

Morphometrical Study on the Sclerotic Inferior Vena Cava in Chronic Lung Disease

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SUMMARY : The purpose of this study is to determine the relationship between chronic lung disease (CLD) and morphological changes in the inferior vena cava (IVC) from postmortem materials. The IVC and pulmonary truncus were obtained from 70 cases with CLD and/or cor pulmonale and from 23 controls. The tissues were processed for light and electron microscopic studies. The adventitia was by far the thickest component of the IVC wall. The total wall, intimal, and adventitial thicknesses were all significantly greater in the CLD cases than in the controls ($p < 0.001$), but there was no significant difference in the ratio of adventitia thickness to wall thickness. The incidence of intimal thickening was 13.0% and 37.3% in controls and in CLD respectively. Electron microscopic examination of the IVC from the CLD cases revealed a marked increase in the amount of extracellular matrix including collagen, elastic fibers and ground substances in the adventitia as compared with the controls. No foam cells were detected in the thickened intima of the IVC.

PA, right ventricular thickness and RV/LV ratio were greater in CLD than in controls. The blood gas levels of the CLD cases indicated obvious hypoxia (PaO_2 54.2 mmHg). This study suggests that increased venous pressure and hypoxia might be implicated in the pathogenesis of phlebosclerosis in patients with CLD.

INTRODUCTION

Phlebosclerosis in aortocoronary vein graft has been reported by many investigators¹⁾²⁾¹³⁾¹⁷⁻²¹⁾. The altered layer consists of modified smooth muscle cells, collagen, and ground substances, thus resembling an early arteriosclerotic lesion, though the occurrence of true arteriosclerosis in grafted vein has been controversial²⁾²²⁾.

It is well known that the right-sided heart failure causes right ventricular hypertrophy and pulmonary arteriosclerosis due to elevated central venous pressure^{1,6)}. Venous thickening

has been observed in the portal veins and inferior vena cava in cases of hepatic cirrhosis and congestive heart failure⁶⁾. Echocardiographic studies have revealed that the inferior vena cava was dilated and did not change caliber during respiration in patients with severe right-sided heart failure¹²⁾¹⁴⁾¹⁵⁾. Phlebosclerosis is clinically significant in consideration of low compliance in patients with cor pulmonale.

To our knowledge, however, detailed morphological studies of the IVC in patients with chronic lung disease (CLD) have rarely been reported. Moreover, the pathogenesis of phlebosclerosis is a matter of recent attention. The purpose of

this study is to examine the IVC from postmortem materials in chronic lung diseases by light and electron microscopy and to carry out a morphometrical analysis.

MATERIALS AND METHODS

The IVC and pulmonary trunci were obtained from 70 autopsy cases in Nagasaki, Japan, with chronic lung diseases and/or cor pulmonale. These disorders were diagnosed according to pathological findings and clinical charts. The 70 cases of CLD included 19 cases of emphysema, 15 of pulmonary fibrosis, 12 of pulmonary tuberculosis, 10 of pneumoconiosis, eight of chronic bronchitis including bronchiolitis, four of bronchiectasis, and two of bronchial asthma. The 43 male and 27 female patients ranged in age from 25 to 98 years (mean 69.0). The controls were 23 patients without significant pulmonary disease who died from short term disorders such as burns, cerebral bleeding, acute cardiac infarction, etc.. The eight male and 15 female control patients ranged in age from 21 to 83 years (mean 49.6). The IVC specimens were excised from the abdominal segment located between the IIIrd and Vth lumbar vertebrae. Pulmonary truncus specimens were taken 2cm distal from the pulmonary valve. The tissues were fixed in a 10% formalin solution, cross-sectioned into three consecutive 5mm lengths, and embedded in paraffin. From each paraffin block, 3 μ m thick sections were cut and stained with hematoxylin-eosin, elastica van Gieson, and Azan-Mallory. Morphometry sections were scanned with a light microscope. The adventitial, intimal, medial and complete vessel wall thicknesses were measured with an ocular micrometer at a magnification of 100. The values used in this study were the averages of the three samples of tissue taken from each location in each of the 93 cases. The ratio of the adventitia to the IVC wall thickness was expressed as AT% (adventitial thickness / wall thickness \times 100) to determine to what extent the adventitia contributed to the thickening.

