LYMPHATIC ANEURYSM OF THE HEART

R.W. Lupinski

National Heart Centre, Department of Cardiothoracic Surgery, Singapore

ABSTRACT

The Annular Subvalvular Left Ventricular Aneurysm (ASLVA) is a rare entity, which occurs usually in young ethnic groups from Sub-Saharan Africa and South India. These aneurysms are situated immediately beneath the mitral and aortic valves and extend around in the substance of fibrous ring, from which valves arise. Their etiology is still obscure.

Fifteen consecutive cases of ASLVA were treated surgically for this heart condition. Their clinical presentations, surgery, histopathology of aneurysmal wall were studied.

Infective diseases with associated mediastinal lymphadenopathy were observed in all patients prior to the time the diagnosis of ASLVA was made. Nine patients had also lymphadenopathy in another region. Sinus of Valsalva Aneurysm was an associated finding in three patients. Dense fibrous tissue was the most common histopathological feature of the aneurysmal wall. Endothelium within the structure of the aneurysmal wall, "compressed" myocardium around the ASLVA wall, dilated and deformed heart lymphatics with lymph extravasation, and lymphatic neovascularization were all found in some histopathology specimens.

Post-inflammatory destruction of mediastinal lymph nodes may obstruct lymph outflow from the heart, cause backwards lymphostasis, damage lymphatic vessels in the heart, and can lead to aneurysm formation. Increased intravascular shear stress triggers release of endothelial growth factors (bFGF, TGF-beta) and leads to neovascularization and tissue fibrosis, the most common feature of aneurysmal wall.

The Annular Subvalvular Left Ventricular Aneurysm (ASLVA) is a rare entity that occurs usually in young ethnic groups from Sub-Saharan Africa and South India. These aneurysms, by definition provided by Abrahams (1), are situated immediately beneath the mitral (submitral aneurysm) or/and aortic valve (subaortic aneurysm, *Fig. 1*) and extend around in the substance of fibrous ring, from which valves arise. As the etiology of ASLVA still remains unknown, several causes have been postulated – congenital weakness of the atrioventricular groove, infective endocarditis, rheumatic arteritis, tuberculosis or syphilis. Tuberculous origin of those aneurysms seems to be the most likely in children. The aim of this study is to elucidate the contribution of infection with mediastinal lymph node enlargement to development of this rare heart condition.

