PULMONARY HYPERTENSION

IN

SYSTEMIC LUPUS ERYTHEMATOSUS

by

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D E C L A R A T I O N

I, Dr. A. Barkhuizen, hereby declare that the work on which this thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other University.

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This thesis is dedicated to **Cindy** *for her love and patience; and* **my parents** *for their unfailing and loyal support of my career.*

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ABSTRACT

66 female SLE patients, attending LUPUS CLINIC at Groote Schuur Hospital, were investigated for the presence of pulmonary involvement and specifically for evidence of pulmonary hypertension. The study of the relationship of pulmonary hypertension with the presence and severity of Raynaud's phenomenon, and with disease activity formed the main aim of the study. A literature review of primary pulmonary hypertension and pulmonary hypertension in systemic lupus erythematosus is presented.

The mean pulmonary artery pressure of the study patients calculated from measurements made during echocardiography was 25.9 mm Hg (SD=10.8, range=6-52), and differed significantly from the 20 control subjects:15.72 mm Hg (SD=5.59, 6-28; $p<0.0001$).

41 patients (62%) were classified as possibly having pulmonary hypertension by combined clinical, radiological, electrocardiographic and echocardiographic criteria. 12 of these patients were considered to have definite primary pulmonary hypertension, and a further 18 had probable primary pulmonary hypertension. 11 had pulmonary hypertension secondary to cardiac disease (3), fibrosing alveolitis (7) and recurrent pulmonary thromboembolism (1). Total ARA criteria differed significantly between these groups, but this assessment could have been influenced by observer bias. No association was found between the category of pulmonary hypertension and presence of Raynaud's phenomenon, or SLE disease activity score. Possible reasons for this lack of association are discussed.

Other forms of pulmonary involvement found were pulmonary infections in 38 patients (57.6%), pleural involvement in 25 (37.9%), cryptogenic fibrosing alveolitis in 9 (13.6%), asthma in 6 (9%), vanishing lung syndrome in 3 (4.6%), acute lupus pneumonitis in 2 (3%), solitary pulmonary nodule in 2 (3%) and pulmonary hemorrhage, pulmonary thromboembolism, COAD and bronchiectasis in 1 each. In conclusion, suggested methods of treatment and future avenues of research are discussed.

ABBREVIATIONS

1^0:	Primary
2^0:	Secondary
AcT:	Acceleration Time
ANF:	Anti-nuclear factor
Anti-DNA:	Anti-double stranded DNA
APL:	Anti-phospholipid antibody
approx:	approximation
ARA:	American Rheumatism Association
ATS:	American Thoracic Society
C3:	3rd component of complement
C4:	4th component of complement
CH50:	Total hemolytic complement
CIC:	Circulating immune complexes
CFA:	Cryptogenic fibrosing alveolitis
CRP:	Clinical, Radiographic, Physiologic score
C-RP:	C-reactive protein
COAD:	Chronic obstructive airways disease
curr:	current
CXR:	Chest Radiograph/X-Ray
Dig ulcer:	Digital ulceration
Durat:	Duration
ECG:	Electrocardiogram
Echo:	Echocardiogram
EDRF:	Endothelium-derived relaxing factor
ENA(Sm):	Extractable nuclear antigen (Smith)
ET-1:	Endothelin-1
FEV1:	Forced expiratory volume in 1 second
FVC:	Forced vital capacity
GSH:	Groote Schuur Hospital
Hb:	Hemoglobin
HLA:	Human Leukocyte Antigen
LV:	Left ventricle
Lymph's:	Lymphocytes
MEP:	Maximum expiratory pressure
MHC:	Major Histocompatibility Complex
MIP:	Maximum inspiratory pressure
MPAP:	Mean Pulmonary Artery Pressure
MRC:	Medical Research Council
MRI:	Magnetic Resonance Imaging
NEJM:	New England Journal of Medicine
NIH:	National Institute of Health
NO:	Nitric oxide
O_2:	Oxygen
PA:	Pulmonary Artery
PFT:	Pulmonary Function Test
PH:	Pulmonary Hypertension
pred:	predicted
PTT:	Partial thromboplastin time
PPH:	Primary Pulmonary Hypertension
PVR:	Pulmonary vascular resistance
RA:	Right atrium
RV:	Right Ventricle
RVET:	Right ventricular ejection time
SD:	Standard deviation

SLE:	Systemic Lupus Erythematosus
TLC:	Total lung capacity
$TLCO_{sb}$:	Single breath carbon monoxide transfer factor
TR:	Tricuspid Regurgitation
UCT:	University of Cape Town
uncorr:	uncorrected
unclass.	unclassified
Vasodil:	Vasodilator
VDRL:	Venereal diseases reference laboratory
VQ:	Ventilation/Perfusion
WCC:	White cell count
WHO:	World Health Organisation

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Chapter 1 BACKGROUND

1.1 Introduction

Systemic Lupus Erythematosus (SLE) is a multisystem disorder characterised by multiple auto-antibodies that participate in immunologically mediated tissue and microvascular damage. The severity, and therefore the morbidity and mortality vary widely between patients. Primary Pulmonary Hypertension (PPH) has been recognised for several decades as a serious disorder of the pulmonary vasculature resulting in cor pulmonale and death.

The co-existence of these two conditions has been documented more recently and, as might be expected, has been shown to be a particularly debilitating combination. Patients often present with advanced irreversible pulmonary vascular disease and palliative care is all that can be offered.

Recent advances in non-invasive pulmonary artery pressure measurement using Doppler echocardiography has allowed earlier diagnosis of pulmonary hypertension. Knowledge about the pathogenetic mechanisms involved, has improved considerably in recent years. This has improved the prospect of developing effective forms of therapy that might influence the prognosis of affected patients. Several forms of treatment have been proposed with some being in regular use.

1.2 Historical Perspective

1.2.1 Primary Pulmonary Hypertension (PPH)

In 1891 Romberg[1] described the autopsy findings of a patient with sclerosed pulmonary arteries without underlying pulmonary or cardiac disease. This is thought to be the first description of PPH.[2] In 1951 Dresdale et al[3] described the clinical and hemodynamic findings in 39 patients with unexplained pulmonary hypertension and coined the term primary pulmonary hypertension.

In 1958 Wood[4] proposed the hypothesis that PPH developed as a consequence of prolonged pulmonary vasoconstriction and suggested the use of vasodilator therapy. During the 1960s the publicity surrounding the appetite suppressant, Aminorex fumarate, as a cause of pulmonary hypertension, alerted the medical community to this condition in its various forms.[5]

In 1970 Wagenvoort and Wagenvoort[6] described the three histological subtypes of PPH: plexogenic, thrombotic and veno-occlusive. In 1973 the current definition of PPH was proposed by the WHO.[7] In 1981 the National Institute of Health (NIH) funded the establishment of a registry for the study of PPH in America. For 5 years, patients from 32 centers were enrolled and followed until 1989, thus providing very useful clinical and long term follow-up data.[8]

Treatment options for patients have been limited due to the advanced stage of the pathology by the time symptoms develop. In the 1980s and 1990s numerous reports of the use of vasodilators appeared.[9-13] The common finding of in situ thrombosis at post-mortem has prompted the use of anticoagulants.[14] In the 1990s, heart-lung, single-, and double-lung transplantation has emerged as salvage therapy for advanced disease.[15-17] The lack of donors and cost of transplantation limit its widespread application. Early diagnosis and treatment, before irreversible heart failure occurs, remains the major objective of management and research protocols.[18,19]

1.2.2 Pulmonary Hypertension in Systemic Lupus Erythematosus

In 1983 Hodson et al[20] described the Cape Town experience with 4 cases of Pulmonary Hypertension (PH) and SLE. These authors were able to find 17 cases of this association in the literature, the earliest being presented in 1964 in the case records of the Massachusetts General Hospital.[21] Several overseas groups have reported their experience with this association.[22-27] In these reports no alternative cause for the PH could be found, favouring the postulate that PPH occurs as a direct consequence of SLE.

1.3 Clinical Features of Primary Pulmonary Hypertension

1.3.1 Definition

PPH is defined by the World Health Organisation (WHO) as a mean pulmonary artery pressure of greater than 25 mm Hg at rest or 30 mm Hg during exercise.[7] By definition there should be no demonstrable cardiac or pulmonary cause for the PH.

1.3.2 History

Dyspnea is the commonest presenting symptom, and was reported in 90% of cases in the NIH registry.[8] The dyspnea worsens progressively as the disease advances, and is aggravated by hypoxemia-induced hyperventilation.

Chest pain is a common symptom. As the coronary arteries are usually normal, it is probably due to relative underperfusion of the hypertrophied right ventricle, or due to stretching of the large pulmonary arteries.

Syncope occurred in 10% of cases in the NIH registry. This usually occurred during or after exercise, and is probably due to a fixed cardiac output. Arrhythmias may also be responsible as severe hypotension can occur during atrial tachyarrhythmias.

10% of the NIH patients had Raynaud's phenomenon. Hoarseness may occur due to compression of the recurrent laryngeal nerve by the enlarged pulmonary artery. Cough and hemoptysis are less frequent symptoms.

At the onset of right ventricular failure, edema develops and upper gastro-intestinal congestive symptoms of distention, nausea, anorexia and wasting become prominent.

1.3.3 Examination

In its early stages no signs are present. A loud pulmonary, and a narrowly split second heart sound, and a right ventricular heave are often the earliest signs. As the disease progresses, signs of right ventricular failure develop: edema, a raised venous pressure with CV waves, a pulsatile liver and the murmur of tricuspid regurgitation. Cyanosis is mild, unless a congenital heart defect has been missed, or re-opening of the foramen ovale has allowed right to left shunting. Clubbing is rare.

1.3.4 Chest Radiograph (CXR)

A CXR is an important part of the diagnostic work-up to exclude pulmonary or cardiac disease. The main and hilar pulmonary arteries were enlarged in 90 % and peripheral pulmonary arteries were pruned in 51 % of the NIH registry cases. The lung fields are usually clear. A normal CXR was found in 6 % of the cases with PH confirmed at cardiac catheterisation.

In 1962 Chang[28] reviewed the chest X-rays of 1085 normal subjects. He reported normal values for the diameter of the right descending pulmonary artery from its lateral aspect to the air column of the bronchus intermedius: 16 mm in males and 15 mm in females. This is measured on an inspiratory film and reduces by 1-3 mm in expiration. These measurements have been incorporated as normal values into radiology textbooks[29-31] and has been measured as part of this study.

1.3.5 Electrocardiogram (ECG)

ECG changes are usually only seen in advanced cases. The ECG abnormalities are mainly those of right ventricular and atrial enlargement: right axis deviation; right bundle branch block pattern; tall R waves, ST segment depression and inverted T waves in V_1-V_2; and tall peaked p waves.[32]

1.3.6 Pulmonary Function Tests (PFT's)

PFT's are performed to exclude obstructive or restrictive lung disease. Mild abnormalities in lung volumes are found due to increased stiffness of the lungs.[8] The transfer factor is often reduced. This is thought to be due to increased capillary-alveolar distance caused by the pulmonary vascular disease or a reduced pulmonary capillary bed.

Hypoxemia is common and is due to ventilation-perfusion mismatches. In the occasional patient it is due to shunting through a patent foramen ovale.

1.3.7 Perfusion lung scan

The perfusion lung scan serves as the most useful, although not sensitive investigation for excluding recurrent pulmonary emboli as the cause of PH. 60 % of patients with PPH have abnormal ventilation/perfusion (VQ) scans, with mostly patchy defects, and in a minority, single subsegmental defects. Segmental and lobar defects are a feature of thromboembolism.[8] D'Alonzo et al[33] were able to differentiate PPH from thromboembolic PH using VQ scans in 25 cases studied. The former had low and the latter high probability scans.

1.3.8 Pulmonary angiogram

Some authors suggest performing pulmonary angiography when the lung scan shows single or multiple, segmental or lobar defects to confidently exclude pulmonary thromboembolism.[2] In PPH there is peripheral pruning of vessels with dilated central vessels, and in chronic thromboembolism there are cutoffs of large proximal vessels or filling defects. Because of the potential side effects of further increasing the pressure and even causing death, the procedure is controversial.[34]

1.3.9 Right heart study

Cardiac catheterisation remains the gold standard for diagnosing PPH. It confidently excludes cardiac disease and allows accurate measurement of the pulmonary artery (PA) pressure. It is also possible to assess vascular responsiveness to vasodilators administered during the procedure.[19,35] This however, may on occassion cause severe hypotension. Cardiac catheterisation has a substantial mortality. The Mayo Clinic reported 5 deaths in 120 patients studied for PH.[34] The NIH registry group had no deaths but severe hypotensive episodes or hemoptysis occurred in 10 of their patients.[8]

1.3.10 Echocardiogram

Echocardiography has emerged as an important noninvasive diagnostic tool in PPH. It excludes cardiac causes of PH eg. silent mitral stenosis and intra-cardiac shunts. It allows visualisation of pulmonary valve motion and characteristic patterns have been described in PH: a rapid opening slope in systole, attenuation or absence of the "a" dip,[36,37] prolongation of the right ventricular pre-ejection period to right ventricular ejection time,[37,38] and midsystolic semi-closure of the pulmonary valve.[36,37]

With the advent of doppler echocardiography, pulmonary artery pressure can now be quantified non-invasively and with acceptable accuracy. The doppler can often detect trivial tricuspid regurgitation (TR), and the measurement of the transtricuspid pressure gradient allows one to estimate the right ventricular systolic and pulmonary artery pressures. In a study by Chan et al[39] this measurement correlated well with PA pressure measured by cardiac catheterisation (r=0,87). Adequate TR signals for pressure gradient estimation were found in 72 % of cases in their study. In other laboratories - including our institution - TR is often not detected, necessitating the use of other measurements for PA pressure estimation.

