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Therapeutic aspects of fat embolism syndrome

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KEYWORDS:
Fat embolism syndrome; FES; intramedullary nailing; respiratory failure; ARDS; cerebral edema; cerebral fat embolism syndrome; fat emboli.

Summary[1] Signs and symptoms of clinical fat embolism syndrome (FES) usually begin within 24–48 hours after trauma. The classic triad involves pulmonary changes, cerebral dysfunction, and petechial rash. Clinical diagnosis is key because laboratory and radiographic diagnosis is not specific and can be inconsistent. The duration of FES is difficult to predict because it is often subclinical or may be overshadowed by other illnesses or injuries.
Medical care is prophylactic or supportive, including early fixation and general ICU management to ensure adequate oxygenation and ventilation, hemodynamic stability, prophylaxis of deep venous thrombosis, stress-related gastrointestinal bleeding, and nutrition. Studies support early fracture fixation as a method to reduce recurrent fat embolism and FES. The main therapeutic interventions once FES has been clinically diagnosed are directed towards support of pulmonary and neurological manifestations and management of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS).

Introduction

Fat embolism syndrome (FES) has been reported to occur in several clinical conditions including bone marrow transplant, pancreatitis, fatty liver and liposuction [1, 2]. However, FES is most commonly associated with long bone fractures. Although fat embolism may occur in up to 90% of trauma patients [3], FES occurs in only 2–5 % of patients with long bone fractures [4]. FES is characterized by both pulmonary and systemic fat embolism [2, 5, 6, 7] and includes a spectrum of subclinical, mild to fulminate presentations [7, 8].

Clinical FES typically involves multiple organ systems; however, the pulmonary, neurological, hematological, and dermatological systems involvement is the most common.

In addition to fat embolization from the initial trauma, long bone fixation may result in additional embolizations and FES. During intramedullary nailing, the intramedullary canal pressure can reach 1000 mm Hg [9]. This elevated pressure during reaming appears to be temporally associated with embolization to the pulmonary circulation when studied with echochocardiography [10]. Once fat is liberated into the circulation and embolizes, the pulmonary microvasculature becomes occluded.

Depending on the size of fat globules, smaller globules may traverse the pulmonary microvasculature and reach the systemic circulation, leading to the common neurological manifestation of FES. Although the pulmonary, cerebral, retinal, and skin microcirculations are typical clinical manifestations of FES, fat embolization can affect any microcir-

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culatory bed. Case reports include acute coronary syndrome presumed to result from fat globules in the coronary microcirculation [11].

Discussion

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) may result from fat emboli occluding pulmonary capillaries [2, 12–16] and biochemical alterations that produce lung injury that directly damages the pulmonary capillary endothelium [2, 12, 13, 17, 18].

Although many patients with long bone fractures develop fat embolism, far fewer develop FES, suggesting that additional factors may be necessary in the development of lung injury. Biochemical fat embolization is associated with the release of free fatty acids (FFAs) [19]. FFAs in the lung are locally hydrolyzed in pulmonary circulation by lipoprotein lipase, which releases toxic substances that injure the capillary endothelium. The release of FFAs increases vascular permeability, producing alveolar hemorrhage, edema, and inactivate the surfactant molecules [20–26]. Ultimately, these pulmonary alterations lead to respiratory failure, resulting in ALI and ARDS.

As fat accumulates in the pulmonary microcirculation and lipoprotein lipase liberates FFAs, disseminated intravascular coagulation (DIC) and platelet aggregation further compound capillary disruption and systemic inflammation.

Fat emboli that pass through the pulmonary vasculature result in systemic embolization, most commonly in the brain and kidneys [27]. Cerebral FES is a rare, yet potentially lethal, complication of long bone fractures. Neurological symptoms vary from confusion with diminished Glasgow Coma Scale (GCS) to encephalopathy with coma and seizures. A clinical diagnosis may be difficult as cerebral FES may be masked by other clinical scenarios [28]. Diffuse encephalopathy, petichial hemorrhages, localized cerebral edema, and white matter changes have also been seen in patients diagnosed with FES. Magnetic resonance imaging (MRI) may be necessary to show the characteristic cerebral lesions of the acute state of FES as opposed to a CT scan, which appears normal [29, 30, 31].