MATERIAL AND METHODS

Fifteen consecutive cases of ASLVA were treated surgically for this heart condition between 1967-1995 at Groote Schuur Hospital, Red Cross War Memorial Children's Hospital and University of Cape Town (South Africa). Patient demographic features (gender, age and region), clinical presentation including evidence of infectious disease, results of investigations (chest x-rays,
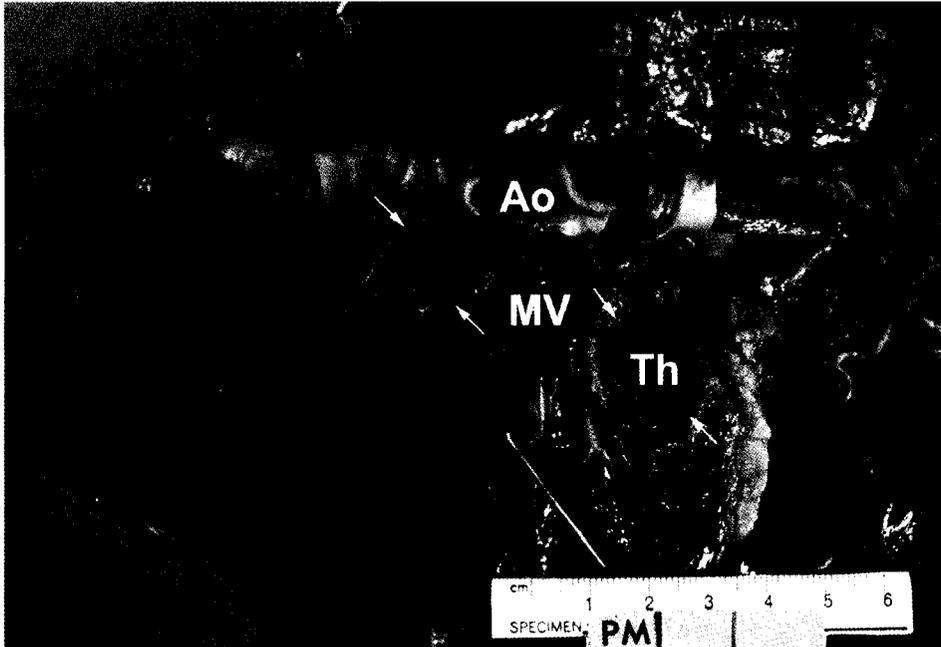
Fig. 1. Subaortic type of ASLVA. on autopsy (between arrows). Dissected left ventricle. Th= thrombus; Ao=aorta; MV=mitral valve.
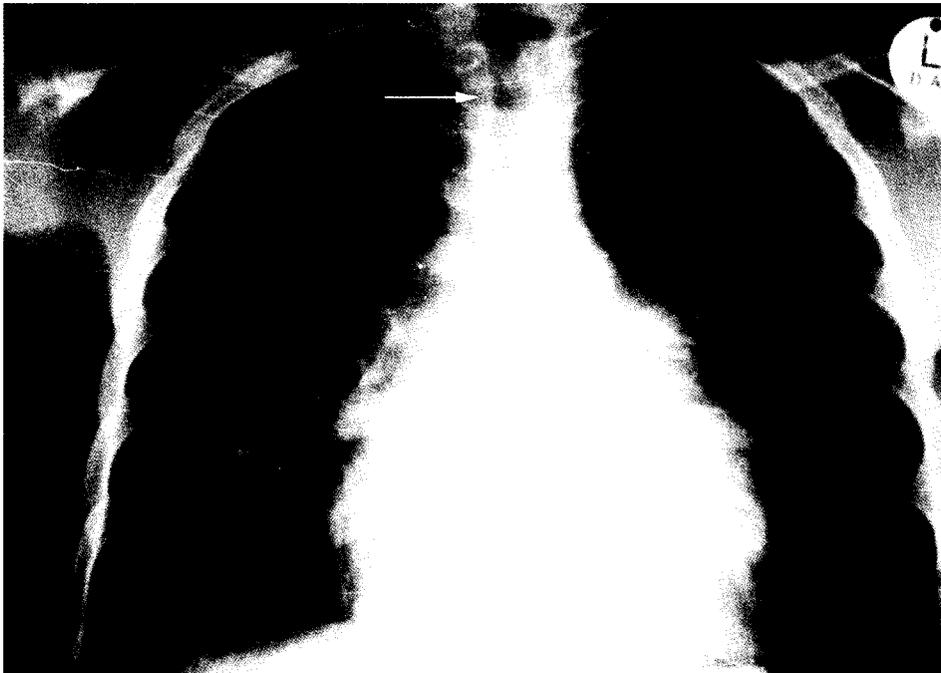
Fig. 2. Chest radiogram showing unusual left heart border. Arrow indicates tracheal compression by spare paratracheal mass, patchy and hazy changes in the right lung middle zone are most probably lymphatic in origin due to obstructed lymph outflow.

TABLE 1
Patients: Demographics and Findings

Patient	Age	Sex	Race	Region	Lesion	Infection	LTH
1	3	m	b	Ciskei	aslva	pulmonary tb	M,I
2	3.5	m	b	W.Cape	aslva	tb myocarditis	M,C
3	6	m	b	Botswana	aslva	tb pericarditis	M
4	8	m	c	W.Cape	aslva	tb	M,C,I
5	9	f	c	W.Cape	aslva	nodal tb, CI	M,C
6	10	f	c	W.Cape	aslva,sv	nodal tb	M
7	11	f	b	Ciskei	aslva,sv	staph.sepsis,O,T	M,C
8	13	f	b	Ciskei	aslva	pleural tb	M
9	14	f	b	Transkei	aslva	occular, nodal tb	M,C,I
10	17	f	b	W.Cape	aslva	pericarditis, CI	M,C
11	19	f	b	Ciskei	aslva	CI, ac.carditis	M,C
12	23	m	c	W.Cape	aslva,sv	aortic root absc.	M
13	25	m	b	Ciskei	aslva	syphilis, CI	M
14	31	m	b	Namibia	aslva	CI, T	M,I
15	35	m	b	Namibia	aslva	hydatid cysts	M

Abbreviations: M=male; f=female; b=black; c=colored, aslva=annular subvalvular left ventricular aneurysm; sv=sinus of Valsalva aneurysm; tb=tuberculosis; CI=chest infection not responding to conventional treatment; T=tonsillitis; O=osteitis; LTH=lymphadenopathy; M=mediastinal; I=inguinal; C=cervical.

blood tests, histopathology reports), surgical or autopsy findings were studied. Lymphadenopathy was detected by clinical examination, external compression of the airway causing "noisy breathing," hoarseness, a swollen face, and was also diagnosed during surgery or autopsy. Chest radiograph may show bronchial/tracheal compression (Fig. 2), atelectasis, unilateral elevation of diaphragm, paratracheal mass or calcification. Patient case notes were retrieved and reviewed.

