DISSERTATION FOR PART III MASTER OF MEDICINE (ANAESTHESIA)

FAT EMBOLISM SYNDROME - A STUDY OF ITS CLINICAL MANIFESTATIONS AND LONG TERM OUTCOME.

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INTRODUCTION

Since Zenker first described the Fat Embolism Syndrome (FES) in 1861, the syndrome continues to be a poorly understood complication of trauma, usually involving fractures of the long bones. Zenker described microscopic fat globules in the pulmonary capillaries of a man who had died of a thoraco-abdominal crush injury (1).

In 1873, Bergman (2) was the first person to describe clinical fat embolism syndrome in a patient with a fractured femur who died with symptoms of confusion, dyspnoea and pyrexia. Since then, not only have many other reports followed, but numerous pathological conditions resulting in similar clinical and patho-anatomical features to the above have been described. These include burns, soft tissue injuries, extracorporeal bypass for open heart surgery, renal transplantation and endoprosthesis surgery. More recently, in 1966, Ashbaugh and Petty (31) described the pathology of the Adult Respiratory Distress Syndrome (ARDS) indicating it to be the common final pathway of many pathological conditions, including FES, resulting in respiratory insufficiency.

The difficulty of clearly defining the FES as a distinct entity from the many conditions which result in ARDS persists still today, but certain features seem to characterise its presentation.

At present, the FES could be defined as a clinically recognisable syndrome of acute respiratory distress with cutaneous, pulmonary and central nervous system manifestations, frequently following trauma associated with long bone fractures.

A consistent aspect of the pathology appears to be a microvascular occlusion by fat macroglobules involving both the pulmonary and systemic vasculature.

The present lack of specific laboratory tests makes the symptom complex of the FES the major factor in distinguishing it as a distinct clinical entity. Whilst investigation into tests for its early detection continues, most progress has been made in the recognition and active and improved management of suspected cases resulting in a favourable outcome in most cases.

The long-term outlook for patients surviving ARDS has not been well evaluated. However it appears that within 6-9 months after ARDS, values for lung volumes (forced vital capacity [FVC], total lung capacity [TLC], ratio of forced expiratory volume in one second to the FVC [FEV1/FVC]) are not significantly different from predicted values. However persistent abnormalities in the diffusing capacity for carbon monoxide (TLCO) have been reported in a fairly high percentage of survivors (3,4). Elliot et al (4) also observed abnormalities of oxygen transfer across the lung with exercise. Since exercise testing is the most sensitive test of pulmonary gas exchange, it was thought appropriate that this long term follow-up study should include such testing to try to ellicit any residual gas exchange abnormalities.

Clearly there exists the need to correlate the details of the ARDS (patient details, precipitating events, course and management of the syndrome) with the long-term outcome of pulmonary function, before we are able to predict the long-term outlook of ARDS.

This study reports the findings of a retrospective study of patients diagnosed as having FES and treated in the Respiratory Unit of Groote Schuur Hospital from 1982 to 1984. The current status and understanding of the FES is reviewed. The long-term effects on the lungs were also evaluated 2-4 years after the illness in those patients who could be traced.

PATIENTS AND METHODS

Twenty patients diagnosed as having Fat Embolism Syndrome (FES) and treated in the Respiratory Intensive Care Unit of Groote Schuur Hospital during the years of 1982 to 1984 were studied.

Patients admitted into the study had evidence of :

(1) musculo-skeletal trauma involving bony fractures

(2) systemic embolisation with cutaneous and/or central nervous system involvement and

(3) pulmonary embolisation as manifested by hypoxaemia and chest radiographic changes.

The data was retrieved from the computerised data bank of the Respiratory Unit. The original folders were then obtained from hospital records and the clinical notes and special investigations reviewed. Where possible patients were traced using data present in their original folders and 9 of the 20 patients agreed to return to the hospital for investigations of pulmonary function. The remaining 11 patients could not, for various reasons, be traced. These studies included static lung volumes; flow-volume measurements; diffusing capacity for carbon monoxide (TLCO) and stage I exercise test.

Details of Tests

(1) Lung volumes were measured on a Godart expirograph (water spirometer) using the helium dilution technique. The spirometer was calibrated by the syringe method.

(2) Flow-volume measurements were done on a 570 wedge spirometer (Med-Science) linked to an X-Y Hewlett Packard 7041M recorder. Volumes were corrected to BTPS.

(3) Diffusing capacity for carbon monoxide were measured using the P.K. Morgan transfer test (single breath technique).

Normal predicted values for all the above tests were obtained from the literature as listed (5,6,7).

Stage I Exercise Test

Exercise testing arises from the engineering principle of testing a system under load conditions. Exercise related symptoms (eg dyspneoa) are often subjective and objectivity may be provided by exercise testing. The stage one test involves progressive incremental exercise to exhaustion during which simple measurements are made at frequent intervals. The maximum power output achieved by the patient is an important objective finding, often conflicting with one's subjective opionion.

The Groote Schuur Hospital (GSH) protocol was used and is as follows :

(1) Preliminary recordings of spirometry (using a Parkinson Cowan CD4 dry gas meter) and ECG (12 lead Hewlett Packard 1513A) were made.

(2) The patients were then made to perform progressive graded exercise to a symptomatic maximum. Workload was incremented by 100 kilopascals per minute using a Siemens Elema

RE20 cycle ergometer.

(3) Measurements of heart rate, blood pressure, ventilation, ear oximetry and endt-idal PCO_2 ($PetCO_2$) were made each minute. A Siemen's Mingograph chart recorder and Hewlett Packard 47201A oximeter (measuring directly from the patient's earlobe) were used in addition to the 12 lead ECG and blood pressure recordings (standard mercury baumanometer). The patient was made to breathe via a Hans Rudolf one-way mouthpiece.

(4) ECG recordings were done immediately post-exercise and at 1, 3, 5 and 10 minute intervals. Spirometry was performed at 5 and 10 minutes post-exercise.

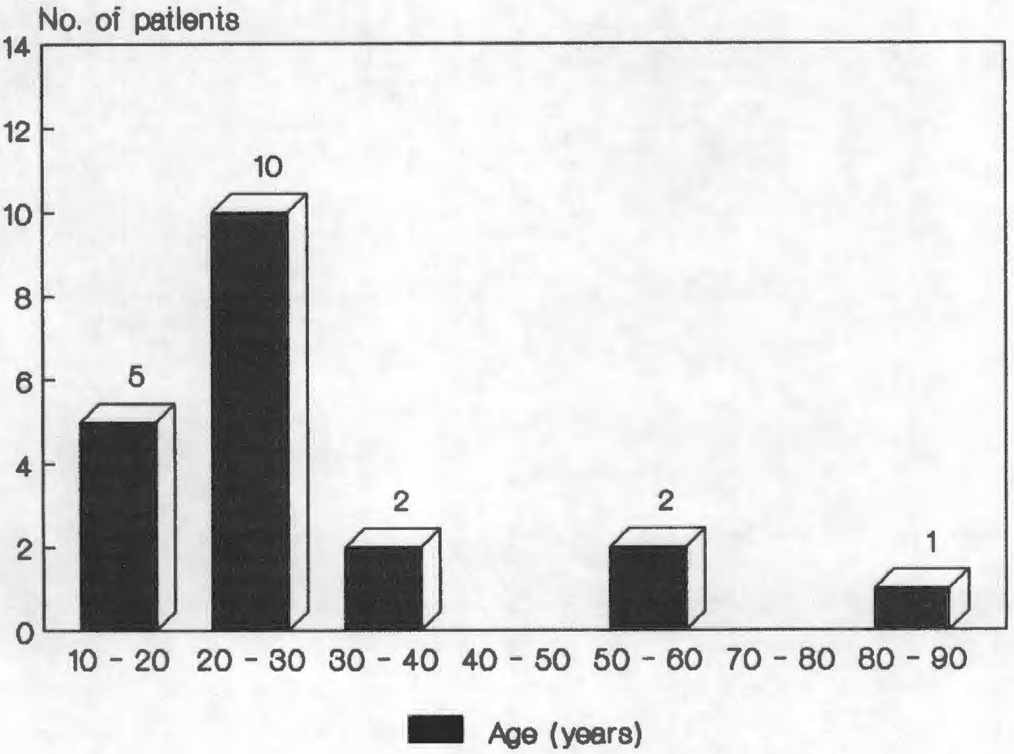
(5) Note was made of the patient's limiting symptoms.

RESULTS

(1) Age and Sex (Table 1)

The patients' age ranged from 16-81 years. Thirteen were males and 7 females. The median age was 25 years. Fifteen out of 20 were 30 years or less of age (75%).

