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# Studies on the Syndrome of Fat Embolization

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**ABSTRACT**

**Three patients, all of whom were well-muscled young adult males who had suffered fractures of long bones, were studied by means of measurement of ventilatory function and arterial blood gases. They had degrees of mental change varying from mild confusion to stupor. Anemia, hypocalcemia, skin petechiae and radiologic pulmonary infiltrates were demonstrated in all three.**

**In the absence of any clinical cyanosis, profound arterial $O_2$ desaturation was demonstrated in all. Physiologic studies indicated that the desaturation was the result of a diffusion defect early in the course of the syndrome and later from venous admixture. The lungs were stiff and the work of breathing was increased. The anemia appeared to be hemolytic in type.**

**It is suggested that anemia, hypocalcemia and arterial $O_2$ desaturation may contribute significantly to the cerebral symptomatology associated with the syndrome of fat embolization.**

**SOMMAIRE**

**Trois jeunes hommes, bien musclés, qui avaient subi des fractures des os longs, furent soumis à une étude portant sur l'évaluation de la fonction respiratoire et de la teneur en gaz du sang artériel. Ils présentaient des anomalies mentales allant de la confusion légère à l'état de stupeur. Chez ces trois patients on pouvait noter de l'anémie, de l'hypocalcémie, des pétéchies et une image radiologique d'infiltrat pulmonaire.**

**Bien qu'ils n'aient présenté, cliniquement, aucune cyanose, on parvint à mettre en évidence une désaturation extrême du sang artériel en $O_2$. L'étude des phénomènes physiologiques a démontré que cette désaturation provenait d'un trouble de la diffusion au début du syndrome et, ultérieurement, d'un mélange de sang veineux. Les poumons étaient rigides et l'effort respiratoire était augmenté. L'anémie était du type hémolytique.**

**Les auteurs estiment que l'anémie, l'hypocalcémie et la désaturation du sang artériel en $O_2$ favorisent nettement l'apparition des symptômes cérébraux qui accompagnent le syndrome d'embolie graisseuse.**

WHILE a certain degree of fat embolism appears to be common following any injury to the bony skeleton,[1] only rarely does the embolism produce clinically recognizable signs and symptoms. The symptom complex which does arise has been subdivided into a pulmonary type characterized by the findings of acute pulmonary edema and a cerebral type with evidence of central nervous system involvement. The varying symptomatology has been ascribed to a combination of a mechanical obstruction of capillaries by fat globules and a delayed chemical action with hydrolysis of neutral fats to fatty acids which in turn have a destructive effect on the endothelium of blood vessels.[2]

Clinical and histological changes diagnostic of fat embolism have been demonstrated following severe trauma without fractures, surgical operations on the viscera, in severe burns, following prolonged anesthesia[3] and from individuals with fatty livers.[4]

The characteristics of the syndrome are outlined in Table I.

The pulmonary infiltration has no very specific appearance. It can be localized, or a variety of

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TABLE I.—CHARACTERISTICS OF THE SYNDROME OF FAT EMBOLIZATION

| |
|---|
| Diffuse pulmonary infiltration |
| Anemia |
| Petechiae |
| Mental changes (confusion—coma) |
| Increased serum lipase |
| Decreased serum calcium |
| Fat in sputum and urine (sizzle test) |
| Decreased $O_2$ saturation without cyanosis |
| Decreased vital capacity |

widely and bilaterally distributed infiltrates can appear.

Anemia has been noted[2, 5] as occurring in the syndrome of fat embolization. Definitive studies on the mechanism of production of this state in patients are not available, although it has been established that a considerable drop in hemoglobin can be explained by the loss of blood into traumatized tissues.[6] Other factors possibly contributing to the anemia are a temporary hemolytic state or intrapulmonary hemorrhage of significant degree. It has been demonstrated that the administration of fatty acids to experimental animals can be followed by profound intrapulmonary hemorrhage.[7]

Petechiae are pathognomonic of the disorder. They occur principally in the axillae and flanks and also in the conjunctiva. Biopsies of these lesions have indicated them to be tiny areas of hemorrhage distal to areas of fat infarction.[3]