Kitabatake et al[40] studied the doppler-derived blood flow characteristics in the right ventricular outflow tract of patients undergoing cardiac catheterisation. Cases with pulmonary hypertension had a rapid acceleration of flow velocity (AcT); a shortened right ventricular ejection time (RVET); and a reduced ratio of AcT/RVET. The AcT and ratio of AcT/RVET were correlated with the catheter data for mean pulmonary artery pressure by means of linear regression analysis. The measurements used were the average of readings from five to eleven consecutive cardiac cycles and importantly did not require the presence of TR. The $\log_{10}$(MPAP) correlated in a linear fashion with these measures, with the following regression equations and correlation coefficients:

Equation 1:	$\log_{10}(MPAP) = -0.0068(AcT) + 2.1$	r=-0.88
Equation 2:	$\log_{10}(MPAP) = -2.8(AcT/RVET) + 2.4$	r=-0.90

Chan et al [39] used the following equation for MPAP:

Equation 3:	MPAP = 79 - (0.45 x AcT).	r=0.85

The r-value was 0.66 but improved to 0.85 for heart rates between 60 and 100.

1.3.11 Magnetic Resonance Imaging (MRI)

MRI with its excellent resolution has recently been used to estimate ventricular mass. Katz et al[41] were able to estimate accurately the ventricular mass of 10 fresh bovine hearts. In healthy volunteers and patients with PPH, the right ventricular myocardial mass was calculated from end-diastolic MRI images of the heart. An RV index - ratio of RV mass and body surface - was determined and correlated with the invasively measured PA pressure with the following regression equation and corrrelation coefficients:

Mean PA pressure = 27.09 +(0.59 x RV index)	r=0.75, p<0.003

1.3.12 Pathology

Wagenvoort and Wagenvoort[6] described three histological subtypes of PPH: plexogenic pulmonary arteriopathy, recurrent microthromboembolism, and pulmonary veno-occlusive disease. The WHO[7] included these types in their position paper on PPH. A recent editorial by Rich[42] questioned the distinction. Other workers in the field, however, are able to distinguish the subtypes on open lung biopsy[43], and found it helpful in categorising patients with unexplained PH. The increased morbidity of open lung biopsy in patients with PH has resulted in limited use of this investigation.

Moser and Bloor[44] caution against accepting a biopsy diagnosis of PPH on the basis of the presence of plexogenic and other characteristic findings. Several cases are sited where lung scans and angiograms identified evidence of chronic major vessel thromboembolism in the so-called PPH cases. Pulmonary thromboendarterectomy was performed on these patients with good results.

1.4 Pathogenesis of Pulmonary Hypertension

1.4.1 Primary Pulmonary Hypertension

Many articles have been published which describe different individual mechanisms at play in PPH. The pathogenesis of PPH is, however, probably multifactorial.

Wood considered pulmonary vasoconstriction to be an important pathogenetic factor.[4] The presence of Raynaud's phenomenon in 10 % of cases with PPH in the NIH registry, lent support to this hypothesis.[8]

In 1988 at the 30th Aspen Lung Conference Hogg[45] postulated that abnormal smooth muscle activation might result in reduced pulmonary vessel diameter, and a raised PA pressure. He suggested that it might be an abnormality of receptor or agonist-receptor interaction, but no proof of this was provided.

In 1989 at the Third Grover Conference on the Pulmonary Circulation, Reid[46] pointed out the importance of the endothelium. It acts as a monitor of homeostasis, and processes mediators on their way to the vessel wall, where they cause structural changes.

Endothelin-1 (ET-1), a potent endothelial derived vasoconstrictor with mitogenic properties, has been the subject of various studies. Increased levels of ET-1 have been implicated in the pathogenesis of such varied disorders as the hepatorenal syndrome, diabetes mellitus, cardiogenic shock, and systemic and pulmonary hypertension.

Stewart et al[47] found increased **circulating** levels of ET-1 in all forms of PH. This could be due to increased release, or reduced clearance of ET-1. In PPH patients, a significantly increased arterial compared to venous level was found, suggesting increased pulmonary release or production of ET-1. The vascular damage found in secondary PH could result in reduced ET-1 clearance.

Cacoub et al[48] demonstrated increased **venous** ET-1 levels in PPH and in the Eisenmenger syndrome. In PPH mean ET-1 levels were higher, despite having lower PA pressures than the Eisenmenger syndrome group. A follow-up study by the same authors[49] using a radioimmunoassay for ET-1 levels in **pulmonary** tissue, demonstrated increased levels both in patients with PPH and the Eisenmenger syndrome compared to controls.

Giaid et al[50] performed immunocytochemical analysis for the distribution of endothelin-1-like immunoreactivity on lung specimens. There was a significant increase in staining in the **vascular endothelium** of the PPH group, and to a lesser extent in the secondary PH group. The endothelium of elastic and muscular pulmonary arteries with severe medial thickening and intimal proliferation had the greatest degree of immunostaining. The staining was shown to a lesser extent in pulmonary capillaries and veins as well as bronchial arteries. No staining was found in systemic vessels of cases with PH and minimal staining was found in control lung specimens.

Subsequently the authors demonstrated endothelin-1 messenger RNA by in situ hybridization. Its distribution matched closely that of the endothelin-1-like immunoreactivity in the lungs of patients with PH. This confirmed the hypothesis that increased ET-1 levels in cases with PH were due to its local production rather than reduced clearance. The initiating stimulus for this increased production is unknown. An unexpected finding was the expression of ET-1 in alveolar epithelial cells, which occurred almost exclusively in patients with pulmonary fibrosis. This suggested a role for ET-1 in other pulmonary diseases where cellular proliferation occurs.

The presence of thrombi in the pulmonary vasculature of cases with PPH has already been mentioned. It may be formed in situ on a damaged endothelium via platelet-endothelium interactions.[51] Disordered fibrinolysis has been demonstrated in PPH by Eisenberg et al,[52] and this may result in reduced clearance of thrombi.

Autoimmune mechanisms may play a role in PPH. The association of PPH with autoimmune disorders such as SLE favors this hypothesis. Raynaud's phenomenon, frequently found in autoimmune diseases, is also reported in PPH.[8]

Many autoimmune diseases have an association with the human leukocyte antigen (HLA) class II determinants of the major histocompatibility complex (MHC). Barst et al[53] found an increased incidence of DR3, DRw52, and DQw2, and a decreased DR5 in children with PPH. In children with congenital heart disease with large shunts resulting in PH, no HLA association was found. In PPH, the specific MHC may be expressed on endothelial cells, and may lead to the induction of cytokines with resultant vascular smooth muscle changes.

In animal models[54] of PH, inflammatory cells are prominent in vessel walls suggesting an immune basis for some of the vascular damage. This has not been found in human cases of PPH. The inflammatory phase of PPH may, however, have been missed if it occurs very early in the disease.

Current researchers suggest that the endothelium is central to the pathogenesis of PPH. In a recent editorial[55] Loscalzo states ".... that pulmonary endothelial dysfunction and abnormal vascular response have an important bearing on the pathogenesis, diagnosis, and treatment of pulmonary hypertension." He however points out, that it is unclear, whether this endothelial dysfunction is a cause, or consequence of the pulmonary hypertensive process.

Pulmonary veno-occlusive disease is a rare form of PPH and is characterised by intimal proliferation and fibrosis of the intrapulmonary veins and venules. It has been described after viral illness, chemotherapy and toxins.[2] Very little is known about its pathogenesis.

1.4.2 Secondary Pulmonary Hypertension

In more than 95% of cases of PH, it is secondary to cardiac, pulmonary or systemic disease. Olivari[2] in a comprehensive review of PH classifies the causes and pathogenetic mechanisms as follows:

a) Cardiac Disease

i. Prolonged increased pulmonary flow exceeding the pulmonary vascular reserve, will result in excessive shear forces causing endothelial damage, intimal proliferation, medial hypertrophy and raised pulmonary vascular resistance, and is mediated by the same substances as PPH. This may occur in left to right shunts through ventricular and atrial septal defects, or a patent ductus arteriosus.

ii. Increased resistance to pulmonary venous drainage with persistently elevated left atrial pressure results in PH. Such increased resistance occurs in:
- left ventricular failure, eg. cardiomyopathy, valvular and ischemic heart disease
- reduced LV compliance, eg. hypertension, hypertrophic cardiomyopathy
- mitral valve disease, eg. mitral stenosis
- left atrial myxoma and
- pulmonary vein stenosis.

b) Pulmonary Parenchymal Disease

This is the commonest cause of PH in adults. Anatomical loss of pulmonary vessels, arteriolar constriction secondary to hypoxemia, and increased viscosity cause a raised pulmonary artery pressure. This occurs in chronic obstructive airways disease, restrictive lung disease, granulomatous disease, and cystic fibrosis.

c) Disease of Respiratory Function

Alveolar hypoventilation with hypoxemia and acidosis results in pulmonary vasoconstriction and pulmonary hypertension. Examples of such diseases are: thoracic cage deformities, sleep apnea syndrome, obesity hypoventilation syndrome, and neuromuscular diseases.

d) Pulmonary Vascular Disease

Anatomical obstruction to pulmonary flow results in increased resistance and pulmonary artery pressure. This occurs in: pulmonary thromboembolism, pulmonary arteritis (Takayasu's disease), collagen vascular disease, sickle cell anemia, schistosomiasis, peripheral pulmonary artery stenosis, and high altitude.

e) Miscellaneous causes with unclear mechanisms include: intravenous drug abuse, appetite suppressants, bush tea, and hepatic cirrhosis.

1.4.3 Pulmonary Hypertension in Systemic Lupus Erythematosus

The pathogenesis of pulmonary hypertension in SLE is unknown. Considering the range of microvascular pathologies and immunological phenomena found in this disease, a multifactorial aetiology is likely. Peripheral vasospasm (Raynaud's phenomenon) is a common early feature of SLE and may reflect a more general tendency to systemic vasospasm affecting organs such as the lungs. If this is indeed the case, it is possible that factors provoking Raynaud's phenomenon may provoke a transient increase in pulmonary vascular resistance. Furthermore, just as the changes in the fingers become fixed and permanent, so pulmonary vasospasm might become irreversible as a consequence of prolonged vasospasm. Several studies have been performed to investigate this relationship and hypotheses.

Cattle, with hyperreactive pulmonary vasculature, at an altitude of 1524 m, have been shown to develop PH when placed into a -5 ^{0}C chamber.[56]

Using single breath carbon monoxide transfer factor ($TLCO_{sb}$) as an indicator of pulmonary blood volume, several investigators have shown changes during cold pressor testing in patients with Raynaud's phenomenon. Vergnon et al[57] immersed the hands and forearms of subjects into 15 ^{0}C water and demonstrated a drop in $TLCO_{sb}$ in both patients with 1^0 and 2^0 Raynaud's, but not in controls. Fahey[58] demonstrated a drop in a 1^0 Raynaud's group and no change in 2^0 Raynaud's or normal controls. Wise et al[59] used whole body immersion at 4 ^{0}C, and found no change in $TLCO_{sb}$ in cases with Raynaud's 2^0 to scleroderma, but found an increase in normals and 1^0 Raynaud's. This was interpreted as redistribution of blood from the peripheral to pulmonary circulation in the latter 2 groups. Due to pulmonary vascular disease in scleroderma group, the pulmonary vasculature could not accomodate the redistributed blood, thus explaining the unchanged $TLCO_{sb}$. Miller[60], using hand immersion, demonstrated an increased $TLCO_{sb}$ in 1^0 Raunaud's, and no change in Raynaud's 2^0 to scleroderma, or in normals. The results from the latter two studies thus differed from the first two. It must, however, be noted that the numbers of patients were small, and the changes noted in $TLCO_{sb}$ were very small (albeit statistically significant). In addition, very few cases with SLE and no cases with PPH or PH were included in the above studies. Performing a similar study in patients with SLE and PH may shed more light on the link between peripheral and pulmonary vasospasm.

The association of antiphospholipid antibodies and SLE is well known. Such patients have a tendency to arterial and venous thrombosis, and this may predispose to the development of PH in patients with SLE.

Immune complex deposition in vessel walls, or T cell mediated vascular injury with vasculitis, frequently occurs in SLE. When this occurs in the pulmonary vasculature, narrowing of the vessels may occur with consequent PH. Quismorio et al[61] found immune complexes and vasculitis in pulmonary vasculature of patients with SLE and PH. Asherson et al[25] suggest that this immune complex deposition demonstrated in the pulmonary vasculature is merely a reflection of its widespread deposition, and that it does not necessarily play a pathogenetic role. In a single case report, a patient with SLE and PH had a reduction in pulmonary artery pressure during a course of cyclophosphamide, which provides putative evidence for pulmonary vasculitis.[62]

Interstitial lung disease may occur in patients with SLE. In advanced disease, a combination of hypoxic pulmonary vasoconstriction and fibrotic damage of vessels may result in PH.

1.5 Management of Primary Pulmonary Hypertension

1.5.1 Exclude secondary causes

The first step in the management of PPH is to confirm the diagnosis, ie. to exclude the secondary causes that are potentially treatable eg. mitral stenosis.

Until more is known about the exact cause and relevant pathogenetic mechanisms, treatment is largely symptomatic and often using a "shotgun" approach.

1.5.2 Oxygen (O2) therapy

If hypoxemia is demonstrated, O_2 supplementation should be considered to reduce pulmonary vasoconstriction, myocardial ischaemia and arrhythmias.

1.5.3 Anticoagulants/antiplatelet agents

Due to the frequent finding of thrombi in pulmonary vessels at autopsy, anticoagulants are widely used and are associated with improved survival when used alone[14], or in combination with vasodilators.[83] Antiplatelet agents may also be beneficial in reducing platelet aggregation and thrombosis, but may increase the risk of bleeding especially if they are combined with anticoagulants.

