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Apparent hypoxic changes in pulmonary arterioles and small arteries in infancy

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SUMMARY The pulmonary arterioles and small arteries were studied and their musculature and its nuclei were quantified in 90 neonates, infants, and young children who had suffered from a variety of clinical and hypoxic conditions immediately before death. Among the 90 cases investigated in this study, 30 were of sudden infant death syndrome (SIDS). No evidence was found to support the view that cases of SIDS are subjected to chronic hypoxia before death as significantly more medial muscle tissue in the pulmonary arterioles and small arteries was found in the chronic hypoxic group compared to the SIDS, non-hypoxic, and acute hypoxic groups. Furthermore, there was no statistically significant difference in the amount of medial muscle tissue of the pulmonary vessels as between the SIDS, non-hypoxic, and acute hypoxic groups. With other signs of acute hypoxia found at the necropsy of SIDS, the results of this study could be considered to support the view that cases of SIDS succumb as a result of an acute episode of hypoxia, or possibly repeated short-duration episodes of acute hypoxia which do not produce pulmonary vascular changes.

Some signs indicating a terminal hypoxic episode have been found in cases of the sudden infant death syndrome (SIDS). These include intrathoracic petechial haemorrhages in the lungs, heart, and thymus. Nevertheless the actual cause of such a hypoxic episode is still speculative. One of the current theories concerning the aetiology of the SIDS is that of Steinschneider (1974). He has suggested that in many cases of sudden infant death there are episodes of prolonged sleep apnoea and while such episodes may be a normal physiological phenomenon, gradually becoming less frequent and completely disappearing within the first year of life, it is possible that such an episode of apnoea may become so prolonged as to cause the death of the child by hypoxia.

Naeye, in 1973, looked for evidence of chronic hypoxia in the lungs of cases of SIDS and in control infants. He reported a pulmonary arteriole abnormality commonly associated with chronic alveolar hypoxia. This took the form of hypertrophy and hyperplasia of the smooth muscle fibres in the small pulmonary vessels. He compared the findings in children living at high altitudes with those living at sea level, working on the assumption that those who lived at high altitudes comprised a chronic hypoxic control group and those who lived at sea level comprised a non-hypoxic control group.

During the past three years in Newcastle upon Tyne we have attempted to measure the size of the small pulmonary vessels in a series of infants, including a group of SIDS cases, and to quantify and compare the degree of hypertrophy or hyperplasia which may or may not be present.

Material and methods

Lung sections were taken from 90 infants and young children. These included 30 cases of the SIDS. The criteria for diagnosis of SIDS were the sudden death of an infant which is unexpected by history, that is, the infant was in apparently good health or gave a history of minor illness immediately before death, and in whom there is no clear and acceptable cause of death at the time of necropsy.

The remaining 60 cases were divided into four groups. Group 1 comprised 15 infants who died as a result of acute respiratory illness of less than one week's duration and were presumably subjected to acute hypoxia during their terminal illness. Within this group were cases of acute bronchiolitis and acute lobular pneumonia. Group 2 comprised 15

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infants who had suffered from a chronic respiratory disease of more than three weeks' duration either as a result of a chronic respiratory infection or associated with congenital heart disease. It was presumed that these cases had suffered from chronic hypoxia during the course of their illness. Group 3 comprised 15 infants who died suddenly from non-respiratory causes such as accident, homicide, etc. This group was presumably not subjected to any significant degree of hypoxia before death. Group 4 comprised neonates who died during the first months of life. In addition to the previously mentioned groups, the study also included five stillborn cases.

In each case between four and six blocks were taken from both lungs; four sections from each block were cut at 5-micron intervals and one of these sections was stained with haematoxylin and eosin. The remaining three sections were stained with special stains, namely, Masson trichrome, Verhoff van Gieson, and Biebrich scarlet with haematoxylin.

Only pulmonary arterioles and small arteries were studied. Only those arteries and arterioles cut in transverse section and in the neighbourhood of a bronchiole were selected for measurement. Pulmonary arterioles were taken to include pulmonary arterial vessels of less than 100 microns in external diameter (Harris and Heath, 1962; Heppleston, 1975), while the pulmonary small arteries included pulmonary arterial vessel of more than 100 μ but less than 200 μ in external diameter. Ten pulmonary arterioles and 10 pulmonary small arteries were studied in each case. The combination of both pulmonary arterioles and small arteries were studied together and will be referred to as group A, ie, from the smallest pulmonary arterioles up to 200 μ arteries.

