Winning at Failure

Modern Management of Cardiogenic Pulmonary Edema

Amal Mattu, MD
Associate Professor, Division of Emergency Medicine
Director, Emergency Medicine Residency Program
Co-Director, Emergency Medicine/Internal Medicine Combined Residency Program
University of Maryland School of Medicine
Baltimore, Maryland

OBJECTIVES

At the conclusion of this presentation, each participant should be able to. . .

1. Describe the limitations of morphine and furosemide in the management of cardiogenic pulmonary edema.
2. Identify medications available for rapid preload reduction and afterload reduction.
3. Discuss the use of noninvasive positive pressure ventilation.

I. Pathophysiology

Definitions
- Leakage of fluid from the pulmonary capillaries and venules into the alveolar space as a result of increased hydrostatic pressure.
- Inability of the left ventricle (LV) to effectively handle its pulmonary venous return

Basic causes
- Excessive venous return (preload)
- Excessive systemic vascular resistance (afterload)
- LV dysfunction
  - Systolic dysfunction
    - Disorders of contractility
    - Disorders of rate and rhythm (arrhythmias)
  - Diastolic dysfunction
    - Inadequate ventricular relaxation (ventricular "stiffening")

A self-perpetuating cycle leads to cardiogenic pulmonary edema:
1. Acute LV systolic dysfunction leads to…
2. Decreased myocardial contractility and cardiac output (CO), leading to…
3. Catecholamine production, leading to…
4. Increased SVR (afterload) and blood pressure, leading to…
5. Increased myocardial wall tension and myocardial oxygen demand, leading to…
6. Myocardial ischemia, leading to…
7. Decreased myocardial contractility and CO **(continues the cycle…)**
8. Diastolic dysfunction, increased pulmonary artery and capillary hydrostatic pressures
9. Transudation of fluid into pulmonary alveoli and interstitium (pulmonary edema), leading to…
10. Hypoxia, leading to…
11. Myocardial ischemia **(continues the cycle…)**
12. Anxiety, leading to…
13. Increased catecholamine production **(continues the cycle…)**
14. Note that as the left side of the heart fails, the right side continues to fill (preload)
15. This produces even greater pulmonary artery and capillary hydrostatic pressures **(continues the cycle…)**

Treatment must be aimed at breaking this cycle!
- Decrease right-sided filling (decrease preload)
- Improve CO and "unload" the left side of the heart (decrease afterload)
  - Results in improved LV diastolic function
- Improve LV systolic function

    - Increase contractility (not usually necessary if steps 1 and 2 are done well)
    - Treat arrhythmias
- By breaking this cycle, fluid is redistributed *out of the lungs*

II. Goals in Management

ABCs, supplemental oxygen, ECG
Pharmacological treatment — major goals
- Decrease right-sided filling (decrease preload)
- Increase left-sided emptying:
    - Decrease SVR (decrease afterload)
    - Improve LV contractility (inotropic support) — sometimes necessary
        - Inotropes have some adverse effects, therefore avoided when possible

III. Preload Reduction

Traditional treatments
- Morphine
- Furosemide
- Nitrates

<u>Morphine</u>
Advantages
- Histamine effect causes some decrease in preload
- Anxiolytic effect may decrease catecholamines
    - Results in a decrease in afterload

Disadvantages
- Limited data (none?) to support the notion of a preload effect
    - At high doses only?
- Respiratory depressant at high doses
- Myocardial depressant at high doses
- Concerns if patient has low blood pressure
    - Myocardial depressant effect
- Histamine-related side-effects may actually *increase* catecholamines
    - Rash/urticaria
    - Nausea/vomiting

Vismara, et al (*Circulation*, 1976)
- Evaluated venous tone in the hand and forearm veins in pulmonary edema patients after administration of morphine
        - Venous tone decreased, i.e. produced venodilation in the hand and forearm

- How does this correlate with preload (*PCWP*)?? Must look at Swann studies…

Lappas, et al (*Anesthesiology*, 1975)
- Evaluated filling pressures of the heart and pulmonary circulation in patients with CAD after IV morphine
  - 2 mg/kg IV morphine (5 mg/min infusion)
  - Left and right heart filling pressures *increased*
  - CI *decreased*

