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Left ventricular hypertrophy in emphysema

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Edwards, C. W. (1973). *Thorax*, **29**, 75–80. **Left ventricular hypertrophy in emphysema.** The role of systemic hypertension in 10 emphysematous subjects with left ventricular hypertrophy was investigated. The medial thickness of the internal mammary artery was used as a parameter of raised systemic blood pressure during life. The pulmonary vasculature, ventricular weights, and the type and severity of emphysema in these patients were also studied. A group of 10 normotensive subjects and a group of 10 subjects with systemic hypertension were used as controls.

The medial thickness of the internal mammary artery was significantly greater in the group of patients with systemic hypertension. Using this criterion it was found that four of the 10 patients with emphysema and left ventricular hypertrophy showed evidence of systemic hypertension. In these patients the pulmonary arterioles and arteries were normal.

Three of the remaining six patients with emphysema and left ventricular hypertrophy showed the changes of hypoxic pulmonary vascular disease. In the other three the pulmonary vasculature showed no abnormality.

The left ventricular weights and total ventricular weights in the patients with emphysema and left ventricular hypertrophy were significantly higher than in the group of patients with systemic hypertension only. There was no correlation between ventricular weights and the type or severity of emphysema.

There appears to be a definite syndrome characterized by emphysema, normal systemic blood pressure, and enlargement of the left as well as the right ventricle. Hypoxic pulmonary vascular disease is not always present.

It is generally accepted that a proportion of patients with chronic pulmonary disease develop left ventricular hypertrophy (*Lancet*, 1971). The mechanism that produces this change is not yet understood, and a detailed anatomical study of such cases has not previously been made. The investigation described in this paper was undertaken primarily to define the role of systemic hypertension in the production of left ventricular hypertrophy in emphysematous patients. The type and severity of the associated emphysema, the size of the right ventricle, and changes in the pulmonary vasculature will also be described. In addition, the feasibility of using the medial thickness of the internal mammary artery as a parameter of systemic hypertension will be discussed.

CASES STUDIED

Material was obtained from selected patients coming to routine necropsy at the East Birmingham Hospital. The patients were divided into three groups of ten.

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Group A consisted of patients with no significant emphysema and no evidence of myocardial hypertrophy (see below). Group B consisted of patients who had been treated for systemic hypertension; they had left ventricular hypertrophy but no significant emphysema at necropsy. Group C consisted of patients with emphysema and left ventricular hypertrophy. Care was taken to exclude subjects with myocardial fibrosis or infarction and those with valvular heart disease. The age and sex of these patients are shown in Tables I, III, and V. The criteria for 'significant' emphysema and myocardial hypertrophy are defined below.

METHODS

ASSESSMENT OF MEDIAL THICKNESS OF INTERNAL MAMMARY ARTERY At necropsy the superior 5 cm of the internal mammary artery on each side was dissected free and fixed in 10% formalin. Great care was taken to avoid crushing the vessel, and in some cases it was necessary to thread a bristle down the lumen before fixation in order to stop it assuming an oval cross-section. After fixation for at least 24 hours five blocks were taken from each artery. Each block consisted of about 0·3 cm of artery with a

variable amount of surrounding fat. Obvious areas of atheroma were avoided, and some cases had to be rejected because of heavy calcification and distortion of the arterial wall. The blocks were embedded in paraffin wax, and sections 5 μm thick were cut and stained with Lawson's elastic-van Gieson stain. By this technique 10 transverse sections of internal mammary artery were available from each case.

Using an eyepiece micrometer, the diameters D_1 and D_2 (Fig. 1) of each of the transverse sections of

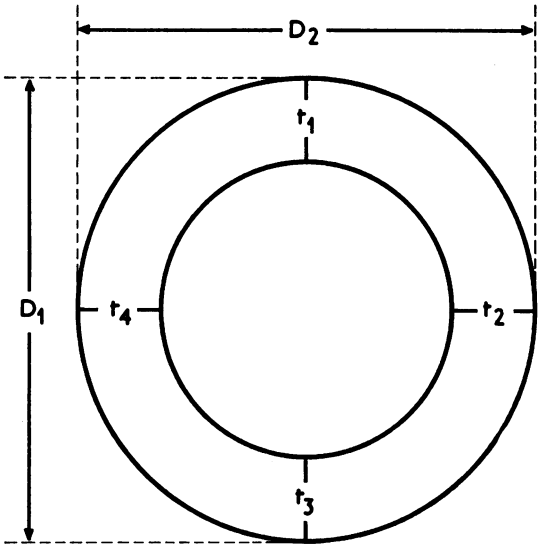

FIG. 1. *A schematic drawing of an arterial vessel showing the internal and external elastic laminae and the measurements taken to calculate the percentage medial thickness (see text).*