The medial muscular area (MA, Fig. 1) was calculated in each pulmonary vessel and studied under constant magnification of × 600 using the equation:

$$MA = \pi(b^2 - a^2)$$

where a = radius of internal elastic lamina

and b = radius of external elastic lamina.

The number of medial muscular nuclei (N) was counted in each blood vessel under study. This number was presumed to represent the number of medial muscle cells in each cross section of pulmonary vessel. Then the medial muscular area (MA) was divided by the number of medial muscular nuclei (N) to diminish the error in calculating MA due to the contraction and dilatation of the pulmonary arterioles and arteries. In addition the ratio MA/N was used as a measure of the size of an arteriole/arterial medial muscle cell.

Results

The age and sex distribution of the groups studied are shown in Table 1. The general lung histology of the SIDS cases has been reported elsewhere (Kendeel, 1976). In the four control groups, the lung histopathology was consistent with the clinical and necropsy findings.

There was no thromboembolic disease or intimal proliferation, infiltration, fibrous/fibroelastic hyperplasia or 'plexiform lesion formation'. There were no changes suggestive of necrotising arteritis or generalised pulmonary haemosiderosis. Such results would indicate a mild degree of pulmonary hypertension resulting from congenital heart diseases in cases studied within the chronic hypoxic group.

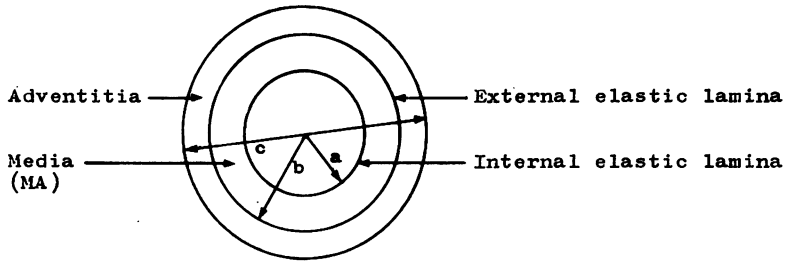

Fig. 1 *Measurements used to calculate the medial musculature in pulmonary arterioles and small arteries.*

a = Radius of internal elastic lamina

b = Radius of external elastic lamina

c = The external diameter of the blood vessel

$MA = \pi (b^2 - a^2)$

Table 1 *Age and sex distributions in the five clinical situations in which the pulmonary arterial and arteriolar media were compared*

Group	*Total*	*Male*	*Female*	*Age (Mean ± SE)*
SIDS	30	12	18	6 weeks – 9 months 4·15 ± 0·4 months
Non-hypoxic	15	6	9	5 weeks – 22 months 5·07 ± 1·42 months
Acute hypoxic	15	8	7	1 month – 24 months 7·42 ± 1·85 months
Chronic hypoxic	15	7	8	1 month – 24 months 6·49 ± 1·96 months
Neonatal	15	8	7	13 hours – 15 days

In each group investigated there were significantly more medial muscle cells in the pulmonary small arteries than in the pulmonary arterioles, and the mean of the size of the medial muscle cells was significantly greater in the small arteries than in the arterioles (Tables 2 and 3; Fig. 2). There was no

Table 2 *Means of the numbers of medial nuclei in small pulmonary arterioles and arteries*[1] ± *standard error*

Group	*Total*	*Arterioles*	*Arteries*	*A*
SIDS	30	13·86 ± 0·35	21·01 ± 0·60	17·45 ± 0·41
Non-hypoxic	15	14·46 ± 0·44	19·42 ± 0·74	16·93 ± 0·53
Acute hypoxic	15	13·83 ± 0·73	18·87 ± 0·62	16·35 ± 0·57
Chronic hypoxic	15	13·98 ± 0·65	22·36 ± 1·44	18·23 ± 0·80
Neonatal	15	10·15 ± 0·36	18·78 ± 0·56	14·47 ± 0·32

[1]Pulmonary arterioles up to 100 μ in external diameter.
Small pulmonary artery: more than 100 μ but less than 200 μ in external diameter.
A = Pulmonary arterioles and small arteries combined, ie, arterial vessel from the smallest arteriole up to 200 μ pulmonary artery