Timmis, et al (*Br Med J*, 1980)
- 0.2 mg/kg IV morphine in AMI patients with severe LV failure (LVF)
- 15 and 45 minutes after injection, BP, HR, *and cardiac index (CI)* were decreased
- No decrease in preload noted
  - Conclusion — no immediate beneficial hemodynamic effect

Hoffman, et al (*Chest*, 1987)
- 57 patients with presumed prehospital diagnosis of pulmonary edema
- 38% had subjective deterioration after receiving morphine
- 46% had objective deterioration after receiving morphine
- no patients receiving NTG *without* morphine had deterioration

Sacchetti, et al (*Am J Emerg Med*, 1999)
- Odds ratios for intubation and ICU admission for pulmonary edema patients
- Morphine — 5:1

Morphine for anxiolysis
- Decrease in catecholamines, afterload
- Why not use a benzodiazepine instead?
  - No concerns with rash/urticaria
  - No concerns with nausea/vomiting
  - Less concern with respiratory depression
  - Less concern with hypotension

Summary for morphine
- Preload reduction
  - No good evidence to support any immediate reduction in preload centrally
  - Nitrates are more effective, safer
- Anxiolysis
  - Side-effect profile favors benzodiazepines

<u>Furosemide</u>
Reduce preload by:
- Removal of total body fluid through renal effect (diuresis)

- However, CPE patients often have significantly reduced renal blood flow (RBF; ~20% of normal) due to elevated afterload
- Furosemide will have a delayed diuretic effect (30-120 minutes)

- Direct vasoactive effect (venodilation) supposedly reduces preload within 5-10 minutes
  - Pickkers, et al (Circulation, 1997)
    - Evaluated effect of furosemide on human forearm and hand veins after administration peripherally
      - Result — local administration of furosemide produced dose-dependent venodilation
        - But does this correlate with reductions in preload *centrally* (reduction in right heart filling, reduction in PCWP, etc.)?? Must look at Swann studies…
  - No convincing studies supporting any immediate effect

  - More studies actually demonstrate an initial *adverse* hemodynamic effect
    - Kiely, et al (*Circulation*, 1973)
      - IV furosemide administered to post-AMI CHF patients
      - Significant reductions in filling pressures occurred *only in patients that had diuresis*
    - Ikram, et al (*Clin Sci*, 1980)
      - IV furosemide produced significant reductions (17%) in CO during the first 90 minutes
      - CO gradually returned to normal after diuresis
    - Nelson, et al (*Eur Heart J*, 1983)
      - IV furosemide (1 mg/kg) administered to AMI patients with LVF
      - Initial adverse hemodynamic effects
        - Increase in SBP, DBP, and HR during first 30 minutes
        - Decrease in CO and stroke volume (SV) during initial 90 minutes
      - Parameters returned to baseline over next 60-90 minutes with diuresis
    - Francis, et al (*Ann Intern Med*, 1985)
      - Class III and IV CHF patients given IV furosemide
      - Produced early activation of the renin-angiotensin system
        - Significant increase in plasma renin, NE, and arginine vasopressin levels
      - Produced early adverse hemodynamic effects
        - Significant increase in HR, SVR
        - Significant decrease in SV
        - Gradual return to baseline with diuresis
    - Kraus, et al (*Chest*, 1990)
      - Effects of IV furosemide on PCWP over 1 hour in patients receiving nitrates (for preload reduction) and captopril (for afterload reduction)
      - Furosemide produced increases in PCWP over initial 15 minutes
      - Then decrease PCWP with diuresis

        - If patients were premedicated with nitrates and captopril, furosemide produced an immediate and sustained decrease in PCWP

Summary for furosemide
- Decreases preload through diuresis, but this is a delayed effect
- No consistent data regarding any immediate direct venodilating effect
- Produces an initial activation of the sympathetic nervous system
    - Increased HR, SVR, myocardial oxygen demand; leading to cardiac ischemia
    - Decreased SV, CO, tissue perfusion
- Produces an initial activation of the renin-angiotensin system

Nitroglycerin (NTG)
Advantages
- Rapid, reliable preload reduction
    - Multiple studies comparing NTG vs. morphine or furosemide for preload reduction
        - NTG clearly superior (faster, safer)
- Moderate/high dosages reduce SVR (afterload) as well
    - Maintains or improves SV and CO
- Multiple forms of administration — topical, SL, IV (be aggressive!)
- Short half-life limits any adverse effects
    - Especially important if prehospital misdiagnosis