RESULTS

Demographics

The 8 male and 7 female patients had a mean age of 15 years (range from 3.0 to 35).

There were 4 colored and 11 black patients (Table 1).

Clinical Presentation

Infections were observed in all patients. Tuberculosis was the most common type of infection and was diagnosed in 8 patients (Table 1). Five had chest infections not responding to conventional treatment. One child had Staphylococcal septicemia associated with pericarditis. One patient had positive serology for syphilis (TPHA, VDRL). Hydatid cysts, aortic root abscess, acute carditis were each diagnosed in one patient. Two of the patients were also treated for tonsilitis.
Mediastinal lymphadenopathy was detected in all patients (Figs. 3,4). Nine

144

Fig. 3 Enlarged aortopulmonary window lymph node marked by dotted lines (anterior view).

Fig. 4. Enlarged subcarinal and right paratracheal lymph nodes marked by dotted lines (posterior view).

patients had also associated lymphadenopathy in another region *(Table 1)*.

Fourteen patients had signs of cardiac failure. Mitral incompetence was associated with aneurysm in 13, aortic incompetence in 5 and mitral stenosis in one patient. Arrhythmias were present in all patients. ECG evidence of myocardial injury, despite unobstructed coronary flow on angiography, was observed in 8 of the patients.

Surgery – Findings and Methods

The aneurysms were identified in the submitral position in 12 cases (4 from the apex, 2 subaortic, and 3 left atrial). Six of these patients had multiple forms of aneurysm. Three patients had associated sinus of Valsalva aneurysm. Neck closure

was performed in 11 cases, resection in 8, and obliteration of the aneurysm in 5. Four patients had mitral valve replacement and one had aortic valve replacement. Six patients required mitral valve repair. Repeat surgery was necessary in 4 children (recurrent aneurysm or mitral valve incompetence)

Histopathology of ASL VA

In all cases the wall of the aneurysm consisted of dense, fibrous tissue *(Fig. 5)*. Necrosis was present in 6, calcification of aneurysmal wall was found in 6 and hyalinization in 2 of the cases. Inflammatory infiltrate was detected in 6, and organisms were present inside macrophages in 2 of the specimens of aneurysmal wall. Neovascularization was reported in 4 cases *(Fig. 6)*.

Fig. 5. Histopathological specimen of ASLVA wall. In the right lower corner thrombus (Th) overlying dense fibrous wall with calcium (Ca) deposition. In the middle - myocardium replaced in part by fibrous scar. In the left upper corner -"compressed" myocardium (My). Dotted line surrounds remnant myocardial vessels within scar tissue.
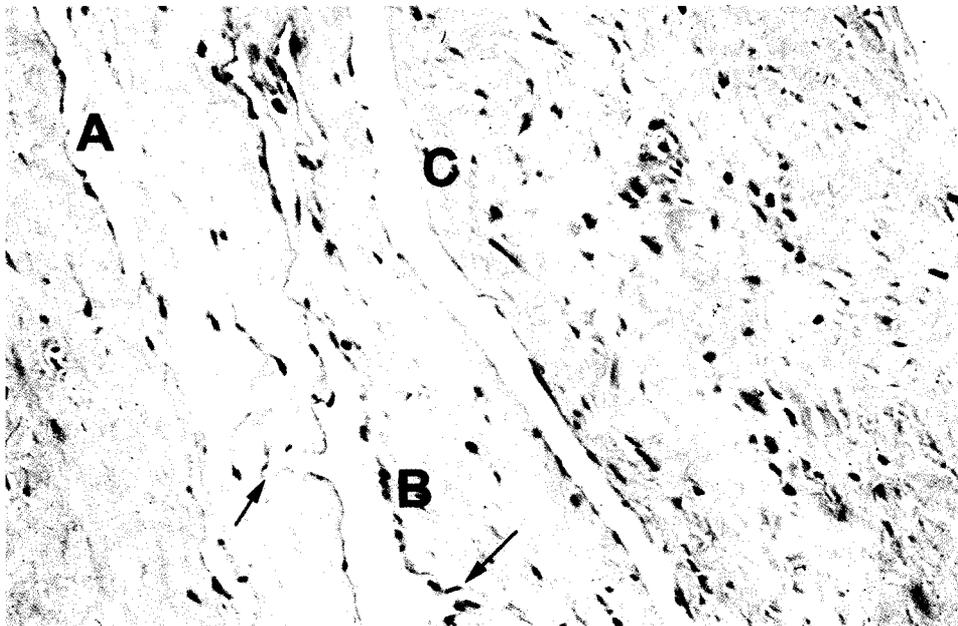