The mental changes occurring in the syndrome are widely variable, ranging from mild euphoria, confusion and paranoia to complete coma. It would appear that victims of "cerebral fat embolism" either succumb or recover with little neurologic defect. The available case reports on recovered individuals mention "sleep disturbance", "headache", "slight spasticity" or "full recovery".[2, 3, 8, 9]

Lipase is released from pulmonary tissues as well as other areas in the body and it is, at least in part, responsible for the transformation of neutral fat to the fatty acids which may possibly result in the generalized vascular damage of the syndrome.[7]

The fatty acids, when formed, tie up calcium as a soap, and the hypocalcemia in itself may contribute to a certain proportion of the symptomatology in two ways. First, a generalized increase in neuromuscular irritability occurs with the hypocalcemic state. Secondly, it has been shown that intracellular cohesion is related to the action of calcium ions.[10] The loss of these ions could conceivably result in a loss of intracellular cohesion with consequent disruption of the endothelial surface of capillaries.

Fat may be found, if diligently searched for, in urine, and in sputum. The fat in urine may be revealed by flaming a loop of liquid over a Bunsen burner where the fat will snap and crackle like fat on a wet frying pan.[11]

Cyanosis has occasionally been noted[2, 9] as occurring in victims of this condition, but measurements of the oxygen saturation of arterial blood have not been previously reported.

In association with the pulmonary changes there seems to be an increase in the stiffness of pulmonary tissues which mediates an increase in respiratory rate and can be measured as a decrease in the total displaceable lung volume.

The following case histories are presented to emphasize the occurrence of anemia and of profound degrees of arterial oxygen unsaturation in the absence of any clinical cyanosis in three victims of this condition.

Arterial pH and carbon dioxide tension were analyzed with the Astrup apparatus and the oxygen tension estimated polarographically.[12] Gas mixtures were, other than when patients were receiving assistance from an IPPB machine, breathed through a Rudolph two-way breathing valve with Bennett seal mouthpiece, and expired air was collected in Douglas bags. This gas was analyzed for oxygen content on a Beckman E-2 magnetic oxygen analyzer and for $CO_2$ content on a Godart Capnograph.

## CASE REPORTS

CASE 1.—A husky 25-year-old oil-field worker was brought into hospital after a fall from an oil rig in which he had sustained a fracture of the right femur which had been treated in the field by closed reduction. Three days later he was transferred to the University of Alberta Hospital because of a stuporous state which had developed quite suddenly over the preceding 12 hours.

On examination he was semicomatose and had unequal pupils through which marked bilateral papilledema was observed. He had petechiae on both sides of the body down to the flanks and on both conjunctivae. The retinas were normal. His breath sounds were harsh but there were no adventitious sounds although the respiratory rate was 40 to 45 per minute. A chest radiograph showed diffuse mottling and his temperature was slightly elevated to 101° F.

On the next day his respiratory rate had risen to 60 per minute and it was observed that when his breathing was assisted by means of a positive pressure machine the respiratory rate dropped to 22 per minute. This was taken to mean that the hyperpnea was mediated by peripheral factors in the lung rather than by a central drive, since the taking over of his work of breathing for him caused such a marked change. A tracheotomy was advised, primarily to facilitate the delivery of the positive pressure assistance. As a preliminary to this, arterial blood was drawn which showed a remarkable degree of arterial oxygen desaturation (69%) in the absence of clinically apparent cyanosis. He was suctioned of large quantities of mucoid, blood-tinged material at the time of tracheostomy. This was in the absence of auscultatory signs of airway obstruction.