TABLE 1: AGE OF PATIENTS



(2) Presenting Bone Fractures (Table II)

Most patients in this study had multiple long bone fractures (60%) but in 8 (40%) isolated fractures were the only injury. This included fracture of the femur (4), tibia and/or fibula (3) and pelvis (1). Fracture of the femur was the commonest bone fracture (70%), followed by fracture of the tibia and/or fibula (55%). Fractures of the pelvis, although not a long bone, have been reported to commonly occur in association with FES, as is shown in this study (35%), and with only one exception were associated with lower limb fractures. Upper limb fractures were commonly associated (30%) but never occurred in isolation. Other fractures listed (ankle, hand, foot, vertebral, ribs) were not considered as long bone. The average number of long bone fractures overall per patient was 2.4.

TABLE II: FRACTURE SITES

Patient	Lower Limb Fem	Lower Limb Tib	Lower Limb Fib	Pelvis	Upper Limb Hum	Upper Limb Rad	Upper Limb Ulna	Other
1	+	+	+	-	-	-	-	-
2	+	+	+	-	-	+	-	# ribs x 2
3	+	+	+	-	-	-	-	
4	+	-	-	+	-	-	-	Dislocated elbow
5	+	-	-	-	-	+	+	
6	+	-	-	-	-	-	-	
7	+	-	-	-	-	-	-	# Facial bone # Ribs x 3
8	-	+	+	-	-	-	-	# T8 vertebra
9	+	-	-	+	-	-	-	
10	+	+	+	-	+	-	-	
11	+	-	-	-	-	-	-	
12	+	+	+	+	-	+	+	# Foot
13	-	+	+	-	-	-	-	
14	+	+(2))	-	+	+	-	-	
15	-	-	-	+	-	-	-	Disruption knee
16	-	+	+	+	-	-	-	
17	-	+(2))	-	-	-	-	-	# Mandible
18	+	-	-	+	-	-	-	# Ribs x 3 # Ankle
19	+	-	-	-	-	-	-	
20	-	+	+	-	+	+	-	# Ankle
Total	14	8*	9**	7	3	4	2	
%	70	40	5	35	15	20	10	

* - 2 were bilateral
** - 1 was bilateral

(3) Clinical Presentation (Table III)

The clinical signs of the FES were divided into **major** and **minor** features. The major features included those of the respiratory system, namely hypoxaemia and radiological changes (characteristically showing bilateral extensive parenchymal opacities), evidence of central nervous system involvement unrelated to head injury and a petechial rash. Minor clinical features included pyrexia in the absence of obvious clinical infection, anaemia (a haemoglobin of less than 10 g/dl) and thrombocytopaenia (platelet count less than 150 000/mm^3). The lowest haemoglobin and platelet count within the first 72 hours after admission were recorded.

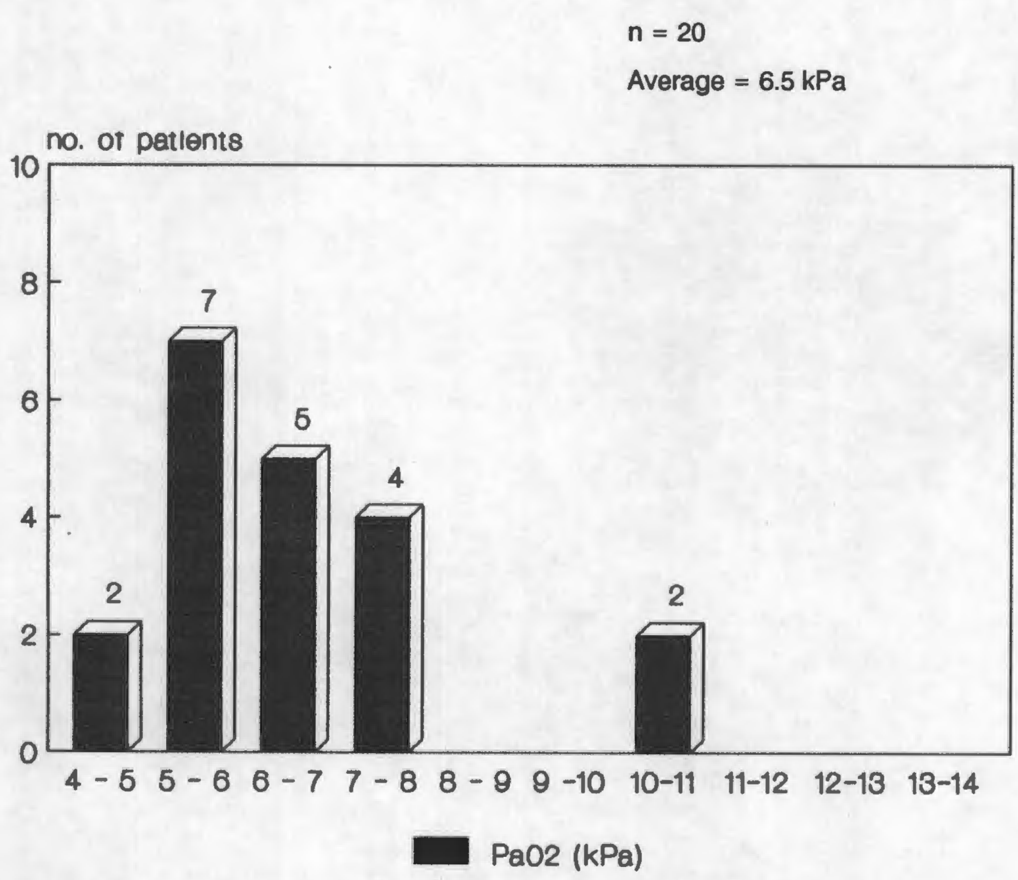
TABLE III : PRESENTING CLINICAL FEATURES

Patient No.	Resp.	CNS	Petechiae	T^o	Hb (< 10 g%)	Platelets (< 150,000/mm^3)
1	+	+	+	+	+	0
2	+	+	+	0	+	0
3	+	+	+	+	+	+
4	+	+	0	+	+	0
5	+	+	+	+	+	0
6	+	+	0	0	0	0
7	+	0	+	+	+	+
8	+	0	+	+	+	+
9	+	+	+	0	+	0
10	+	0	+	+	+	0
11	+	+	0	+	+	0
12	+	+	0	+	+	+
13	+	+	0	+	+	0
14	+	0	+	0	0	+
15	+	+	+	+	0	0
16	+	0	+	0	+	0
17	+	+	0	+	0	0
18	+	0	+	+	+	+
19	+	+	0	+	0	0
20	+	0	+	0	+	+
Total	20	13	13	14	15	7
%	100	65	65	70	75	35

respiratory intensive care unit for management. Thirteen patients (65%) developed neurological signs attributable to FES and the same number had clinical evidence of petechiae. The commonest minor feature was found to be a low haemoglobin (75%). Other minor clinical features such as electro-cardiographic changes, retinal changes (fat globules in retinal vessels), lipuria, increased serum lipase activity and jaundice have been reported to occur with FES, but were not specifically reported in these patients.

Eighteen of the 20 patients presented with arterial oxygen tension (PaO_2) below 8 kPa (see Table IV). Two patients presented with initial PaO_2 of between 10 and 11 kPa but both of these were on supplemental oxygen via a facemask at the time. The average PaO_2 on admission was 6.5 kPa.