vessel were measured. These measurements were made at right angles to each other from the external elastic lamina of one side to the external elastic lamina on the opposite side. The thickness of the media at four points (t_1, t_2, t_3, t_4—Fig. 1) was also measured. The mean diameter D_m and the mean medial thickness t_m of the internal mammary artery in each subject were then calculated. The medial thickness of the internal mammary artery was expressed as a percentage of the diameter using the formula

$$\frac{t_m}{D_m} \times 100$$

EXAMINATION OF PULMONARY VASCULATURE Six to eight random blocks were taken from the right lung in each case. The blocks were embedded in paraffin wax, and sections 5 μm thick were cut and stained with haematoxylin and eosin and Lawson's elastic-van Gieson stains.

The muscle coats of the muscular pulmonary arteries were then examined. Muscular pulmonary arteries are defined as arterial vessels, 100 to 1,000 μm in diameter. They have a muscular media and well-defined internal and external elastic laminae (Brenner, 1935). In normal subjects the medial coat is circular, and longitudinal muscle bundles are not present in the intima. In this investigation vessels of less than 300 μm in diameter were examined. This was because most of the vessels in the sections were of this size, and also because there is a large amount of information available on vessels of this size (Hasleton, Heath, and Brewer, 1968).

The medial thickness of the muscular pulmonary arteries was measured in the same way as described for the internal mammary arteries. Again two measurements of the diameter were taken at right angles to each other (Fig. 1). The thickness of the media was expressed as a percentage. In addition the presence or absence of intimal longitudinal muscle was noted. Only vessels which were nearly circular in section were used in this study.

The pulmonary arterioles were also examined. In normal subjects these vessels are defined as arterial vessels less than 100 μm in diameter. Their walls consist of a single elastic lamina, and there is no muscular media except at their origins from muscular pulmonary arteries. The presence or absence of a muscle coat in these vessels was noted.

ASSESSMENT OF VENTRICULAR SIZE The method of Fulton, Hutchinson, and Jones (1952) was used. The atria, valves, and great vessels were removed, and then the free wall of the right ventricle was dissected off and weighed. The left ventricle and the interventricular septum were weighed together. Before the specimens were weighed the epicardial fat was trimmed away.

The upper limit of normal for right ventricular weight was taken to be 65 g, and for the left ventricle and septum 190 g.

ASSESSMENT OF TYPE AND SEVERITY OF EMPHYSEMA A point counting technique similar to that described by Dunnill (1962) was used. At necropsy the right lung was removed with great care in order to avoid tearing the pleura. The lung was then distended with formalin and fixed at a constant pressure of 25 cm of 10% formalin using the apparatus described by Heard (1966). After fixation for at least 48 hours the lung was cut into slices approximately 2 cm thick. Each slice was immersed in a dish of water with the medial side uppermost, and a transparent plastic grid ruled in 1-cm squares was laid over it. The percentage of lung tissue involved by emphysema was estimated by the aggregate number of intersections overlying normal lung parenchyma and abnormal air space in each slice. In addition the type of emphysema at each point—centrilobular or panacinar—was recorded. In each lung about 500 points were counted.

A significant degree of emphysema was taken to be present if more than 5% of the lung was involved.

RESULTS

The ventricular weights and the medial thicknesses of the internal mammary arteries and muscular pulmonary arteries in the individual cases of groups A, B, and C are shown in Tables I, III, and V. The means, ranges, and standard deviations of these values are shown in Tables II, IV, and VI. The type of emphysema and the percentage of lung involved in group C are shown in Table V. The pulmonary vascular changes found in group C are also shown in Table V.

TABLE I

VENTRICULAR WEIGHTS AND MEDIAL THICKNESSES OF INTERNAL MAMMARY ARTERIES AND MUSCULAR PULMONARY ARTERIES IN NORMAL SUBJECTS (GROUP A)

Case	Age and Sex	LV	RV	LV + RV	LV / RV	IM	MPA
A1	77F	70	26	96	2·7	11·1	6·8
A2	88F	98	36	134	2·7	12·2	4·4
A3	88F	130	35	165	3·7	10·9	4·6
A4	69M	130	60	190	2·1	11·2	4·3
A5	64F	136	56	192	2·4	11·9	3·8
A6	60F	140	40	180	3·5	11·4	6·0
A7	67M	140	40	180	3·5	10·2	5·1
A8	65M	144	48	192	3·0	11·3	3·9
A9	80F	160	40	200	4·0	11·3	6·5
A10	71M	160	70	230	2·3	11·8	5·2

LV = weight of left ventricle and interventricular septum (g).
RV = right ventricular weight (g).
IM = mean medial thickness of internal mammary artery expressed as a percentage of the diameter.
MPA = mean medial thickness of muscular pulmonary arteries expressed as a percentage of the diameter.
The subjects are arranged in ascending order of left ventricular weight in Tables I to VI.