Caution — hypotension, acute mitral regurgitation (MR), aortic stenosis (AS), pulmonary hypertension, Viagra

Summary for NTG
- Better than morphine or furosemide for preload reduction
- Safer than morphine or furosemide for preload reduction (especially important in the prehospital setting — see below)
- SL NTG provides rapid and effective initiation of treatment
    - Followed by topical NTG if moderate symptoms
    - Followed by IV NTG if severe symptoms or in extremis

IV. Afterload Reduction

Results in increased CO, restores RBF
- Nitroglycerin
    - SL and moderate/high dose IV
    - Excellent single agent for simultaneous preload and afterload reduction
- Nitroprusside
    - Especially useful for acute MR, severe hypertension
- Hydralazine
- ACE-inhibitors
    - Down-regulate the renin-angiotensin system

- Decrease adrenergic tone and afterload
- Improve LV relaxation and CO
- Treatment of choice for chronic CHF
- Useful for acute CHF exacerbations also

ACE-inhibitors

Barnett, et al (*Curr Ther Res*, 1991)
- 25 mg SL captopril if BP > 110
- 12.5 mg SL captopril if BP < 110
- Decreased PCWP (preload) noted by 10 minutes
- No change in HR, mean arterial pressure (MAP)
- 12 additional patients with florid pulmonary edema had significant improvement/complete resolution of dyspnea by 15 minutes
    - 8/12 patients — abrupt increase in diuresis *without the use of a diuretic* (due to improved RBF)

Langes, et al (*Curr Ther Res*, 1993)
- IV captopril infusion in moderate decompensated CHF or pulmonary edema patients
- Onset of action by 6 minutes
- Decreased SBP, PCWP (preload)
- Increased CO
- No adverse effects

Varriale, et al (*Clin Cardiol*, 1993)
- Hemodynamic response to 1.25 mg IV enalaprilat in patients with severe CHF + MR
- Increased CO and SV
- Decreased MAP and SVR (afterload)
- Decreased PCWP (preload)
- Decreased the magnitude of MR

Hamilton, et al (*Acad Emerg Med*, 1996)
- Randomized double-blind controlled study
- 48 patients with pulmonary edema
    - treated with NTG, furosemide, morphine
- 25 mg SL captopril if SBP > 110
- 12.5 mg SL captopril if SBP 90-110
- Clinically significant reduction in “distress scores” by 30 minutes

Sacchetti, et al (*Am J Emerg Med*, 1999)
- Odds ratios for intubation and ICU admission for pulmonary edema patients
- SL captopril — 0.28:1

Other studies
- Brivet, et al (*Eur J Clin Invest*, 1981)
    - PO captopril

- Haude, et al (*Int J Cardiol*, 1990)
  - SL captopril
- Sacchetti, et al (*Am J Emerg Med*, 1993)
  - SL captopril in hemodialysis patients with pulmonary edema
- Tohmo H, et al (*Eur Heart J*, 1994)
  - IV enalaprilat
- Annane, et al (*Circulation*, 1996)
  - IV enalaprilat
- *Hemodynamic and subjective improvements can be seen in 6-12 minutes!*

Southall JC, et al (abstract—*Acad Emerg Med*, 2004)
- Safety of ED use of SL captopril in NYHA Class 4 patients
  - No increased incidence of hypotension
  - No increased need for vasopressors
  - Decreased ICU length of stay (29 hours vs. 78 hours)

Summary for ACE-inhibitors
- Rapid reduction in afterload *and preload*
- Rapid reduction in subjective level of distress (decreased anxiety)
- Decreased need for intubation, ICU use
  - Increased bed availability, decreased hospital costs
- Combination with NTG exceeds benefit of either drug alone
- Acceptable alternative to IV NTG in patients with pulmonary edema
  - Works well even as a single agent if patients that can't tolerate NTG
    - Patients with severe MR, AS
    - Patients taking Viagra

V. Combination Preload and Afterload Reduction

<u>Natriuretic peptides</u>
- Hormone-like substances produced by myocardium
  - Modulate diuresis, natriuresis, vasodilation, venodilation
- Activated and synthesized by the ventricle during heart failure
  - Heart may not be capable of producing adequate concentrations under acute stress (e.g. decompensated CHF)