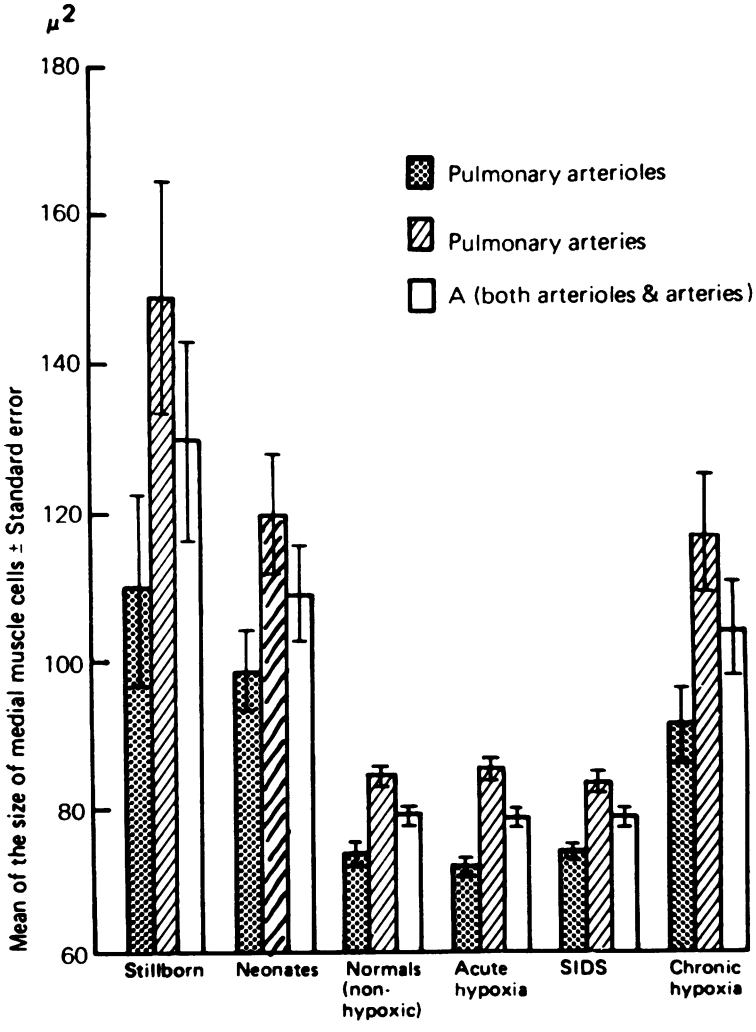

Fig. 2 *Mean of the size of medial muscle cells ± standard error in pulmonary arterioles, small arteries, and both (A) in six clinical situations.*

Table 3 *Statistical comparison between pulmonary arterioles and small arteries[1] in each group studied*

	Neonatal (15 cases)	*Non-hypoxic (15 cases)*	*Acute hypoxic (15 cases)*	*Chronic hypoxic (15 cases)*	*SIDS (30 cases)*
Number of medial nuclei	$t = 12{\cdot}66$ df = 28 $P < 0{\cdot}001$	$t = 5{\cdot}79$ df = 28 $P < 0{\cdot}001$	$t = 5{\cdot}17$ df = 28 $P < 0{\cdot}001$	$t = 5{\cdot}71$ df = 28 $P < 0{\cdot}001$	$t = 10{\cdot}21$ df = 58 $P < 0{\cdot}001$
Size of medial muscle cells	$t = 2{\cdot}12$ df = 28 $P < 0{\cdot}05$	$t = 6{\cdot}02$ df = 28 $P < 0{\cdot}001$	$t = 7{\cdot}44$ df = 28 $P < 0{\cdot}001$	$t = 2{\cdot}97$ df = 28 $P < 0{\cdot}01$	$t = 6{\cdot}16$ df = 58 $P < 0{\cdot}001$

[1]Pulmonary arteriole: up to 100 μ in external diameter.
Pulmonary small artery: less than 200 μ but more than 100 μ in external diameter.

Table 4 *Comparison of pulmonary arteriolar muscle cell size in five different clinical situations*