TABLE IV : ARTERIAL OXYGEN TENSION (PaO2)

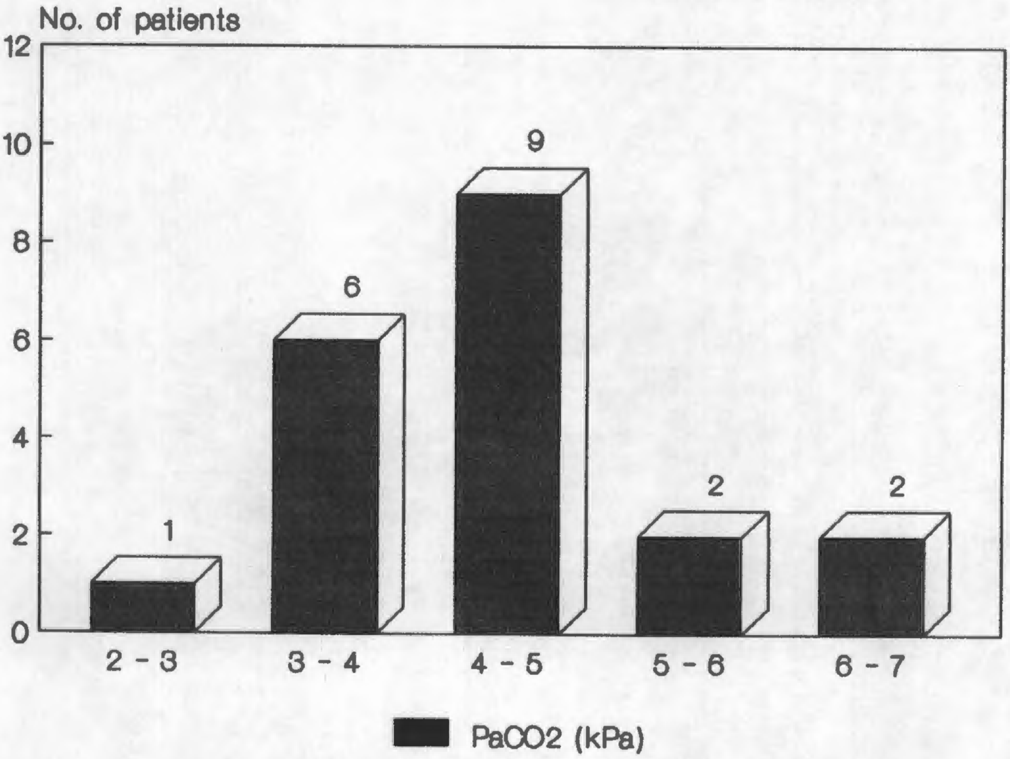


The initial arterial carbon dioxide tensions ($PaCO_2$) averaged at 4.2 kPa overall on admission (see Table V), and overall reflects a degree of alveolar hyperventilation. Two patients however had elevated $PaCO_2$'s on presentation.

TABLE V : ARTERIAL CARBON DIOXIDE TENSION (PaO2)

n = 20

Average = 4.2 kPa



Radiological changes in all patients showed chest X-rays which were consistent with ARDS, usually one of diffuse patchy consolidation involving both lungs (Figure 1 a and b).

FIGURE 1 (a) : MILD LUNG INVOLVEMENT

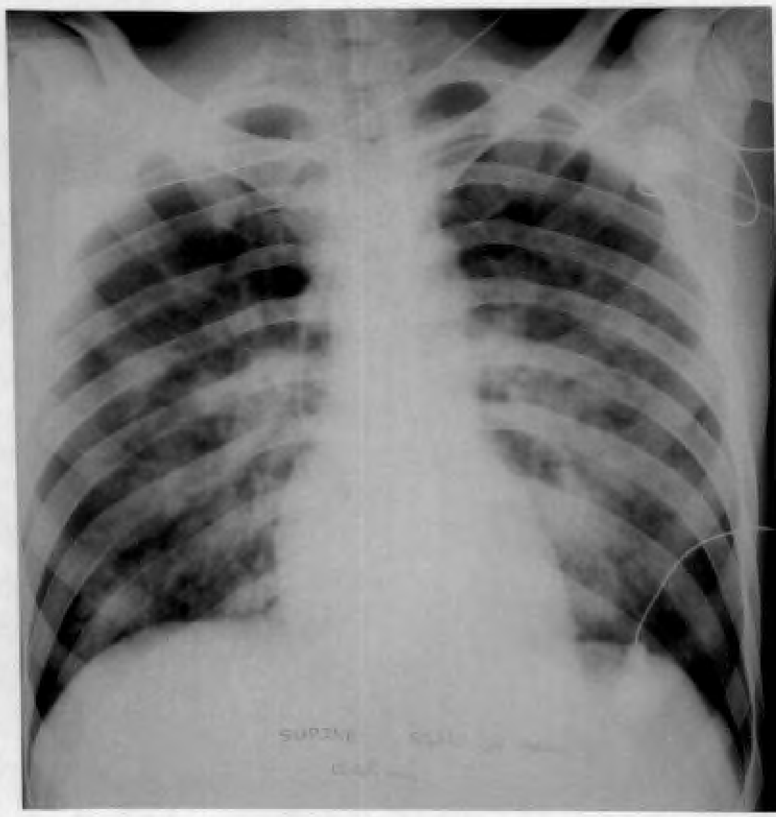
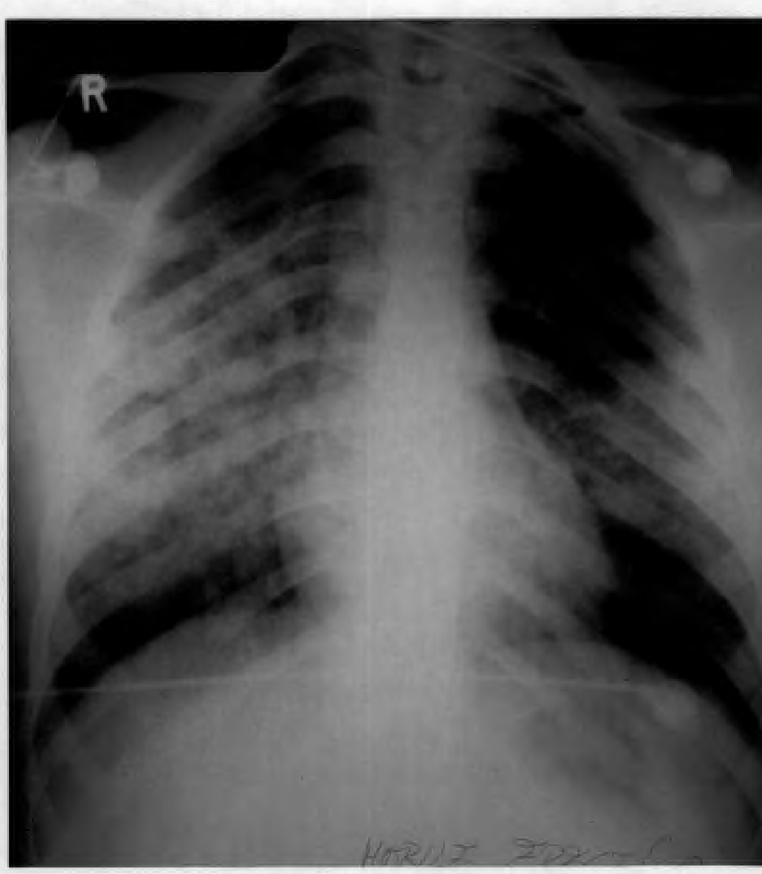


FIGURE 1 (b) : SEVERE LUNG INVOLVEMENT



Neurological manifestations were present as diffuse encephalopathic changes in 13 patients (65%). Two of these patients, in addition, had evidence of focal lesions (I had decreased movement of the right arm and another a dilated pupil on the one side), and 2 patients had frank grand mal seizures. One patient had paraparesis below the spinal level of T8 secondary to an injury sustained in the accident, but had no neurological abnormalities attributable to the FES. The duration of neurological abnormalities ranged from 1-43 days. In only 4 patients did the abnormalities persist for more than 10 days. The average duration of neurological deficit was 9.9 days and 7 of these 13 patients had resolved completely within 4 days. Four of these patients, including those with focal signs and seizures, had special investigations (3 CT scans and 1 carotid angiogram), but no focal lesions could be demonstrated in any.

An elevated temperature (within the first 48 hours) was recorded in 14 patients (70%). Of these, 11 were $38^{o}C$ or greater.