For electron microscopic observation, IVC specimens were taken from six CLD and six control cases and fixed in 1.5% glutaraldehyde

immediately after excision during autopsy. The tissues were then processed for electron microscopic examination. Ultra thin sections were stained with uranyl acetate and lead citrate and examined with a JEM 100B electron microscope. The heart weights, anterior wall thicknesses of the left and right ventricles and blood gas levels (PaO₂, PaCO₂) were also recorded during autopsy and from clinical charts.

RESULTS

The structure of the inferior vena cava is shown in Fig. 1. The adventitia was by far the thickest component of the IVC wall. There was little smooth muscle present in the media. The intima consisted of a single layer of endothelial cells and subendothelial connective tissue. The adventitial smooth muscle bundle was well developed in the IVC.

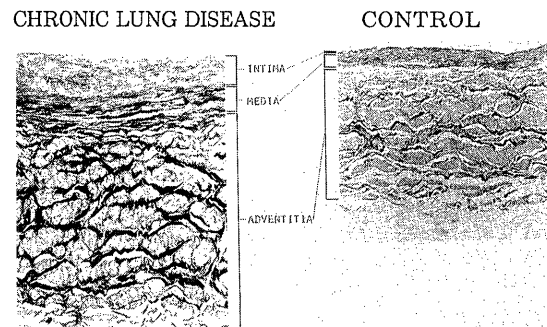


Fig. 1. The comparison of IVC in CLD and controls. (EVG, identical magnification)

Fig. 1 compares the IVC from the CLD cases with those from the control cases. Table 1 and 2 present detailed measurements of the IVC. Basically, the IVC from the CLD cases were much thicker than those from the control cases. The degree of phlebosclerosis was most remarkable in pneumoconiosis, and followed by chronic bronchitis (bronchiolitis), pulmonary fibrosis, pulmonary emphysema, pulmonary tuberculosis and bronchiectasia in turn. The total wall, intimal, and adventitial thicknesses were all significantly greater in the CLD cases than in the control cases ($P < 0.001$), but there was no significant difference in the AT%. Two types of intimal thickening were present. One was a dif-

Table .1 Measurements of the IVC in CLD and Control

	n	IVC wall thickness(μ)	ADV(μ)	media(μ)	intima(μ)	incidence of intimal thickening(%)	%ADV/IVC
CLD	70	1072 \pm 213	765 \pm 162	233 \pm 116	20.9 \pm 44.1	37.3	72.2 \pm 7.7
control	23	813 \pm 164	570 \pm 143	188 \pm 73	1.8 \pm 5.1	13.0	69.9 \pm 6.9
p value		< 0.001	< 0.001	NS	< 0.001	< 0.05	NS

CLD ; 50 \pm 21 yrs, σ / ρ = 0.69, control ; 69 \pm 11 yrs, σ / ρ = 1.68

IVC : interior vena cava, ADV : adventitia, CLD : chronic lung disease

Expressed as mean \pm SD

Table 2. Measurements of the VIC in Each Disease

	n	I V C			
		IVC(μ)	ADV(μ)	media(μ)	intimal thickening(%)
pul. emphysema	19	1051 \pm 214 ^{***}	739 \pm 124 ^{***}	261 \pm 145	53 ^{**}
pul. fibrosis	15	1069 \pm 221 ^{***}	766 \pm 125 ^{***}	254 \pm 110	43 [*]
pul. tuberculosis	12	1031 \pm 198 ^{**}	764 \pm 203 ^{**}	165 \pm 76	33
pneumoconiosis	10	1179 \pm 121 ^{***}	880 \pm 129 ^{***}	235 \pm 79	20
chr. bronchitis	8	1155 \pm 204 ^{***}	837 \pm 186 ^{**}	244 \pm 91	38
bronchiectasia	4	1032 \pm 201 [*]	680 \pm 121	278 \pm 79	25
bronchial asthma	2	789 \pm 69	527 \pm 90	217 \pm 4	0
control	23	813 \pm 164	570 \pm 142	188 \pm 73	13