Treatment

A specific treatment for FES does not currently exist [32]. Treatments with heparin, dextran, and corticosteroids have not been shown to reduce the morbidity or mortality as treatments for FES [1, 33]. However, when given prophylactically, corticosteroids (methylprednisolone) may have beneficial effects [34–38]. The mainstay of treatment for FES is supportive [32], therefore, prevention, early diagnosis, and adequate symptom management are paramount.

Although long bone fracture fixation is the main cause of fat embolism and FES, early fracture fixation may be critical in reducing recurrent liberation of fat into the circulation as a result of fracture movement [39].

Early fixation of long bone fractures within 24 hours has documented a reduction in the incidence of FES in patients who are stable enough to undergo surgery [40]. In addition, as patients with polytrauma are at risk of other forms of respiratory failure (atelectasis, pneumonia) and multiple system organ failure (MSOF), early fixation and patient mobilization may reduce complications [41]. Experimentally, increasing intramedullary pressure [42] has been shown to increase fat embolization. Methods to reduce intramedullary pressure and embolization during reaming have been developed, which include venting or applying a vacuum during reaming to limit the elevation of intramedullary pressure and thus reduce the incidence of fat embolization [43, 44].

Respiratory failure from FES is characterized as permeability edema with decreased compliance similar to oleic acid lung injury [15]. Gas exchange abnormalities include shunt and increased dead space from atelectasis and alveolar flooding comparable to ALI and ARDS from other causes [45–47].

The general goals of ALI and ARDS management focus on maintaining acceptable gas exchange while limiting ventilator-associated lung injury (VALI).

Supportive pulmonary therapies may include enhancement of spontaneous breathing and cough, early patient mobilization, utilization of positive end-expiratory pressure (PEEP), and a reduction in the use of sedation and neuromuscular blocking agents (NMBAs). By utilizing ventilator modes that allow spontaneous breathing and cough, patients are not mandated to conform to a clinician-set I:E ratio; rather, the patient may spontaneously breathe freely and interact with the ventilator. Traditionally, spontaneous breathing in patients with ALI or ARDS is discouraged, forcing the patient to adapt to predetermined ventilator settings. Controlled ventilation frequently requires heavy sedation or NMBAs to synchronize the patient with the ventilator, particularly in the management of patients diagnosed with FES and associated neurological manifestations.

Forms of ventilation that require excessive sedation and NMBAs preclude detailed assessment

and the ability to perform serial neurological examinations. In addition, excessive sedation or NMBA usage eliminates spontaneous breathing and the diaphragm's potential to facilitate dependent lung ventilation [48,49]. Data suggest spontaneous breathing may play a vital role during mechanical ventilation. Improvements in V/Q matching, alveolar recruitment, and cardiac output are often seen when effective spontaneous breathing is introduced during mechanical ventilation [48, 50, 51]. Elimination of spontaneous breathing and cough may result in additional ventilator days, adverse hemodynamic effects, ventilator-associated complications, and cost [52–54].

Recent data suggest PEEP may protect and even delay the onset of VALI [55]. Required PEEP levels to maintain end-expiratory lung volume in ALI or ARDS and limit shear forces may be substantial (>20 cmH_2O). Although the exact level of PEEP required to completely eliminate cyclic airway closure and shear force is unknown, studies demonstrate a wide spectrum of airway pressures exist within the acutely injured lung [56–60]. These studies suggest recruitment is a 'pan inspiratory' phenomenon and may require pressures of 30 cmH_2O or greater to fully recruit lung regions and prevent tidal shear stress [61]. An alternative to controlled ventilation is Airway Pressure Release Ventilation (APRV) which combines spontaneous breathing and an open lung method to optimize lung volume [62]. APRV allows patients to breathe comfortably, decreasing sedation needs and facilitating neurological examinations. Spontaneous breathing improves ventilation to dependent lung regions recruiting these regions without increasing applied airway pressure [48–51]. Patients with severe chest trauma and fat embolism have been successfully managed with APRV at R Adams Cowley Shock Trauma Center in Baltimore, Maryland as standard of care for multi-trauma patients since 1994. In addition to mechanical ventilation, more severe pulmonary dysfunction may benefit from prone positioning or extracorporeal membrane oxygenation [63].

Support of patients with FES and neurological complications is directed towards neurological examinations, including frequent monitoring of GCS and the patient's status. Patients with FES may develop cerebral edema, leading to rapid deterioration [64]. In such cases, ICP monitoring may be beneficial and should be considered [65]. In general, trauma patients should not have their neurological examination obscured by excessive sedation or NMBAs in order to allow them to tolerate mechanical ventilation [66]. Therefore, sedation and analgesia should be chosen carefully to optimize patient comfort while preserving neurological examination. Furthermore, the utilization of a sedation/agitation scale may provide consistency of examinations for neurological function as affected by sedation or analgesia.