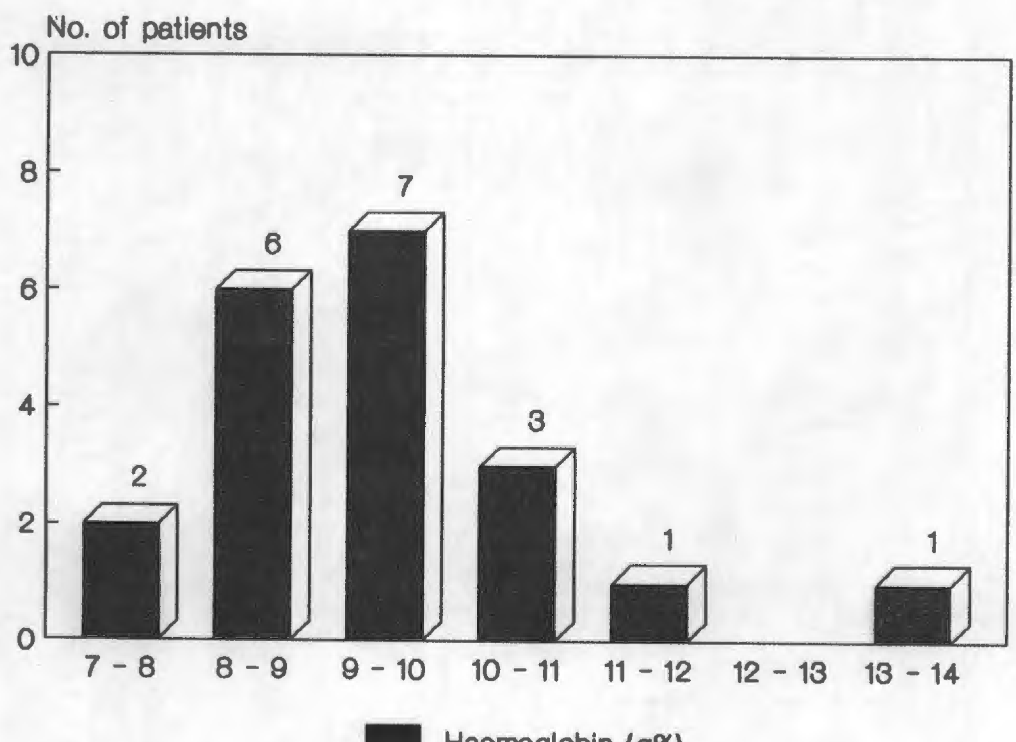
The commonest minor feature to be present was a low haemoglobin, with 15 patients (75%) having a level less than 10g%. The range was 7.4-13.5g% and the average haemoglobin level was 9.5 (see Table VI).

TABLE VI : HAEMOGLOBIN

n = 20

Range 7.4 - 13.5 g%

Average = 9.5 g%



Platelet counts of less than 150 000/mm^3 were considered to be inappropriately depressed and were present in 7 patients (35%), the lowest values being 90 000/mm^3.

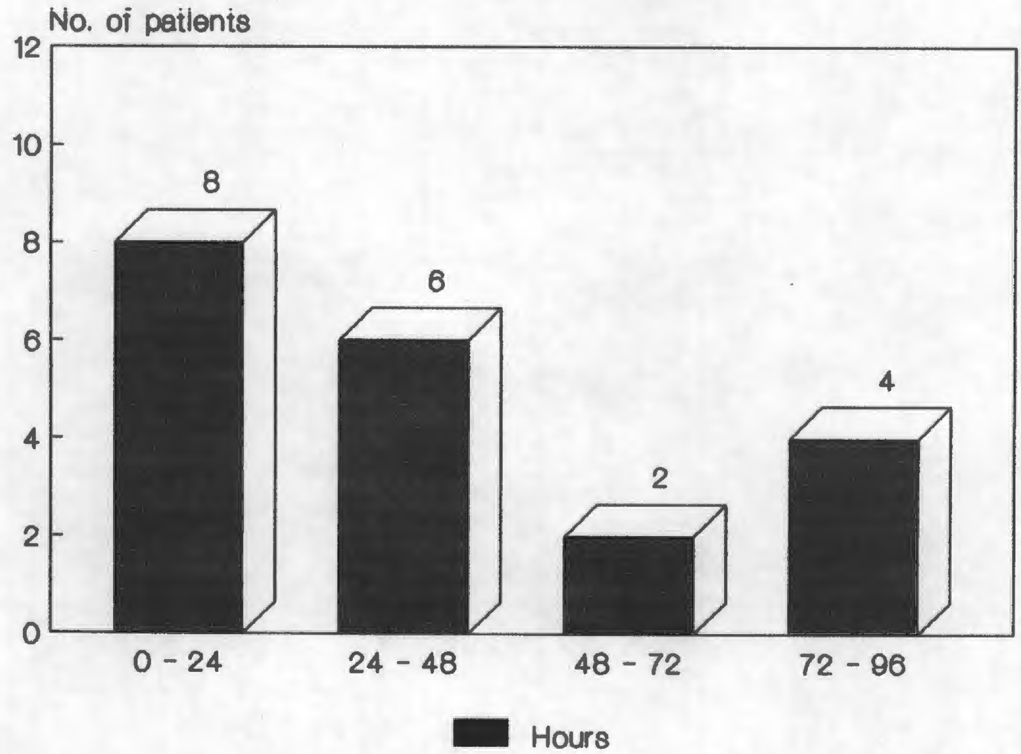
(4) Injury to Presentation Time Interval (Table VII)

The onset of symptoms from the time of injury was considered. Fourteen of the 20 patients (70%) presented within 48 hours of sustaining the injury. All 20 patients presented within 96 hours of the injury.

TABLE VII : INJURY TO PRESENTATION TIME INTERVAL

n = 20

Median = 24 - 48 hours



(5) Management

(a) Early Management

Early fracture immobilisation was performed on all patients in the Trauma Unit. This necessitated a general anaesthetic in several patients for debridement of wounds, reduction and immobilisation of the fractures. Four of the patients were transferred to Groote Schuur Hospital from outlying hospitals after initial management there.

(b) Management (Intensive Care Unit)

Respiratory management was aimed at reversing the hypoxaemia and patients were treated either with Continuous Positive Airways Pressure (CPAP) via a facemask or they were electively ventilated using Intermittent Positive Pressure Ventilation (IPPV) with Positive End Expiratory Pressure (PEEP). Indications for IPPV were (i) an inability to protect the airway; (ii) poor patient co-operation; (iii) an inability to apply the facemask; (iv) inadequate alveolar ventilation and (v) inadequate oxygenation on CPAP.

CPAP

Ten patients were treated with CPAP initially. This was administered via a Capp CPAP machine (a locally manufactured, low resistance apparatus, providing a continuous high flow, inspiratory-boosted supply of oxygen-enriched humidified air, water valve PEEP.) Six of the 10 patients had no CNS symptoms at all and 3 had mild neurological symptoms only. One of the latter was intubated and received IPPV after his neurological symptoms had deteriorated. The average number of days of patients requiring CPAP was 3 and the average stay of this group of patients in the ICU was 5.8 days. The range was from 1 to 4 days.

IPPV

Eleven patients (including the failed CPAP) required IPPV and PEEP. Five of these 11 patients later required tracheostomy, the main indicator for this being an anticipated length of 7 or more days of intubation. The average number of days of IPPV was 7.7 and the average stay of this group in the ICU was 10.2 days. Nine of these 11 patients had significant neurological symptoms ranging from drowsiness and confusion to deep coma responding to pain only. The remaining 2 patients had no neurological symptoms but required intubation and ventilation for severe respiratory failure. The average duration of tracheostomy was 9.6 days, and the range 1 to 14 days.

Corticosteroids

Twelve of the patients (60%) received corticosteroid therapy as part of their early management. Approximately 30 mg/kg body weight of methylprednisolone or an equivalent dose of another preparation was used. No specific protocol or steroid formulation was used. No suitable comparisons of the steroid versus the non-steroid treated group could be made other than that of a shorter duration of stay in the ICU in the group not receiving steroids (6.9 days versus 8.2 days). No significance could be demonstrated for this (Student's t test).

(6) Overall Outcome

All patients survived their stay in the Intensive Care Unit and were eventually discharged from the hospital. Four patients developed significant secondary bacterial respiratory infections as evidenced by continued pyrexia, positive bacterial cultures on tracheal aspirates and clinical and radiological evidence of pulmonary infection. All 4 patients had received steroids in their management at some time. However, no significance could be attributed to this (Chi-squared test). The presumptive causative organism in all 4 patients was staphylococcus aureus. Two of these patients had prolonged stays in the ICU (20 and 26 days), 1 of these was complicated by the development of a bronchopleural fistula. The latter patient received 14 days of IPPV, 5 of which required very high levels of PEEP (from 15-25 cms of water).

As mentioned previously, prolonged neurological abnormalities persisted for more than 10 days in 4 patients, but all eventually returned to normal before discharge from hospital.

(7) Pulmonary Function Studies - long-term follow-up

Of the 9 patients who returned to participate in the studies, 2 were unable to manage the exercise studies (one was paraplegic and the other had residual damage to a leg). The 9 patients were fairly representative of the original group of patients, being well matched for age and mode of respiratory management (Table VIII). Five of them had been treated with CPAP and 4 by IPPV. One of the latter patients was in fact the patient who developed a bronchopleural fistula and secondary bacterial infection.No significant difference could be shown in the average duration of ICU stay between the 2 groups (Students t).

