Effect of exposure to 15% oxygen on breathing patterns and oxygen saturation in infants: interventional study

K J Parkins, C F Poets, L M O'Brien, V A Stebbens, D P Southall

Abstract

Objective: To assess the response of healthy infants to airway hypoxia (15% oxygen in nitrogen).
Design: Interventional study.
Settings: Infants' homes and paediatric ward.
Subjects: 34 healthy infants (20 boys) born at term; mean age at study 3.1 months. 13 of the infants had siblings whose deaths had been ascribed to the sudden infant death syndrome.
Intervention: Respiratory variables were measured in room air (pre-challenge), while infants were exposed to 15% oxygen (challenge), and after infants were returned to room air (post-challenge).
Main outcome measures: Baseline oxygen saturation as measured by pulse oximetry, frequency of isolated and periodic apnoea, and frequency of desaturation (oxygen saturation ≤80% for ≥4 s). Exposure to 15% oxygen was terminated if oxygen saturation fell to ≤80% for ≥1 min.
Results: Mean duration of exposure to 15% oxygen was 6.3 (SD 2.9) hours. Baseline oxygen saturation fell from a median of 97.6% (range 94.0% to 100%) in room air to 92.8% (84.7% to 100%) in 15% oxygen. There was no correlation between baseline oxygen saturation in room air and the extent of the fall in baseline oxygen saturation on exposure to 15% oxygen. During exposure to 15% oxygen there was a reduction in the proportion of time spent in regular breathing pattern and a 3.5-fold increase in the proportion of time spent in periodic apnoea ($P < 0.001$). There was an increase in the frequency of desaturation from 0 episodes per hour (range 0 to 0.2) to 0.4 episodes per hour (0 to 35) ($P < 0.001$). In 4 infants exposure to hypoxic conditions was ended early because of prolonged and severe falls in oxygen saturation.
Conclusions: A proportion of infants had episodes of prolonged (≤80% for ≥1 min) or recurrent shorter (≤80% for ≥4 s) desaturation, or both, when exposed to airway hypoxia. The quality and quantity of this response was unpredictable. These findings may explain why some infants with airway hypoxia caused by respiratory infection develop more severe hypoxaemia than others. Exposure to airway hypoxia similar to that experienced during air travel or on holiday at high altitude may be harmful to some infants.

Introduction

A reduction in the partial pressure of inspired oxygen may increase the risk of apparent life threatening events and sudden death in infancy.[1–4] Airway hypoxia can be caused by respiratory tract infection.[5] It may also be caused by a change to a higher altitude[3] and air travel. The partial pressure of inspired oxygen on commercial aeroplanes is only 110 to 130 mm Hg; this corresponds to a fraction of inspired oxygen of 0.15 to 0.17 at sea level.[6] Little is known about the physiological effects of airway hypoxia on respiratory function in infants. In adults acute airway hypoxia has pronounced effects on the control of breathing during sleep,[7] and respiratory control and oxygenation are considered to be more vulnerable to the effects of hypoxia and other insults during infancy. We became interested in the effects of airway hypoxia on respiratory control in infants after two sets of parents attending our outpatient clinic reported that their infants had died of the sudden infant death syndrome after intercontinental flights; one infant had died between 14 and 19 hours after a flight and the other had died between 40 and 41 hours later.

In this study we exposed clinically healthy infants to 15% oxygen in nitrogen to discover the effects of airway hypoxia on arterial oxygenation and on the frequency of isolated and periodic apnoeic pauses. We also wanted to determine if there was a subgroup of infants who would develop potentially significant hypoxaemia during exposure to 15% oxygen.

Subjects and methods

Subjects

Thirty four infants (20 boys) were enrolled in the study. Twenty one were recruited by structured sampling of births at an obstetric unit run by general practitioners and 13 by approaching families who were receiving support in caring for an infant after a previous infant had died of the sudden infant death syndrome. The two groups were matched for age at the time of the study (mean age 3.1 months, SD 1.7 months for the group recruited from the obstetric unit and 1.8 months for the group of infants whose siblings had died of the sudden infant death syndrome). To be enrolled, infants had to have been born at term and have no history of respiratory distress or congenital anomalies; later, one infant was found to have ß thalassaemia minor but it

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was considered inappropriate to exclude him retrospectively. Twelve mothers had smoked during their pregnancies, half of these were mothers of children whose deaths had been ascribed to the sudden infant death syndrome.