1.5.4 Vasodilators

Vasodilator agents remain the mainstay of PH treatment. Calcium channel blockers have been used with varying success. Controversy still exists over the need to confirm vasoresponsiveness.[63] This unfortunately entails performing cardiac catheterisation with its inherent risks to patients with raised PA pressure. Rich[12] recommended using high dose calcium channel blockers in hemodynamic testing, to identify responsive patients for long term treatment. Calcium channel blockers are, however, not without side effects, particularly hypotension. Noncardiogenic pulmonary edema, possibly due to leaky capillaries, has also been reported following the use of high doses of calcium channel blockers.[64]

Adenosine reduces pulmonary vascular resistance and PA pressure.[65] It compares favorably to nifedipine[11] and these drugs may be used in combination.[9] The disadvantage of adenosine is the lack of an oral formulation.

Uren et al[10] demonstrated some reduction in pulmonary vascular resistance (PVR) and PA pressure with acetylcholine, calcitonin gene-related peptide and nicardipine, but no response to substance P. Apart from nicardipine, these agents are all endothelium-dependent vasodilators and administered parenterally.

Prostaglandins cause vasodilation. In several forms of severe PH, including the toxic oil syndrome, a prostacycline-stable analogue (Iloprost) was infused with good effect.[66] Aerosolised prostacycline (PGI_2) similarly reduced the PA pressure in ventilated patients with the adult respiratory distress syndrome (ARDS).[67]

Endothelium-derived relaxing factor (EDRF), a potent vasodilator, has been shown to be nitric oxide (NO). It is rapidly inactivated by binding with hemoglobin. When inhaled, it diffuses into the pulmonary interstitium and acts directly on the vascular smooth muscle, causing vasodilation and a reduced PA pressure. This has been demonstrated in sheep,[68] as well as in patients with ARDS,[69] severe PPH,[70] and chronic obstructive airways disease.[71] Currently it has limited clinical usefulness due to its rapid inactivation. Administration via inhalation is preferable to the oral or parenteral route as it acts locally on the diseased vasculature without systemic effects.

1.5.5 Immunosuppression

Immunosuppressive agents have been used for PPH when a collagen vascular disease is present.[62] The lack of effect in most patients is not unexpected, as little inflammation is evident in most cases assessd by open lung biopsy or at post-mortem examination.

1.5.6 Transplantation

Transplantation has become a viable treatment option for advanced cases of PPH, with the recent improvements in treatment of rejection and improved surgical expertise. Parquin et al[15] found no difference in the actuarial survival between heart lung and double lung transplantation for severe PPH. Frist et al[16] performed single lung transplantation on five patients with severe PH (two with PPH) and all were alive at mean follow-up of 412 days. Despite severe preoperative right ventricular dysfunction, in all cases the pulmonary vascular resistance normalized, and full cardiac recovery occurred postoperatively. This may be attributed to the transplanted lung receiving >85 % of the cardiac output. In view of the universal shortage of organs, single lung transplantation is now the preferred surgical treatment.

Higenbottam et al[17] reported the survival data of 44 patients with PPH, treated with long term intravenous prostacycline while waiting for heart-lung transplantation. The patients were pre-tested for vasoresponsiveness, and those with the least vasodilation, had the best survival figures when treated with prostacycline. At a glance this seems paradoxical, and contrasts with the survival data of vasodilators reported by Rich et al[83]. The responsible mechanism is probably prostacycline's powerful inhibition of platelet aggregation, rather than vasodilation. The prostacycline reduced the monthly mortality risk by 66%, as compared to the 18% reduction achieved with heart-lung transplantation. The advantage to the patient of transplantation is that the constant intravenous infusion can be discontinued. Prostacycline however buys time in these patients for a donor to become available.

In view of the poor survival rates of clinically evident PPH, better tests are required for earlier diagnosis of PPH. As the pathogenesis becomes known, more specific and practical therapeutic modalities may become available.

Chapter 2 STUDY

2.1 Aim

The aim of this study was to evaluate patients with SLE for pulmonary involvement - in particular the presence of pulmonary hypertension - and to investigate the relationship of peripheral vasospasm (Raynaud's phenomenon) to pulmonary vasospasm.

2.2 Hypotheses

The study tested the following hypotheses:

1. Pulmonary hypertension is more common in SLE than previously recognised.

2. Pulmonary hypertension is strongly associated with the presence of peripheral vasospasm in SLE.

3. Pulmonary hypertension is associated with active SLE.

2.3 Study Design

A case study of patients attending LUPUS CLINIC over a 15 month period to determine the prevalence of pulmonary involvement including pulmonary hypertension and the associations mentioned above.

2.4 Definitions

The following criteria were used to define:

2.4.1 Systemic Lupus Erythematosus

At least 4 of following 11 American Rheumatism Association (ARA) Criteria[72]:

1. Malar rash
2. Discoid rash

3. Photosensitivity
4. Oral ulcers
5. Arthritis: non-erosive arthritis involving at least 2 or more peripheral joints
6. Serositis: pleuritis - history, rub or effusion or pericarditis - rub, ECG or effusion
7. Renal: persistent proteinuria > 0.5 g/day or 3+ on paper stick testing
8. Neurologic: seizures or psychosis
9. Haematologic: haemolytic anaemia with reticulocytosis or leucopenia <4000/mm^3 or lymphopenia <1500/mm^3 or thrombocytopenia <100 000/mm^3
10. Immunologic: increased anti-DNA antibody levels or increased ENA(Sm) or false positive serological test for syphilis for at least 6 months
11. Anti-nuclear antibody (ANF): abnormal titre

Patients with an overlap syndrome or a mixed connective tissue disease were excluded.

2.4.2 Pulmonary Hypertension

Major and minor criteria were used to define PH.

Major criteria:

1. Direct measurement by Swan Ganz catherization: mean PA pressure > 25 mm Hg

2. Echocardiograph: mean PA pressure > 40 mm Hg

Minor criteria:

1. Chest Radiograph: enlarged pulmonary arteries, right ventricle or both as judged by a chest radiologist

2. Clinical features: one or more of palpable and/or loud P2, RV heave and/or RV failure

3. Electrocardiograph: two or more of tall R in RV leads and AVR; deep S in I,II,III; small q in V1; RBBB; R axis; RV strain; and p > 1,5 mm tall

4. Histology: hypertrophied pulmonary arteries/arterioles on open lung biopsy, or at autopsy, assessed on pathological criteria

The pulmonary hypertension group was divided into:

Definite pulmonary hypertension - At least one major criterion

Probable pulmonary hypertension - Echo PAP: 20 - 40 and 1 or more minor criteria

Possible pulmonary hypertension - Echo PAP: 20 - 40 and no minor criteria

Pulmonary hypertension was further subdivided into:

Primary - absence of any known cause of pulmonary hypertension and

Secondary - presence of one of the following conditions:

Heart disease eg. mitral stenosis, L to R shunts

Pulmonary thromboembolism

Interstitial lung disease:

- radiographic diffuse infiltrate
- restrictive lung defect (FVC < 66 % predicted)
- TLCO < 66 % predicted
- biopsy evidence

Obstructive lung disease:

- radiographic hyperinflation
- FEV1/FVC < 75 % predicted
- TLC > 120 % predicted
- RV/TLC > (predicted ratio+10%)

2.4.3 Pulmonary Involvement

Acute infections: bronchial - cough productive of purulent sputum with no evidence of consolidation clinically or on CXR, and treated with antibiotics

pneumonia - cough productive of purulent sputum with evidence of consolidation clinically or on CXR, usually requiring admission

pulmonary tuberculosis - radiographic evidence and usually microbiological confirmation

Pleural: pleuritic chest pain, pleural rub or pleural effusion (clinically or on CXR)

Fibrosing alveolitis: dyspnea, clubbing and crackles, diffuse infiltrate on CXR, restriction on PFT's and reduced TLCO, and histological diagnosis (if available)

Pulmonary hemorrhage: hemoptysis presumed to be due to diffuse pulmonary vasculitis (capillaritis), once known causes of hemoptysis have been excluded

Vanishing lung: diaphragmatic weakness as evidenced by small lung volumes clinically and on CXR, reduced maximum inspiratory and expiratory mouth pressures (MIP's and MEP's), and absence of interstitial involvement

Bronchiectasis: chronic sputum production with crackles and CXR abnormality (ring shadows and tramlining)

Acute lupus pneumonitis: acute dyspnea, crackles, pulmonary infiltrate on radiograph not due to fluid or infection, and rapid response to corticosteroids.

2.4.4 Raynaud's Phenomenon

A three colour change of the skin of the digits to white, blue or red, usually on cold exposure.

2.4.5 Raynaud's Severity

A visual analogue score was used to grade the patient's perception of the severity of peripheral vasospasm on the study day. A score of 0 = no vasospasm up to 10 = extreme vasospasm was used. The grading took into account the current weather/temperature, the duration of vasospasm, and the severity of vasospasm as witnessed by colour changes and interference with hand function.

2.4.6 The Physician's global assessment of disease activity

Disease activity was graded on a visual analogue scale from 0 - 10. A score of 0 = inactive up to 10 = highly active was used, according to a combination of the following clinical and laboratory criteria.

Clinical criteria: Arthritis/arthralgias, Raynaud's phenomenon, active skin involvement, mouth ulcers, serositis, and neuropsychiatric manifestations.

Laboratory criteria: Renal-proteinuria, and casts
Hematologic-anemia, thrombocytopenia and leukopenia/lymphopenia
Immunologic-increased immune complexes and hypocomplementemia

2.4.7 Clinical, Radiographic, Physiologic (CRP) Score[73]

0 = no dyspnea after 30 minutes activity
2 = 5 flights of stairs , 10 minutes activity
4 = 2 km level , 3 flights of stairs
6 = 400 m to 2 km level , 2 flights of stairs
8 = 100 to 400 m level , bedmaking
10 = 50 to 100 m level , 1 flight of stairs
scrubbing , factory work
12 = 15 to 50 m level , housework
14 = 6 to 15 m level , light work
16 = walking < 6 m , minor effort , prolonged talking
18 = eating , writing
20 = at rest

2.5 Methods

2.5.1 Study Patients

Female patients attending the weekly LUPUS CLINIC were recruited randomly by the investigator, and were fully evaluated for current pulmonary involvement. A current respiratory and rheumatological history was obtained and a clinical examination was performed. (See Appendix A)

2.5.2 Controls

An echocardiogram was performed on age matched healthy female volunteers to ascertain a normal range for the PA pressure measurements using the AcT and RVET method.

2.5.3 Laboratory Investigations

Blood tests for serological and activity markers and the anti-phospholipid antibody were performed if not previously performed in the preceeding 3 months. (See Appendix B) Urine dipstix and microscopy was performed. Urine results obtained at the previous visit were used if the patient was menstruating on the study day.

2.5.4 Chest Radiograph

A postero-anterior inspiratory CXR was performed on all the patients, using the same apparatus in the Respiratory Clinic Radiology Department. All current and available past chest films were reviewed by the same chest radiologist without any clinical or laboratory information. On the current film particular care was taken to measure the diameter of the right descending pulmonary artery. Pulmonary and cardiac abnormalities were recorded on the Data Sheet (Appendix A).

2.5.5 Electrocardiogram (ECG)

A standard twelve lead ECG was performed on a MAC 15 computerised ECG machine (Marquette Electronics Inc.) and analysed for relevant abnormalities (See definitions).

2.5.6 Pulmonary Function Tests

A flow-volume loop and single breath carbon monoxide transfer factor ($TLCO_{sb}$) were performed on the Masterlab Jaeger automated system, (Jaeger, Wurzburg). The American Thoracic Society (ATS) standardised criteria[74] were adhered to. Volumes were reported in millilitres and as percentage predicted (% pred) using the predicted values of Schoenberg et al[75] and the $TLCO_{sb}$ predicted values were taken from Cotes.[76] The $TLCO_{sb}$ was corrected for hemoglobin using the formula of Cotes et al.[77] Results were further reported as normal, mild, moderate and severe. (See Appendix C) MIP's and MEP's were performed using a pressure gauge manometer as described by Black and Hyatt[78].