Nesiritide
- Recombinant form of B-type natriuretic peptide (normally produced in the ventricle)
  - These substances modulate diuresis, natriuresis, vasodilation, and venodilation
- Early studies in decompensated CHF
  - Dose-related decreases in PCWP (preload) and SVR (afterload) as well as increases in CI
  - *No increase in HR or arrhythmias*

- Symptomatic improvements

Mills, et al (*J Am Coll Cardiol*, 1999)
- Randomized, double-blind, placebo-controlled study of nesiritide infusion in patients with decompensated CHF; *manufacturer-supported*
- Significant reductions in PCWP and SVR
- Significant increases in SV and CI
- No effect on HR
- Beneficial effects evident at 1 hour and sustained throughout (24 hour) infusion

Colucci, et al (*N Engl J Med*, 2000)
- Randomized double-blind placebo-controlled study of nesiritide infusion in patients with decompensated CHF; *manufacturer-supported*
- Dose-related decrease in PCWP
- Subjective improvements in clinical status
- Most common side-effect was dose-related hypotension (usually asymptomatic)

VMAC Investigators (*JAMA*, 2002)
- Randomized double-blind placebo-controlled trial of intravenous nesiritide vs. NTG added to "standard treatment" in decompensated CHF; *manufacturer-supported*
- "Standard treatment" ≠ "optimal treatment"
  - No mention of aggressive use of nitrates, ACE-Is, NIPPV
- Mean baseline PCWP was 28 mm Hg
- Evauated patients at 3 hours and 24 hours
  - Results at 3 hours
    - Decrease in PCWP by 5.8 (nes.) vs. 3.8 (NTG)
    - No subjective improvement in patients' status
  - Results at 24 hours
    - Decrease in PCWP by 8.2 (nes.) vs. 6.3 (NTG)
    - No difference in dyspnea
    - Some improvement in "global clinical status" (never specified what this is!)
      - Admitted this was a non-validated scoring system
- Subsequent analyses…
  - Trend towards increased mortality with nesiritide
    - 19% for nesiritide vs. 13% for NTG at 90 days (p=0.08)
  - Questions regarding cost-effectiveness
    - 40x more expensive than NTG
    - Duration of hospital stay 2 days longer for nesiritide patients vs. NTG
    - But…decreased readmission rate for nesiritide patients (among survivors)
  - Sackner-Bernstein, et al (*Circulation*, 2005)
    - Meta-analysis of five randomized trials of nesiritide in acutely decompensated heart failure (1269 total patients)

        - Included FDA data from VMAC and other trials
            - Nesiritide associated with worsening renal function
            - No increase in need for hemodialysis, but…
            - Increase in need for medical intervention for renal function (11.1% vs. 4.2%)
    - Their conclusion:
        - "When added to standard care in patients hospitalized with acutely decompensated CHF, nesiritide improves hemodynamic function and some self-reported symptoms more effectively than intravenous NTG or placebo."

    - ***My conclusion:***
        - "When added to ***sub-optimally treated*** patients hospitalized with acutely decompensated CHF, nesiritide ***provided no improvement in mortality or subjective improvement in dyspnea and barely*** improved hemodynamic function and some ***undescribed*** self-reported symptoms more effectively than ***sub-therapeutic doses of*** intravenous NTG or placebo."

    - **Cost of nesiritide: $456 per 1.5 mg vial!** (approx. enough for 24 hours of treatment)
        - (*The Medical Letter* 11/12/02)

VI. Inotropic Support

Choices
- Catecholamines
    - Dopamine
    - Dobutamine
- Phosphodiesterase inhibitors
    - Amrinone
    - Milrinone
- Intra-aortic balloon pump (bridging device before PTCA/CABG)

<u>Catecholamines</u>
Dopamine
- Low dosages (< 5 mcg/kg/min) — vasodilation
- Moderate dosages (5-10 mcg/kg/min) — inotropic
- High dosages (10-20 mcg/kg/min) — vasoconstriction (increase afterload)
- Moderate and higher dosages are arrhythmogenic

Dobutamine
- Inherent vasodilator properties
- Positive inotrope
- Arrhythmogenic (probably less than dopamine)
- Higher dosages associated with tachycardia