Fig. 6. Dynamics of changes within the ASLVA wall. Direction of tensile forces from left towards right part of specimen illustrates degree of deformation and size of the vessels - narrowing and compression of the vessels (A,B,C) by surrounded fibrous tissue, almost acellular in the left part. Arrows indicate two "tooth-like" processes of neovascularization.

	Fibrosis	Necrosis	Inflam. infiltrate	Organism	Calcium	Hyalini- zation	Endothe- lium	Thrombus	Neovasc- ularization	LN	Pericar- dium
TABLE 2 Histopathology of Aneurysmal Wall											
1	+	+					+	+			
2	+	+									+
3	+				+	+					
4	+	+	+			+			+		
5	+		+					+			
6	+	+	+	+	+		+		+	tb	
7	+	+							+		+
8	+		+	+				+			
9	+				+						
10	+				+						
11	+	+				+	+				
12	+				+		+		+		
13	+							+		r	
14	+		+		+			+		r	
15*				Ech							

Abbreviations: Inflam.=inflammatory; LN= lymph node; tb=tuberculosis; r=reactive; Ech=Echinococcus granulosus; *=patient has no histopathology specimen or report available.

Endothelium was the structure of aneurysmal wall in 4 cases. In one, the endothelium had been damaged with associated extravasation of the lymph into the myocardium *(Fig. 7, Lymphatics Deformation)*.

Pericardium was part of the aneurysmal wall in 2, and reactive lymph nodes were found within 2 of ASLVA specimens. In another specimen, a tuberculous lymph node was present. Thrombus within the ASLVA sac was found in 6 of the cases.

DISCUSSION

The Annular Subvalvular Left Ventricular Aneurysm (ASLVA) is a rare entity that occurs predominantly in young people almost exclusively from poor

socioeconomic groups in Sub-Saharan Africa (82% of reported cases) and South India, but has also been reported from Europe (mainly oriental and black immigrants), North America, Japan and Australia (2).

These aneurysms are usually left ventricular and are situated below the mitral and aortic valves and extending into the substance of the fibrous ring, from which the valves arise. Abrahams introduced the term "Annular Subvalvular Left Ventricular Aneurysm" in 1962 to describe this condition (1). Other terms used in the literature to describe ASLVAs are subannular, subvalvar, non-ischemic subannular, Bantu aneurysm, and supernumerary chambers of the left ventricle. The neck of an ASLVA is usually wide (0.5 to 5cm). Submitral, subaortic, left atrial wall, heart apex or a combination ASLVA cases have also been described. ASLVAs seldom coexist with sinus of Valsalva aneurysm (three cases from this study). The aneurysmal sac adjectives vary and are "finger-like," "windsock," "golf-ball," or "diverticular." Some of the ASLVAs may contain thrombus, which can be detected on echocardiography. Several causes for ASLVA have been suggested: anomalous coronary arteries, congenital weakness of the atrio-ventricular valve ring, trauma, rheumatic arteritis, endocarditis, syphilis, tuberculosis. All of these have been thought to be associated with development of ASLVA, but in those cases could not be identified as a causative factor. Tuberculous origin of those aneurysms seems to be the most likely in children. This study shows that infections associate with ASLVA more commonly and were observed in each patient reported here. These infections, which were developed prior to the diagnosis of ASLVA, seem to spread by means of lymphatic channels and cause damage to mediastinal lymph nodes. Mediastinal lymphadenopathy was detected in all patients from this report. Enlarged, inflamed or sclerotic and calcified mediastinal lymph nodes can cause obstruction of the lymph outflow from the lungs, and also from the heart.