2.5.7 Echocardiogram (Echo)

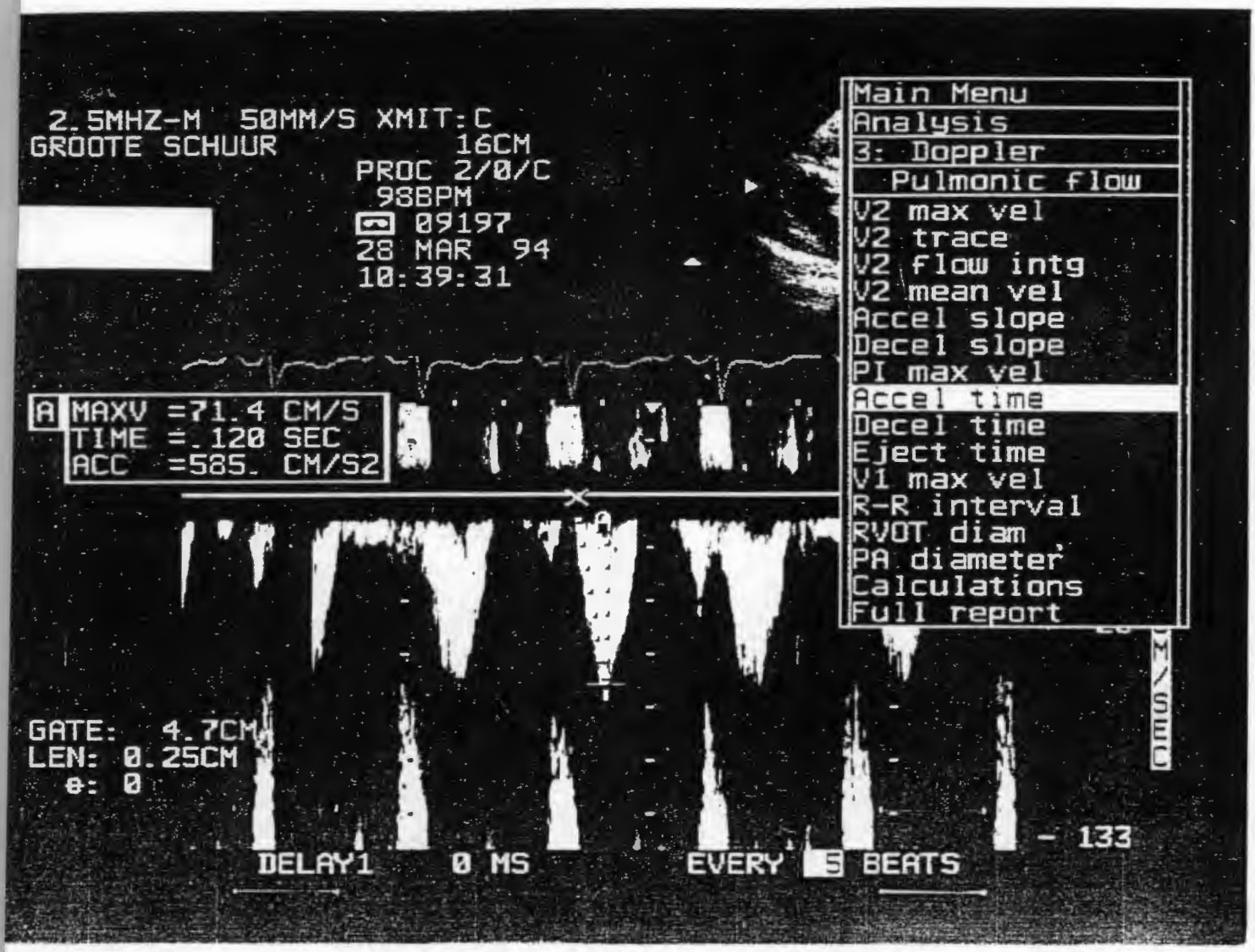
An echocardiogram was performed using a Hewlett Packard Sonos 500 machine with a 2.5 MHz transducer. An M-mode echo was performed to identify any cardiac abnormality and measure the cardiac output. A continuous wave doppler was performed to identify TR and to estimate the PA pressure. In most cases the RV outflow tract was also sampled, and the pulmonary artery acceleration time (AcT) and right ventricular ejection time (RVET) during four to five cardiac cycles was recorded. See fig 2.1. The regression equation 3 described in Chapter 1.3.10 was used to calculate the PA pressure.

2.5.8 Folder Review

Finally all available hospital and Lupus Clinic records were reviewed for past pulmonary involvement.

Figure 2.1

Echocardiographic doppler tracing of pulmonary artery outflow tract to demonstrate the measurement of AcT and RVET



2.5.9 Statistical Analysis

A data sheet was used to record all data (see appendix A) and entered on the MRC computer. The SAS/BASE and SAS/STAT software (SAS Institute Inc, Cary, N.C., USA) was used for univariate and multivariate analysis by the MRC statisticians. For all analyses, $p < 0.05$ was considered to be statistically significant. Depending on the sample size, the Chi square approximation test was used for samples with more than 5 observations per cell, or the Fisher exact 2-tailed test for less than 5 observations per cell.

2.6 Ethical Considerations and Funding

Informed consent was obtained from all patients and control subjects included in the study. (Appendix D) Permission for the study was granted by the Ethics and Research Committee of the University of Cape Town Medical School. Funding was obtained from the Medical Research Council and the Nellie Atkinson fund.

2.7 Results

2.7.1 Study Period

The study was conducted between November 1992 and February 1994 at the Lupus Clinic at Groote Schuur Hospital and the University of Cape Town, South Africa. Approximately 120 patients with SLE are regularly followed at this clinic which serves as the major academic referral centre in the Western Cape.

2.7.2 Study Patients

The study patients consisted of 66 females fulfilling 4 or more of the 1982 ARA criteria for SLE. There were 60 coloured and 6 black patients with a mean age of 39 years (SD=11.5, range=14.4-72.4). The mean disease duration was 9 years (SD=7.3, range=0.5-36.4). 3 patients refused to participate in the study.

2.7.3 History

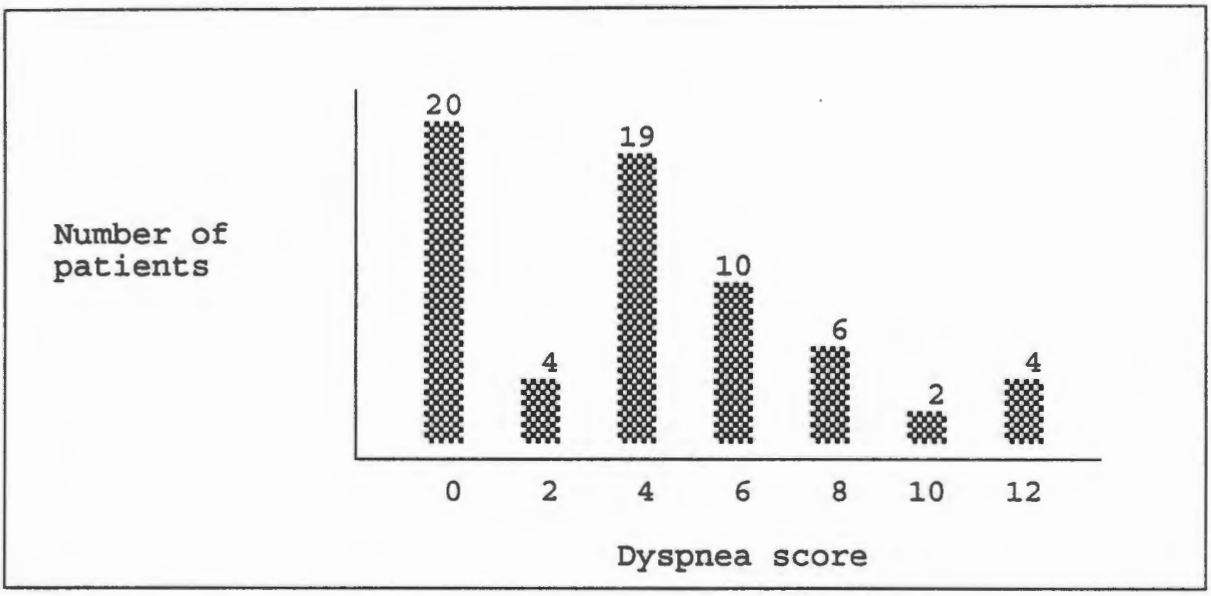
Smoking History

There were 31 life-time non-smokers. The 15 ex-smokers had a mean smoking history of 7.5 (SD=9.9) pack-years (range=1-30) and the 20 current smokers had a mean history of 8.1 (10.1) pack-years (range=1-40).

Respiratory History

The mean CRP dyspnea score was 4. See Figure 2.1

Figure 2.1
Mean dyspnea score

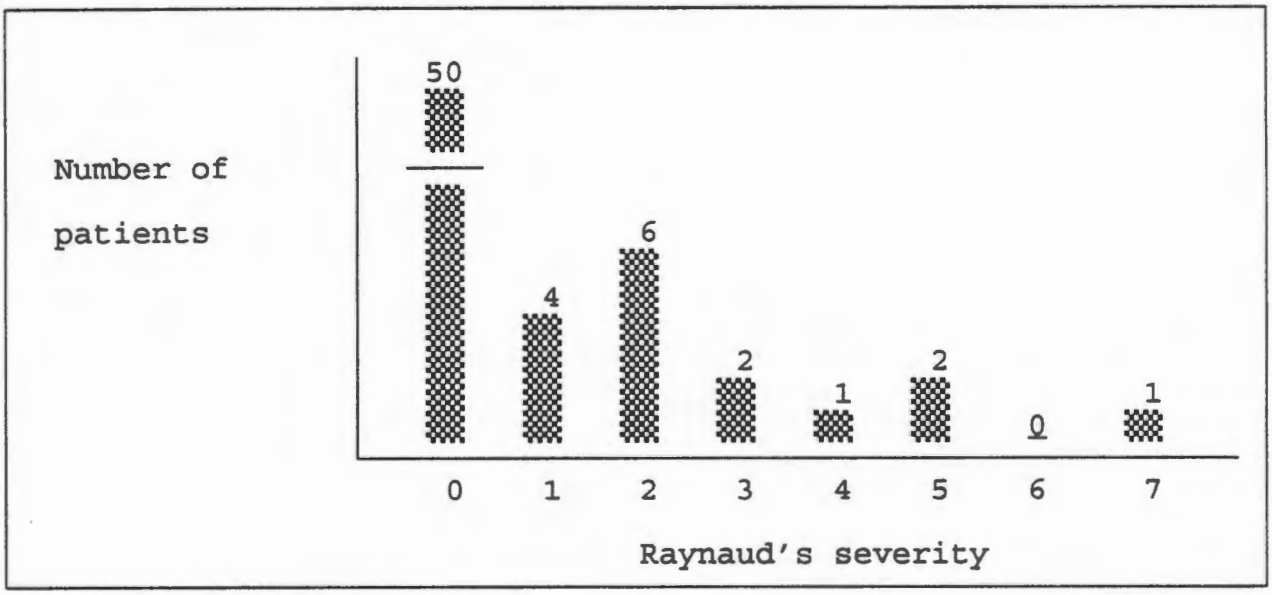


A dry cough occurred in 6 (7.1.%). 13 (15.5%) had a cough productive of mucoid sputum. In 7 (8.3%) it was purulent and in 3 (3.6%) it was bloodstained during the preceeding 3 months. Some patients produced more than one type of sputum. 16 (19%) had been treated for bronchitis in the corresponding period and none were on anti-tuberculous treatment. Pleuritic chest pain was present on the study day in 20 patients (23.8%).

Rheumatological History

On the study day 16 (24.2%) reported the presence of Raynaud's with a mean severity score of 2.6. (See Figure 2.3) A total of 38 (57.6%) had reported Raynaud's phenomenon at some stage in their illness.

Figure 2.3
Raynaud's severity



Photosensitivity was reported in 42 (63.6%) and arthritis/arthralgias in 46 (69.7%). Digital ulceration had occurred in the past in 11 (16.7%) and was present on the study day in 2 (3%).

Treatment

Medications that had been, or were in use for the treatment of SLE and its complications are summarised in Table 2.1.

Table 2.1
Medications used in study patients

Medication	Number of patients	(% total)	Duration in months	SD	Range
Cortico-steroids					
current:	34	(51.5)	49	44.2	5-216
past:	28	(42.2)	47.8	59.8	9-336
never:	16	(24.2)			
Chloroquine					
current:	21	(31.8)	32	29.2	3-129
past:	16	(24.2)			
never:	31	(47)			
Azathioprine					
current:	3	(4.5)			
Cyclophosphamide					
current:	5	(7.6)			
past:	6	(9.1)			
Warfarin	4	(6.1)			
Aspirin	6	(9.1)			
Vasodilators	5	(7.6)			

2.7.4 Examination

A malar rash was present in 8 (12.1%) and a discoid rash in 15 (22.7%). None had painless oral ulceration. Raynaud's was observed in 15 (22.7%) and objective synovitis in 15 (22.7%).

None had clubbing or a pleural rub, and 12 (18.2%) had end-inspiratory crackles.

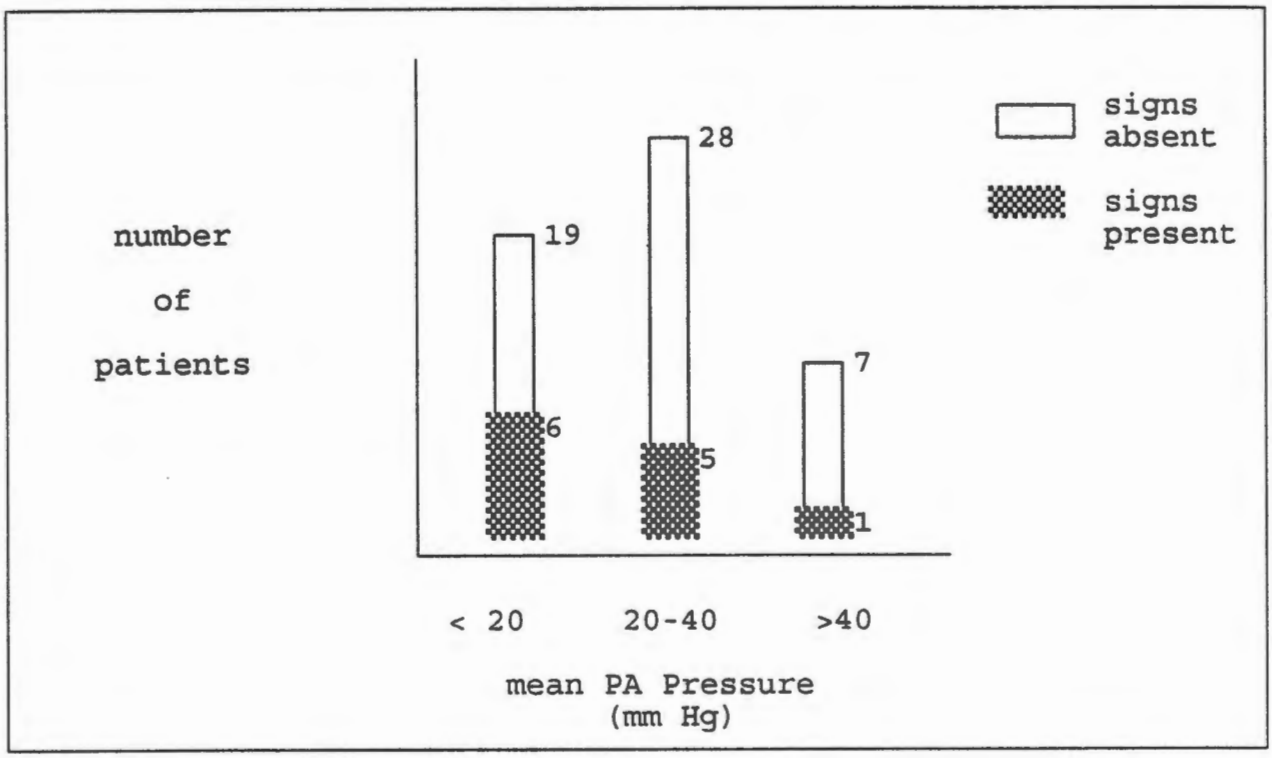
Peripheral edema was found in 1 (1.5%), a raised JVP in 1 and an enlarged liver in 5 (7.6%).
Signs of pulmonary hypertension are summarised in Table 2.2.