In the week before the study no infant had had an illness with fever, but four developed respiratory infections; two additional infants had coughs from previous infections. One infant died suddenly three weeks after the study at age 2 months. Her two older half-siblings had allegedly died of the sudden infant death syndrome. All three deaths were later identified as infanticide.

We had intended to study infants who had undergone apparent life threatening events. The first four infants enrolled after such events, however, had abnormally low baseline values of oxygen saturation in room air and thus could not be subjected to airway hypoxia. Apparent life threatening events in two other infants were found to be due to epilepsy[8] and intentional suffocation.[9] For these reasons we decided to concentrate on infants without a history of apparent life threatening events.

Informed consent

Parents were sent a standard letter which briefly discussed the methods and purpose of the study, including the potential relevance of the research to the mechanism that might be responsible for some deaths from the sudden infant death syndrome. A self addressed envelope and reply form were included. If families were interested in participating they were contacted and arrangements were made to discuss the project in more detail. This happened either at the family's home or by telephone, and when possible both parents were involved. Information was presented to parents on the relation between the administration of 15% oxygen and airline flights, holidays at altitude, and the sudden infant death syndrome.

All parents were aware that an overnight physiological recording of their infant's oxygen saturation and respiratory variables would be done at home before their child was exposed to hypoxic conditions in hospital. Parents were informed that this recording would be analysed to ensure that values were within normal limits before the infant was exposed to 15% oxygen. All parents knew that an experienced paediatrician would be present throughout the infant's exposure to 15% oxygen, and that exposure would end if the infant's oxygen saturation dropped to $\leq 80\%$ for ≥ 1 minute. Where applicable parents were informed that this had been necessary during previous recordings in this study. Parents were aware that they could withdraw their baby from the study at any time without explanation. After this discussion parents were given another information leaflet and were asked to sign a consent form. Each of the families in which exposure to 15% oxygen was ended early because of hypoxaemia of $\leq 80\%$ for ≥ 1 minute was advised against taking their infants on flights or to high altitude until they were older than 12 months. This study was approved by the local research ethics committees.

Measurement of respiratory variables

Three tape recordings were made over two nights for each infant. Signals recorded were oxygen saturation in beat-to-beat mode (N200 pulse oximeter, Nellcor, Hayward, CA), pulse waveforms for validation of the accuracy of saturation measurements, and abdominal breathing movements with a volume expansion capsule placed on the abdominal wall (Graseby Medical, Watford). Recordings were made at 60 to 120 m above sea level. Infants were placed in their normal sleep position (lateral or supine). The first recording (pre-challenge) was made in room air in the infant's home; the results were checked to verify that the infant had normal baseline oxygen saturation values ($\geq 94\%$) before the second recording. The second and third recordings were made in hospital 1 to 4 days later (median 26 h). The second recording (challenge) took place in an oxygen tent[10] into which a medical gas mixture of 15% oxygen in nitrogen (British Oxygen Company, London) was delivered to maintain a monitored fraction of inspired oxygen of 0.15 to 0.16. Respired oxygen and carbon dioxide were monitored by a cannula on the upper lip (Elisa Duo, Engström, Stockholm) to confirm that rebreathing did not occur. Transcutaneous monitoring of the partial pressure of carbon dioxide was done at frequent intervals (Microgas, Kontron Instruments, Watford). Ambient temperature was maintained at 22°C to 26°C. Infants and monitors were observed continuously by an experienced paediatrician. According to our protocol, exposure to hypoxia would end if oxygen saturation fell to $\leq 80\%$ for ≥ 1 minute. After the challenge infants were returned to room air and the third recording (post-challenge) was made throughout the rest of the night.

Recordings were printed and analysed manually by experienced technicians blind to the changes in inspired oxygen. Periods of regular and non-regular breathing patterns were identified[11]; a regular breathing pattern has been shown to be closely related to quiet sleep.[12] Apnoeic pauses lasting ≥ 4 s were identified; these were classified by duration (4 s to 7.9 s, 8 s to 11.9 s, and ≥ 12 s[13]) and by whether they were isolated or appeared in periodic apnoea (episodes of three or more pauses, each separated by < 20 breaths[11]).

Baseline oxygen saturation, heart rate, and respiratory rate were measured only during episodes of a regular breathing pattern.[11] Periods when oxygen saturation fell to $\leq 80\%$ for ≥ 4 s (desaturation) were identified throughout the recordings; these were classified as to whether they were associated with an apnoeic pause.[13] Mean values of transcutaneous partial pressure of carbon dioxide were calculated.