Fat from long bones and subcutaneous tissue is composed of neutral fat including triglyceride, glycerol, and long chain fatty acids. Unsaturated fatty acids constitute 60–80% of acid elements [67]. FFAs are normally bound to serum albumin with only 1% in the unbound state [46]. They can produce tissue injury and inflammation, and are particularly toxic to capillary endothelium [15, 45, 68]. Oleic acid has been implicated as a key component in fat embolism and the development of ALI and ARDS [69–71]. Although albumin can bind oleic acid and render it non-toxic, albumin binding may be prevented or limited during fat embolization [69, 70].

Oleic acid may have a role in ARDS. Elevated plasma and broncoalveolar lavage oleic acid levels have been documented in patients with ARDS and are associated with increased vascular permeability, increased extravascular lung water, and inhibition alveolar fluid reabsorption [72].

Generally, the management of patients with FES includes adequate resuscitation to limit or prevent persistent shock states. Also, overaggressive reaming of the femoral canal should be avoided in femoral shaft fractures. Resuscitation remains a key element in the management of critically ill, polytrauma patients. Intraoperatively, these patients should be handles carefully and prolonged surgeries > 6 hours duration should be avoided.

Although the form of volume expansion used for resuscitation may or may not be relevant, some data suggest that albumin binding to oleic acid diminishes its edemogenic potential [73, 74]. Goodman found that human serum albumin has several binding sites for FFA and estimated that each gram of albumin can bind up to 110 mg of long-chain fatty acid [75].

Since fatty acids, such as oleic acid, are one of the factors involved in the development of ALI and ARDS, fluid resuscitation with albumin solutions may be beneficial. In addition, the use of albumin when combined with furosemide in patients with ALI and ARDS tends to improve oxygenation and may decrease ventilation duration. A recent meta-analysis of albumin therapy in general suggests improved mortality of acutely ill hospitalized patients [76].

In patients with fulminate FES causing obstructive shock and right ventricular failure, hemodynamic support with dobutamine, in addition to volume, may be superior in restoring RV-PA coupling and cardiac output over norepinephrine [77]. Other

agents to consider may include nitric oxide to lower pulmonary arterial pressure and unload the right ventricle.

Conclusion

The outcome in patients with FES who receive supportive care is generally favorable with mortality rates of less than 10% [78].

Pulmonary, neurological, and retinal abnormalities generally resolve completely. General management is supportive in nature and focuses on early fixation and mobilization. Organ support includes shock resuscitation and gas exchange support, which balances lung recruitment and limits the potential for VALI. Ideally, neurological support would include the ability to conduct a clinical neurological examination.