Lymph backflow, loss of valvular function of lymphatic vessels due to increased intravascular pressures can lead to pathological dilatation and deformation of lymphatic vessels.

Patients predominantly present in congestive cardiac failure due to mitral incompetence and/or myocarditis, and sometimes with associated aortic incompetence. Only a small percentage of patients are asymptomatic, where the diagnosis of ASLVA is made accidentally, for example during evaluation of cervical lymphadenopathy. Almost all symptomatic patients have arrhythmias. Supraventricular tachycardia, atrial fibrillation, first degree heart block, nodal tachycardia, nodal bradycardia, ventricular premature beats or ventricular tachycardia, have all been reported. RBBB, LBBB and generalized low voltage on ECG were present in all patients in this series. These arrhythmias and conduction delay disturbances can be explained on a basis of the lymphatic nature of conduction tissue (3). Fibrosis with an apparent endothelial cell sheath surrounding the conduction system was first noticed by Keith and Flack in 1906 and described by Curran in 1909, who emphasized its lymphatic nature (4). The ECG can sometimes reveal features of myocardial ischemia/damage. These are predominantly seen in latero-posterior leads. Coronary angiography typically confirms normal coronary arteries despite myocardial damage.

A non-specific histopathological picture of the ASLVA wall with replacement of the surrounding heart muscle by dense scar tissue or extensive fibrosis, hyalinization, necrosis, calcification, neovascularization, inflammatory infiltrate was observed in each specimen of ASLVA wall.

Endothelium was the structure of the aneurysmal wall in only four cases reported here. Rupture of a lymphatic vessel with extravasation of lymph observed in one histopathological specimen (Table 1, patient 11), was reported earlier (5). Descriptions of ASLVAs of a vessel shape as "finger-like"
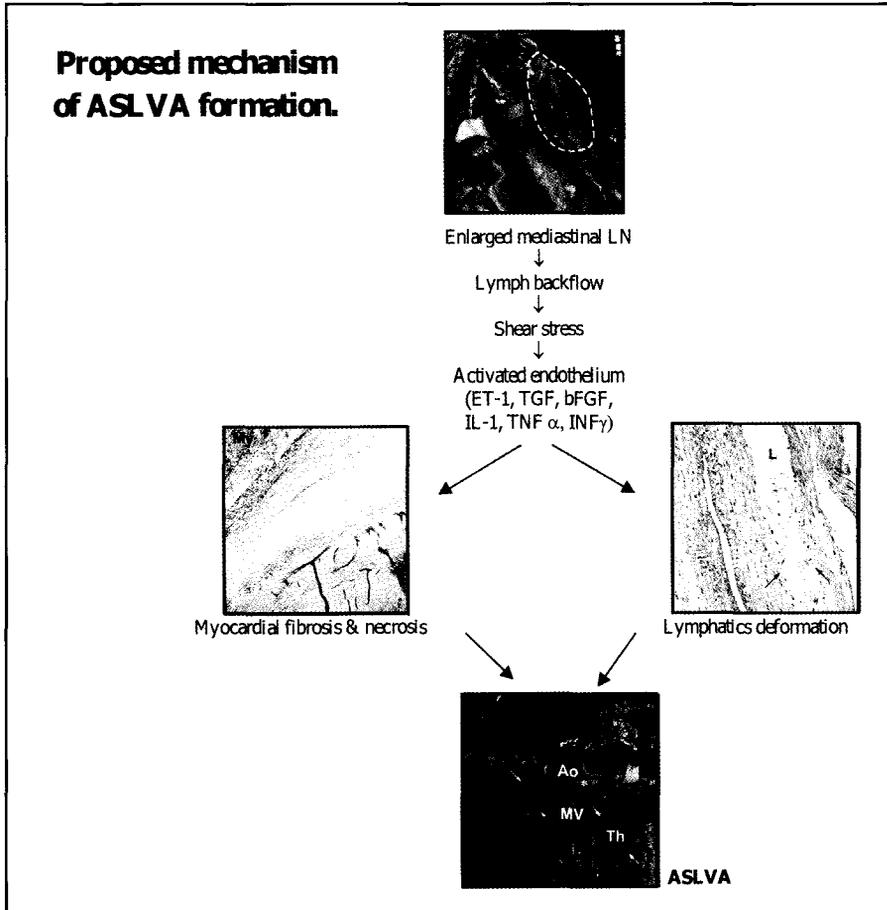
Fig. 7. Proposed mechanism of ASLVA formation. [Modified from Lupinski et al (5)].

or "windsock" have been frequently used in the literature and in our surgical notes to describe the findings.