p value (compared with control) * p<0.05, ** p<0.01, *** p<0.001

fuse type of intimal thickening (Fig. 2a), and the other a plaque type (Fig. 2b). The incidence of intimal thickening was 13.0% in the control IVC and 37.3% in the CLD IVC. Recanalization was occasionally observed in the thickened intima of the IVC of the CLD cases. There was no significant difference between male and fe-

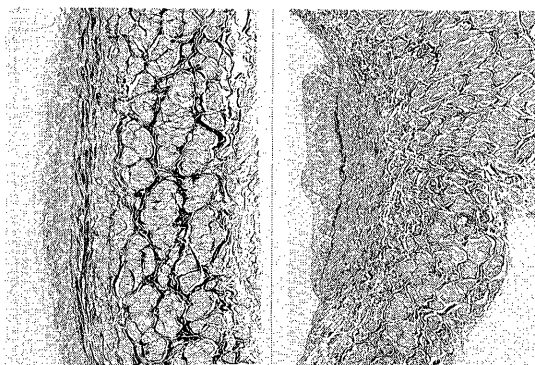


Fig. 2. Two types of intimal thickening were present.

- a) diffuse intimal thickening (EVG, \times 110)
 b) plaque type intimal thickening (EVG, \times 110)

male in the severity of phlebosclerosis, and there was no correlation with aging.

Electron microscopic examination of the IVC from the CLD cases revealed a marked increase in the amount of extracellular matrix in the adventitia as compared to the controls (Fig. 3). However, there was no significant increase in the number of smooth muscle cells. The volumes of collagen and elastic fibers and ground substances had also increased significantly, contributing greatly to venous sclerosis. Fibroblasts were sometimes present in both the intima and adventitia. An abundance of glyco-gen particles was observed in the cytoplasm of the adventitial smooth muscle cells. Myeline configuration was frequently encountered in the thickened intima of the IVC (Fig. 4). Table 3 lists the pulmonary artery thickness and the measurement of heart. Pulmonary arteries from the CLD cases were thicker, caused in the part by diffuse fibromuscular intimal thickening. Pulmonary arteriosclerosis was well correlated with phlebosclerosis of IVC in each case of CLD. No significant differences in heart weight or left ventricular wall thickness were

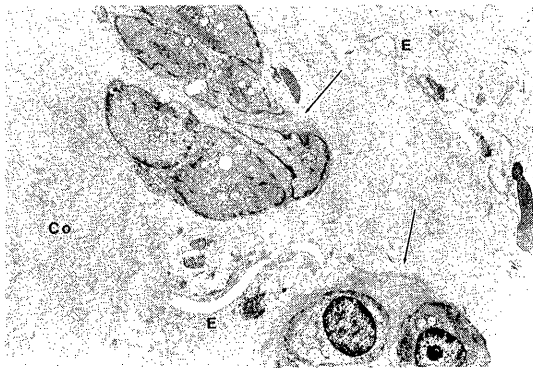


Fig. 3. Ultrastructure of the adventitia from a CLD case. The amount of extracellular matrix was increased. Smooth muscle cells were surrounded by a thick layer of basement membrane-like material (arrow). E; elastic fiber Co; collagen fiber ($\times 9,800$)