Results are presented as median and range, or mean and standard deviation. Statistical analysis was performed using the Wilcoxon matched pairs test for paired data and the Mann-Whitney U test for the group comparisons. Correlations were assessed by Spearman's rank test.

Results

There was no significant difference in any variable between infants who were recruited from the obstetric unit and those from families in which an infant had previously died of the sudden infant death syndrome. Only two variables, respiratory rate and heart rate, were correlated with age. Results from the pre-challenge, challenge, and post-challenge recordings are shown in the table.

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Results of tests on infants done before, during, and after exposure to 15% oxygen. Values are medians (range)

				P values		
	Pre-challenge	Challenge	Post-challenge	Pre-challenge *v* challenge	Challenge *v* post-challenge	Pre-challenge *v* post-challenge
Measurements:						
Oxygen saturation (%)	97.6 (94.0 to 100)	92.8 (84.7 to 100)	97.5 (90.0 to 100)	<0.001	<0.01	>0.05
Heart rate/min	123 (105 to 140)	131 (107 to 146)	130 (99 to 144)	<0.01	>0.05	<0.05
Respiratory rate/min	30 (21 to 53)	32 (20 to 58)	31 (18 to 55)	>0.05	>0.05	>0.05
Percentage of time spent in regular breathing pattern	27 (0 to 53)	16 (0 to 44)	25 (7 to 83)	<0.001	<0.001	>0.05
No of episodes of desaturation/h	0 (0 to 0.2)	0.4 (0 to 35)	0 (0 to 0)	<0.001	<0.01	>0.05
Apnoea:						
Percentage of time spent in periodic apnoea	0.7 (0 to 31)	2.4 (0 to 35)	0.2 (0 to 11)	<0.001	<0.001	<0.05
Longest episode of periodic apnoea (min)	1.4 (0.9 to 20.5)	4.3 (0.4 to 34.8)	1.4 (0.5 to 4.8)	<0.01	<0.05	>0.05
Isolated apnoeic pauses/h	6.2 (0 to 13)	7.3 (0 to 19)	7.9 (0 to 17)	>0.05	>0.05	>0.05
Percentage of apnoeic pauses ≥8 s	9.0 (0 to 33)	1.8 (0 to 47)	4.9 (0 to 50)	<0.001	<0.05	>0.05

The mean duration of the pre-challenge recordings was 7.7 (SD 2.1) hours. Data from these recordings were similar to data already reported.[13 14] Baseline oxygen saturation was ≥94% in all infants, and only one infant had episodes of desaturation (three episodes, longest duration 11 s).

The mean duration of the recordings during the challenge was 6.3 (SD 2.9) hours. When compared with pre-challenge values, oxygen saturation during the challenge was lower (median difference −4.9%); this drop was highly variable (range −9.3% to 0.7%). Respiratory rates did not change significantly, but heart rates were 8 beats per minute higher ($P<0.01$); both rates were inversely correlated with age. Mean partial pressures of carbon dioxide during the challenge were within the normal range at 5.0 (SD 0.6) kPa. There was a significant decrease in the proportion of time spent in the regular breathing pattern, and a 3.5-fold increase overall in the proportion of time spent in periodic apnoea ($P<0.001$). There was a weak positive correlation between baseline oxygen saturation and amount of time spent in periodic apnoea ($r_s=0.44$, $P<0.01$) during challenge. The frequency of isolated apnoeic pauses did not change significantly. Pauses tended to be shorter than during pre-challenge recording, with a decrease from 9.0% to 1.8% in the proportion lasting ≥8 s; none of the apnoeic pauses lasted ≥20 s.

There was a significant increase in the number of times desaturation occurred per hour during hypoxia ($P<0.001$); 21 out of 34 (62%) recordings had episodes of desaturation. A median of 96% of episodes of desaturation (range 16% to 100%) were associated with apnoeic pauses and were short (median average duration 5.0 s, range 4.0 s to 7.2 s). The median of the average of the lowest oxygen saturation value occurring during desaturation was 72% (67% to 76%).