Inflammatory infiltrate within ASLVA wall specimens was also frequently observed in ASLVA wall specimens. Organisms were present within two thrombus specimens inside macrophages.

Thrombus formation within the aneurysmal sac varies and depends on direct contact between lymph and blood. Lymph does not contain all necessary clotting factors. Fibrinogen and prothrombin in lymph are always less than in plasma, but platelets are absent resulting in a lack of thromboplastin for coagulation. If the ASLVA sac has no communication with blood, coagulation of lymph does take place but takes longer than the normal clotting process. Coagulated lymph forms frothy, friable clot, which consists of many yellowish-orange granules as was observed during necropsy in one of the reported patients (*Fig. 1*, the clot's color became brownish after several days in formalin). The other "frothy" clot was observed during surgery of submitral and apical aneurysms (*Table 2*, patient 8). Once ASLVA ruptures into the heart chambers, the lacking clotting factors are supplemented, and normal thrombus is formed (6). Laminated structure of the thrombus, frequently observed in ours and other

reported cases, is probably formed gradually from the surface towards the inner level according to the infiltration manner of the lacking clotting blood factors. However, sometimes ASLVA does not rupture and forms an intracardiac structure. This usually happens in cases of subaortic aneurysms with no communication to left ventricle as it was found in two cases from this study.

There are some published reports from Russian investigators of the heart lymphatic system describing the histopathology of experimental cardiac lymphostasis in dogs and rabbits (7). Their description of myocardial injury during lymphostasis is very similar to that observed in ASLVA reported here and from the literature. Fibrosis of the myocardium, necrosis, neovascularization, inflammatory infiltrate were all seen in animal histopathological specimens. The only difference is that hyalinization and calcification within the ASLVA wall has not been found in animals. However, the reported duration of this experimental lymphostasis lasted only 30 days compared with months to years of medical history in ASLVA patients. In one reported case, a patient developed calcification within ASLVA over a 3-year follow up period. External compression of coronary vessels by dilated lymphatics and by extravasated lymph from ruptured vessels during experimental lymphostasis can lead to myocardial ischemia followed by tissue necrosis. Reduction in the coronary artery lumen was observed at necropsy in three hearts and was due to "extrinsic pressure and not to any intraluminal obliterative process." This seems to be an explanation of frequently present (including 8 of the patients from this manuscript) Q waves and T wave abnormalities on ECG despite unobstructed coronary flow on angiography.

Proposed Mechanism of ASLVA Formation (Fig. 7)

Immunobiology of shear stress

Shear stress can lead to injury of endothelium and surrounding tissue (8). Shear stress changes endothelial cell shape and is responsible for cytoskeletal remodeling (9). It also regulates cell survival by inhibition of cell growth-sustained activation of p53, which induces the up-regulation of growth arrest and DNA damage inducible protein 45 (GADD 45) and p21. The resulting inhibition leads to endothelial cell cycle arrest and cell death (10). This could explain why endothelial cells *(Table 2)* lined just a few of the ASLVA walls reported here. Shear stress also activates Endothelin-1 gene expression in endothelial cells by inducing an early transient upregulation followed by a sustained suppression resulting in contraction and dilatation of the vessel *(Fig. 6)*.

Activated lymphocytes during infection and endothelium during shear stress release lymphokines and cytokines, which trigger certain immunobiological reactions. The evolving damage-repair process of endothelium and surrounding tissue leads to fibrosis. TGF (Transforming Growth Factor), bFGF (basic Fibroblast Growth Factor), and TNF-alpha stimulate fibroblasts to excessive collagen production (9). TGF and bFGF are both responsible for neovascularization during tissue repair processes (11,12). Activated lymphocytes and endothelium during shear stress release Interferon gamma (INF gamma) and TNF alpha-cytokines, which stimulate tissue damage and necrosis (9). Extensive fibrosis was the finding in all ASLVA wall specimens and necrosis was observed in many of them *(Table 2, Fig. 5)*. It has also been noted in experimental cardiac lymphostasis in animals that intensity of pathological changes within vascular wall were mainly determined by intensity and exposition for lymphostasis (shear stress), while etiologic factors were less important.