Table 2.2
Signs of PH

Signs	Number of cases	(% total)
Palpable P2	5	(7.6)
RV lift	7	(10.6)
Loud P2	8	(12.1)
TR	0	(0)

7 had only one sign of pulmonary hypertension, 2 had two, and 3 had three signs. 6 patients with clinically suspected PH had a normal PA pressure. (See figure 2.3)

Figure 2.4
Correlation between signs of PH and measured PA pressure



2.7.5 Pulmonary Function Tests (Table 2.3)

65 cases were able to perform PFT's. Results are shown in Table 2.3.

Table 2.3
Pulmonary function tests in 65 patients with SLE

PFT:	Mean	SD	Range	%pred.
FEV1	2110	512	1080-3000	84.4
FVC	2598	569	1600-3790	85.5
TLCO	15.64	3.72	6.07-25.1	64.7
Hb corr. TLCO	17.54	4.02	7.18-26.67	72.3
KCO	4.66	0.90	2.57-7.35	85.6
MIP	62.4	23.5	25-125	75.71
MEP	93.5	24.15	50-160	63.29

These measurements were subdivided according to severity as shown in Table 2.4.

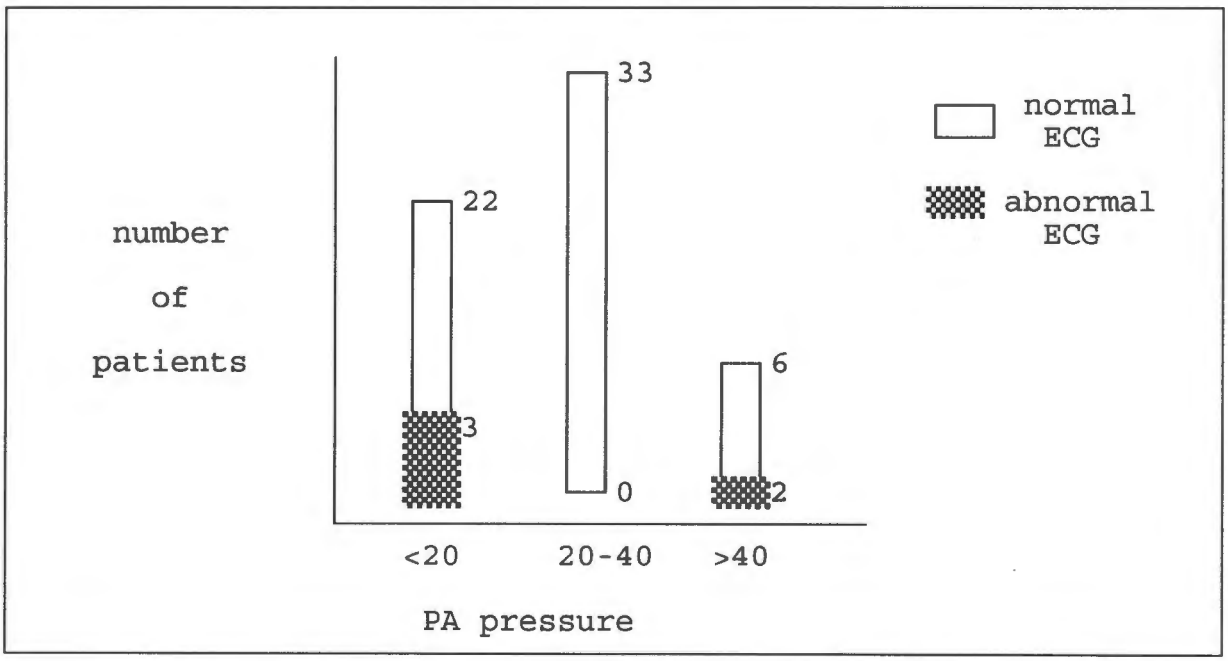
Table 2.4
Severity of abnormal PFTs

	Normal [cases(N)]	(%)	Mild	(%)	Moderate	(%)	Severe	(%)
Restriction	46	(70.8)	15	(23.1)	3	(4.6)	1	(1.5)
Obstruction	64	(87)	1	(1.5)	0	(0)	0	(0)
TLCO	13	(20)	27	(41.5)	23	(35.4)	2	(3)
TLCO corr.	22	(34.4)	26	(40.6)	16	(25)	0	(0)

2.7.6 Electrocardiogram

In 5 patients (7.6%) the ECG was abnormal. 1 had a RBBB pattern, 3 had evidence of right atrial enlargement and 1 had right ventricular enlargement and strain pattern. None had more than one abnormality. The ECG abnormalities and corresponding PA pressures are shown in Figure 2.5.

Figure 2.5
ECG abnormality



2.7.7 Chest Radiograph

The commonest abnormalities were pleural fluid or thickening, noted in 23 (34.9%) and evidence of past tuberculosis in 8 (12.1%). 6 (9.1%) had features of pulmonary hypertension, 5 (7.6%) of cryptogenic fibrosing alveolitis, and 1 (1.5%) of vanishing lung.

Other radiographic abnormalities noted were pericardial effusions in 4, fluid overload in 7, atelectasis in 2 and a calcified mediastinal node and accessory right inferior fissure in 1 case.

2.7.8 Echocardiogram

Study patients

The echocardiogram was of very poor quality in 1 patient (1.5%) and the best estimate possible was a mean of 6 mm Hg which was used in the further analysis. Tricuspid regurgitation was present in 15 (23%) and in 9 the PA pressure could be estimated from it. This TR derived PA pressure measurement was used in the later analyses in only 4 patients where it was the only measurement available. In 2 the PA pressure was only reported as being < 19 and a value of 19 was used. In the remainder the values derived from equation 3 (Chapter 1.3.10) using the AcT were used in the statistical analyses.

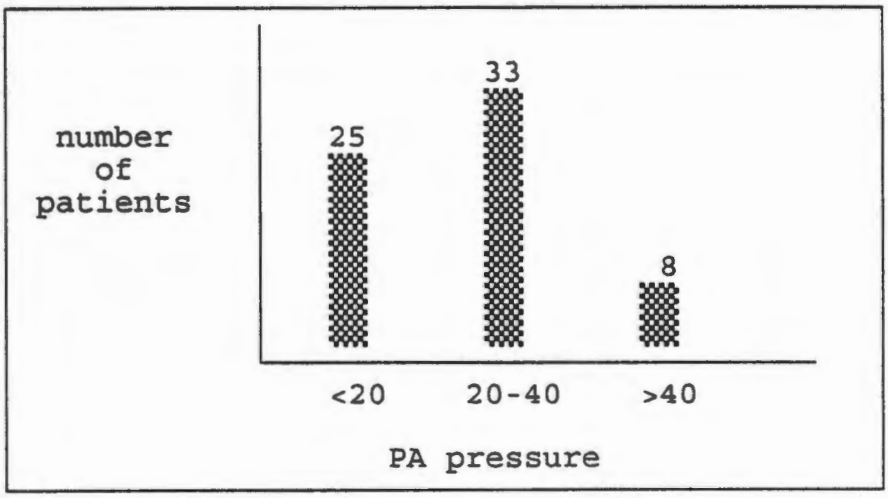
The acceleration and ejection times were obtained from 4 to 5 cardiac cycles and recorded in 49 patients and is shown in Table 2.5.

Table 2.5
Echocardiographic measurements

	Mean	(SD)	Range
Study patients			
ACT	116	29.7	30-210
RVET	284	44.8	140-420
PA pressure	25.9	10.8	6-52
Controls			
ACT	141	16.3	10-210
RVET	304	32.3	210-380
PA pressure	15.7	5.59	6-28

The patients were divided into 3 groups according to the measured PA pressure. (fig 2.6)

Figure 2.6
Pulmonary artery pressure groups



Controls

20 healthy age matched controls (mean age=38.2 ;range=22.2-72) consented to an echocardiogram. The echo failed in 1 due to poor PA doppler signals. None had tricuspid regurgitation. See Table 2.5 for results.

2.7.9 Blood results (Table 2.6)
The results of the blood investigations are summarised in Table 2.6.

Table 2.6
Blood investigations

Test	Number tested	Mean	Range	SD	Abnormal %
ANF	62	500*	0-2500	N/A	51 (82.3)
ENA	62	20 000*	160-160 000	N/A	59 (95.2)
Anti-DNA	65	20.28	0-139	28.68	21 (32.3)
CIC	61	12	2-77	14.5	34 (55.7)
C-RP	66	1.5	0-8.1	1.6	39 (59.1)
CH50	60	184.5	70-300	77.5	24 (40)
C3	46	97.2	30-166	30.2	14 (30.4)
C4	43	20.8	8-35	22.7	9 (20.9)
APL	61	13.2	0-98	21.3	(See text)
Hb	65	11.4	7.4-18	1.9	13 (20)
WCC	65	6454	1900-18100	2902	14 (21.5)
Lymph's	62	1534	132-4163	1015	34 (54.8)
Platelets	65	281523	74000-684000	113134	4 (6.2)

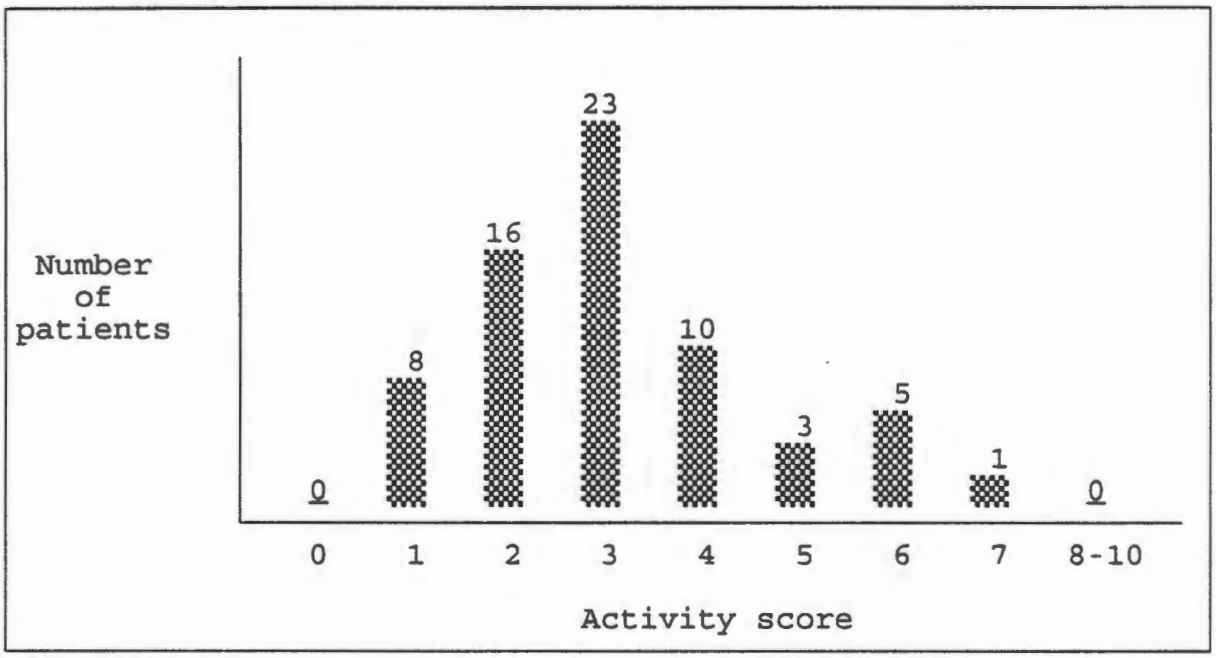
(* = Median value given)

36 patients (59%) had a normal APL-IGG titre. 12 (19.7%) had a low titre, 13 (21.3%) a moderate titre and none a high titre.

2.7.10 Physician's global assessment of disease activity (Fig. 2.7)

The mean disease activity count was 3 ranging from 1 to 7.