He was carried on continuous assisted respiration for eight days and then on gradually decreasing amounts of assistance as his oxygen saturation and measurements of ventilation improved (see Table II). Twelve days after admission he was breathing without assistance. His pulmonary care was complicated by a

TABLE II.—BLOOD GAS STUDIES—CASE 1

| | Day 4 | | Day 5 | | Day 9 | | | Day 11 | | | Day 22 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Room air | Tracheotomy | Room air | 40% $O_2$* | Room air | 40% $O_2$* | 100% $O_2$* | Room air | 40% $O_2$* | 100% $O_2$* | Room air |
| $pO_2$ | 32.0 | | 38.0 | 239.0 | 39.0 | 69.0 | 132.0 | 36.0 | 120.0 | 132.0 | 76.0 |
| $O_2$ saturation (%) | 69.0 | | 73.0 | 100.0+ | 75.0 | 92.0 | 100.0 | 71.5 | 100.0+ | 100.0+ | 94.0 |
| A–a $O_2$ gradient (mm. Hg) | — | | 68.0 | 20.0 | 61.0 | 221.0 | 518.0 | 49.0 | 222.0 | 620.0 | 8.0 |
| $pCO_2$ | 45.0 | | 32.0 | 39.0 | 37.0 | 39.0 | 38.0 | 39.0 | 43.0 | 40.0 | 38.0 |
| pH | 7.41 | | 7.41 | 7.36 | 7.42 | 7.37 | 7.37 | 7.43 | 7.37 | 7.41 | 7.40 |
| $\dot{V}$ | (not measured) R.R. 60 per min. | | 25.0 | 14.0 | 33.4 | 16.01 | 20.0 | 28.6 | 15.6 | 18.0 | 10.0 |

*Biochemical and hematological data*

| | | | |
|---|---|---|---|
| Hb | 6.4 g.% | Schumm test | + |
| Plasma Hb | 4.9 mg.% | Serum bilirubin | 1.5 mg.% |
| Urinary hemosiderin | ++ | Serum $Ca^{++}$ | 7.9 mg.% |
| Urinary fat | +++ | Reticulocytes | 9.4% |

*=assisted breathing with IPPB machine.
$\dot{V}$=minute ventilation (litres per minute).

severe infection with *Staphylococcus aureus* and *Pseudomonas aeruginosa*. This was treated with polymixin B and kanamycin by nebulization and by penicillin in doses of 50,000,000 units daily intravenously. He was finally discharged 79 days after admission, with his fracture healed and with no neurologic or pulmonary abnormalities.

The laboratory work showed him to be anemic and hypocalcemic and he had fat in his urine. The hematologic tests were suggestive but were not really diagnostic of a hemolytic state.

CASE 2.—A husky 25-year-old man sustained a badly contaminated open fracture of the left tibia-fibula and a closed fracture of the left femur. He was transfused extensively prior to admission (five litres) and then admitted to hospital. His respiratory rate and temperature were both increased, but there were no abnormal physical findings at that time. That evening, under general anesthesia, his wound was extensively debrided and the tibia was pinned and encased in plaster. The next morning his respiratory rate was 36, and he had a few rales in the right lower lung which were associated with a radiologic infiltrate in the same area. His arterial oxygen saturation when measured was 78% and he was therefore given oxygen therapy, primarily by mask but with occasional positive pressure assistance. On the next day petechiae were first observed. On this regimen of treatment plus antibiotics, he improved temporarily, his chest cleared and measures of oxygen saturation and ventilation returned to virtually normal figures (Table III). He then relapsed, however, into a toxic febrile state and on the 17th hospital day he suddenly died.

At postmortem examination there were scattered globules of fat throughout most tissues of the body but no specific localized findings.

Laboratory studies showed an anemia and hypocalcemia. The hematologic studies revealed a low serum iron, and one reading of the serum hemoglobin was quite markedly elevated. His vital capacity was decreased with a normal expiratory flow rate—the findings of a pure restrictive ventilatory defect.

TABLE III.—BLOOD GAS STUDIES—CASE 2

| Blood gas studies | Day 3 | Day 7 | | Day 14 | |
|---|---|---|---|---|---|
| | | Room air | 40% $O_2$ | Room air | 100% $O_2$ |
| $pO_2$ | 43.0 | 49.0 | 90.0 | 70.0 | 256.0 |
| $O_2$ saturation (%) | 78.0 | 83.0 | 97.0 | 93.8 | 100.0 |
| A–a gradient | — | 37.0 | 167.0 | 15.0 | 294.0 |
| $pCO_2$ | 36.0 | 37.5 | 40.0 | 38.0 | 42.0 |
| pH | 7.40 | 7.42 | 7.44 | 7.39 | 7.36 |
| $\dot{V}$ | Not measured R.R. 36 | 13.5 | 7.5 | 8.5 | 9.0 |