Biomechanics of viscous flow

The biomechanical effect of shear stress on vascular endothelium (viscoelastic struc-

ture) is obvious and depends upon pressure, fluid viscosity, degree of flow obstruction, wall strength and Young's modulus for vascular wall. In physiology, Hook's law applies stating that strain of vascular wall is proportional to intravascular pressure and intensity of flow. If pressure rises, Hagen-Poiseuille's law applies. This states that during partial obstruction of the vessel the magnitude of its dilatation is proportional to fluid viscosity and flow. Huber's strain criterion explains that the rupture of the vessel depends on wall endurance, hoop and shear stress. The rupture of vessel or aneurysmal wall may occur when strain rate exceeds wall endurance. All of these biomechanical laws are nicely represented in one of the histo-pathological specimens of ASLVA's wall *(Fig. 6)*. In this specimen, normal lymphatic vascular endothelium is present in one section, and dilated and ruptured vessel in another. Direction of tensile forces from the lower towards upper part illustrates the degree of deformation and the size of the vessels, narrow and destroyed, surrounded by almost acellular fibrous tissue in the lower part and regular lumen in the upper part.

CONCLUSION

1. Post-inflammatory destruction of mediastinal lymph nodes may obstruct lymph outflow from the heart, cause backwards lymphostasis and cause damage to lymphatic vessels of the heart.
2. Increased intravascular pressure triggers shear stress-related structural changes in lymphatic vessels and in the myocardium similar to those obtained in experimental lymphostasis.
3. Annular Subvalvular Left Ventricular Aneurysm has a lymphatic origin.

ACKNOWLEDGMENT

REFERENCES

1. Abrahams, DG, CJ Barton, WP Cockshott, et al: Annular subvalvular left ventricular aneurysms. Q. J. Med. 31 (1962), 345-360.
2. Lupinski, RW, S Vosloo, U Lupinska: Association of annular subvalvular left ventricular aneurysm in children with tuberculosis–a possible aetiological relationship. S. Afr. Med. J. 86 (1996), C212-217.
3. Uhley, HN, SE Leeds, MA Sung, et al: Subendocardial lymphatics of the canine heart. A possible role of the lymphatics in the genesis of conduction disturbances and arrhythmias. Am. J. Cardiol. 29 (1972), 367-371.
4. Curran, AJ: A constant bursa in relation with the bundle of His, with studies of the auricular connection of the bundle. Anat. Rec. 3 (1909), 618.
5. Lupinski, RW, S Shankar, KY Wong, et al: Annular Subvalvular Left Ventricular Aneurysm associated with cardiac lymphostasis. Lymphology 34 (2001), 30-32.
6. Fantl, P, JF Nelson: Coagulation in lymph. J. Physiol. 122 (1953), 33-37.
7. Zerbino, DD, AS Gavrish: Transformation in the lymphatic system of the heart and myocardium in congestion with lymph. Arkh. Patol. 37 (1975), 30-35.
8. Malek, AM, GH Gibbons, VJ Dzau, et al: Fluid shear stress differentially modulates expression of genes encoding basic Fibroblast Growth Factor and Platelet-derived Growth Factor B chain in vascular endothelium. J. Clin. Invest. 92 (1993), 2013-2021.
9. Malek AM, IW Lee, SL Alper, et al: Regulation of endothelin-1 gene expression by cell shape and the microfilament network in vascular endothelium. Am. J. Physiol. 273 (1997), C1764-C1774.
10. Lin, K, PP Hsu, BP Chen, et al: Molecular mechanism of endothelial growth arrest by laminar shear stress. Proc. Natl. Acad. Sci. USA 97 (2000),9385-9389.
11. Nicod, LP: Cytokines. Overview. Thorax 48 (1993) 660-667.
12. Liu, NF, QL He: The regulatory effects of cytokines on lymphatic angiogenesis. Lymphology 30 (1997), 3-12.

Richard W. Lupinski, MD, PhD
Department of Cardiothoracic Surgery
National Heart Centre
Mistri Wing, 17 Third Hospital Avenue
Singapore 168752
Fax: +65 62243632
E-mail: rilup2@signet.comm.sg