TABLE VIII : G.S.H. FES STUDY - LONG TERM FOLLOW-UP

(2 - 4 YEARS)

	FOLLOW-UP GROUP	TOTAL
Patients (n)	9	20
Median age (years)	22	25
Respiratory Mx (patients)		
CPAP	5	10
IPPV	4	11
I.C.U. stay (average days)	6.3	8.2 (NS Student 't')

The results are seen in Table IX and X can be summarised as follows. Studies of lung volumes (in particular FVC, FEV1, TLC, RV) and diffusing capacity (TLCO) for all 9 patients fell within the normally accepted predicted values (5,6,7). The wide range of predicted normals for residual volume is due to the relatively large values of the standard deviations when compared to the mean.

TABLE IX

PULMONARY FUNCTION STUDIES - RESULTS

NO.	FVC (ml)				FEV1 (ml)				TLC (ml)				RV (ml)				TLCO (ml/mm Hg/min)			
	Act	Pred	2SD	% Pred	Act	Pred	2SD	% Pred	Act	Pred	2SD	% Pred	Act	Pred	2SD	% Pred	Act	Pred	2SD	% Pred
1	4700	5410	1190	87	3900	4400	880	89	5830	6740	1340	86	650	1330	760	49	32.6	37.4	10.2	087
2	5160	4610	1200	112	3960	3540	800	112	6140	6020	1340	102	1150	1420	760	81	36.1	30.5	10.2	119
3	4570	4620	1200	99	4480	3780	900	118	7400	5970	1340	124	2510	1350	760	186	37.0	33.7	10.2	110
4	3680	3700	870	99	3320	3230	650	103	3920	4870	970	80	760	1170	630	65	26.4	25.6	6.6	103
5	5650	5160	1190	109	5350	4260	880	126	7155	6530	1340	110	1605	1360	760	118	40.2	37.3	10.2	108
6	3950	3090	870	128	2900	2740	650	106	4570	3850	960	119	1090	760	640	143	24.6	27.1	7.2	91
7	3950	3190	870	124	3500	2760	650	127	4825	3960	960	122	840	780	640	108	28.2	26.7	7.2	106
8	4500	3550	870	127	3350	3030	650	111	5560	4710	960	118	1335	1160	640	115	25.4	28.4	7.2	89
9	4200	3940	1190	107	3000	3100	880	97	5255	5600	1340	94	1170	1660	760	70	31.8	25.6	10.2	124
Average				110				110				106				104				104

Key : Act = actual
Pred = predicted
2SD = 2 standard deviations
% Pred = % predicted normal
No. = patient number

FVC = forced vital capacity
FEV1 = forced expired volume in 1 second
TLC = total lung capacity
RV = residual volume
TLCO = diffusing capacity for carbon monoxide (single breath)

TABLE X : PULMONARY FUNCTION STUDIES - FLOW VOLUME LOOP

	PEFR (l/min)			PIFR (l/min)			MEF50 (l/sec)		
No.	Act	Pred	2SD	Act	Pred	2SD	Act	Pred	2SD
1	558	511	157	312	332	146	6.55	5.4	2.17
2	521	437	144	334	307	144	4.83	4.32	1.9
3	639	453	144	372	313	144	6.86	4.77	2.0
4	440	353	105	370	266	110	5.4	4.24	1.59
5	612	499	155	360	326	146	8.5	5.38	2.16
6	318	311	98	288	247	110	3.3	3.88	1.52
7	460	327	101	325	256	110	4.65	3.85	1.51
8	395	337	103	320	250	110	4.0	4.05	1.55
9	475	395	136	380	275	146	4.3	3.86	1.79

Key: PEFR - Peak Expiratory Flow Rate
PIFR - Peak Inspiratory Flow Rate
MEF50 - Maximum Expiratory Flow Rate at 50% of Vital Capacity
Act - Actual
Pred - Predicted
2SD - 2 Standard Deviations
No. - Patient Number

Exercise Test

The 7 patients having the stage 1 exercise test were followed up from 19 months up to 51 months after their episodes of FES (the average was 39 months - just over 3 years later). (Results are shown in Table XI). Figure 1 and 2 (page 18) are results of patient no. 7, showing how heart rate and ventilation are plotted against work load in each patient during exercise. Predicted maximum values for heart rate, work load and and ventilation are calculated from nomograms (42). In this example (Fig 1), the patient has normal heart rate response, reaching the predicted maximum. Fig 2 shows a normal ventilatory response, not reaching the ventilatory limit. Five of the 7 patients had normal tests, of which two were completely normal exercise tests and three were normal but submaximal, that is, they did not reach their predicted maximum workload. Leg fatigue was the common cause for this, but lack of encouragement and apprehension resulting from previous injuries may have contributed to the submaximal efforts. One of these 3 patients became mildly hypertensive during exercising. Two of the 7 tests were abnormal. One patient had an inappropriately elevated heart rate prior to and throughout the study. Possible causes for this could be primarily cardiac in origin, or secondary to metabolic or endocrine disorders (e.g. hyperthyroidism) or drug-related to name but a few. We were unfortunately unable to get the patient to return for further investigations.

TABLE XI : STAGE I EXERCISE TESTS

n	Age	*%	Reason for stopping	SaO2 (%)	PetCO2 mmHg	Abnormal results	Remarks
1	23	65	Leg fatigue	97	34-38	Mildly increased HR response	Submaximal test below ave. fitness
2	33	60	Leg fatigue	96-97	35-42	Elevated HR response Mildly hypertensive BP response	Submaximal test - unfit subject. Mildly hypertensive on exercise
3	17	100	Leg fatigue	96-97	34-40	None	Normal exercise test
4	23	75	Sore feet	96-98	36-42	Elevated heart rate at rest and during exercise	Mildly reduced exercise capacity with probable circulatory limitation for tachycardia not apparent
5	20	60	Leg fatigue	95-97	30-35	Mild hyperventilation on exercise	Submaximal test - no limiting factors
6	21	15	Leg fatigue	97	26-31	Marked hyperventilation on trivial exercise with low PetCO2	Submaximal test - cause not apparent but suggestive of anxiety
7	42	100	Leg fatigue Dyspneoa	96-97	33-34	Became hypotensive and fainted 4 mins post-exercise	Normal test Post-exercise syncope (? venous pooling)

*% = % predicted maximum power output
SaO2 and PetCO2 - ranges given
SaO2 - arterial oxygen saturation
PetCO2 - partial pressure of end-tidal CO2

FIGURE 1:

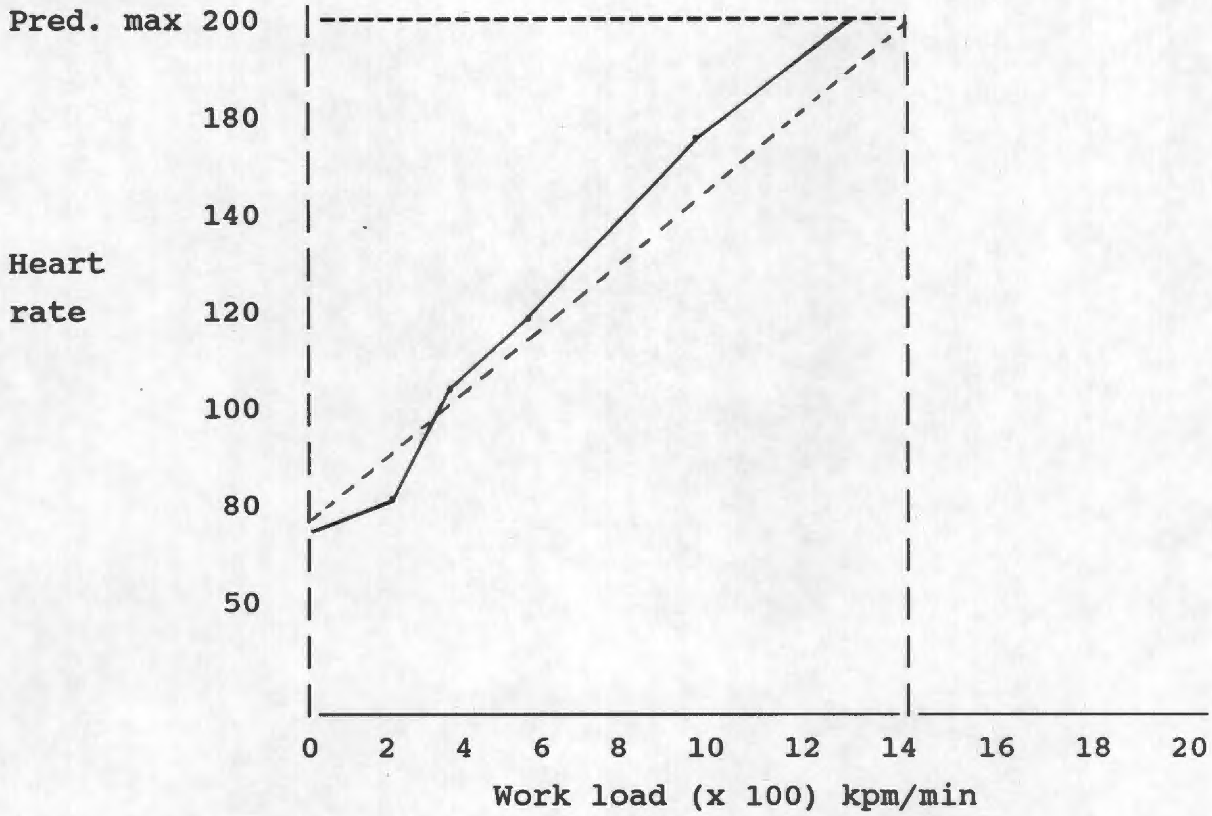
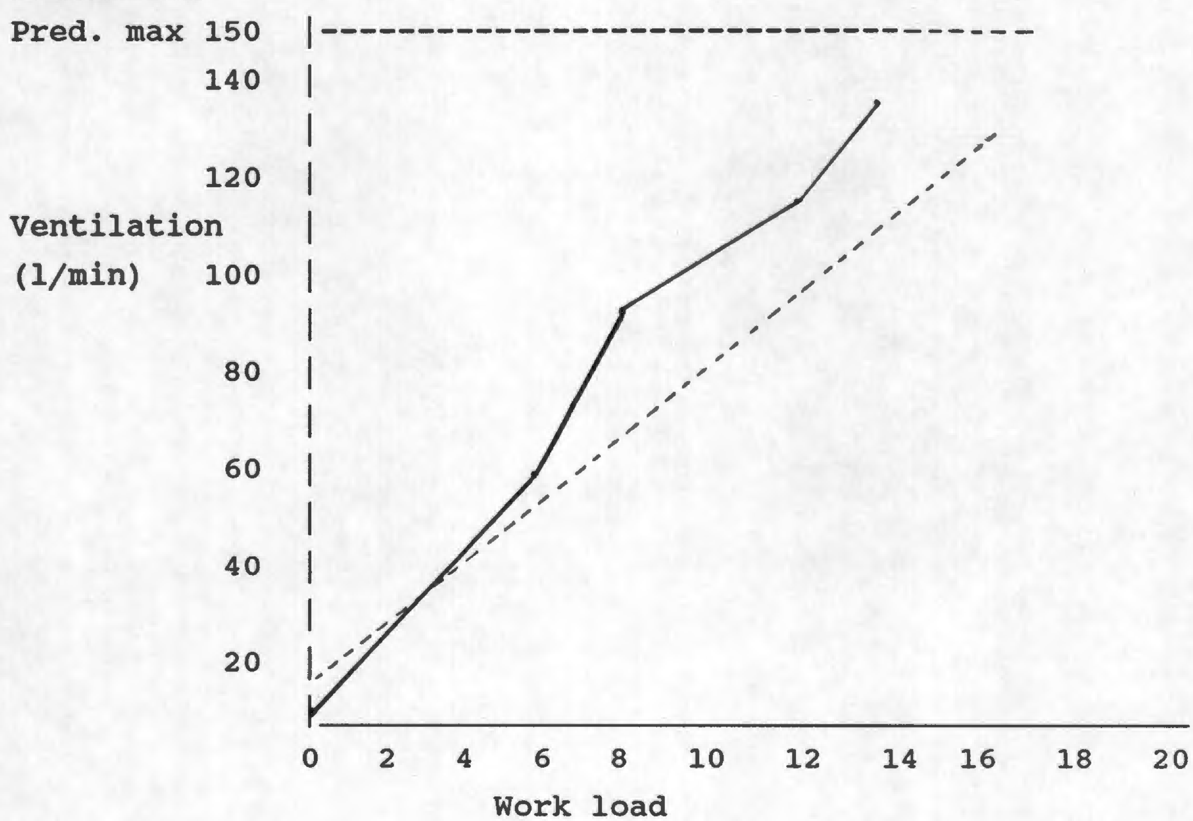


FIGURE 2 :



The second patient had evidence of hyperventilation with a low end-tidal PCO_2 recording, for which no cause other than anxiety could be attributed.

Of importance was the fact that no desaturation occurred in any of the patients during exercise, and a normal ventilatory response was found in all but the 1 patient. In addition, ECGs remained normal throughout the studies in all patients, with the exception of the patient who had the inappropriate tachycardia.

DISCUSSION AND LITERATURE REVIEW

The relative lack of specific early laboratory tests and the similarity of its clinical presentation to that found in the context of severe multiple trauma, make the diagnosis of FES today, one based on a high index of suspicion secondary to its clinical presentation. The importance of its recognition and the aggressive management of FES, has been shown to favour a rapid full recovery in the majority of cases.

The purpose of this study is to highlight experience of this ICU in the diagnosis, presentation, management and outcome of the syndrome. The findings are discussed in the context of the current understanding of the syndrome, and the long-term outcome of this particular syndrome on pulmonary function is considered.

Pathogenesis

FES is a relatively infrequent complication of musculo-skeletal trauma manifesting as a variant of the ARDS. The syndrome presents clinically as one of severe respiratory insufficiency with an associated multi-system response to trauma, in particular, involving metabolic, haematological and probable endocrine responses as well.

Two theories have been postulated to explain the pathogenesis of the FES :

(a The Marrowglobular or Mechanical Theory and

(b) The Metabolic Theory.

The Marrowglobular or Mechanical Theory (29) describes the embolic marrow fat derived from the fracture site of the long bone as the central pathophysiologic agent. It is thought that a disruption in the adipose tissue of the marrow space with traumatic opening up of venous channels and a transient rise in marrow pressure above venous pressure, leads to venous embolisation of marrow fat and tissue thromboplastins. This fat is then trapped in the pulmonary vascular bed at a capillary level, some of it traversing the arteriovenous communications, reaching the general circulation. The fat and thromboplastins concentrated in the pulmonary vascular bed then serve to activate the clotting cascade, enhance platelet aggregation and the release of vasoactive substances with subsequent complement activation and leucocyte aggregation in the pulmonary parenchyma. The embolised neutral fat is converted by lipases (produced by the pneumatocytes) to free fatty acids. These are directly toxic to the alveolar cells (especially type II) with resultant diminished surfactant production, leading to intra-alveolar oedema, haemorrhage and atelectasis (10). The final common pathway of the pulmonary response to injury results in the "shock lung" scenario with critical impairment of gas exchange.

Contrasting with this is the **Metabolic Theory**, based on the alteration of lipid stability as a result of chemical or mechanical action on the blood. A significant rise in serum lipids (mainly free fatty acids and triglycerides) can be demonstrated following trauma. Baker et al (8) and McNamara et al (9) have shown that an increase in free fatty acids followed a rise in the catecholamines in the bloodstream after trauma and stress. The esterification of free fatty acids in the liver and spleen appears to be depressed after severe trauma and sepsis, so this "clearing" mechanism becomes defective and increased free fatty acids enter and are filtered out by the lungs (30). Nixon and Brock-Utne (11) showed a significant correlation between arterial hypoxaemia and a rise in free fatty acid levels in patients with fractures. Irrespective of their source, these fat globules are trapped in the lung filter resulting in the secondary lung parenchymal damage.

At our present level of understanding, it seems that the mechanical theory probably explains the basis of the mechanism by which the FES is triggered and if severe enough will account for its early presentation clinically. The subsequent multisystem cascade would incorporate the metabolic response of trauma, resulting in the familiar pulmonary insufficiency and metabolic changes observed clinically, usually after an initial temporal delay varying between 24 to 48 hours.

Incidence

The incidence of FES is tremendously variable, and is probably largely due to a differing awareness of the syndrome as a clinical entity.

At autopsy, morphological fat embolism is observed much more frequently in patients dying soon after accidental injury, a varying incidence of between 45-89% having been observed in multiple fractures (12,13). Tachakra demonstrated a significant incidence of arterial hypoxaemia in patients who had had long bone fractures without any other injuries (14). However the full blown FES in cases of long bone fractures of the lower limb has been described to occur in 3-6% of these patients (15,16,17,18) with more recent studies (19,20) giving a lower incidence around 1%, which probably is a result of earlier recognition and more active early treatment of the long bone fractures. In multiple fractures associated with pelvic injuries, an incidence of between 5-10% has been quoted (21,22).