The mean duration of the post-challenge recordings was 4.5 (SD 1.9) hours. All variables returned to pre-challenge values except for heart rate (which remained significantly raised) and the proportion of time spent in periodic apnoea (which was significantly reduced). Exposure to hypoxia was ended early in six infants. Analysis of the recordings showed that for four of the six the decision to end exposure early was appropriate. Oxygen saturation had been ≤80% for ≥1 minute in three infants. Oxygen saturation had been ≤80% for only 45 seconds in another infant but it had been <60% for two thirds of the time. Oxygen saturation values in the other two infants could not be interpreted because of movement artefact; a decision to withdraw these two infants from exposure to hypoxia was therefore inappropriate. However, while watching the monitoring the mother of one of these infants requested that her baby be returned to room air.

Withdrawal occurred after 1.9 to 5.2 hours (median 3.1 h) of hypoxic exposure in the four infants for whom it was appropriate; none of the infants woke spontaneously during their prolonged hypoxaemia. They were clinically well after withdrawal, although one received low flow oxygen (fraction of inspired oxygen 0.28) for the next hour to maintain oxygen saturation ≥94%. None had recently had a respiratory illness; one was the sibling of an infant who had died of the sudden infant death syndrome. Their ages were similar to those of the complete sample. Three of the four, however, had had low baseline values of oxygen saturation during the challenge; they were three of the six infants in the complete sample who had values <90% during the challenge. The fourth did not have any periods of a regular breathing pattern during the challenge so baseline values could not be measured. None of the four infants who were withdrawn from exposure had prolonged apnoeic pauses on their recordings.

Discussion

Main findings and limitations of the study

These healthy 1 to 6 month old infants had highly variable and unpredictable responses to acute airway hypoxia; some infants became hypoxaemic to such a degree that their exposure to hypoxia was ended.

Some limitations of this study should be considered. We gave priority to describing the effects of several hours of acute airway hypoxia on sleeping infants, rather than to identifying the mechanisms of the observed responses. We tried to interfere as little as possible with the infants' normal sleep patterns and decided against recording electroencephalograms, electro-oculograms, or quantifying ventilation. This prevented us from collecting precise information about the reasons why some infants developed severe hypoxaemia when exposed to 15% oxygen. Possible explanations include hypoventilation[15] or increased inequalities between ventilation and perfusion.[16] We do not know why the infants who became severely hypoxaemic did not wake up. We do not know whether our experimental conditions are identical to those of air

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Key messages

- A reduction in inspired oxygen concentration to 15% can induce severe prolonged hypoxaemia in a small proportion of infants
- Prediction of which infants will become hypoxaemic does not appear possible from analysing oxygenation or the respiratory pattern of infants breathing room air at sea level
- The way in which an infant responds to airway hypoxia may contribute to understanding the relation between respiratory infections, hypoxaemic episodes, and the sudden infant death syndrome
- Airline travel and holidays at high altitude may result in hypoxaemia in a small proportion of infants

travel and its effect on respiratory responses in infants. However, we could not find any data to suggest that there is a difference between a reduction in alveolar oxygen pressure due to reduced barometric pressure or due to a reduced fraction of inspired oxygen during constant atmospheric pressure. To address these issues infants would have to be studied during an airline flight or at high altitude.

Previous studies and possible relevance of these findings to the sudden infant death syndrome

Median values of baseline oxygen saturation during exposure to 15% oxygen in nitrogen in this study were similar to values measured by Lozano et al in 189 infants and young children born and living at 2640 m (93.3%, SD 2.1).[17] The range of values found in the study of Lozano et al was much narrower than the range found in our study. This difference in interindividual variability in baseline values may have occurred because the infants studied by Lozano et al might have been both genetically and environmentally adapted to airway hypoxia, whereas our infants were not. This idea is supported by the results of a study done in Lhasa (altitude 3660 m) which found that indigenous Tibetan infants had mean oxygen saturation values of 87% to 88% during sleep, while Chinese infants, who had recently moved to the region, had values of only 76% to 80%.[3] The lack of a genetic adaptation to high altitude has been proposed as the most likely cause for the disproportionately high rate of sudden deaths in infants soon after they have been moved to higher altitude.[3 4] High interindividual variability in the respiratory response to airway hypoxia may also explain why a proportion of infants with respiratory tract infections have low baseline values of oxygen saturation or an excessively high number of hypoxaemic episodes, or both.[5]

There was no difference in the response to airway hypoxia in infants with a sibling whose death had been ascribed to the sudden infant death syndrome or in infants without such a family history. This is in accordance with other studies which failed to find evidence for a disturbance in respiratory control or function in the siblings of infants who had died of the sudden infant death syndrome,[18 19] and reinforces doubts about the appropriateness of using such infants for investigations into the pathophysiology of the syndrome.