Bibliography

1. **Dudney TM, Elliott CG** (1994) Pulmonary embolism from amniotic fluid, fat, and air. *Prog Cardiovasc Dis*; 36(6):447–474.
2. **Levy D** (1990) The fat embolism syndrome. A review. *Clin Orthop Relat Res*; 261:281–286.
3. **Riska EB, Myllynen P** (1982) Fat embolism in patients with multiple injuries. *J Trauma*; 22(11):891–894.
4. **Glover P, Worthley L** (1999) Fat Embolism. Critical Care and Resuscitation; 1:276–284.
5. **Sevitt S** (1977) The significance and pathology of fat embolism. *Ann Clin Res*; 9(3):173–180.
6. **Peltier LF** (1988) Fat embolism. A perspective. *Clin Orthop Relat Res*; 232:263–270.
7. **Fabian TC, Hoots AV, Stanford DS, et al** (1990) Fat embolism syndrome: prospective evaluation in 92 fracture patients. *Crit Care Med*; 18(1):42–46.
8. **Hagley SR** (1983) The fulminant fat embolism syndrome. *Anaesth Intensive Care*; 11(2):167–170.
9. **Wenda K, Runkel M, Degreif J, et al** (1993) Pathogenesis and clinical relevance of bone marrow embolism in medullary nailing—demonstrated by intraoperative echocardiography. *Injury*; 24 Suppl 3:73–81.
10. **Mellor A, Soni N** (2001) Fat embolism. *Anaesthesia*; 56(2):145–154.
11. **Bokhari SI, Alpert JS** (2003) Probable acute coronary syndrome secondary to fat embolism. *Cardiol Rev*; 11(3):156–159.
12. **Benatar SR, Ferguson AD, Goldschmidt RB** (1972) Fat embolism—some clinical observations and a review of controversial aspects. *Q J Med*; 41(161):85–98.
13. **Riseborough EJ, Herndon JH** (1976) Alterations in pulmonary function, coagulation and fat metabolism in patients with fractures of the lower limbs. *Clin Orthop Relat Res*; 115:248–267.
14. **Müller C, Rahn BA, Pfister U, et al** (1994) The incidence, pathogenesis, diagnosis, and treatment of fat embolism. *Orthop Rev*; 23(2):107–117.
15. **Fonte DA, Hausberger FX** (1971) Pulmonary free fatty acids in experimental fat embolism. *J Trauma*; 11(8):668–672.
16. **Feingold K, Hardardottir I, Grünfeld C** (1998) Beneficial effects of cytokine induced hyperlipidemia. *Z Ernährungswiss*; 37 Suppl 1:66–74.
17. **Saldeen T** (1979) Blood coagulation and shock. *Pathol Res Pract*; 165(3):221–252.
18. **Hofmann S, Huemer G, Salzer M** (1998) Pathophysiology and management of the fat embolism syndrome. *Anaesthesia*; 53 Suppl 2:35–37.
19. **Nakata Y, Tanaka H, Kuwagata Y, et al** (1999) Triolein-induced pulmonary embolization and increased microvascular permeability in isolated perfused rat lungs. *J Trauma*; 47(1):111–119
20. **Broe PJ, Toung T, Margolis S, et al** (1981) Pulmonary injury caused by free fatty acid: evaluation of steroid and albumin therapy. *Surgery*; 89(5): 582–587.
21. **Ehrhart IC, Hofman WF** (1981) Oleic acid dose-related edema in isolated canine lung perfused at constant pressure. *J Appl. Physiol*; 50(6):1115–1120.
22. **Fredrickson DS, Gordon RS Jr** (1958) Transport of fatty acids. *Physiol. Rev*; 38(4):585–630.
23. **Gemer M, Dunegan LJ, Lehr JL, et al** (1975) Pulmonary insufficiency induced by oleic acid in the sheep: a model for investigation of extracorporeal oxygenation. *J Thorac Cardiovasc Surg*; 69(5):793–799.
24. **Hoak JC, Connor WE, Warner ED** (1966) Thrombogenic effects of albumin-bound fatty acids. *Arch Pathol*; 81(2):136–139.
25. **Kay E, Weilly H, Genton E, et al** (1971) Consumption coagulopathy in the canine oleic acid model of fat embolism. *Surgery*; 69:533–541.
26. **Spragg R, Abraham JL, Loomis WH** (1982) Pulmonary platelet deposition accompanying acute oleic-acid-induced pulmonary injury. *Am Rev Respir Dis*; 126(3):553–557.
27. **Richards RR** (1997) Fat embolism syndrome. *Can J Surg*; 40(5):334–339.
28. **Parizel PM, Demey, HE, Veeckmans G, et al** (2001) Early diagnosis of cerebral fat embolism syndrome by diffusion-weighted MRI (starfield pattern). *Stroke*; 32(12):2942–2944.
29. **Satoh H, Kurisu K, Ohtani M, et al** (1997) Cerebral fat embolism studied by magnetic resonance imaging, transcranial Doppler sonography, and single photon emission computed tomography: case report. *J Trauma*; 43(2):345–348.
30. **Stoeger A, Daniaux M, Felber S, et al** (1998) MRI findings in cerebral fat embolism. *Eur Radiol*; 8(9):1590–1593.
31. **Citerio G, Bianchini E, Beretta L** (1995) Magnetic resonance imaging of cerebral fat embolism: a case report. *Intensive Care Med*; 21(8):679–681.
32. **Weisz GM** (1974) Fat embolism. *Curr Probl Surg*; 1–54.
33. **Worthley LI, Fisher MM** (1979) The fat embolism syndrome treated with oxygen, diuretics, sodium restriction and spontaneous ventilation. *Anaesth Intensive Care*; 7(2):136–142.
34. **Schönfeld SA, Ploysongsang Y, DiLisio R, et al** (1983) Fat embolism prophylaxis with corticosteroids. A prospective study in high-risk patients. *Ann Intern Med*; 99(4):438–443.