An interesting feature of our study was the fact that the majority of patients fell within the first 3 decades of life. The median age of our group was 25 years (average age 27 years) with 75% of cases being less than 30 years of age. Traditionally this is explained by claiming that this age group has the greatest likelihood of sustaining major injury. Geunter's series of 54 patients with clinical evidence of FES had an average age of 27.3 years (23). An analysis of a three year period (1984-1986) revealed that of 8155 patients admitted to Groote Schuur Hospital's Trauma Unit following motor traffic accidents (i.e. pedestrian or passengers of motor vehicles or motor cycles), the average age was 29 years. No significant difference in age between this group or those with FES in this study could be shown (Students t test). Moore et al (19) had an average age of 23 years old in his group of 17 patients with

FES, however he points out that 147 out of 321 (45.7%) with respiratory failure after thoracic and/or long bone injuries but who did not satisfy criteria for respiratory failure due to the FES alone, fell outside the first 3 decades of life. Although one might consider other patho-anatomical or biochemical causes which may predispose young adults to FES after long bone fractures, it seems that their vulnerability of sustaining a major injury is the most likely attributable factor.

Pattern of Injuries

Results of this study show that fat embolism syndrome occurs almost always but not exclusively with long bone fractures of the lower limb. In addition, most patients had more than one long bone fracture, with an average of 2.4 per patient in this study. There is also a high correlation of pelvic and multiple long bone fractures of the lower limb (30%). Fracture of the femur was the single most common long bone fracture associated with FES.

This corresponds with other studies like that of Geunter and Braun (23) whose series of 54 patients had an average of 2.7 fractures per patient and Moore et al (19) whose series of 17 patients had an average of 2.4 long bone fractures per patient. In this latter study, all but 1 patient had fractures of the lower limbs or pelvis. Alho (24) quotes an average of 2.5 fractures of the pelvis and lower extremities per patient in a series of 17 FES cases. Lepisto (37) reported in a series of 70 patients that 88.5% of FES patients had lower limb fractures compared to 53.7% in the control group of patients suffering multiple trauma.

We conclude that FES is almost always associated with lower limb fractures particularly of the femur (70% of our cases had femoral fractures), but can occur with any isolated long bone fracture. In addition, there remains a high association of FES where long bone lower limb fractures and pelvic fractures occur together (30% of cases).

Clinical Presentation

In this particular series, the full-blown syndrome was clearly apparent, as evidenced by the fact that all patients had significant hypoxaemia and diffuse radiological changes on admission, necessitating their admission to the Respiratory Intensive Care Unit for the appropriate management.

Gurd (25) classified the clinical features into major and minor criteria. The major criteria included respiratory signs (hypoxaemia and radiological changes) cerebral signs and a petechial rash.

The occurrence of marked encephalopathic changes in FES is one of its characteristic features. The literature reports incidences of up to 85% of FES having neurological disorders (26,27,28) It usually presents as an encephalopathic state, typically an acute confusional state with impaired consciousness at some time. However, focal features are not uncommon, usually co-existent with severe impairment of the level of consciousness, including apraxia, hemiplegia, scotomata and conjugate eye deviation. Jacobson et al (26) reported in their study that patients who had focal signs tended to present earlier with neurologic features and had relatively less risk for pulmonary involvement and did not develop fever, than those presenting with diffuse encephalopathy. He theorised that the difference in the 2 groups could be explained on the two accepted models of fat embolism, concluding that those with focal signs represented the mechanical theory with early fat embolisation and those with diffuse encephalopathy represented the biochemical theory with its later and more diffuse pathogenic mechanisms. Jacobson also confirmed the favourable long-term outlook for recovery as far as neurological deficits were concerned, as we have found in this study.

Macroscopic and microscopic examination of the brain in FES have shown that there is widespread petechial eruption (macroscopically), and multiple haemorrhagic lesions consisting of embolic intra-vascular fat in the lumen of minute vessels of the brain with associated perivascular haemorrhages (12). Although it seems as if the neurological abnormalities may be improved by oxygen therapy, they are generally not influenced by the latter, and often persist after reversal of the hypoxaemia thus cerebral hypoxia should be considered only a minor contributing factor in this regard (26,30)

The presence of petechiae has always been a very characteristic and significant clinical feature in the FES which is often sufficient evidence to clinch the diagnosis of FES in the context of the patient's injuries and clinical presentations. Oh and Mital (29) quote a figure of 50-60% of cases as having petechiae, the same figure quoted by Pellegrini (30). The petechiae usually occur 24-28 hours after the fracture was sustained. Geunter and Braun (23) gave an incidence of 72% of patients in a series of 54 as having petechial rashes. In this series 13 patients (65%) had evidence of petechiae, and occurred most commonly on the eyelids or conjunctivae. Rarely a diffuse petechial rash occurs. Although a thrombocytopaenic origin for the petechiae has been supported by some, only 5 of the 13 patients with rashes had significantly lowered platelet counts (< than $150000/mm^3$). Biopsies of skin lesions have demonstrated embolic fat with capillary damage and local haemorrhage (12).

Thrombocytopaenia per se is one of the minor criteria mentioned by Gurd (25). Others include tachycardia, pyrexia, retinal changes, urinary changes (increased urea/oliguria/fat globules in the urine) anaemia (out of proportion to measured blood loss), fat globules in the sputum and an elevated sedementation rate.

In this retrospective study, only the platelet counts (the lowest level within 48 hours of admission), the presence of pyrexia, and serum haemoglobin levels were reviewed as minor criteria. The diagnostic value of fat in the sputum, urine and blood have all been questioned (23,30) and are thought to be of doubtful value.

The significance of thrombocytopaenia however is doubtful as a decrease in platelet count usually occurs to some extent after major trauma. It seems that neutral fats and tissue thromboplastins released from the fracture site activate the clotting cascade and platelet aggregation occurs. In addition, the suppression of the fibrinolytic system in the injured patient (22) then aggravates the accumulation of fat macroglobules, platelets, erythrocytes, leucocytes and fibrin which are passively concentrated in the lung by virtue of its filtering action on venous blood.

Pyrexia has long been listed as a minor criterion provided one has excluded other sources of infection. Eleven of the 20 patients exhibited pyrexia (greater than $37^{o}C$) in the early post-injury period in this study, but this remains a non-specific feature.

Anaemia, out of proportion to that expected from the injuries sustained and the blood loss observed, is also regarded as a minor criterion. It is thought to be secondary to the aggregation of blood components with the fat macroglobules and fibrin which are filtered out in the lung as well as pulmonary haemorrhage. The extent to which occult blood loss occurs in large long bone fractures may be a significant contributing factor accounting for the large drop in haemoglobin.

Onset of Clinical Presentation

Clinical presentation of FES generally followed within 48 hours of the injury sustained (70% of cases). The remaining 30% all presented within 96 hours. Sevitt (12) quotes figures of 60% presenting within 24 hours and 85% in 48 hours post fracture. The temporal delay is due to the evolving effects of vasoactive substances released in the lung and hydrolysis of neutral fats to toxic free fatty acids.

However, if specifically looked for, arterial hypoxaemia will be found to be present from an early post-injury stage (up to 30 minutes after the injury) and is often the only abnormality in subclinical fat embolisation. Symptoms directly referable to the respiratory system are often not present until the PaO_2 falls below 65 mmHg (8.5 kPa), and tachypnoea and cyanosis may never actually be present.

These changes are readily explained by mechanical pulmonary vascular occlusion. Gas exchange is partially returned to normal by autoregulatory redistribution of ventilation effected by local bronchoconstriction in areas of decreased blood flow. The delayed clinical manifestations in the full-blown FES is then explained on the basis of the free fatty acid toxicity and its consequences described earlier.

In this study most patients presented with a severe degree of hypoxaemia (average 6.6 kPa) (Table IV), with only two patients not having arterial oxygen tensions less than 8.0 kPa, both of whom were on supplemental oxygen via a facemask at the time of the initial blood gas being taken. Most patients had evidence of alveolar hyperventilation (ave. $PaCO_2$ 4.2 kPa). Two patients had the unusual findings of an elevated $PaCO_2$, 1 had profuse bronchial secretions at the time and the other was an elderly man with significant pre-existing lung disease (Table V).

At present the commonly abnormal laboratory test results have consistently lacked specificity. These include anaemia, thrombocytopaenia, hypoalbuminaemia, hypocalcaemia, fat globules in the blood, urine or sputum and elevated blood lipase levels. Chan et al (41) however carried out a Cryostat technique for detecting neutral fat droplets in rapidly frozen clotted blood and reported good correlation of positive tests in patients with overt FES (100%) or multiple fractures (85%). However, 50% of patients with no clinical symptoms were also positive. This test could be of some use clinically in identifying "at risk" patients at an early stage.