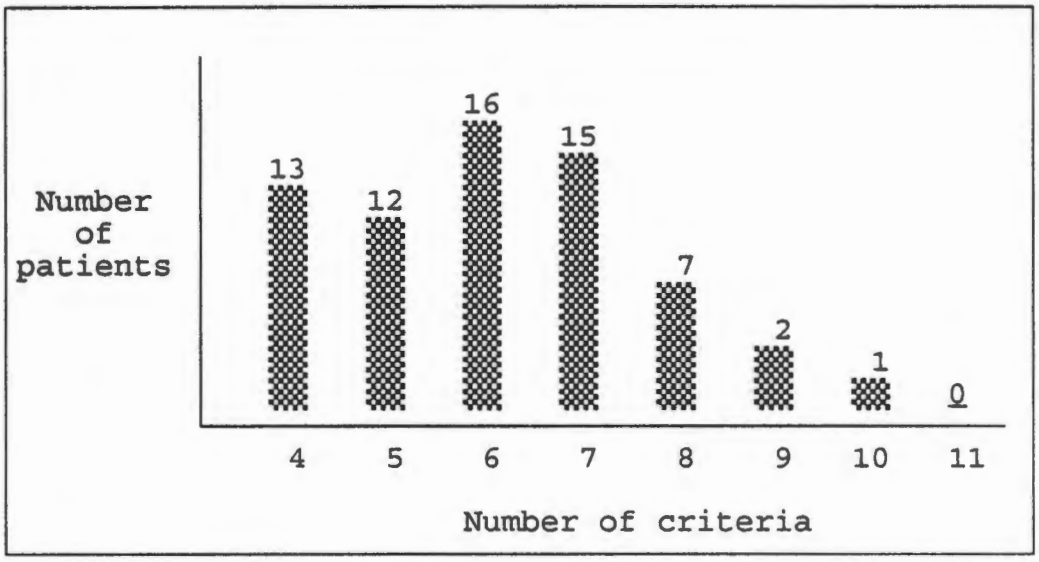
Figure 2.7
Physician's global assessment of disease activity



2.7.11 ARA Criteria (Figure 2.8)

The mean total criteria was 6. The commonest clinical ARA criteria were: arthritis in 54 (81.8%), photosensitivity in 42 (63.6%) and a malar rash in 36 (54.5%). The commonest laboratory criteria were positive ANF in 65 (98.5%), ENA in 64 (97%) and lymphopenia in 36 (54.5%).

Figure 2.8
ARA criteria



2.7.12 Outpatient Visits/Admissions

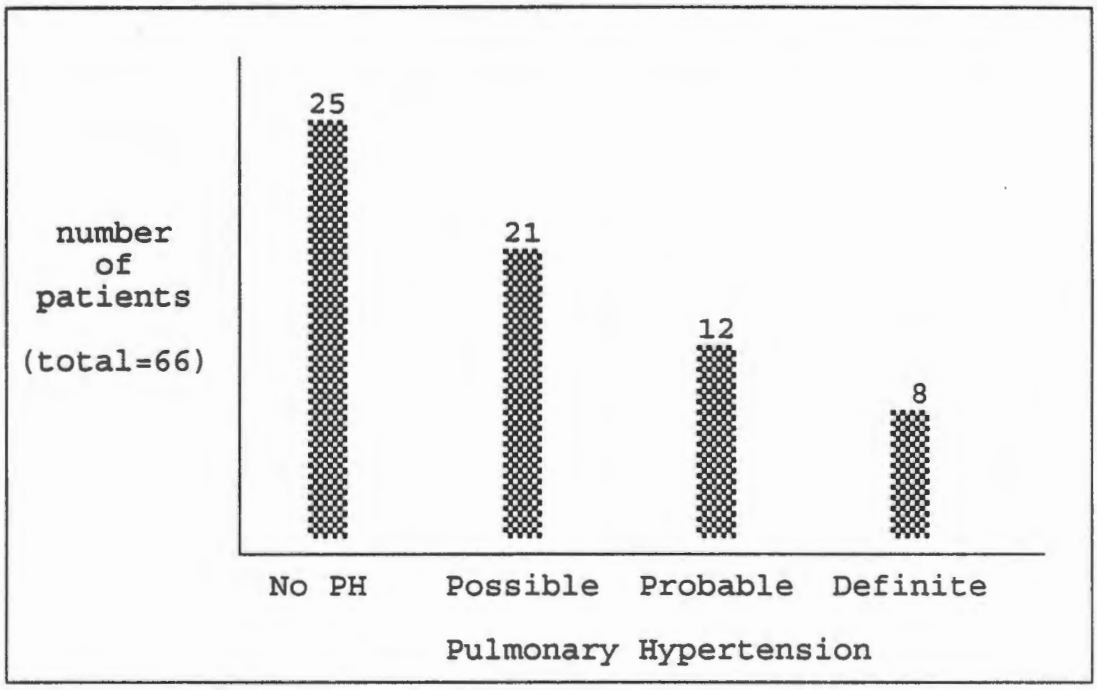
The patients had attended Lupus Clinic for a mean of 43.1 visits (range=2-267) for a mean duration of 7 years (range=0.1-34.7).

Only 7 patients had never been admitted to hospital. The mean number of admissions for SLE related illnesses was 3.2 (range=0-14).

2.7.13 a) Pulmonary Hypertension - possible, probable or definite (fig 2.9)

41 patients (62%) were classified as having possible, probable or definite PH by combined clinical, radiological, ECG and echocardiographic criteria as defined in Chapter 2.4.2.

Figure 2.9
Pulmonary hypertension groups according to combined clinical, radiological, ECG and echocardiographic criteria



2.7.13 b) Primary and secondary pulmonary hypertension (fig 2.10)

Definite Primary Pulmonary Hypertension

12 of the 41 patients considered to have possible, probable or definite PH were classified as definite primary pulmonary hypertension on the basis of a negative perfusion scan and no secondary cause being present.

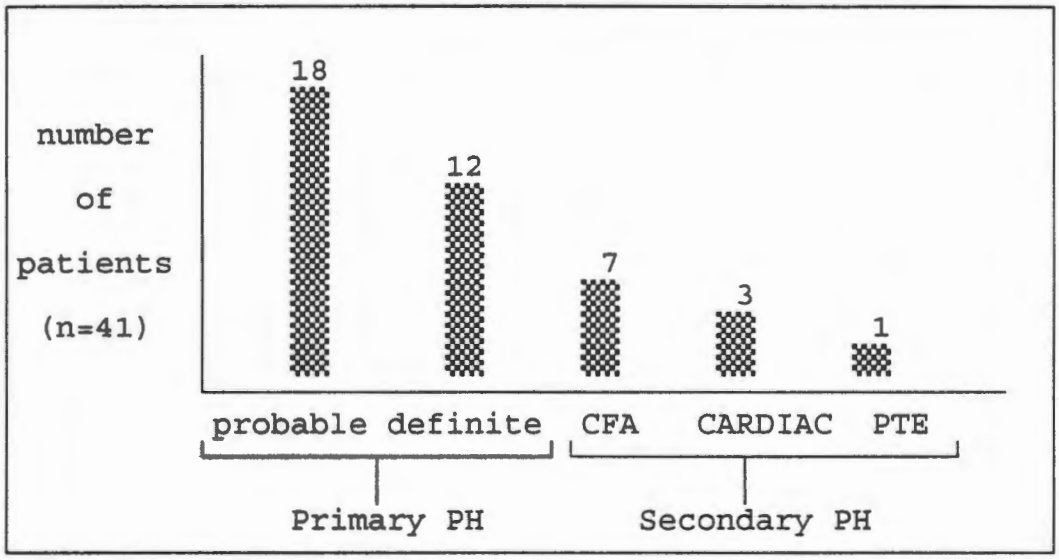
Probable Primary Pulmonary Hypertension

18 cases could be placed in the probable PPH group as no secondary cause was present, and there was a very low clinical index of suspicion of thromboembolism in them, but perfusion lung scans had not been performed.

Secondary Pulmonary Hypertension

11 patients were classified in the secondary pulmonary hypertension group. 3 patients were secondary to cardiac disease on the basis of echo features of diastolic dysfunction. 7 patients had CFA and 1 had recurrent thromboembolism.

Figure 2.10
Primary and Secondary Pulmonary Hypertension



2.7.13 c) Clinical features of patients with PH

Of the 41 patients with pulmonary hypertension 25 patients were dyspneic; 5 had a palpable P_2 and 6 a loud P_2; 4 had an RV lift; 2 had pedal edema; and 4 had a raised JVP. In 1 case the ECG had evidence of RA and RV enlargement. On the radiograph 7 were thought to have enlarged pulmonary arteries and 4 enlarged right ventricles; only 3 cases had a right descending pulmonary artery more than 15 mm. (This measurement was possible in 59 radiographs.)

2.7.14 Other forms of Pulmonary Involvement in SLE

Pleural involvement had occurred at some time in their history in 25 patients (37.9%). In these patients 80% had experienced chest pain, 24% had an audible rub, 60% clinical evidence of an effusion and 80% radiological evidence of pleural involvement.

Pulmonary infections had occurred in 38 patients (57.6%). The commonest was bronchitis occurring in 27 (multiple in 15). Pneumonia had occurred in 16 (13 needing a single admission, and 3 needing 2, 3 and 6 admissions respectively). Pulmonary tuberculosis had occurred in 5.

The patients with infections had received immunosupressives for a mean of 54.3 months. In contrast, the patients without infections, had received it for a mean of 34.3 months. This difference was not significant. (Chi-square approx. p=0.1990) The smoking history was similar for the patients with infections (mean 4.68 pack-year) and without infections (mean 3.52 pack-year; Chi-square approx. p=0.851)

Cryptogenic fibrosing alveolitis was present in 9 (13.6%). 7 (78%) had a cough, 5 (56%) were dyspneic, none were clubbed, and all had end-inspiratory crackles. Chest radiograph revealed small lungs in 6 (67%) and an infiltrate in 8 (89%). Pulmonary function tests confirmed restriction in 8 (89%) and all had a reduced TLCO. Only 1 case had a bronchoscopy performed to confirm the diagnosis.

Vanishing lung was present in 3 (4.6%); all were dyspneic, had small lungs on CXR and had markedly reduced MIP's and MEP's.

Pulmonary thromboembolism, unrelated to the antiphospholipid antibody syndrome, had previously been confirmed in 1 patient (1.5%) by ventilation/perfusion scanning.

Other forms of pulmonary involvement included: acute lupus pneumonitis in 2, pulmonary hemorrhage in 1 , asthma in 6, smoking induced COAD in 1, bronchiectasis in 1, and a solitary pulmonary nodule (probably a granuloma) in 2.

Chapter 3 DISCUSSION OF RESULTS

3.1 Statistical Analysis

3.1.1 Pulmonary Artery Pressures in SLE

The mean pulmonary artery pressure of SLE patients was significantly higher than in control subjects (25.90 vs 15.72; Chi square approximation test, **p = 0.0001**).

3.1.2 Association between the presence and severity of Raynaud's Phenomenon and Pulmonary Hypertension (Table 3.1)

There was no difference in the presence of Raynaud's phenomenon whether current or past, or in the Raynaud's severity score, between the patients with pulmonary hypertension and those without. Similarly no differences were noted with respect to Raynaud's and the pulmonary artery pressure subgroups.

Table 3.1
Raynaud's in PH groups

PH	Total Number	presence of Rayn. (N cases)	severity > 1 (N cases)
No PH	25	13	4
Possible	21	14	6
Probable	12	5	3
Definite	8	6	3
Fisher's exact test		p = 0.185	p = 0.457
PA Pressure	N	severity > 1	
<20	25	4	
20 - 40	33	9	
>40	8	3	
Chi-square approx.		p = 0.395	

3.1.3 Association between Disease Activity and PH (Table 3.2)

The different pulmonary hypertension groups did not differ with respect to the physician's global assessment of disease activity. However there was a trend towards a higher disease activity score in patients with higher PA pressures (Chi square approx.; p=0.0642)

Table 3.2
Disease activity score in Pulmonary Hypertension groups

PH	N	mean activity score
No PH	25	2.69
Possible	21	3.16
Probable	12	3.25
Definite	8	3.63
Chi-square approx.		p = 0.1583

PA pressure	N	mean activity score
<20	25	2.68
20 - 40	33	3.18
>40	8	3.63
Chi-square approx.		p = 0.0642

3.1.4 Differences in Clinical features and Laboratory parameters between the pulmonary hypertension groups (Table 3.3, 3.4, 3.5)

In the different pulmonary hypertension groups a significant difference in the **uncorrected $TLCO_{sb}$**; and in the **CXR right pulmonary artery diameter** was noted. The TLCO was lowest in "probable" and "definite PH" as can be expected. The low TLCO level of the "No PH" group is probably due to the inclusion of patients with fibrosing alveolitis in this group. The differences in the PA diameter can possibly also be explained on this basis. See Table 3.3

Table 3.3
TLCO and PA diameter in PH

PH	mean TLCO (% pred)	mean right PA diam.
No PH	70.02 %	12.6 mm.
Possible	91.90 %	10.9 mm.
Probable	52.98 %	13.8 mm.
Definite	63.87 %	12.1 mm.
Chi-square approx.	p = 0.0163	p = 0.0268

The **total ARA criteria** in the different groups almost reached significance. See Table 3.4

Table 3.4
ARA criteria in PH

PH	N	mean total ARA criteria
No PH	25	5.50
Possible	21	6.47
Probable	12	6.17
Definite	8	6.63
Chi-square approx.		p = 0.0717

No significant difference was noted between the PH groups with respect to the **miscellaneous variables** shown in Table 3.5.