35. **Lindeque BG, Schoeman HS, Dommisse GF, et al** (1987) Fat embolism and the fat embolism syndrome. A double-blind therapeutic study. *J Bone Joint Surg Br*; 69(1):128–131.

36. **Alho A, Saikku K, Eerola P, et al** (1978) Corticosteroids in patients with a high risk of fat embolism syndrome. *Surg Gynecol Obstet*; 147(3):358–362.

37. **Shier MR, Wilson RF, James RE, et al** (1977) Fat embolism prophylaxis: a study of four treatment modalities. *J Trauma*; 17(8):621–629.

38. **Stoltenberg JJ, Gustilo RB** (1979) The use of methylprednisolone and hypertonic glucose in the prophylaxis of fat embolism syndrome. *Clin Orthop Relat Res*; 143:211–221.

39. **Gossling HR, Donohue TA** (1979) The fat embolism syndrome. *JAMA*; 241(25):2740–2742.

40. **Bone LB, Johnson KD, Weigelt J, et al** (1989) Early versus delayed stabilization of femoral fractures: a prospective randomized study. *J Bone Joint Surg*; 71:336–340.

41. **Brundage SI, McGhan R, Jurkovich GJ, et al** (2002) Timing of femur fracture fixation: effect on outcome in patients with thoracic and head injuries. *J Trauma*; 52(2):299–307.

42. **Kropfl A, Davies J, Berger U, et al** (1999) Intramedullary pressure and bone marrow fat extravasation in reamed and unreamed femoral nailing. *J Orthop Res*; 17(2):261–268.

43. **Pitto RP, Schramm M, Hohmann D, et al** (1999) Relevance of the drainage along the linea aspera for the reduction of fat embolism during cemented total hip arthroplasty. A prospective, randomized clinical trial. *Arch Orthop Trauma Surg*; 119(3–4):146–150.

44. **Pitto RP, Koessler M, Kuehle JW** (1999) Comparison of fixation of the femoral component without cement and fixation with use of a bone-vacuum cementing technique for the prevention of fat embolism during total hip arthroplasty. A prospective, randomized clinical trial. J Bone Joint Surg Am; 81:831-843

45. **Peltier LF** (1956) Fat embolism. III. The toxic properties of neutral fat and free fatty acids. *Surgery*; 40(4):665–670.

46. **Moylan JA, Birnbaum M, Katz A, et al** (1976) Fat emboli syndrome. *J Trauma*; 16(5):341–347.

47. **Gossling HR, Pellegrini VD Jr** (1982) Fat embolism syndrome: a review of the pathophysiology and physiological basis of treatment. *Clin Orthop Relat Res*; 165:68–82.

48. **Wrigge H, Zinserling J, Neumann P, et al** (2003) Spontaneous breathing improves lung aeration in oleic acid-induced lung injury. *Anesthesiology*; 99(2):376–384.

49. **Neumann P, Hermann W, Zinserling J, et al** (2005) Spontaneous breathing affects the spatial ventilation and perfusion distribution during mechanical ventilatory support. *Crit Care Med*; 33:1090–1095.

50. **Putensen C, Zech S, Wrigge H, et al** (2001) Long-term effects of spontaneous breathing during ventilatory support in patients with acute lung injury. *Am J Respir Crit Care Med*; 164(1):43–49.

51. **Sydow M, Burchardi H, Ephraim E, et al** (1994) Long-term effects of two different ventilatory modes on oxygenation in acute lung injury. Comparison of airway pressure release ventilation and volume-controlled inverse ratio ventilation. *Am J. Respir Crit Care Med*; 149(6):1550–1556.

52. **Kress JP, Pohlman AS, O'Connor MF, et al** (2000) Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med*; 342(20):1471–1477.

53. **Kollef MH, Levy NT, Ahrens TS, et al** (1998)The use of continuous i.v. sedation is associated with prolongation of mechanical ventilation. *Chest*; 114(2):541–548.

54. **Ely EW, Baker AM, Dunagan DP, et al** (1996) Effects on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. *N Engl J Med*; 335(25):1864–1869.

55. **Valenza F, Guglielmi M, Irace M, et al** (2003) Positive end-expiratory pressure delays the progression of lung injury during ventilator strategies involving high airway pressure and lung overdistention. *Crit Care Med*; 31(7):1993–1998.

56. **Pelosi P, Goldner M, McKibben A, et, al** (2001) Recruitment and derecruitment during acute respiratory failure: an experimental study. *Am J Respir Crit Care Med*; 164(1):122–130.

