Myocardial ischaemia in infancy and childhood

C. L. BERRY

*From The Institute of Child Health and The Hospital for Sick Children,
Great Ormond Street, London*

SYNOPSIS Examination of 135 consecutive necropsy specimens has shown that ischaemic myocardial injury is not uncommon in infancy and childhood. The extent of the myocardial change has been assessed by a technique of staining with acid fuchsin, first described by Selye (1958). The significance of the findings is discussed.

Histological changes are slow to develop in myocardial ischaemia, and studies by Jennings, Sommers, Smyth, Flack, and Linn (1960) have shown that almost all the severely ischaemic muscle cells are dead several hours before histological evidence of necrosis is present. Although Jennings, Sommers, Kaltenbach, and West (1964) have demonstrated that these changes may be accelerated after resumption of circulation through the damaged area, a considerable time elapses before conventional histological techniques allow a firm diagnosis of ischaemic injury to be made. Further, Niles, Bitensky, Chayen, Cunningham, and Braimbridge (1964), in an investigation of biopsy material from patients undergoing extensive cardiac surgery, have shown by histochemical techniques that changes in cellular biochemistry occur rapidly in the myocardium during these procedures.

A technique that would demonstrate early ischaemic injury or an injury not sufficiently severe to cause necrosis would be of great value in assessing the state of the myocardium in conditions where death had occurred before histological changes could develop. Such a technique should be applicable to post-mortem tissues obtained at varying times after death and be sufficiently simple to be included in routine work. These two considerations eliminate many quantitative and qualitative chemical and histochemical techniques which are capable of showing early myocardial injury.

In 1958 Selye, and Nielsen, Renaud, Lemire, and Selye used such a technique to evaluate toxic cardiac necroses in experimental animals. This method stains fibres which have suffered ischaemic injury with acid fuchsin; this change is apparent before any loss of striation.

Fuchsinophilic material first appears in a patchy distribution along the Z bands. With increasing damage it involves more of the sarcoplasm until the

whole fibre is stained deep red. These damaged areas contrast with uninvolved tissues which are stained by methyl green (Figs. 1 and 2). This method was used by Poley, Fobes, and Hall (1964) to examine the heart in patients dying suddenly, all of whom had a previous history of myocardial infarction. The same authors established, by experimental work in dogs, that fuchsinophilia of the whole fibre was produced after interruption of the circulation for half an hour; they also discussed the possible underlying mechanisms of the technique.

In the very young coronary artery disease is seldom a significant factor in myocardial ischaemia. Inadequate perfusion of the coronary arteries or imperfect oxygenation of the blood are generally more important. In this context Burnard and James (1961) have demonstrated hypoxia of left atrial blood in infants with an Apgar score of less than 7 while breathing air. An investigation of necropsy material was made in order that the incidence of ischaemic injury in this age group might be determined.

METHODS

One hundred and thirty-five consecutive cases were studied. In 40 of these whole heart slices were examined in the remainder blocks were taken from each ventricle and the septum. All blocks were taken at a level mid-way between the atrio-ventricular sulcus and the apex.

After fixation in buffered 10% formalin, tissues were embedded in paraffin and sections cut at 5 μ .

The sections were stained as follows:

- 1 Hydrate to distilled water.
- 2 Stain for 15 min. in solution A¹ which is prepared on the day of use. The working solution is made up of 10 ml. stock solution, 40 ml. distilled water, 0.2 ml. 1% oxalic acid. The stock solution is made up of 1 g. cresyl fast violet in 500 ml. distilled water; filter after one hour.
- 3 Rinse in running water for 10 minutes.
- 4 Mordant for 15 min. in solution B (1% phosphotungstic acid, filtered).

FIG. 1.

FIG. 1. *Fuchsinophilia (pale areas) in the region of the Z bands. $\times 2.5$ from 150 (yellow filter).*

FIG. 2.

FIG. 2. *More extensive changes. $\times 2.5$ from 320 (green filter).*

- 5 Rinse in running water for three minutes.
- 6 Stain for approximately 30 min. in a 60°C. oven in solution C, with mechanical stirring. Solution C is made up of 20 ml. acid fuchsin 0.01%, 15 ml. 0.01% orange Gr, 15 ml. 0.01% methyl green, 0.2 ml. 1% oxalic acid.
- 7 Rinse in 0.5% glacial acetic acid.
- 8 Dehydrate in alcohols.
- 9 Clear in xylol and mount in Canada balsam or synthetic medium.

This is essentially the method of Poley *et al.* (1964) but mechanical mixing at stage 6 improved the reproducibility of results. A positive and negative control were included with each batch of slides stained.

RESULTS

In no instance was 'conventional' evidence of recent myocardial injury present.

The cases were divided into three groups related to the degree of fuchsinophilia present (Table I). The 39 cases in group I were considered to show no significant change. In view of the surprisingly large number of cases showing myocardial injury (96) the mode of death of each individual with ++ or +++

changes was determined from witnesses and case nursing records.

TABLE I

POST-MORTEM CHANGES OBSERVED BY PRESENT METHOD

Group No.	Changes	Number of Cases
I (- or $\pm$)	No fuchsinophilia, or minimal partial staining of occasional fibres	39
II (++)	Fuchsinophilia in part or all of the fibre's length, in a patchy distribution	19
III (+++)	Fuchsinophilia involving the entire fibre and the majority of fibres	77

Five main categories were apparent and the numbers in each group are shown in Table II. In this connexion, 'multiple cardiac arrests' are defined as three distinct episodes of cardiac arrest with at least two hours between the first and last. 'Cardio-respiratory failure' is used as a term to include those cases in which intermittent positive pressure respiration was necessary to maintain adequate ventilation

for 24 hours or more; in most cases cardiac arrest occurred terminally. Hypotension must have been recorded for 12 hours before death. 'Convulsions' indicates generalized convulsions for 24 hours or more. In those cases in which sudden death occurred no attempt at resuscitation was made. Two cases were excluded, as a note was made at post-mortem examination that the myocardium was damaged by open chest massage; a study of tissue deliberately subjected to crushing injury had shown that trauma produces fuchsinophilia.