TABLE II

MEANS, RANGES AND STANDARD DEVIATIONS OF VALUES FOR GROUP A SHOWN IN TABLE I

	LV	RV	LV + RV	LV / RV	IM	MPA
Mean	131	48	175	3·0	11·3	5·1
Range	70–160	26–70	96–230	2·1–4·0	10·2–12·2	3·8–6·8
Standard deviation	26·2	12·6	35·4	0·62	0·53	1·01

TABLE III

VENTRICULAR WEIGHTS AND MEDIAL THICKNESSES OF INTERNAL MAMMARY ARTERIES AND MUSCULAR PULMONARY ARTERIES IN SUBJECTS WITH SYSTEMIC HYPERTENSION (GROUP B)

Case	Age and Sex	LV	RV	LV + RV	LV / RV	IM	MPA
B1	67F	205	75	280	2·7	15·8	5·5
B2	58M	215	65	280	3·3	14·2	5·3
B3	65M	230	55	285	4·2	14·0	5·3
B4	71M	230	65	295	3·5	14·5	5·6
B5	70M	230	95	325	2·4	15·0	4·8
B6	50M	240	100	340	2·4	14·3	4·9
B7	75F	250	75	325	3·3	15·8	6·4
B8	69M	260	60	320	4·3	14·9	5·3
B9	70M	280	75	355	3·7	13·0	5·1
B10	68M	290	120	410	2·4	14·3	6·5

TABLE IV

MEANS, RANGES, AND STANDARD DEVIATIONS OF VALUES FOR GROUP B SHOWN IN TABLE III

	LV	RV	LV + RV	LV / RV	IM	MPA
Mean	243	79	322	3·2	14·6	5·4
Range	205–290	5·5–120	280–410	2·4–4·3	13·0–15·8	4·6–6·5
Standard deviation	25·8	19·4	38·5	0·688	0·7	0·598

MEDIAL THICKNESS OF INTERNAL MAMMARY ARTERY

The external diameter of the upper end of the internal mammary artery varied between 2 and 3 mm from patient to patient. Histologically the vessel showed the typical appearance of an elastic systemic artery (Fig. 2). The internal elastic lamina was well marked, and the media consisted of circular muscle fibres with numerous elastic fibres between them. No definitive external elastic lamina could be seen, but elastic-van Gieson staining showed a sharp line of demarcation between the adventitia and the media. There was a variable amount of intimal fibrosis, but this did not appear to be any more marked in the hypertensive cases. The adventitia consisted of a narrow band of collagen, and this in turn was surrounded by fat.

The mean medial thickness of the internal mammary artery in the normal subjects was 11·3% of the external diameter, with a range of 10·2% to 12·2% (Table II). In the hypertensive subjects

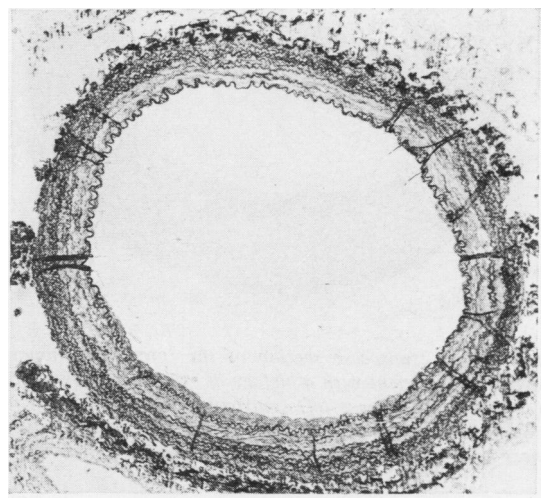

FIG. 2. *A transverse section of the internal mammary artery of a patient with no history of systemic hypertension and no significant emphysema or myocardial hypertrophy at necropsy (case A3). The mean medial thickness was* 10·9%. *Elastic-van Gieson* ×27.