	Neonatal	*Non-hypoxic*	*Acute hypoxic*	*Chronic hypoxic*	*SIDS*
Neonatal	—	$t = 4{\cdot}33$ df = 28 $P < 0{\cdot}001$	$t = 4{\cdot}70$ df = 28 $P < 0{\cdot}001$	$t = 0{\cdot}94$ df = 28 $P < 0{\cdot}1$	$t = 4{\cdot}29$ df = 43 $P < 0{\cdot}001$
Non-hypoxic	$t = 4{\cdot}33$ df = 28 $P < 0{\cdot}001$	—	$t = 0{\cdot}96$ df = 28 $P\ 0{\cdot}1$	$t = 3{\cdot}75$ df = 28 $P < 0{\cdot}001$	$t = 0{\cdot}37$ df = 43 $P\ 0{\cdot}5$
Acute hypoxic	$t = 4{\cdot}70$ df = 28 $P < 0{\cdot}001$	$t = 0{\cdot}96$ df = 28 $P\ 0{\cdot}1$	—	$t = 4{\cdot}20$ df = 28 $P < 0{\cdot}001$	$t = 1{\cdot}5$ df = 43 $P\ 0{\cdot}1$
Chronic hypoxic	$t = 0{\cdot}94$ df = 28 $P\ 0{\cdot}1$	$t = 3{\cdot}75$ df = 28 $P < 0{\cdot}001$	$t = 4{\cdot}20$ df = 28 $P < 0{\cdot}001$	—	$t = 3{\cdot}71$ df = 43 $P < 0{\cdot}001$
SIDS	$t = 4{\cdot}29$ df = 43 $P < 0{\cdot}001$	$t = 0{\cdot}37$ df = 43 $P\ 0{\cdot}5$	$t = 1{\cdot}5$ df = 43 $P\ 0{\cdot}1$	$t = 3{\cdot}71$ df = 43 $P < 0{\cdot}001$	—

significant correlation between the age and the number or size of medial muscle cells of the pulmonary vessels examined in any group under study. The size of the medial muscle cells of the pulmonary arterioles was significantly greater in the neonatal and chronic hypoxic groups than in the non-hypoxic, acute hypoxic, and SIDS groups, and there was no significant difference between the SIDS, non-hypoxic, and acute hypoxic groups (Table 4). Similarly, there was no significant difference between the neonatal and chronic hypoxic groups. A similar significant grouping of changes was noted when the size of medial muscle cells in the pulmonary small arteries was calculated; namely, there was a significant difference between those of the neonatal and chronic hypoxic groups and those of the non-hypoxic, acute hypoxic, and SIDS groups.

Discussion

It has been reported that infants are usually born with both thick pulmonary arterioles and thick small arteries (Dammann and Ferencz, 1956; Wagenvoort, 1960; Harris and Heath, 1962). Dammann and Ferencz (1956) recorded that the small pulmonary arteries of the newborn have thick media and adventitia and they have small lumens and appear similar to systemic vessels. Within a few months a relative and absolute thinning out of the pulmonary vascular wall and widening of the lumen occurs. As a result of these pulmonary vascular changes there is a progressive decrease in pulmonary arterial resistance so that a low arterial pressure is adequate to perfuse the lungs.

A similar conclusion can be reached from our results. These confirm the presence of a thick media in the pulmonary arterioles and small arteries in stillbirths and newborn infants, and our data suggest that this relatively thick media is mostly due to the large size of medial muscle cells rather than to a large number of medial muscle cells. The gradual thinning of the wall of the pulmonary arterioles and small arteries which takes place in infancy appears to be due to atrophy of individual medial muscle cells, while no significant reduction in the number of medial muscle cells in these pulmonary vessels can be demonstrated.

Chronic hypoxia is known to cause muscularisation of pulmonary arterioles and probably causes hypertrophy of medial muscular tissue in larger pulmonary arteries in adults (Wagenvoort, 1960; Harris and Heath, 1962; Hasleton *et al.*, 1968; Naeye, 1968, 1973). In infants and young children this study shows that chronic hypoxia causes thickening of the muscular media of pulmonary arterioles and small arteries. Such thickening might be the result of either

the slowing or even the cessation of the normal thinning of pulmonary arteriolar and arterial walls in infancy, or an absolute hypertrophy of individual medial muscle cells, or both.

This study did not show any significant difference in the amount of medial muscular tissue of the pulmonary arterioles and small arteries between the SIDS, non-hypoxic, and acute hypoxic groups. But it did show a significant difference in the amount of medial muscular tissue of those pulmonary vessels between the chronic hypoxic group and the SIDS, non-hypoxic, and acute hypoxic groups. Such results tend to rule out the suggestion that cases of SIDS have been subjected to chronic hypoxia before death but do not exclude the possibility of single or repeated short-duration episodes of acute hypoxia before death.

Accordingly, our results are in disagreement with the general conclusions of Naeye (1973). Nevertheless they do not invalidate the general conclusions of Steinschneider (1972, 1974) with respect to repeated short episodes of sleep apnoea.

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