*Biochemical and hematological data*

| | |
|---|---|
| Hb | 10.3 g.% |
| Serum Hb | 23.2 mg.% |
| Urinary hemosiderin | + |
| Urinary urobilinogen | +++ |
| Urinary fat | + |
| Serum Fe | 45 (TIBC: 240%) |
| Serum calcium | 8.8 mg.% |
| Vital capacity | 2.1 l. |
| Maximal expiratory flow rate | 250 l./min. |

$\dot{V}$=minute ventilation (l. per min.).

CASE 3.—A 32-year-old man fractured his right femur and some of his ribs in an automobile accident. There were no significant physical findings on his first day in hospital—the respiratory rate was 22, the temperature 100° F. Two days later rhonchi were heard in the left base, his chest radiograph indicated a localized infiltrate and his respiratory rate had risen to 32 per minute. At this time general anesthesia was deferred, a Steinmann's pin was inserted into his left leg and his cast renewed. He was noted to be very slightly confused and irritable. He did not appear to be cyanosed but an oxygen determination on arterial blood showed profound desaturation (51%). He was placed on oxygen therapy and nebulization with occasional assistance administered. On the next day showers of petechiae were apparent on his flanks but his chest signs had cleared. By the 14th hospital day his oxygen saturation was normal and his measures of ventilation greatly improved (Table IV). The petechiae had disappeared.

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TABLE IV.—BLOOD GAS STUDIES—CASE 3

| | Day 2 | | Day 4 | | | Day 14 |
|---|---|---|---|---|---|---|
| | Room air | 100% $O_2$ (unassisted) | Room air | 40% $O_2$ | 100% $O_2$ | Room air |
| $pO_2$ | 25.0 | 62.0 | 43.0 | 130.0 | 360.0 | 73.0 |
| $O_2$ saturation | 51.0 | 93.0 | 78.0 | 100+ | 100+ | 94.5 |
| A-a gradient | 66.0 | 436.0 | 46.0 | — | 190.0 | 16.0 |
| $pCO_2$ | 34.0 | 29.7 | 32.0 | 30.0 | 32.0 | 42.0 |
| pH | 7.44 | 7.48 | 7.47 | 7.53 | 7.51 | 7.43 |
| $\dot{V}$ | 18.9 | 10.1 | 16.2 | — | — | 10.3 |

*Biochemical and hematological data*

| | |
|---|---|
| Hb | 9.8 g.% |
| Plasma Hb | 270 mg.% |
| Urinary fat | negative |
| Schumm test | + |
| Red cell volume | 14.1 c.c./kg. |
| Red cell survival | 10 days |
| Serum calcium | 7.8 mg.% |
| Vital capacity | 1.6 l. |
| Maximal expiratory flow rate | 55 l./min. |

$\dot{V}$ = minute ventilation (l. per min.).

The laboratory work once again showed anemia and hypocalcemia. No fat was found in the urine or sputum, but the hematologic results did show a very significantly increased rate of destruction of red cells in keeping with a hemolytic state. His initial restricted vital capacity of 1.6 l. increased to 3.3 l. in the two weeks and the rate of air flow changed markedly from 55 to normal values of 500 l. per minute.

## DISCUSSION

Fig. 1 depicts the oxygen-carrying capacities of the arterial blood of the three patients described. In comparison to a normal individual with a hemoglobin value of 15.0 g., 95% of which is oxyhemoglobin, it can be seen that all of these patients had profound degrees of hypoxia compounded by desaturation superimposed on a decrease in total red cell mass.

Initially it was puzzling that cyanosis was not evident in these extremely desaturated individuals. However, since it is generally accepted that for blueness of the skin to be apparent 5 g. of reduced hemoglobin should be present in the visible peripheral blood, part of the lack of cyanosis can be ascribed to the anemia alone. Normally a good proportion of the visible blood is venous (containing, of course, much more reduced hemoglobin than the arterial blood). We have indirect evidence that in these patients the peripheral vascular bed was probably widely dilated so that most of the vessels seen were filled with arterial blood. In Case 3, an indirect estimation of cardiac output suggested that it had to be something over 30 l. This was done by applying the Fick principle[13] to the known oxygen consumption and arterial oxygen content of his blood and assuming that the venous blood contained no oxygen at all.