In this light, the most important diagnostic criteria remain the simultaneous occurrence of certain clinical symptoms and signs and the emphasis it seems, will remain as such until more specific laboratory tests can be developed. This, in turn, will depend on a clearer understanding of the pathogenesis of the syndrome.

Management and Outcome

The primary aim of the management was to reverse the hypoxaemia and secondarily, general supportive management. Most patients requiring IPPV had associated severe neurologic abnormalities (9 out of 11) with compromised levels of consciousness. Slow resolution of the neurological abnormalities, together with severe pulmonary involvement and especially secondary respiratory infection, necessitated prolonged respiratory support and ICU stay. The decision on whether CPAP or IPPV was to be used in the management could not be attributed to the degree of pulmonary involvment, since there was no significant difference in the PaO2 on admission of patients treated with either CPAP or IPPV (Chi-sqaured test). The mode of ventilatory support was thus determined predominantly by the neurological state of the patient and their ability to co-operate.

Although in this study all patients survived, the fact that 3 patients required 3 weeks or more of intensive care treatment and that 1 patient developed a bronchopleural fistula, indicates that FES is associated with a significant morbidity and in many previous reports in the literature, a significant mortality as well. In his review of the literature Lepisto (37) gives reported mortality rates of between 2% to 4.2% of cases with FES. Peltier (21) reported a 5.5% mortality directly related to fat embolism in 5265 deaths among 236 861 trauma patients over a 10 year period. Since World War II the reported mortality has shown a gradual decline from 4.2% in Wilson's study (15) to recent reports like that of Geunter et al (23) who had no mortalities in a series of 54 patients.

The commonest complication during the ICU stay in this study was secondary bacterial respiratory infection which occurred in 20% of cases and resulted in the need for prolonged mechanical respiratory support. The other significant complication was the persistence of neurological abnormalities previously mentioned, all of whom returned to complete normality.

Steroids

Since Ashbaugh and Petty's work in 1966 (31) the general impression is that steroids given in large doses and as early as possible after the injury has been sustained, may favourably influence both the severity and possible incidence of the FES. Rokkanen et al (32) were the first to use steroids prophylactically, administering the 10 mg/Kg doses of methyl prednisolone every 8 hours to multiple trauma patients in the emergency room. They noticed a reduction in the incidence of FES from 6 out of 15 patients in the control group to 1 out of 14 patients in the treated group. Schonfeld et al (33) showed in a prospective, randomized double-blind study of high risk patients with long bone fractures, a significant difference between the steroid treated (0 out of 21) and placebo treated patients (9 out of 41). He also expressed the need for sequential clinical evaluation of patients at high risk, and that petechial eruption was the most significant factor diagnostic of the syndrome and because of the potential pulmonary morbidity, this may warrant corticosteroid treatment in the right setting.

The current explanation of corticosteroids' beneficial effect is thought to lie in their blockade of leucoaggregation in the lung (complement-mediated) and thus preventing or reducing lung injury that results secondary to this (34).

In a recent study from Pretoria University, Lindeque et al (38) also confirmed in a randomized double-blind study that methylprednisolone (30 mg/kg body mass) given routinely to patients admitted with long bone fractures offers advantages in the maintenance of PaO_2 values and a reduction in the incidence of FES. He stresses the monitoring of PaO_2 levels to be the most sensitive early indicator of the developing syndrome and that Gurd's classical criteria tend to occur too late to effect early reversal with appropriate resuscitation. In addition, he found that serum-free fatty acid levels were stabilized and/or reduced by methylprednisolone, but was unable to demonstrate any relationship between the development of FES with activation of serum complement (C5a), nor could they demonstrate reduction of C5a after the administration of methylprednisolone. Lindeque, however, stresses that basic early aggressive management of long bone fractures is still the most important therapeutic and preventative tool.

Kallenbach, in another very recent study (39), confirmed the beneficial effect of prophylactic methylprednisolone in stabilizing the PaO_2 and reducing the incidence of FES (10 of the 40 in the placebo group developed FES. compared to only 1 out of 40 cases in the methylprednisolone group). He also confirmed the high incidence of significant hypoxaemia seen in patients after long bone fractures, the majority of which do not progress to the full blown syndrome. However, one fatality occurred due to infection and this was from the methylprednisolone group.

Wolfe et al showed that in patients developing ARDS following gastric aspiration, the occurrence of Gram negative pneumonia within 5 days after aspiration was significantly greater in those patients treated with steroids compared to thos not receiving steroids (40).

Twelve of the 20 patients received steroids in this study but no specific protocol regarding type, dosage and time of administration was used. There was no significant difference in the outcome of the steroid treated versus non-steroid treated group if one looked at the rate of resolution of respiratory symptoms and length of stay in the ICU (Student's t test).

However, as mentioned earlier in this study, all 4 patients who developed significant secondary respiratory infections had in fact received steroids as part of their management. Despite the fact that statistical significance could not be demonstrated, probably due to the fact that small numbers were involved, I feel that caution should be taken in the use of steroids either in the early or late management of FES.

At this stage, although it is apparent that there are beneficial effects to be had following prophylactic steroids in reducing the progression and severity of the hypoxaemia and the incidence of the FES, the potential harm resulting from their use has not been adequately defined. Therefore, especially as regards their possible serious adverse effects on the host's immune defence system, one cannot recommend high dose steroid therapy as rational treatment until more and better information is obtained.

Pulmonary Function Tests - Long-term Follow-up

Alberts et al (35) reviewed follow-up results on 131 episodes of ARDS that occurred in 129 patients. There was a wide diversity of the etiology of these ARDS episodes. These patients were reviewed clinically 2 months or longer after the acute event. The overall results favoured a very positive long-term functional outlook for such patients. Within a few months the great majority are without dyspnoea on exertion and had normal chest X-rays. However almost 30% demonstrated hypoxaemia at rest when last studied and almost 50% demonstrated reduction in the diffusing capacity for carbon monoxide.

Thus far there have been no long-term follow-up studies on the pulmonary function of patients who developed ARDS secondary to the Fat Embolism Syndrome specifically. The results of this study indicate that some years after the event (average 39 months), no long-term impairment of pulmonary function could be shown, attributable to the pre-existing ARDS. In particular, no abnormalities of diffusing capacity and of pulmonary function during exercise could be ellicited and that the two abnormal exercise studies could not be attributed to pulmonary limitation and would require further assessment to explain these. This suggests that this particular form of ARDS associated with the FES to be potentially fully reversible with early and appropriate management.

It is difficult to make any comparison between Albert's study and ours mainly because of the differing etiologies of the ARDS and the difference in time elapsed before the patients were clinically re-evaluated in the 2 groups. Further prospective long-term follow-up studies in the clinical re-evaluation of ARDS patients would be useful in determining which patients to be at high risk of developing long-term pulmonary complications.

CONCLUSION

This retrospective analysis has once again confirmed FES to be a specific clinical entity frequently encountered in predominantly young adult patients with multiple fractures, mostly involving the lower limbs and pelvis.

Diagnosis of the entity depends on a high index of clinical suspicion and the presence of 2 or more of the major clinical features (hypoxaemia and lung parenchymal infiltrations, neurological deficit, and petechial rash). In addition, the presence of one or more minor features, particularly pyrexia, thrombycytopaenia and anaemia, are commonly found to be present. The presence of petechiae seems to be a highly characteristic feature of the FES although not always present.

Prompt early management of the hypoxaemia and our knowledge that corticosteroids, if given early and in large doses, may reduce the incidence and severity of FES. However, an awareness that the use of corticosteroids may be associated with an increased susceptibility of patients to secondary infection should be borne in mind. This study also suggests that the neurological and respiratory complications which account for the most of the morbidity associated with FES to be largely reversible in the long-term as is illustrated by this present follow-up study of lung function discussed above. This form of ARDS associated with the FES seems to be particularly amenable to treatment and rapid reversal, especially if one considers that the overall mortality from ARDS itself is quoted to be as high as 50% or more (36) and that it occurs unpredictably and often in previously healthy individuals. Future studies should look more closely at the long-term effects of ARDS and in particular, compare those with differing aetiologies of the syndrome. Continued research into the FES is likely to be directed toward the identification of the population at risk of developing ARDS and the detection of early indicators of the evolving syndrome which may in turn broaden our knowledge of the possible pathogenesis of ARDS. As these become known, so might we be able to detect the "at risk" patients and take the appropriate preventative or palliative measures in our overall management. A suitably controlled clinical trial of corticosteroids can then be conducted to establish their proper role in the treatment of this potentially catastrophic problem.

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