The most frequent cause of airway hypoxia in infants is respiratory infection (particularly bronchiolitis). We and others have shown that a small proportion of infants with such infections may progress to developing life threatening hypoxaemic episodes.[5 20] Respiratory infections have also been linked with the sudden infant death syndrome in a number of studies.[21]

Ethical issues

Was it ethically justified to expose healthy infants to 15% oxygen? Many infants travelling on aeroplanes or to holidays at high altitude are exposed to similar or even more markedly reduced partial pressures of inspired oxygen. Yet this exposure is considered safe. We were aware of anecdotal evidence of a small number of cases of the sudden infant death syndrome occurring after air travel, and of the observations made in Tibet.[4] We considered that information on this important issue should ideally have been gathered before infants were permitted to travel by air. We found no evidence that such studies had been done. Information collected by British Airways showed that one infant had died during a flight from Hong Kong to Britain (NJ Byrne, personal communication). Our protocol was designed to allow us to identify immediately any potentially harmful degree of hypoxaemia, hypoventilation, or effects on cardiac rhythm; infants were observed continuously by an experienced paediatrician who followed strict guidelines on when to end an infant's exposure to hypoxia. We must also emphasise that although the siblings of infants whose deaths had been ascribed to the sudden infant death syndrome were already being monitored at home, the majority of the infants in this study had not been seen in our clinic before the study. Their families were, therefore, unlikely to feel conscious or unconscious pressure to comply with our request for participation.

Clinical implications

We have shown that a small number of infants may become hypoxaemic during several hours of exposure to a fraction of inspired oxygen of 0.15 to 0.16. We could not, for ethical and humanitarian reasons, determine whether this would have progressed to clinically apparent cyanotic episodes if exposure had continued. Unfortunately, there was no physiological or clinical variable in this study which would help identify infants who might develop clinically important hypoxaemia during later exposure to airway hypoxia. We believe that additional research is urgently needed into the effects on infants of prolonged airline flights or holidays at high altitude. Our findings may contribute to an understanding of the possible relation between respiratory infection with resulting airway hypoxia and some sudden deaths in infancy.

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Contributors: DPS formulated the hypothesis and obtained funding for the study, he is also guarantor for the study. CFP, VAS, and DPS designed the protocol. DPS supervised the collection of clinical data which was largely collected by KJP and LMO. Parents were informed and supported by KJP. CFP, VAS, and LMO prepared the data and did the statistical analysis. CFP led the writing of the paper with the involvement of all authors. KJP produced the first draft of the paper.

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Conflict of interest: None.

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Commentary: Safety of participants in non-therapeutic research must be ensured

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When retrospectively evaluating research what matters is not the harm that actually resulted from the research, but the risk to which researchers exposed participants when all the knowledge available at the time is taken into account. At least five questions are relevant to this discussion.

Was there known to have been a risk to participants before the study began, and what was the magnitude of that risk as evaluated by the evidence available at the time?

There was evidence that a reduction in the pressure of inspired oxygen might be causally related to sudden infant death [1] at the time Parkins and colleagues began their study. Is it reasonable to impose a risk of death on healthy infants to gain more knowledge about physiological responses to hypoxia? It could be argued that monitoring procedures removed this risk. Even if the study design were perfect, the chance of human and mechanical error[2] could not be entirely removed.

This study is an example of non-voluntary, non-therapeutic research. It is generally accepted that the risk posed to participants by such research must be minimal.[3 4] The Royal College of Physicians suggests that participants in this type of research should be exposed to no more risk than that taken by a passenger flying on an aeroplane.[3] Indeed, the justification presented by the researchers for exposing normal infants to hypoxia is that "[m]any infants travelling on aeroplanes or to holidays at high altitude are exposed to similar or even more markedly reduced partial pressures of inspired oxygen. Yet this exposure is considered safe."

There are several problems with this argument. In the first place, researchers may have access to information which is not available to the public. Flying in an aeroplane may be more dangerous for some people—for example, those with emphysematous bullae. If an airline or responsible authority was unaware of the risks to travellers with emphysema they might allow them to travel on aeroplanes without restrictions. However, this would not provide justification for an interventional study which exposed these travellers to lower air pressures.