57. **Crotti S, Mascheroni D, Caironi P, et al** (2001) Recruitment and derecruitment during acute respiratory failure: a clinical study. *Am J Respir Crit Care Med*;164(1):131–140.

58. **Gattinoni L, Bombino M, Pelosi P, et al** (1994) Lung structure and function in different stages of severe adult respiratory distress syndrome. *JAMA*; 271(22):1772–1779.

59. **Medoff BD, Harris RS, Kesselman H, et al** (2000) Use of recruitment maneuvers and high-positive end-expiratory pressure in a patient with acute respiratory distress syndrome. *Crit Care Med*. 28(4):1210–1216.

60. **Cakar N, van der Kloot T, Youngblood M, et al** (2000) Oxygenation response to a recruitment maneuver during supine and prone positions in an oleic acid-induced lung injury model. *Am J Respir Crit Care Med*; 161(6):1949–1956.

61. **Hickling KG** (1998) The pressure-volume curve is greatly modified by recruitment. A mathematical model of ARDS lungs. *Am J Respir Crit Care Med*. 158:194–202.

62. **Habashi N** (2005) Other approaches to open-lung ventilation: Airway pressure release ventilation. *Crit Care Med*; 33 [Suppl]: S228–S240.

63. **Webb DP**, **McKamie WA**, **Pietsch JB** (2004) Resuscitation of fat embolism syndrome with extracorporeal membrane oxygenation. *J Extra Corpor Technol*; 36(4):368–370.

64. **Meeke RI, Fitzpatrick GJ, Phelan DM** (1987) Cerebral oedema and the fat embolism syndrome. *Intensive Care Med*; 15:147–148.

65. **Sie MY, Toh KW, Rajeev K** (2003) Cerebral fat embolism: an indication for ICP monitor? *J Trauma*; 55(6):1185–1186.

66. **Lobato RD, Rivas JJ, Gomez PA, et al** (1991) Head-injured patients who talk and deteriorate into coma. Analysis of 211 cases studied with computerized tomography. *J Neurosurg*; 77:161–162.

67. **Boyd HM, Peltier LF, Scott JR, et al** (1956) Fat embolism. II. The chemical composition of fat obtained from human long bones and subcutaneous tissue. *Surgery*; 40(4):661–664.

68. **Hagerty CS** (1938) Experimental embolic glomerulonephritis produced with human fat, fatty acids and calcium soaps. *Arch Pathol*; 25:24–34.

69. **Jacobs RR, Wheeler EJ, Jelenko C III, et al** (1973) Fat embolism: a microscopic and ultrastructure evaluation of two animal models. *J Trauma*; 13(11):980–993.

70. **Derks CM, Jacobovitz-Derks D** (1977) Embolic pneumopathy induced by oleic acid. A systematic morphologic study. *Am J Pathol*; 87(1):143–158.

71. **Beilman G** (1995) Pathogenesis of oleic acid-induced lung injury in the rat: distribution of oleic acid during injury and early endothelial cell changes. *Lipids*; 30(9):817–823.

72. **Vadasz I, Morty RE, Kohstall MG, et al** (2005) Oleic acid inhibits alveolar fluid reabsorption: a role in acute respiratory distress syndrome? *Am J Respir Crit Care Med*; 171(5):469–479.

73. **Agnantis N**, **Gyras M**, **Tserkezoglou A**, **et al** (1988) Therapeutic effect of bovine albumin in the experimental fat embolism syndrome. *Respiration*; 53(1):50–57.

74. **Hofman WF, Ehrhart IC** (1985) Albumin attenuation of oleic acid edema in dog lung depleted of blood components. *J Appl Physiol*; 58(6):1949–1955.

75. **Goodman D** (1958) The interaction of human serum albumin with long-chain fatty acid anions. *J Am Chem Soc*; 80:3892–3902.

76. **Vincent JL, Navickis RJ, Wilkes MM** (2004) Morbidity in hospitalized patients receiving human albumin: a meta-analysis of randomized, controlled trials. *Crit Care Med*; 32(10):2029–2038.

77. **Kerbaul F, Rondelet B, Motte S, et al** (2004) Effects of norepinephrine and dobutamine on pressure load-induced right ventricular failure. *Crit Care Med*; 32(4):1035–1040.

78. **Fulde GW, Harrison P** (1991) Fat embolism—a review. *Arch Emerg Med*; 8(4):233–239.

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