TABLE II
MODE OF DEATH¹

<i>Mode of Death in Cases Showing Myocardial Injury</i>	<i>Number of Cases</i>
Multiple cardiac arrests	32
Cardio-respiratory failure	26
Hypotension	10
Convulsions	11
Sudden	15

¹Two cases excluded (see text).

DISCUSSION

In many of the cases in this series the mode of death is itself sufficient to have caused anoxic change in the myocardium. Comparison of cases in group I with those in groups II and III shows that this is not an entirely adequate explanation of the results. Table III illustrates this point. Each pair of cases is matched for age at operation, maturity, and length of operative procedure. Those in the left-hand column are cases in which no attempt at spontaneous post-operative respiration was made, and in which intermittent positive-pressure respiration was continued until death. The right-hand column is composed of patients who were returned to the ward, noted to be in a state of respiratory difficulty, and mechanically ventilated after an interval. Significant fuchsinophilia is confined to those cases in the right hand column.

Group I (no change) includes one death as the result of convulsions; this case had been maintained by relaxation and intermittent positive-pressure respiration from the time of the second seizure. The absence of myocardial damage in this child contrasts with the 11 cases in groups II and III which had not been ventilated.

Of the 10 cases of hypotension examined, nine fell into group II and one in group III. Possibly lowered coronary perfusion pressure is less likely to cause extensive damage than anoxia in this group of patients with normal vessels. However, the progressive deterioration in cardiac function noted clinically in these patients may be due to myocardial injury.

TABLE III

POST-OPERATIVE COURSE

<i>No Spontaneous Respiration, Intermittent Positive-pressure Respiration Maintained from Theatre</i>		<i>Spontaneous Respiration with Subsequent Respiratory Difficulty. Intermittent Positive-pressure Respiration</i>	
<i>Diagnosis</i>	<i>Degree of Fuchsinophilia</i>	<i>Diagnosis</i>	<i>Degree of Fuchsinophilia</i>
Tracheo-oesophageal fistula, oesophageal atresia	±	Tracheo-oesophageal fistula, oesophageal atresia	+++
Tracheo-oesophageal fistula, oesophageal atresia	—	Tracheo-oesophageal fistula, oesophageal atresia	+++
Tracheo-oesophageal fistula, oesophageal atresia	—	Tracheo-oesophageal fistula, oesophageal atresia	+++
Transposition of great arteries	±	Transposition of great arteries	+++
Tracheo-oesophageal fistula, oesophageal atresia	—	Diaphragmatic hernia	+++

The diagnoses in the 15 cases in which sudden death occurred are shown in Table IV. In this group the myocardial injury is probably not due to the mode of death. All showed severe changes (group III).

The three cases of anaemia were known to have haemoglobin levels in excess of 5 g. % on the day before death and 3.5 g. % or less on the day of death. Six other selected cases of leukaemia in which adequate data were available were then examined. In two, with haemoglobin levels in excess of 6 g. % at death, there was no evidence of ischaemic change. The remainder, with haemoglobin levels of 4 g. % or less at death, showed ischaemic injury, as indicated by this technique.

TABLE IV

CASES OF SUDDEN DEATH

<i>Probable Immediate Cause of Death</i>	<i>Diagnosis</i>	<i>Number of Cases</i>
Anaemia	Aplastic anaemia	1
	Acute leukaemia	2
Airway obstruction	Aspiration of vomit	2
	(1) Hirschsprung's disease	
	(2) Tracheo-oesophageal fistula, oesophageal atresia	
	Cerebral tumour	2
Impaired coronary perfusion	'Viral' pneumonitis	2
	Atheroma of the coronary vessels	1
	Dissection of the pulmonary artery	1
	Total anomalous pulmonary venous drainage	2
	Transposition of the great arteries	2

The child with atheroma of the coronary vessels resembles those cases reported by Poley *et al.* (1964) in having long-standing myocardial fibrosis but no recent evidence of infarction demonstrable by conventional methods.

Those cases in which airway obstruction was the cause of death provide evidence for the rapidity with which myocardial change may occur.

The infant with pulmonary artery dissection had a rapidly progressive narrowing of the vessel with infarction of part of the right lung. In this case it seems possible that the eventual pulmonary blood flow was insufficient to maintain adequate myocardial perfusion. The remaining four cases had conditions in which myocardial damage might theoretically have occurred at any time. It has been shown by Cumming (1963a, b) that there is a striking lability of right-to-left shunts in congenital heart disease after various pharmacological agents and possibly some similar physiological changes are involved, precipitating an irreversible myocardial insult.

These findings confirm the necessity for prompt and adequate ventilation in all conditions in which respiratory exchange is impaired.

The damage to the myocardium in anaemic patients suggests the practice of withholding transfusion until haemoglobin levels are low is not with-

out risk. In thalassaemia, myocardial failure, unassociated with transfusion, is a common cause of death (Engel, 1964) and ischaemic insults may contribute to the myocardial changes present.

The importance of poor coronary perfusion is not sufficiently emphasized in children and the cardiac reserve is assumed to be adequate. It is probable that ischaemic injury to the myocardium is not uncommon in severely ill children, although fortunately this is generally reversible.

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