Table 3.5
Miscellaneous variables and the PH groups

Variable	Test	p-value
Dyspnea score	Chi-square approx.	0.5282
Disease(Durat)	Chi-square approx.	0.6286
Smoking(curr)	Fisher's Exact	0.527
Smoking(past)	Fisher's Exact	1.000
Anticoag.	Fisher's Exact	1.000
Immunosupp.	Chi-square approx.	0.6374
Chloroquine	Chi-square approx.	0.5931
Vasodil.	Fisher's Exact	0.776
Dig. ulcer.	Fisher's Exact	0.951
FEV1	Chi-square approx.	0.3987
FVC	Chi-square approx.	0.6168
Anti-DNA	Chi-square approx.	0.8401
C-RP	Chi-square approx.	0.2575
CH50	Chi-square approx.	0.9264
C3	Chi-square approx.	0.2711
C4	Chi-square approx.	0.7736
CIC	Chi-square approx.	0.4086
APL	Chi-square approx.	0.8169
WCC	Chi-square approx.	0.7168
Lymph.	Chi-square approx.	0.8318

3.1.5 Differences in Clinical features and Laboratory parameters according to PA pressure level (Table 3.6, 3.7)

In the different pulmonary artery pressure groups there was a significant difference in the **total number of ARA criteria**. See Table 3.6

Table 3.6
ARA criteria in PA pressure groups

PA pressure	N	mean total ARA criteria
<20	25	5.44
20 - 40	33	6.30
>40	8	6.63
Chi-square approx.		p = 0.0440

There was no significant difference between the groups with respect to the **variables** shown in Table 3.7.

Table 3.7
Miscellaneous variables and the PA pressure groups

Variable	Test	p-value
Disease(durat)	Chi-square approx.	0.6059
Smoking(curr)	Chi-square approx.	0.932
Smoking(past)	Chi-square approx.	0.917
Anticoag.	Fisher's Exact	1.000
Immunosupp.	Chi-square approx.	0.5705
Chloroquine	Chi-square approx.	0.5773
Vasodil.	Fisher's Exact	0.817
Dig. ulcer.	Fisher's Exact	1.000
FEV1	Chi-square approx.	0.2699
FVC	Chi-square approx.	0.5133
TLCO(uncorr)	Chi-square approx.	0.2744
Anti-DNA	Chi-square approx.	0.5991
C-RP	Chi-square approx.	0.1859
CH50	Chi-square approx.	0.5007
C3	Chi-square approx.	0.4979
C4	Chi-square approx.	0.5721
CIC	Chi-square approx.	0.5319
APL	Chi-square approx.	0.6795
WCC	Chi-square approx.	0.2495
Lymph.	Chi-square approx.	0.7940

3.2 Discussion

3.2.1 Pulmonary Hypertension in Systemic Lupus Erythematosus

41 (62%) of the 66 patients studied were shown to have echocardiographic evidence of altered pulmonary blood flow velocities and/or altered transtricuspid pressure gradients compatible with pulmonary hypertension. Estimates of pulmonary artery pressure made upon the basis of these variables provided categorisation of 12 patients (29%) as having definite primary pulmonary hypertension, 18 (44%) as probable primary pulmonary hypertension and a further 11 (27%) as secondary pulmonary hypertension. Recognising the limitations of the echocardiographically derived pulmonary artery pressures, discussed in chapter 3.3.1, the study seems to support the observations made previously of an increased incidence of pulmonary hypertension not explained by other forms of lung disease in SLE.[20-27] The finding of significantly lower pressures in the normal volunteers acting as controls, further strengthens this conclusion.

Support for the concept that the higher than expected incidence of pulmonary hypertension is the result of occult pulmonary vascular disease, is the disproportionate reduction in the $TLCO_{sb}$ in patients with SLE compared with reduction in lung volumes. The majority of patients had normal or only mildly reduced volumes but the $TLCO_{sb}$ was reduced by a greater percentage overall. 25% of patients had moderate to severely reduced $TLCO_{sb}$, even when corrected for hemoglobin. The latter correction increased the $TLCO_{sb}$ from a mean of 15.64 to 17.54. ($p=0.0001$) Thus anemia, a common problem in SLE, was responsible for a significantly reduced $TLCO_{sb}$. The remainder may be the result of pulmonary vascular disease.

The definitions of possible, probable and definite pulmonary hypertension used in this study, were defined according to currently accepted non-invasive tests.[39,40] They need to be validated by larger studies with direct measurement of pulmonary artery pressure. This study confirmed the low sensitivity of physical signs and other non-invasive tests.

The pulmonary artery measurements could have been validated with right heart catheter data, but this would have made the study more invasive, and less acceptable to the patients. They are further supported by the normal values found in normal controls.

3.2.2 The association between Raynaud's phenomenon and pulmonary hypertension

The results of this study do not support the second hypothesis that pulmonary hypertension is strongly associated with peripheral vasospasm. Raynaud's occurred in 52% of patients with no pulmonary hypertension, 67% of possible, 42% of probable and 75% of definite pulmonary hypertension.

The study failed to show an association between current or past digital ulceration and pulmonary hypertension. It is unlikely that the use of vasodilators could have masked the association as similar proportions of patients in each PH group were on vasodilators.

3.2.3 The association between disease activity and pulmonary hypertension

Various disease activity indices have been devised in SLE using combined clinical and laboratory parameters.[79,80] These indices were considered too time consuming for use in this study. An attempt at an approximate allocation of disease activity was however made, firstly, with the individual laboratory investigations available and, secondly, the physician's global assessment using the combined clinical and laboratory findings listed in Chapter 2.4.6.

The study failed to find an association between pulmonary hypertension and indices of disease activity in SLE. There was a trend toward an association of the physician's global assessment of disease activity and increasing certainty of PH: no PH, possible, probable, to definite PH, but this did not reach statistical significance. (p=0.1583) The global assessment of the three pressure groups showed a similar trend, but still did not reach significance. (p=0.0642)

It is possible that these trends are the result of observer bias as the study was not blinded. Thus higher activity scores may have been allocated to cases with pulmonary hypertension and higher PA pressures, even though these were not included in the original list of activity markers. Alternatively the results may support the hypothesis, but failed to reach statistical significance because the numbers were too small especially in the "definite" and ">40" pressure groups.

3.2.4 The association between total ARA criteria and pulmonary hypertension

The total number of ARA diagnostic criteria in the pulmonary artery pressure groups reached significance.(p= 0.044) The total criteria in the different pulmonary hypertension groups almost reached significance. (p= 0.0717)

The higher total criteria is often said to reflect disease duration. Comparing the pulmonary hypertension and pulmonary artery pressure groups with disease duration, however, failed to show such a tendency.

The number of criteria generally increases as the disease involves more systems. The tendency described above may therefore reflect the fact that SLE, being a multisystem disorder, affects more organs as it progresses, and that pulmonary hypertension occurs as part of this multisystem disease.

3.2.5 Other pulmonary involvement found in study patients

Pulmonary infections occur commonly in patients with SLE. The commonest infection in this study was bronchitis. It is likely that the 27 cases recorded is an underestimate, as many infections would have been treated by private practitioners, and not reported in the hospital folders. Pneumonia occurred in 16 cases, with multiple admissions in 3. Despite the high local prevalence of tuberculosis, only 5 cases had been treated for pulmonary tuberculosis.

The reason for frequent infections is probably multifactorial: decreased immunity which is well recognised in SLE; treatment with immunosupressives; smoking; and underlying lung disease may all play a role. We were unable to confirm these associations in this study.

Pleural involvement occurred in a third of the patients. This too might be an underestimate, as pleural disease may be transient and self-limiting and the signs may thus be missed. Several CXR's and reports were also missing, contributing to a possible underestimate of radiologically confirmed pleural involvement.

Cryptogenic fibrosing alveolitis occurred in 9 patients (13.6%). The clinical features were similar to "lone CFA" ie. CFA occurring without a collagen vascular disorder. The only exception was the absence of clubbing found in the SLE patients. 5 cases were on treatment with corticosteroids, alone, or in combination with azathioprine.

Vanishing lung, a well recognised pulmonary manifestation of SLE[81], is thought to result from a combination of diaphragmatic weakness, pleural thickening, and basal parenchymal fibrosis. Three patients were identified, and in one it was successfully treated with corticosteroids.

Only one patient with pulmonary thromboembolism was identified. In view of the reported high prevalence of the lupus anticoagulant in SLE,[82] (40% in this series) more cases of thromboembolism might have been expected. However, the concentrations of APL was a low titre in half, and only moderate titre in the remainder. Minor episodes of thromboembolism may easily be missed, or the diagnosis overlooked as chest pain is a common occurrence in SLE, and is not routinely investigated. Minor dyspnea may also be attributed to anemia, or inactivity, which is often seen in chronically ill patients. However, in the few patients with elevated pulmonary artery pressures in whom perfusion scans were performed, no evidence of pulmonary thromboembolism were found.

The single case of pulmonary hemorrhage was confidently diagnosed on clinical evidence of episodic minor hemoptysis, dyspnea, iron deficiency anemia, and transient alveolar filling patterns on CXR.

3.3 Limitations and short-comings of the current study

3.3.1 Measurement of pulmonary artery pressures

A criticism of the study is that in most patients (51) tricuspid regurgitation(TR) could not be found in the echocardiography laboratory, necessitating calculation of the mean PA pressure from the less accurate AcT and RVET methods. In only 9 was the pulmonary artery pressure derived from TR. This low pick-up rate of TR may be the result of relative lack of observer skill, or perseverance due to time constraints, or due to a true low incidence of TR.

In the majority of patients, the pulmonary artery pressures were derived from the AcT and RVET described in chapter 1.3.10. This method has important limitations:

- -The AcT and RVET are measures of intracardiac blood-flow velocities that are altered by pressure changes, but also by changes in heart rate and haematocrit. The influence of the latter variables were not specifically looked at, and may have affected the measurements of the patients, and not of the normal controls.
- -The AcT and RVET measurements may vary from beat to beat, and the average from 4 - 5 cardiac cycles were used. Some studies report using up to 11 cardiac cycles for these measurements. Had we used 11 cycles, the results may have been more accurate, but 5 cycles were regarded as adequate.
- -Finally, the measurement of AcT and RVET are not routinely performed in our echocardiography laboratory, and are operator dependent. Inter- and intra-observer variability should therefore have been tested for, and ideally compared with invasively measured right heart pressures to validate the results obtained from our echocardiography laboratory.

3.3.2 Exclusion of alternative causes of Pulmonary Hypertension

The distinction between 1^{0} and 2^{0} pulmonary hypertension is important, as different pathogenetic mechanisms are involved, and treatment will differ. Pulmonary thromboembolism was not excluded by pulmonary angiograms or V/Q scans in all patients with pulmonary hypertension, as there was often no clinical suspicion of this condition. This weakens the study, as recurrent pulmonary thromboemboli may be asymptomatic. However, the probability of pulmonary thromboemboli accounting for the majority of patients with pulmonary hypertension in this study seem low.

In SLE, the variety of other forms of lung involvement that may be present, makes the study of isolated pulmonary vascular disease more difficult. The high incidence of these other lung conditions (37.9% had past history of pleural involvement, 57.6% pulmonary infections, 13.6% CFA and 4.6% vanishing lung) means that it is advisable to assume that such conditions, in a high proportion of cases, might have contributed to the development of apparently isolated pulmonary hypertension. In this study reasonable although not exhaustive attempts were made to recognise 2^0 PH occurring in the presence of likely thromboembolism or interstitial lung disease or cardiac disease. However, minor degrees of these might have been present. It remains speculative whether more invasive and expensive testing would have provided a more useful result, albeit more accurate. For interstitial lung disease, an open lung biopsy might be useful; in pulmonary thromboembolism, a V/Q lung scan and pulmonary angiogram would be viewed as definitive confirmation; and for heart disease, a cardiac catheterisation would have ensured greater certainty about the contributions of these conditions to pulmonary hypertension. It is worth noting that in the CFA group the mean PA pressure was 30 mm Hg and that 1 patient had a mean PA pressure > 40. The cost of performing full ventilation/perfusion scans as part of this study, especially in the asymptomatic individuals, could not be justified. This significantly reduced the confidence with which cases were classified as 1^0 or 2^0 pulmonary hypertension.

3.4 Conclusions and recommendations for future research

This study has confirmed the frequent involvement of the lung in SLE, and using the echocardiograph has identified intracardiac blood-flow velocity alterations compatible with pulmonary hypertension in a higher proportion of patients than previously recognised. In most patients this appeared to represent specific involvement of the pulmonary vasculature rather than being due to other forms of lung disease. As perfusion lung scans were not performed in all the cases, the role of thromboembolism can not be excluded. However, positive confirmation of thromboembolism was present in only one case.

Contrary to expectations, no association between the presence of Raynaud's phenomenon or digital ulceration, (considered to be indicators of peripheral vasospastic activity) and pulmonary hypertension was observed. In addition the presence of pulmonary hypertension bore no relationship to indicators of disease activity. The severity of pulmonary hypertension, however, appeared to relate positively to the extent of multisystem involvement in SLE.

The usefulness of certain diagnostic criteria for PH was disappointing. For example, although in patients with relatively isolated pulmonary vascular involvement, the reduction in $TLCO_{sb}$ and diameter of the right descending pulmonary artery on CXR both bore a positive relationship to severity of PH, these features were of less value in all patients with SLE, as they were adversely affected by other forms of lung disease present in the patients eg. CFA, vanishing lung syndrome and pulmonary thromboembolism.

The common occurrence of PH in SLE raises questions about appropriate follow-up and treatment. Follow-up studies of the natural history and longterm prognosis of PH in SLE are required. Our experience has confirmed that in several patients the disease is progressive and fatal. Echocardiography provides a safe, non-invasive method for following the course of pulmonary vascular involvement and the efficacy of treatment. With further refinements of non-invasive technology, right heart catheter confirmation of PH will become less necessary. However, pulmonary angiography and perfusion lung scans should be used more frequently to exclude recurrent pulmonary thromboembolism.

Another future avenue of research should be to attempt to identify SLE patients at risk of developing PH at a stage when it may be detected only as inducible pulmonary vasospasm. The change in the membrane and capillary component of $TLCO_{sb}$ during a cold pressor test, may identify cases with pulmonary vasospasm. Double blind, randomised control studies will then be needed to assess the long term effects of early treatment of patients identified in this manner.