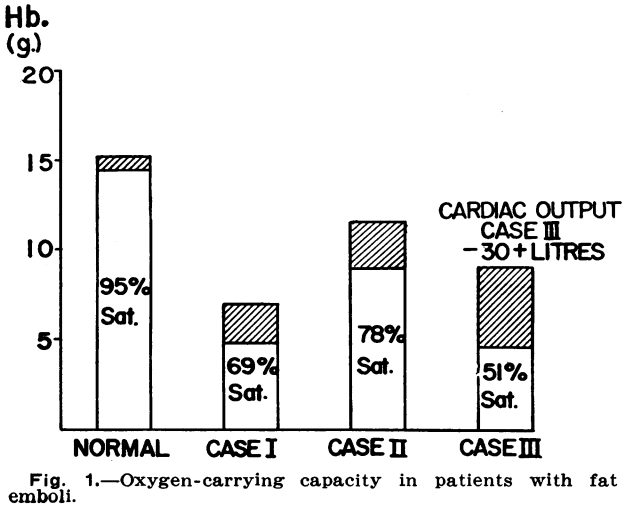


Fig. 1.—Oxygen-carrying capacity in patients with fat emboli.

This is a truly phenomenal level of blood flow and it would seem obvious that the lack of visible cyanosis in these patients was due to a combination of anemia and grossly increased blood flow, leading to or associated with dilatation of the peripheral vascular bed.

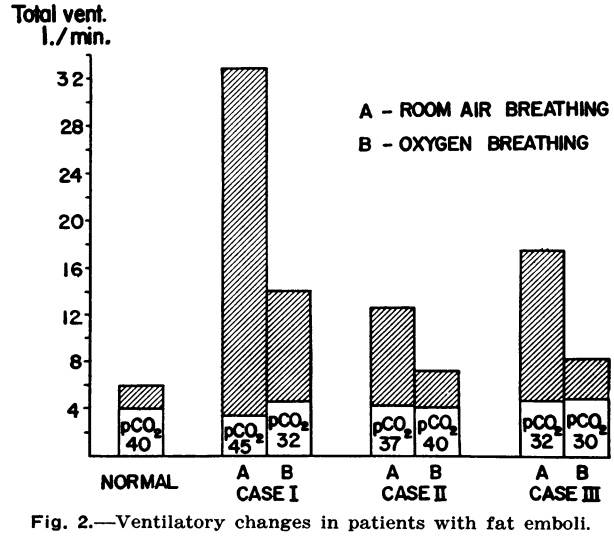


Fig. 2.—Ventilatory changes in patients with fat emboli.

Fig. 2 represents the ventilatory changes in these patients. The normal situation is first depicted, in which a total volume of approximately 6 l. of air is moved, producing a $CO_2$ tension of 40 mm. Hg. Effective alveolar ventilation is usually two-thirds of total ventilation and may be monitored in a dynamic sense by the level of carbon dioxide tension in arterial blood. As alveolar ventilation in relationship to total $CO_2$ production increases, the $CO_2$ tension decreases.

The first patient when breathing on his own, despite the movement of an extremely large amount of air, had a ventilation which was largely ineffective (the shaded portion in Fig. 2 represents dead space ventilation). This is partly because in association with stiffening of the lung tissues his work of breathing was increased and the act of breathing was associated with increased $CO_2$ production. When mechanical assistance to the respiratory muscles was given, the total ventilation dropped but effective alveolar ventilation increased, resulting in an increased elimination of $CO_2$, as

monitored by the arterial $CO_2$ tension levels. In the other two patients administration of oxygen resulted in a very significant drop in the total ventilation which was associated with an alveolar ventilation that remained normal.