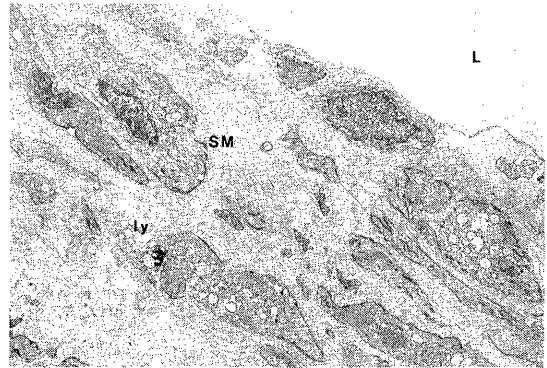


Fig. 4. Ultrastructure of fibromuscular intimal thickening. Arrows indicate cell debris. No foam cells were present. L; lumen SM; smooth muscle cell ly; lysosomal body ($\times 12,300$)

Table 3. PA Thickness and Heart it CLD and Control

	n	PA (μ)	intimal thickness(μ)	heart weight(g)	RV thick-ness(mm)	LV thick-ness(mm)	RV/LV ratio
CLD	70	1058 \pm 201	64.2 \pm 39.1	340 \pm 71	4.1 \pm 2.0	12.4 \pm 3.1	0.38 \pm 0.33
control	23	730 \pm 181	18.5 \pm 12.8	340 \pm 110	3.1 \pm 1.2	13.6 \pm 3.6	0.23 \pm 0.07
p value		< 0.001	< 0.001	NS	< 0.01	NS	< 0.05

mean \pm SD, PA : truncus of pulmonary artery, RV : right ventricle, LV : left ventricle

noted. The right ventricular thickness and RV/LV ratio were greater in the CLD cases than in the control cases ($P < 0.01$). The blood gas levels of the CLD cases (PaO_2 54.2, PaCO_2 50.6mmHg) indicated pulmonary failure.

The %VC and %FEV 1.0 were 46.3 and 67.6 respectively in the CLD cases. The mean values of the PaO_2 and PaCO_2 were 54.2mmHg and 50.6mmHg in the CLD cases and the 90.4mmHg and 33.7mmHg in the control cases respectively.

DISCUSSION

Previous studies indicated a positive correlation between raised intravenous pressure and the development of phlebosclerosis. The present study showed that there was significant venous thickening in the IVC from CLD patients. Adventitial fibromuscular thickening was especially conspicuous and contributed greatly to

the phlebosclerosis of the IVC. Ultrastructurally, collagen proliferation seemed to play a more important role in adventitial thickening than smooth muscle cell proliferation.

Compliance to the venous wall would be expected to decline in the sclerotic IVC of the CLD patients. KATO *et al.*¹¹⁾ have suggested that the low compliance of the peripheral venous wall is reversible and functional in cor pulmonale. Moreover, the compliance of the peripheral capacitance vessels decreased gradually as the brachial venous pressure increased. Echocardiographic studies¹²⁾¹⁴⁾¹⁵⁾ have shown little caliber change in the IVC during respiration in patients with failure of the right side of the heart. The present study confirmed the theory that decreased compliance of sclerotic IVC in CLD patients is organic and irreversible since the IVC from such patients exhibited marked vessel wall thickening.

The pathogenesis of intimal sclerosis in veins has received little attention. Several factors are supposed to be implicated in the pathogenesis of venous sclerosis in CLD patients. Increased venous pressure is one of the pathogenetic factors, although it is still lower in degree than normal arterial blood pressure. Histologically, even the physiological increases in hydrostatic pressure induce medial hyperplasia in veins taken from the lower limbs as well as intimal lesions²³⁾. The phlebosclerotic lesions in venous varicosities are presumably the response of the vein to increases in hydrostatic pressure.