Currently treatment with anticoagulants and vasodilators are advised only for patients with established PH. Patients with significant interstitial lung disease might in addition benefit from corticosteroids alone or in combination with azathioprine or cyclophosphamide.

In conclusion, I believe that the main value of the study was the early detection of minor degrees of elevation of the pulmonary artery pressure in a significant number of patients with SLE. These patients have not yet developed irreversible vascular damage and will be the subject of future research.

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APPENDIX A **PULMONARY MANIFESTATIONS IN SLE** 62

PATIENT DATA

card 1 ☐☐ 2
group no (case=1;control=2) ☐ 3

STUDY NO ___ *study no* 4 ☐☐☐ 6

SURNAME _____ 7 ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐ 26

NAME _____ 27 ☐☐☐☐☐☐☐☐☐☐ 37

FN _____ 38 ☐☐☐☐☐☐☐☐ 45

DOB __/__/19__ 46 ☐☐☐☐☐☐ 51

RACE/SEX _ w/m=1 w/f=2 c/m=3 c/f=4 a/m=5 a/f=6 b/m=7 b/f=8 ☐ 52

CURRENT VISIT
Date __/__/199_ 53 ☐☐☐☐☐☐ 58

HISTORY

Date of 1st symptom __/__/19__ 59 ☐☐☐☐☐☐ 64

Respiratory

Dyspnoea score (0 - 20) __ 65 ☐☐ 66

Cough
- Dry y=1 n=2 ☐ 67
- Mucoid y n
- Purulent y n ☐ 69
- Bloodstained y n

Pleuritic chest pain y n ☐ 71

Smoking
- Ex-Pack years ___ 72 ☐☐☐ 74
- Current-Pack years ___ 75 ☐☐☐ 77

Bronchitis in past 3 months y=1 n=2 ☐ 78

On anti-TB treatment y n ☐ 79

Rheumatologic

card 1 ☐☐ 2

study no 3 ☐☐☐ 5

Photosensitivity y n ☐ 6
Arthritis/arthralgia y n

Raynaud's severity 0/1/2/3/4/5/6/7/8/9/10 8 ☐☐ 9

Other

Ischemic heart disease y=1 n=2 10

Digital ulcers in past y n 11
currently y n

Treatment

Anticoagulants Warfarin y=1 n=2 13
Disprin y n

Vasodilators y n 15

Immunosup n=2 y=1 16

Indication Lupus y=1 n=2 17
Resp y n

Duration __ years 19 20

Drug Pred at __ mg/day 21 22
Aza at ___mg/day 23 25
Cyclop at ___mg/day 26 28
___mg/month 29 32
Other _____ y=1 n=2 33

Response Lupus y=1 n=2 N/A=x 34
Resp y=1 n=2 N/A=x

EXAMINATION

Malar rash y=1 n=2 36
Discoid rash y n
Oral ulcers y n 38

Raynaud's observed y n 39
Arthritis/Synovitis y n
Digital ulcers y n 41

RESP

Clubbing y=1 n=2 42
End-insp crackles y n
Pleural rub y n 44

COR

45 ☐☐☐ ~ ☐☐☐ 50

BP ___/___

RV Failure

Oedema y=1 n=2 ☐ 51
Raised JVP __ cm 52 ☐ 53
Hepar span __ cm 54 ☐ 55

Pulm HT

Palpable P2 y=1 n=2 ☐ 56
RV lift y n

Loud P2 y n ☐ 58
TI y n

Investigations

Urine	1	2	3	4
Protein	+	++	+++	nil
Blood	+	++	+++	nil
Casts	+	++	+++	nil

☐ 60
☐ 62

card 1 ☐☐ 2

study no 3 ☐☐☐ 5

PFT's

	patient	pred	HB corrected
FEV1	6 ☐☐☐☐ 9	10 ☐☐☐☐ 13	
FVC	14 ☐☐☐☐ 17	18 ☐☐☐☐ 21	
FEV1/FVC	22 ☐☐ 23	24 ☐☐ 25	
TLCO	26 ☐☐ , ☐☐ 29	30 ☐☐ , ☐☐ 33	34 ☐☐ , ☐☐ 37
MIP's	38 ☐☐☐ 40	41 ☐☐☐ 43	
MEP's	44 ☐☐☐ 46	47 ☐☐☐ 49	

ECG

RBBB y=1 n=2 ☐ 50
RA+ y n ☐
RV+ y n ☐
RV strain y n ☐ 53

ECHO

Failed n=2 y=1 — 54

TI — y=1 n=2 — 55

PAP — N/A=xx — 56–57

<19	y=1	n=2	N/A=x
20-39	y	n	N/A
>40	y	n	N/A

CXR

Pulm HT	y=1	n=2		61
CFA	y	n		62
Vanishing lung	y	n		63
Pleural fluid/thickening	y	n		
Old TB	y	n		65
Other _____	y	n		66

card — 1–2

study no — 3–5

Blood tests

ANF	____	6–9
ENA	_____(Sm)	10–15
Anti-DNA	___	16–18
CIC	__%	19–20
C-RP	__,_	21–24
CH50	___	25–27
C3	___	28–30
C4	___	31–33
APL	___(IGM)	34–36
	___(IGG)	37–39
PTT test	____	40–42
control	____	43–44
mix	____	45–46
VDRL	____	47–50
TPHA + ve		51 (y=1 n=2 N/A=x)
Hb	__,_	52–54
WCC	_____	55–59
Lymph count	_____	60–64
Platelets	_____	65–70

Disease Activity on Physician's global assessment

0/1/2/3/4/5/6/7/8/9/10 71 ☐☐ 72

FOLDER REVIEW *card* 1 ☐☐ 2

study no 3 ☐☐☐ 5

Date of 1st visit __/__/19__ 6 ☐☐/☐☐/☐☐ 11

no of visits ___ 12 ☐☐☐ 14

no of admissions ___ 15 ☐☐☐ 17

ARA Criteria

Malar rash		y=1	n=2		☐ 18
Discoid rash		y	n		☐
Photosensitivity		y	n		☐
Oral ulcers		y	n		☐ 21
Non-deforming arthritis >/= 2 joints		y	n		☐ 22
Serositis	pleuritis	y=1	n=2		☐ 23
	pericarditis	y	n		☐
Renal	casts	y	n		☐ 25
	protein	y	n		☐
CNS	seizures	y	n		☐ 27
	psychosis	y	n		☐
HEM	hemolytic anemia	y=1	n=2		☐ 29
	WCC < 4000	y	n		☐
	L's < 1500	y	n		☐
	Platelets < 100 000	y	n		☐ 32
Immunologic	Anti-DNA	y	n	N/A=x	☐ 33
	ENA(sm)	y	n	N/A	☐
	False + VDRL	y	n	N/A	☐ 35
ANF		y	n		☐ 36

TOTAL : __/11 37 ☐☐ 38

RESPIRATORY INVOLVEMENT

Worst dyspnoea score

MRC grade 0 1 2 3 4 N/A=x 39
CRP (0 - 20) __ N/A=xx 40 41

Pleural n=2 y=1 42

pain y=1 n=2 N/A=x 43
rub y n N/A
effusion clinically y n N/A
CXR y n N/A 46

INFECTIONS n=2 y=1 47

Bronchitis no of abiotic courses 48 49
Pneumonia no of admissions 50 51
TB no of courses 52 53

PULM THROMBOEMBOLISM n=2 y=1 54

suspected onset 55 60

clinical y=1 n=2 61
nuclear med y n N/A=x
APL associated y n N/A 63

card 1 2

study no 3 5

CFA n=2 y=1 6

suspected onset __/__/199_ 7 12

cough y=1 n=2 13
dyspnoea y n
clubbed y n
end insp crackles y n 16

CXR restricted y n 17
R-N infiltrate y n

PFT restricted y=1 n=2 19
reduced TLCO y n

PO_2 __,_ kPa N/A=xx,x 21 , 23

__% sat N/A=xxx 24 26

Histology TBB y=1 n=2 N/A=x 27
Lavage y n N/A
OLB y n N/A 29

PULM HT n=2 y=1 30
possible=1 probable=2 definite=3 31

suspected onset __/__/199_ 32 37

1 0 y=1 n=2 38

2 0 cardiac y n 39
CFA y n
Thrombo-embolism y n 41

dyspnoea y n 42
palpable P2 y n
loud P2 y n
RV lift y n 45

RVF Oedema y=1 n=2 46
JVP y n
Hepar y n 48

ECG RA+ y n 49
RV+ y n
RBBB y n 51

CXR PA+ y n 52
RV+ y n

1st ECHO PAP __ N/A=xx 54 55
<19 y=1 n=2 N/A=x
20-39 y n N/A
>40 y n N/A 59 60
Swan Ganz PAP __ N/A=xx

VANISHING LUNG n=2 y=1 61

dyspnoea y=1 n=2 62
CXR y n 63
PFT MIP's __ N/A=xxx 64 66
MEP's __ N/A=xxx 67 69

TLCO __ N/A=xx,xx 70 , 73

OTHER _____ y n 74

69

Treatment

card 1 ☐☐ 2

study no 3 ☐☐☐ 5

Anticoagulants __ years 6 ☐☐ 7
Vasodilators __ years 8 ☐☐ 9

Immunosupp n=2 y=1 ☐ 10

Indication Lupus y=1 n=2 ☐ 11
Resp y n ☐

Drug pred y n ☐ 13
aza y n ☐
cyclophos y n ☐
other_____ y n ☐ 16

Duration years ___ 17 ☐☐ 18
no of flares ___ 19 ☐☐ 20

Response Lupus y=1 n=2 N/A=x ☐ 21
Resp y n N/A ☐

Raynaud's y n ☐ 23

Digital ulcers/gangrene y n ☐ 24

Ischemic heart disease y n ☐ 25

Worst PFT's

Date __/__/19__ 26 ☐☐‖☐☐‖☐☐ 31

	patient	pred	HB corrected
FEV1	32 ☐☐☐☐ 35	36 ☐☐☐☐ 39	
FVC	40 ☐☐☐☐ 43	44 ☐☐☐☐ 47	
FEV1/FVC	48 ☐☐ 49	50 ☐☐ 51	
TLCO	52 ☐☐ , ☐☐ 55	56 ☐☐ , ☐☐ 59	60 ☐☐ , ☐☐ 63
MIP's	64 ☐☐☐ 66	67 ☐☐☐ 69	
MEP's	70 ☐☐☐ 72	73 ☐☐☐ 75	

ADDENDUM

group no (case=1;control=2) ☐ 1

STUDY NO 2 ☐☐☐ 4

Current - Imm.sup duration (months) 5 ☐☐☐ 7

- CQ y=1 n=2 ☐ 8

duration (months) 9 ☐☐☐ 11

PFT's

	patient	pred
KCO	12 ☐,☐☐ 14	15 ☐,☐☐ 17

ECHO

AC1	18 ☐,☐☐ 20	ET1	21 ☐,☐☐ 23
AC2	24 ☐,☐☐ 26	ET2	27 ☐,☐☐ 29
AC3	30 ☐,☐☐ 32	ET3	33 ☐,☐☐ 35
AC4	36 ☐,☐☐ 38	ET4	39 ☐,☐☐ 41
AC5	42 ☐,☐☐ 44	ET5	45 ☐,☐☐ 47

PAP 48 ☐☐ 49

%SF 50 ☐☐ 51 CO 52 ☐☐ 53

CXR

R PA diameter 54 ☐☐ 55

ant ribs no 56 ☐☐,☐ 58

post ribs no 59 ☐☐,☐ 61

cardiac diameter 62 ☐☐,☐ 64

thoracic diameter 65 ☐☐,☐ 67

Blood tests

CIC 68 ☐☐,☐ 70

Past - Imm.sup duration (months) 71 ☐☐☐ 73

- CQ y=1 n=2 ☐ 74

duration (months) 75 ☐☐☐ 77

APPENDIX B

Laboratory Reference Values

ANF:	>/= 40	
Anti-DNA:	0 - 15 ug DNA bound/ml serum	
APL-IGG:	0 - 10 u/ml	normal
	10 - 20 u/ml	low titre
	20 - 100 u/ml	moderate titre
	> 100 u/ml	high titre
C3:	85 - 195 mg/ml	
C4:	12 - 36 mg/ml	
CH50:	160 - 220 mg/ml	
CIC:	0 - 7%	
C-RP:	undetectable mg%	
ENA:	0 - 320	
Hb:	11.6 - 15.6 g/dl	
Lymph:	1.2 - 4.0 x 10^9 /l	
Platelets:	164 - 432 x 10^9 /l	
PTT:	> 1.5 Control	
TPHA:	negative	
VDRL:	negative	
WCC:	4 - 11 x 10^9 /l	

APPENDIX C

Pulmonary Function Tests

	Normal	Mild	Moderate	Severe
FEV1	> 80	60 - 79	41 - 59	< 40
FVC	> 80	60 - 79	51 - 59	< 50
Ratio	> 75	60 - 74	41 - 59	< 40
TLCO	> 80	60 - 79	41 - 59	< 40

Values are expressed as % predicted.

Hb Corrected $TLCO_{sb}$ formula[77]

$$\text{Hb Corrected TLCO} = \frac{\text{Observed TLCO} \times (10.22 + \text{Hb})}{1.7 \times \text{Hb}}$$

Smoking History

1 Pack-year = one packet of 20 cigarettes per day for one year

APPENDIX D

CONSENT FORM

I, _____ hereby give my consent to be
involved in this clinical study. I understand that this consent is voluntary and that my future care will not be prejudiced should I not agree to the study.

All the information gathered will be used for research purposes and I agree to it being published in medical journals or presented at clinical meetings provided the investigators adhere to accepted standards of medical confidentiality.

Signed on __/__/199_ at Groote Schuur Hospital.

Subject: _____

Witness: _____