In the second place, even when information on risk is available some people behave recklessly; it would be opportunistic for researchers to take advantage of such behaviour. A prospective interventional study of behaviour during actual drink driving would be unethical even if resuscitation were available and there were no shortage of willing participants.

There is a related problem that occurs when judgments about the reasonableness of risk are based on assumptions drawn from behaviour. People judge that some risks are worth taking, but it is up to them to make that evaluation. Though driving a car or flying in an aeroplane does entail risk, it is wrong to assume that a person would take on this risk to participate in research. This is illustrated by the public's reaction to the scandal surrounding bovine spongiform encephalopathy. People may choose not to engage in an activity with a very small risk of death if they perceive that the benefits are outweighed by the risks. Were the parents in this study explicitly told that participation entailed a small risk to their infant's life? Participants must be scrupulously informed of such risks.

Standards of practice cannot be used to define the appropriate level of safety that should be provided to participants in research. We should look to the inherent risk. There are some concerns raised by this study by Parkins et al. Firstly, why was a saturation of ≤80% for

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≥1 minute chosen as the criterion for ending exposure to hypoxia, and what evidence is there that it is safe to expose infants to hypoxia? Hypoxia was clearly clinically significant in some infants who were described as becoming "severely hypoxaemic." Indeed, one required supplemental oxygen for 1 hour.

Secondly, the methods section states: "Infants and monitors were observed continuously by an experienced paediatrician. According to our protocol, exposure to hypoxia would end if oxygen saturation fell to ≤80% for ≥1 minute." The results section states: "Oxygen saturation had been ≤80% for ≥1 minute in three infants." It is not clear from the protocol whether there was a definite upper limit to the time an infant might spend at an oxygen saturation below 80%. How long had oxygen saturation been ≤80% in these infants?

Thirdly, part of the reason for performing this study was because the researchers became aware of two infants who had died after travelling on an intercontinental flight. Why then did the follow up of infants exposed to hypoxia last only about 10 hours, given that one infant died 40 hours after travelling by aeroplane?

Should any non-human or epidemiological research, systematic overview, or computer modelling have been done before the study to better estimate the risk to participants or to eliminate the need to use human participants?

Piglets have been used as models for the physiological response of infants to hypoxia.[1]

Could the risk have been reduced in any other way?

Researchers could have asked parents of infants who were scheduled to travel on aircraft if their infants could participate. This increases the infants' risk by increasing their total exposure to hypoxia, but these infants and their parents would have the most interest in the results of the study. The results might have been relevant: parents of those infants who tolerated hypoxia poorly might have decided not to expose their infant to the risk of air travel.

Were the potential benefits of this study worth the risks? Was the study design adequate to increase understanding of responses to hypoxia in infants in aircraft and at high altitude?

The authors assert that there is nothing to suggest that a reduction in the fraction of inspired oxygen in reduced barometric pressure (as occurs in an aeroplane) does not have the same effect as a reduction in the fraction of inspired oxygen in constant atmospheric pressure (as in their experiment). Yet they admit that further study during an airline flight or at high altitude (or presumably in a hypobaric chamber) will be necessary. This raises a question about the design of their study: why wasn't the study done under the conditions described above instead of exposing some infants to risk in what must be described as a preliminary study?

Were the infants' parents made aware of all the relevant evidence, in particular evidence of the extent of the risk to the infants, and could the parents decide freely to participate or not based on the evidence of risk?

Concerns were expressed by the editorial committee before the paper was accepted for publication that because some parents already had a therapeutic relationship with the authors they might feel conscious or unconscious pressure to participate in the study. This is a difficult issue to evaluate because potential participants who are in a therapeutic relationship with the investigators may have the most to gain from a study and may have the strongest desire to participate for reasons of rational self interest or altruism. However, the Declaration of Helsinki requires that "informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship."[5]

I have raised concerns in this commentary over whether the risk to the infant was fully disclosed to parents. Doctors should now have serious concerns about infants being exposed to even mild hypoxia. The study by Parkins et al addresses an important issue and will no doubt add to the information available on the effects of hypoxia on infants. A balance must always be struck between discouraging relevant research which might eliminate continuing harm and making that research as safe and ethical as possible.