Drawbacks to the catecholamine class

- Tachycardia/arrhythmias, especially at higher dosages
- Increased myocardial oxygen consumption, ischemia
- Patients with severe CHF have very high endogenous circulating levels of plasma catecholamines
    - Tolerance develops rapidly, higher dosages are needed
        - Higher dosages produce adverse effects
    - Causes dopamine/dobutamine to be less effective inotropes

<u>Phosphodiesterase inhibitors</u>

- Work independent of adrenoreceptor activity and plasma catecholamine levels
- No development of tolerance
- Induce inotropic support as well *as decreased preload and afterload*
- Amrinone — disappointing results
- Milrinone — excellent results

Milrinone

- 7 studies comparing milrinone to dobutamine in patients with severe decompensated CHF (including post-AMI patients)
    - Similar or greater increase in SV/CI
    - Greater reduction in PCWP (preload) and SVR (afterload)
    - No increase in myocardial oxygen consumption
    - Less tachycardia
- Drawbacks — occasional arrhythmias, more expensive, no proven change in mortality

<u>Summary for inotropic support</u>

- Catecholamines (dopamine, dobutamine) may require large dosages in severe CHF
    - Tachycardia, arrhythmias, increased myocardial oxygen consumption
- Milrinone provides preload and afterload reduction in addition to inotropic support
    - Superior to dobutamine for the patient with borderline hypotension

VI. Noninvasive Positive Pressure Ventilation (NPPV)

Physiology

- Maintains positive airway pressure during entire respiratory cycle
    - Maintains patency of stiff fluid-filled alveoli, prevents collapse during exhalation
        - Decreases work of breathing
            - Less energy spent trying to reopen collapsed alveoli
        - Improves oxygen and carbon dioxide exchange
    - Increases intrathoracic pressure
    - Decreases preload and afterload (and increases CO)

Two types

- Continuous positive airway pressure (CPAP)
  - Single airway pressure is maintained throughout all phases of respiratory cycle
- Bilevel positive airway pressure (BiPAP)
  - Allows for separate control in inhalation and exhalation
  - Higher pressures can be applied during inspiration and lower pressures during exhalation
    - Greater patient comfort

CPAP associated with reduced need for endotracheal intubation

- Rasanen, et al (*Am J Cardiol,* 1985)
- Bersten, et al (*N Engl J Med*, 1991)
- Lin, et al (*Chest*, 1995)
- Pang, et al (*Chest*, 1998)

CPAP associated with reduced ICU length of stay and hospital costs

- Holt, et al (*Anaesth Intens Care*, 1994)
- Sacchetti, et al (*Am J Emerg Med*, 1999)

BiPAP associated with reduced need for endotracheal intubation

- Sacchetti, et al (*Acad Emerg Med*, 1995)
- Masip, et al (*Lancet*, 2000)
- Wigder, et al (*Am J Emerg Med*, 2001)

BiPAP associated with reduced ICU length of stay

- Sacchetti, et al (*Am J Emerg Med*, 1999)

CPAP vs. BiPAP in acute cardiogenic pulmonary edema patients

- Mehta, et al (*Crit Care Med*, 1997)
  - BiPAP associated with more rapid improvements in VS, but…
  - BiPAP associated with increased rate of myocardial infarction
    - Study was criticized because BiPAP group was sicker, had more chest pain patients
- Levitt (*J Emerg Med*, 2001)
  - BiPAP vs. mask ventilation for cardiogenic pulmonary edema
  - No increase in rate of myocardial infarction for BiPAP group
- Cross (*Emerg Med J*, 2003)
  - CPAP vs. BiPAP in undifferentiated acute respiratory failure
  - No increase in rate of myocardial infarction or mortality in subgroup analysis of pulmonary edema patients

Summary for noninvasive positive pressure ventilation

- Decreased work of breathing
- Improved oxygen and carbon dioxide exchange
- Improved preload, afterload, and CO
- Reduced need for endotracheal intubation
- Reduced ICU length of stay

- Reduced hospital costs

Must be used early to maximize the benefit!

VII. Prehospital Treatment

Differential diagnosis for the patient with severe dyspnea and hypoxia is vast

- Most common in older adults patients
  - Decompensated heart failure/cardiogenic pulmonary edema
  - Pneumonia
  - Asthma exacerbation
  - COPD exacerbation
  - Pulmonary embolus
- Clinical assessment is difficult, often unreliable
  - Prehospital limitations — no thermometer, no x-ray

Is empiric treatment safe? With which drugs?