TABLE V

VENTRICULAR WEIGHTS AND MEDIAL THICKNESSES OF INTERNAL MAMMARY ARTERIES AND MUSCULAR PULMONARY ARTERIES IN SUBJECTS WITH EMPHYSEMA AND LEFT VENTRICULAR HYPERTROPHY (GROUP C)

Case	Age and Sex	LV	RV	LV+RV	LV/RV	IM	MPA	Emphysema[1] %	HPVD[1]
C1	73M	205	87	292	2·4	14·5	5·2	13 CL	−
C2	55M	240	100	340	2·4	11·2	5·5	22 PA	−
C3	75M	242	64	306	3·8	14·2	6·3	15 CL	−
C4	52M	250	100	350	2·5	11·4	6·1	12 PA	−
C5	65M	302	100	402	3·0	11·9	6·1	28 PA	+
C6	59M	316	92	408	3·4	11·6	5·2	17 CL	+
C7	70M	325	160	485	2·0	9·3	6·8	19 PA	+
C8	57M	350	174	524	2·0	13·8	6·5	38 PA	−
C9	74M	360	138	498	2·6	10·4	3·2	8 PA	−
C10	73M	410	104	514	3·9	13·2	5·6	20 PA	−

[1] The percentage of lung substance involved by emphysema and the presence of hypoxic pulmonary vascular changes are shown. PA = panacinar emphysema; CL = centrilobular emphysema; HPVD = hypoxic pulmonary vascular disease.

TABLE VI

MEANS, RANGES, AND STANDARD DEVIATIONS OF VALUES FOR GROUP C SHOWN IN TABLE V

	LV	RV	LV + RV	LV/RV	IM	MPA
Mean..	300	112	412	2·8	12·2	5·7
Range	205–410	64–174	292–524	2·0–3·9	9·3–14·5	3·2–6·8
Standard deviation	61·3	32·6	83·9	0·659	1·63	1·04

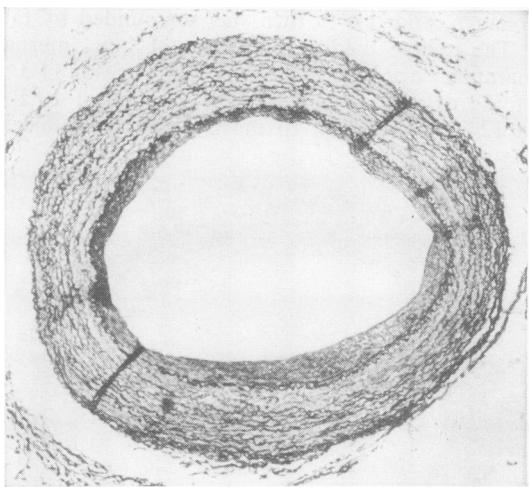

FIG. 3. *A transverse section of the internal mammary artery of a patient with a history of systemic hypertension (case B8). There was left ventricular hypertrophy but no significant emphysema at necropsy. The mean medial thickness was* 14·9%. *Elastic-van Gieson* ×27.

(group B) the mean medial thickness was 14·6% with a range of 13·0% to 15·8% (Table IV). This difference was highly significant ($P<0·01$). Even without measurement there was obvious hypertrophy of the media in the hypertensive subjects (Fig. 3). Of the subjects with left ventricular hypertrophy and emphysema (group C) there were four who showed medial hypertrophy of the internal mammary artery. These were cases C1, C3, C8, and C10 (Table V).

PULMONARY VASCULATURE The mean medial thickness of the muscular pulmonary arteries in group A was 5·1%, in group B 5·4%, and in group C 5·7%. There was no statistically significant difference between these groups, and all the figures obtained fell within the normal range of 2·8 to 6·8% (Heath and Best, 1958).

In group C, however, three of the cases (C5, C6, and C7) showed evidence of hypoxic pulmonary vascular disease. There was longitudinal muscle in the intima of the muscular pulmonary arteries and muscularization of pulmonary arterioles. Such changes were not seen in the pulmonary arterial vessels of groups A and B nor in the remaining cases of group C.

VENTRICULAR WEIGHTS The mean weight of the left ventricle in group A was 131 g, and in group B, 243 g. In group C the mean left ventricular weight was 300 g, which was significantly higher than in group B ($P<0·05$). The mean total ventricular mass was 175 g in group A, 322 g in group B, and 412 g in group C. Again the figure for group C was significantly higher than for group B ($P<0·01$).

The mean value of the ratio LV/RV was 3·0 in group A, 3·2 in group B, and 2·8 in group C. There was no statistically significant difference between these figures.

TYPE AND SEVERITY OF EMPHYSEMA The type and severity of emphysema in the individual cases of group C are shown in Table V. Three of these cases had centrilobular emphysema and the rest had panacinar emphysema; there were no cases in which the two types occurred together. There was no correlation between the amount of lung

involved and the ventricular weights, the medial thickness of the internal mammary artery or the medial thickness of the pulmonary arteries.