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3 Royal College of Physicians. *Research on healthy volunteers: a working party report*. London: RCP, 1986.
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Commentary: Ethical approval of study was warranted

Vivian Hughes

Research Ethics Committee, North Staffordshire Royal Infirmary, Stoke on Trent ST4 6QG

Vivian Hughes, *chairman*

When the research ethics committee first reviewed the project proposed by Parkins and colleagues our immediate reaction was to reject the proposal because of fears about the possible danger to infants involved in the study. After our initial discussion, however, we recognised that the study might provide important information, not only on the sudden infant death syndrome but also on the safety of air travel for infants. It was also clear that the study could not be done on participants other than infants. We decided to invite Professor Southall to attend a committee meeting to respond to our concerns about doing non-therapeutic research on infants. The potential for risk had been made clear in the original submission; we hoped that Professor Southall would provide further information on the degree of risk that it was anticipated that infants would be exposed to.

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Professor Southall attended the meeting on the 26 August 1992. After the meeting, committee members were convinced of the importance of the study, and reassured about the degree of monitoring and supervision that would occur during the infants' exposure to hypoxia. We were assured that exposure would end immediately if a baby became ill or experienced an unacceptably long period of apnoea or hypoxia and that appropriate treatment would be given if required. It was also established that parents would be informed of the nature and potential risks of the study in easily understood terms and that no coercion would be used to persuade parents to allow their infants to participate in the study.

The initial protocol indicated that only families in which an infant had died of the sudden infant death syndrome or in which an infant had had an apparent life threatening event would be asked to participate. We were later requested to permit the inclusion of a control group of healthy infants who had no known risk factors. This caused further heart searching debate, but we accepted that these healthy infants would be at less risk than those from families in which an infant had previously died of the sudden infant death syndrome or had had an apparent life threatening event; the control group was also exposed to less danger than a young child would be on a transatlantic flight. The committee was satisfied that all parents would be approached in a sympathetic manner and that requests for participation would include contacting the family's general practitioner.

Committee members were fully aware of the strict guidelines on the involvement of children in non-therapeutic research. We were also concerned about the potential for harm. However, after a final discussion, and after scrutinising the modified parent information and consent forms, we were convinced that the study should be allowed to proceed. We also feel that we would make the same decision today.

Authors' reply

K J Parkins, C F Poets, L M O'Brien, V A Stebbens, D P Southall

We considered that many healthy infants are exposed to airway hypoxia without apparent difficulties while travelling on airline flights or during holidays at high altitude when we assessed the risks that infants between the ages of 1 and 6 months would be exposed to in our study. It is not thought of as reckless to take infants on aeroplanes or on holidays at high altitude; no guidelines state that healthy infants should not be exposed to these activities.

Reviewing the literature in 1992 we found that non-indigenous infants born at altitude were at an increased risk of sudden death and mountain sickness.[1] We had also undertaken[2] and were aware of studies[3] linking airway hypoxia to apparent life threatening events. We also knew of two infants who had died of the sudden infant death syndrome shortly after an airline flight. We thought that by studying healthy infants in an environment of controlled hypoxia we might be able to elucidate issues relevant to the sudden infant death syndrome, apparent life threatening events, and the effects of respiratory infection. We did not believe that this information could be obtained through animal experiments (such as those mentioned in the commentary by Savulescu; these were published 3 years after our study began).

Research on children with cystic fibrosis has shown that hypoxia at sea level can accurately predict oxygen saturation during air travel.[4] Other studies have examined oxygen saturation at high altitude but mainly in indigenous populations which have a genetic adaptation to living in hypoxic conditions.[5] We considered performing our study in a hypobaric chamber but felt that this would cause difficulties in monitoring the infants, and might increase the risks to the infants because of difficulties in access.

Asking parents of infants who were scheduled to fly on aircraft to participate in the study might have created alarm or anxiety in parents before any results were known. Access to information about infants who are scheduled to fly is protected and difficult or impossible to obtain.

The facts about the study and its risks were presented clearly to the families. Parents were initially contacted by letter from a doctor who was not involved in their clinical care (KJP). They were invited to contact us for further information using a prepaid envelope. A more detailed discussion with a member of the research team then occurred and the parents were given written information. If they agreed to participate, consent was obtained. All parents were aware that there was a potential risk of their infant's blood oxygen saturation falling during exposure to 15% oxygen. They knew that their baby would be closely monitored by an experienced paediatrician and that if blood oxygen saturation fell below a threshold value the exposure would be ended. Before consenting to participate and when appropriate, families were informed that a proportion of infants studied earlier in the project had had episodes of desaturation when exposed to 15% oxygen. The families of those infants who had episodes of desaturation during our study were advised against taking the infant on an aeroplane or to high altitude until the infant was older; this is a potential benefit of being included in the study. All families knew that we had concerns about the safety of infants during airline travel; they knew that these concerns included a small risk of sudden death. Parents knew that they could withdraw their child from the study at any time without needing to justify their decision.