The possible causes of hypoxia can be listed as alveolar hypoventilation, a defect in diffusion, an abnormality of the relationship between ventilation and perfusion, or venous admixture. The various possibilities may be distinguished with fair accuracy by determining alveolar and arterial oxygen tensions and calculating A–a oxygen tension gradients at three levels of oxygenation. If desaturation is due to hypoventilation, no appreciable gradient exists at any level of oxygenation and $CO_2$ retention is usually evident. Any increase in A–a gradient must, therefore, be due to some other mechanism. Lilienthal *et al.*[14] suggested that one might distinguish between a diffusion defect and venoarterial admixture by measurement of the effective alveolar-arterial gradient at two levels of oxygenation, one of which produces significant desaturation of arterial blood. Low levels of inspired $O_2$ exaggerate the effects of impaired diffusion and minimize the effects of veno-arterial admixture. Veno-arterial admixture, thus delineated, may be either through actual anatomical communications or the result of reduction in the ventilation-perfusion ratios. If due to uneven ventilation, the gradient is eliminated by administration of 100% oxygen, since, during pure oxygen breathing, even minimally ventilated alveoli eventually attain an oxygen tension approaching atmospheric pressure. Therefore, the A–a gradient measured during the inspiration of pure oxygen may be taken as a measure of shunting of blood from the venous to the arterial side of the circulation.[15]

The studies on these patients during the course of their disease indicated that initially the desaturation was principally mediated by a diffusion defect which, later in the course, as the desaturation became less profound, was mainly from veno-arterial shunting of blood.

The therapeutic implications as far as administration of oxygen is concerned are obvious. It is particularly noteworthy that in view of the lack of clinical cyanosis in these patients oxygen would not under normal circumstances have been administered. The successful use of carbon dioxide in the treatment of cerebral fat embolism has been recently reported,[16] and one would wonder how much of the improvement or lack of clinical deterioration was due to 10% $CO_2$ and how much to the 90% oxygen with which the carbon dioxide was mixed.

## SUMMARY

The case reports of three young men who suffered fractures and had varying degrees of anemia, hypocalcemia, petechiae and variable central nervous system signs are presented. It is noted in particular that they all had very significant degrees of arterial oxygen desaturation in the absence of clinical cyanosis and that they had evidence of profound stiffening of their lungs. It is suggested that a large proportion of the nebulous symptomatology which arises in this syndrome may be a result of severe cerebral anoxia, possibly exaggerated by a hypocalcemic state and by a profound increase in the work of breathing.

The co-operation and assistance of Drs. Gordon Cameron, Cooper Johnston and Olaf Rostrup in carrying out these studies are gratefully acknowledged.

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## PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

### THE REAL PRACTICAL PHYSICIAN

But in acquiring this habit of observation and thought you must not be conscious of doing so, for this "self-training, self-suspicion and self-discipline" consists in absolute concentration on the work which you are doing at the moment, the cultivation of a desire for knowledge for the sake of knowledge alone, and the putting behind you of all desire to generalize or theorize without a thorough sifting of the facts. You must not constantly be looking for the practical application of the knowledge you acquire. Be content to acquire it, resting assured that the practical application will come in some form later. To neglect any opportunity of becoming acquainted with the more scientific side of your profession is to place yourselves in the position of those short-sighted men who, in the time of Soranus, failed to see the necessity for the study of anatomy.

For "anatomy" substitute—or rather to "anatomy" add—chemistry, physics, physiology, bio-chemistry, pathology, bacteriology: these occupy to-day the place that anatomy did in those far distant times. Through them our methods of diagnosis and treatment are being revolutionized. The efficiency of the modern hospital is now gauged, not alone by the number of beds it contains, by the brightness and airiness of its wards, or by the sumptuousness of its furnishings, all-important as these are. Its true efficiency as a school for the training of the future practitioner, as a centre for research, and above all as an institution for the healing of the sick, is measured by the number and the completeness of equipment of its laboratories, and by the skill of the men who direct them. In like manner the real practical physician of to-day is the man who has at his command a knowledge of, and the ability to apply, every aid which science can afford him.—B. P. Watson, *Canad. Med. Ass. J.*, 4: 479, 1914.