DISCUSSION

When the mass of the left ventricle cannot be measured the diagnosis of systemic hypertension at necropsy can be extremely difficult. Blood pressure readings during life are often not available and in any case may not give an accurate indication of the situation during life if recorded when the patient was ill and in hospital. Examination of the kidneys is fraught with pitfalls because of the various lesions that occur in these organs, particularly in old people. For these reasons a method similar to that of Barrett (1963) was used to try to assess the presence of systemic hypertension during life. Barrett studied the medial thickness and area of the branches of superior mesenteric artery and found that medial hypertrophy occurred in response to systemic hypertension. In this investigation the medial thickness of the internal mammary artery was used, mainly because this vessel can be easily dissected out when the sternum is reflected at necropsy.

As the results show, the media of the internal mammary artery is thicker in subjects with systemic hypertension. This is quite obvious on microscopic examination, and with a little practice measurement is not necessary. Although an increase of medial thickness from 11·3 to 14·6% of the diameter may not appear to be very great, in absolute terms it indicates an increase of almost 30%. There are, however, limitations to this technique; it is not applicable when there is gross atheroma or heavy calcification, and some cases had to be excluded from the series because of these changes.

Four of the subjects with emphysema and left ventricular hypertrophy (group C) showed medial hypertrophy of the internal mammary artery. It would therefore seem reasonable to infer that these subjects suffered from systemic hypertension, even though only one (C10) was known to have had a persistently raised blood pressure during life. Cases C3 and C8 died a few hours after admission to hospital with exacerbations of chronic bronchitis and cardiac failure, and therefore their blood pressure readings, although within the normal range, were not reliable for the present purposes. Case C1 died of a cerebral haemorrhage in the casualty department and no blood pressure readings were recorded. In the six remaining cases of group C (C2, C4, C5, C6, C7, and C9) the medial thickness of the internal mammary artery was within the normal range. It appears, therefore, that although these patients had large left ventricles they did not have high systemic blood pressures during life.

The pulmonary vasculature of these six cases showed features of great interest. In three of them (C5, C6, and C7) there was longitudinal muscle in the intima of the muscular pulmonary arteries and muscularization of the pulmonary arterioles, changes which may be attributed to the effects of chronic hypoxia (Hasleton *et al.*, 1968). The findings in the other three cases (C2, C4, and C9), however, are difficult to interpret. There was no evidence of either pulmonary or systemic hypertension, and yet there was unequivocal left and right ventricular hypertrophy. No explanation for this can be offered at present, but it is of interest that Heath, Edwards, Winson, and Smith (1973) were unable to produce hypoxic pulmonary vascular disease in adult rats exposed to low barometric pressures for long periods, although the animals did show hypertrophy of the right ventricle and thickening of the media of the pulmonary trunk.

The results of the present study give no clue to the mechanism involved in the production of left ventricular hypertrophy in emphysema. A strong stimulus to myocardial hypertrophy appears to be at work in these cases, because the left ventricular and total ventricular weights in these cases were significantly higher than in the patients with systemic hypertension only. Arterial hypoxaemia, hypercapnia, high cardiac output, bronchopulmonary anastomoses, and anatomical continuity between the right and left ventricular muscle have been suggested (Rao, Cohn, Eldridge, and Hancock, 1968). Certainly there is no relation between the degree or type of emphysema and the size of the left ventricle. Arterial hypoxaemia appears to be of importance, because Peñaloza and Sime (1971) found left ventricular hypertrophy in patients with severe chronic mountain sickness.

One mechanism that is worth investigating further is that put forward by Spencer (1968). He suggests that there is reversal of blood flow in the bronchial veins in patients with raised systemic venous pressure. Venous blood flows from the bronchial veins into pulmonary veins by way of anastomotic channels and thus bypasses the right ventricle and increases the work load of the left ventricle. The differential left and right ventricular flow studies of Cudkowicz, Calabresi, Nims, and

Gray (1959) and of Nakamura *et al.* (1961) support this hypothesis.

In conclusion it may be said that systemic hypertension is the cause of left ventricular hypertrophy in some patients with emphysema. In other cases with left ventricular hypertrophy and emphysema, however, systemic hypertension is not a factor. These cases are characterized by an anatomical syndrome of emphysema, very high left ventricular weight, and high total ventricular weight. Hypoxic pulmonary vascular disease is not always present. The mechanism that produces left ventricular hypertrophy in these cases is not yet fully understood, but further investigations are being carried out in this department.

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