The degree of airway hypoxia that is safe for infants to be exposed to is unknown. We considered known baseline oxygen saturation levels at altitude[6] and normal ranges for episodes of desaturation in healthy infants[7] to guide us somewhat empirically in choosing a threshold value of oxygen saturation of $\leq 80\%$ for ≥ 1

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minute. Airway hypoxia was discontinued as soon as possible in each infant who showed this degree of desaturation; it should be remembered that this required the tent to be opened and the gas mixture to be removed from around the baby. No infant remained at ≤80% in 15% oxygen for longer than 126 seconds.

Of the four infants in whom exposure to hypoxia was discontinued early, one infant had a sibling who had died of the sudden infant death syndrome and was already being monitored at home. Oxygen saturation levels in all four infants remained within the normal range during subsequent monitoring. We believed that monitoring the infants for a longer period in hospital would not have been ethically appropriate because they might be exposed to additional risks (for example, the risk of acquiring an infection in hospital). The two infants who had died following an aircraft flight were not monitored so we are unaware of the duration and degree of hypoxaemia to which they might have been exposed.

Although Savulescu's commentary raises the spectre of human or mechanical error, we took every precaution to ensure that the infants were safe. These included the use of a special medical gas mixture of 15% oxygen and 85% nitrogen instead of air diluted with nitrogen, continuous monitoring of the partial pressure of inspired carbon dioxide to identify rebreathing, and continuous monitoring of the partial pressure of inspired oxygen to ensure adequate ventilation of the tent with the gas mixture. The study was done in a room near the intensive care unit. There was also continuous surveillance by an experienced paediatrician of the readings from the pulse oximeter, transcutaneous monitoring of the partial pressure of carbon dioxide, monitoring of respiratory movement, and electrocardiography.

Although Milner reports in his editorial that British Airways identified no deaths on the undisclosed number of flights involving infants, this is low quality information. It is not accurate, as shown by the personal communication cited in our paper. Infant stimulation and the attention paid to an infant during an airline flight may delay potentially serious consequences of the flight until after the plane's arrival. British Airways would not have access to information on infants after arrival and did not seem to know about either of the two cases of the sudden infant death syndrome that were described in our report.

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Lowering blood homocysteine with folic acid based supplements: meta-analysis of randomised trials

Homocysteine Lowering Trialists' Collaboration

Participants in the collaboration are listed at the end of the paper

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Abstract

Objective: To determine the size of reduction in homocysteine concentrations produced by dietary supplementation with folic acid and with vitamins B-12 or B-6.

Design: Meta-analysis of randomised controlled trials that assessed the effects of folic acid based supplements on blood homocysteine concentrations. Multivariate regression analysis was used to determine the effects on homocysteine concentrations of different doses of folic acid and of the addition of vitamin B-12 or B-6.

Subjects: Individual data on 1114 people included in 12 trials.

Findings: The proportional and absolute reductions in blood homocysteine produced by folic acid supplements were greater at higher pretreatment blood homocysteine concentrations ($P<0.001$) and at lower pretreatment blood folate concentrations ($P<0.001$). After standardisation to pretreatment blood concentrations of homocysteine of 12 μmol/l and of folate of 12 nmol/l (approximate average concentrations for Western populations), dietary folic acid reduced blood homocysteine concentrations by 25% (95% confidence interval 23% to 28%; $P<0.001$), with similar effects in the range of 0.5-5 mg folic acid daily. Vitamin B-12 (mean 0.5 mg daily) produced an additional 7% (3% to 10%) reduction in blood homocysteine. Vitamin B-6 (mean 16.5 mg daily) did not have a significant additional effect.

Conclusions: Typically in Western populations, daily supplementation with both 0.5-5 mg folic acid and about 0.5 mg vitamin B-12 would be expected to reduce blood homocysteine concentrations by about a quarter to a third (for example, from about 12 μmol/l to 8-9 μmol/l). Large scale randomised trials of such regimens in high risk populations are now needed to determine whether lowering blood homocysteine concentrations reduces the risk of vascular disease.

Introduction

Epidemiological studies have consistently reported that patients with occlusive vascular disease have higher blood homocysteine concentrations than

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