Arterialization of grafted saphenous veins in coronary by-pass operations causes drastic changes to the veins, such as atheroma, intimal thickening and medial hypertrophy. TAKEBAYASHI *et al.*²²⁾ worked on the comparative studies with artery on the atherogenesis. They pointed out that true atherosclerotic changes, implying elastic hyperplasia, are rarely induced in vein by-pass grafts. For one reason, the nature of the venous wall is different from that of the arterial wall, and reactions to increased pressure differ between veins and arteries. The endothelial cells of vena cava tend to have a large number of Weibel-Palade bodies which, in turn, create an antithrombogenic effect⁷⁾. The venous wall contains more type I collagen than the arterial wall, and material permeability of veins is higher than in arteries²²⁾.

In this study we could not clarify the morphological changes of vasa vasorum, but the role of vasa vasorum and lymphatics cannot be ignored. Veins are supplied much more abundantly with vasa vasorum and lymphatics than arteries are⁹⁾. Though the vein contains poorly oxygenated blood, well developed vasa vasorum carries arterial blood into substance of the vein walls and compensates this need. CARSON *et al.*³⁾ studied on the role of vasa vasorum in preserving venous endothelial integrity. They concluded that the endothelium of the grafted vein is very sensitive to the loss of the vasa vasorum blood supply. In the patients with CLD, the arterial blood was markedly hypoxic and the central venous pressure was supposed to be increased constantly, implying that the vasa vasorum is at stake of collapsing

in the inner layer of the vena cava. Also hypoxia may induce vasospasm in vasa vasorum. Moreover, hypoxia is regarded to be one of risk factors for atherosclerosis⁵⁾⁸⁾¹⁰⁾²⁴⁾. As for lymphatics, FUNAKI *et al.*⁴⁾ suggested the role of lymphatic flow disturbance on initiating an experimental intimal thickening of jugular veins in rabbit by placing polyethylene tube cuff around veins.

It is concluded that adventitial fibromuscular thickening contributed greatly to phlebosclerosis of IVC in patient with CLD and that the increased venous pressure and hypoxemia might be implicated in its pathogenesis.

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REFERENCES

- 1) BARBORIAK, J. J., PINTAR, K., and KORNS, M. E. : Atherosclerosis in aortocoronary vein grafts. *Lancet* ii : 621-624, 1974.
- 2) BULKLEY, B. H., and HUTCHINS, G. M. : Accelerated " Atherosclerosis ". A morphologic study of 97 saphenous vein coronary artery bypass graft. *Circulation* 55 : 163-169, 1977.
- 3) CORSON, J. D., LEATHER, R. P., BALKO, A., NARAYNSINGH, V., KARMODY, A. M., and SNAH, D. M. : Relationship between vasa vasorum and blood flow to vein bypass endothelial morphology. *Arch. Surg.* 120 : 386-388, 1985.
- 4) FUNAKI, C., NAITO, M., NAKAYAMA, Y., HAYASHI, T., KUZUYA, M., ASAI, K., and KUZUYA, F. : Experimental intimal thickening of jugular veins by investment in rabbits. *J. Jpn. Atheroscler. Soc.* 15 : 1471-1473, 1987.
- 5) FRITH, C. H., MCMURTRY, I. F., ALEXANDER, A. F., and WILL, D. H. : Influence of hypertension and hypoxemia on arterial biochemistry and morphology in swine. *Atherosclerosis* 20 : 189-206, 1974.
- 6) GEHRINGER, E. : Venous atheroma. *Arch. Pathol.* 48 : 410-420, 1949.
- 7) CHADIALY, F.N. : Ultrastructural Pathology of the Cell and Matrix, Ed. 2, Butterworths, London, Boston, Sydney, Wellington, Durban, Toronto, 1982.
- 8) Guyton, J. R., and KARNOVSKY, M. J. : Smooth

