R=1.0. If R is less than 1 it will be even lower.

Jean-Paul Richalet gave us a brisk over-view of Operation Everest III (Comex) of which he was the leader. Eight male subjects, having pre-acclimatized in the Valot Hut on Mt. Blanc, spent 30 days in the chamber eventually reaching the equivalent pressure of Everest summit on a number of occasions. There were 14 teams working on as many projects (or more) so only a few can be mentioned. Altitude cough was documented and was a problem despite comfortable temperature and humidity. Blood volume and left atrial diameters were reduced. They were able to get some results up to four days post exposure. Hb was back to normal at four days (altitude training enthusiasts please note) but PA pressure was still elevated, as was HVR and ventilation. Maximum heart rate was blunted at altitude but returned to normal rates quickly on return to normal pressure. A disturbing feature was that there were three cases of transient ischaemic attacks, fortunately with no long term effects. Ben Levine gave us an erudite paper on cerebral autoregulation at altitude. The conclusion was that altitude impairs this function probably because of the hypoxic vasodilatation.

Annabel Nicol and David Collier told us briefly about the science done on the recent “Medical Expeditions” trip to Kangchenjunga. 65 members plus a climbing team of

7 were involved in about 20 projects on themes including Respiratory, Cardiovascular, Sensory and Humoral. Data was collected in London and on the trek out. Observations were repeated at the Northern Base Camp (5100 m) soon after arrival and in some cases after a further period of acclimatization at this altitude or above. Finally we had a debate on the limiting factors to exercise at high altitude between Peter Wagner and Loring Rowell moderated by Jack Reeves. The debate turned on the role of cardiac output and if it is important in limiting exercise. The result, inconclusive.

The second poster session, with again the best ten selected for presentation, ended the formal part of the meeting. Again there were far more posters than I, at least, could digest, some 89 in this session. Perhaps we need three poster sessions or to limit the numbers of posters, though I hope not. The facilities for viewing were much superior to those at Lake Louise.

Prediction of AMS was studied by Markus Hoefer who used a 10 minute period of breathing 10% O_2 and noting the change in ventilation as a measure of HVR. He found this correlated with subsequent AMS scores. The change in heart rate during this time was an even better predictor. Most workers have not found a correlation of HVR with AMS but the use of a longer period of hypoxia may account for the difference. Peter Bartsch had a poster on the latest episode in the sumatriptan for altitude headache story. In a placebo controlled trial the results were not very clear since many in the placebo group improved. However it was considered that sumatriptan did confer some benefit at least in male subjects. Another poster from this group, the results of a questionnaire in 926 mountaineers, confirmed the common impression that migraine sufferers were more likely to have a history of AMS but since they tended to take a slower ascent plan, they did not actually have higher AMS scores than migraine free mountaineers. A poster by Hillenbrand and the Birmingham group failed to show a significant protective effect of progesterone for AMS in a group of 20 subjects. Andrea Ponchia had a poster giving further evidence of the low risk of moderate altitude (up to 2900 m) for asymptomatic patients with myocardial ischaemia. A poster that attracted considerable attention was by Bill Hayward who found that human sexual intercourse, at moderate altitude (1650 m), did not increase cerebral blood flow (using transcrainial Doppler) despite a rise in heart rate of 51 bpm at orgasm.! So that’s all right.

Evenings Entertainments

As relaxation after the hard day’s work the organizers laid on some very good evening talks. Scot Parazynski gave us a wonderfully illustrated talk about “Life in Space, Life on Earth” about space flights, space walks and views of Earth from space. Charlie Houston gave us a splendid personal view of his long and distinguished climbing and altitude research life. John Severinghaus delivered a moving tribute to Niels Lassen with whom he had worked on cerebral blood flow and who has contributed so much to our understanding in that area of physiology and Oswald Oelz gave us a typically idiosyncratic and self depreciating account of his “High Adventures”. On the final night a banquet was followed by a party at which undiscovered talent, singing and dancing were displayed by a number of delegates. I am happy to report that the 11th Hypoxia Symposium was as successful as any previous one and there is every sign that the outlook for the next millennium is good.

Jim Milledge Chorleywood
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