- muscle cell proliferation in the occluded rat carotid artery. *Am. J. Pathol.* 94 : 585-602, 1979.
- 9) HAM, A. W., and CORMACK, D. H. : Vein and venule. In *Histology*, p. 606-611, Ed. 8, J. B. Lippencott Company, Philadelphia, Tronto, 1979.
 - 10) JAENKE, R. S., and ALEXANDER, A. F. : Fine structural alterations of bovine peripheral pulmonary arteries in hypoxia-induced hypertension. *Am. J. Pathol.* 73 : 377-398, 1973.
 - 11) KATO, M., SAIKI, S., SUZUKI, T., OGINO, T., KOJIMA, A., KOEDA, T., INOMATA, H., NAKAI, K., MOTOYAMA, A., and KIMURA, T. : Studies on compliance of the peripheral capacitance vessels in patients with congestive heart failure. *Respiration and Circulation* 25 : 1023-1028, 1977. (in Japanese).
 - 12) KAUDE, J. V., and JAKOBSON, P. : Chronic congestive heart failure : Observations at abdominal ultrasound with a comparison of abdominal veins in healthy individuals. *Angiology* 33 : 198-204, 1982.
 - 13) MCGEACHIE, J. K., PRENDERGAST, R. J., and MORRIS, P. : Vein grafts for arterial repair : an experimental study of the histological development of the intima. *Ann. of Royal College of Surgens of England* 65 : 85-89, 1983.
 - 14) MORENO, F. L. L., HGAN, A. D., HOLMEN, J. R., PRYOR, T. A., STICKLAND, R. D., and CASTLE, C. H. : Evaluation of size and dynamics of the inferior vena cava as an index of right-sided cardiac function. *Am. J. Cardiol.* 53 : 579-585, 1984.
 - 15) REIN, A. J. J. T., LEWIS, N., FORST, L., GOTSMAN, M. S., and LEWIS, B. S. : Echocardiography of the inferior vena cava in healthy subjects and in patients with cardiac disease. *Isr. J. Med. Sci.* 18 : 581-585, 1982.
 - 16) SCOTT, R. W., and GARVIN, C. F. : Cor pulmonale ; Observations in fifty autopsy cases. *Am. Heart J.* 22 : 56-63, 1941.
 - 17) SHAND, J. E. G., RICHARDSON, M., BELBECK, L. W., JULIAN, J., and GUNSTENSEN, J. : Early changes in venous arterial autografts ; a scanning electron microscope study. *Canadian J. Surg.* 26 : 149-153, 1983.
 - 18) SMITTEN, K., STENMAN, S. and SCHEININ, T. M. : Connective tissue change in syngeneic aortal vein grafts in rats. *Acta Chir. Scand.* 146 : 253-260, 1980.
 - 19) SPRAY, T. L., and ROBERTS, W.C. : Changes in saphenous veins used as aortocoronary bypass grafts. *Am. Heart J.* 94 : 500-516, 1977.
 - 20) STEIN, A. A., ROSENBLUM, I. R. A., and LEATHER, R. : Intimal sclerosis in human veins. *Arch. Pathol.* 81 : 548-551, 1966.
 - 21) STUART, M., and MAGAREY, F. R. : The graft veins in venous hypertension. *J. Path. Bact.* 79 : 319-323, 1979.
 - 22) TAKEBAYASHI, S., SHIRAIISHI, M., and HARADA, K. : Vein : A comparative study with artery on the atherosclerosis. *The Cell* 13 : 406-413, 1981. (in Japanese).
 - 23) TITUS, J. L., and KIM, H. S. : Blood vessels and lymphatics. In Kissane, J. M. (Editor) : *Anderson's Pathology*, p. 714-720, The CV Mosby Company, ST Louis, Tronto, Princet on, 1985.
 - 24) TURTO, H., LINDY, S., UITTO, J., HEILIN, P., GARBARSCHE, C. and LORENZEN, I. B. : Increased collagen prolyl hydroxylase activity in the aortic wall of rabbits exposed to chronic hypoxia. *Atherosclerosis* 33 : 379-384, 1983.