- Hoffman, et al (Chest, 1987)
  - Compared NTG, furosemide, morphine in 57 presumed prehospital pulmonary edema patients
  - Best outcome with NTG
  - Adverse effects noted in patients receiving furosemide
    - > 25% of patients later required fluid *repletion*, some hypotensive
    - Significant electrolyte abnormalities developed in some
  - 23% of patients were misdiagnosed and didn't have pulmonary edema, inappropriately treated
    - Worse outcome in patients receiving furosemide and/or morphine
    - Patients that received NTG alone had no adverse effects
- Kosowsky, et al (*Prehosp Emerg Care*, 2001)
  - Evaluated prehospital use of CPAP for 19 presumed pulmonary edema patients
  - 6/19 (32%) were misdiagnosed and didn't have pulmonary edema, inappropriately treated
    - No adverse effects to using CPAP in these patients
- Wuerz, et al (*Ann Emerg Med*, 1992)
  - Evaluated outcomes in 599 prehospital presumed decompensated CHF patients
  - 18% of patients were misdiagnosed, inappropriately treated for CHF
    - Asthma, COPD, pneumonia, bronchitis
    - Patients receiving NTG alone — 2.2% mortality
    - Patients receiving morphine and/or furosemide (± NTG) — 21.7% mortality
  - Asthma, COPD, pneumonia, bronchitis patients treated with bronchodilators — 3.8% mortality
    - CHF patients that were misdiagnosed and "inappropriately" treated with bronchodilators — no increased mortality

VIII. Summary

- Treatment should be based concept of fluid *redistribution*
- NTG — first-line agent
  - IV NTG is excellent single-agent
- ACE-inhibitors — second-line agent
  - In addition to or instead of NTG
- Furosemide — third-line agent
  - After preload and afterload reduction
- Morphine — no indication!
  - No *proven* benefit, potential harm
  - Preload reduction — NTG more effective
  - Anxiolysis — benzodiazepines have fewer side effects
- Nesiritide
  - May prove useful for patients not responding to "optimal treatment" *pending more studies*
  - May be useful for patients that cannot tolerate NTG or ACE-inhibitors
- Inotropic support
  - Milrinone better than dobutamine from hemodynamic standpoint
  - No difference in mortality amongst the various choices
- Noninvasive positive pressure ventilation
  - Produces more rapid improvement, decrease intubations, decreased length of ICU stay, decreased hospital costs
  - Consider *early* use
- Prehospital treatment
  - Increased morbidity and mortality if misdiagnosed and treated with morphine and/or furosemide
  - Consider limiting treatment to NTG, bronchodilators, NPPV (if available)

References

Anderson JL, Askins JC, Gilbert EM, et al. Occurrence of ventricular arrhythmias in patients receiving acute and chronic infusions of milrinone. Am Heart J 1986;111:466-74.

Annane D, Bellissat E, Pussare E, et al. Placebo-controlled, randomized, double-blind study of intravenous enalaprilat efficacy and safety in acute cardiogenic pulmonary edema. Circulation 1996;94:1316-24.

Barnett JC, Zink KM, Touchon RC. Sublingual captopril in the treatment of acute heart failure. Curr Ther Res 1991;49:274-81.

Beltrame JF, Zeitz CJ, Unger SA, et al. Nitrate therapy is an alternative to furosemide/morphine therapy in the management of acute cardiogenic pulmonary edema. J Card Fail (1998) 4:271-9.

Bersten AD, Holt AW, Vedig AE, et al: Treatment of severe cardiogenic pulmonary edema with continuous positive pressure delivered by face mask. N Engl J Med 1991;325:1825-30.

Biddle TL, Yu PN. Effect of furosemide on haemodynamic and lung water in acute pulmonary edema secondary to myocardial infarction. Am J Cardiol 1979;43:86-90.

Bradley TD, Holloway RM, McLaughlin PR, et al. Cardiac output response to continuous positive pressure in congestive heart failure. Am Rev Respir Dis 1991;145:377-82.

Brivet F, Delfraissy JF, Giudicelli JF, et al. Immediate effects of captopril in acute left ventricular heart failure secondary to myocardial infarction. Eur J Clin Invest 1981;11:369-73.

Burger AJ, Elkayam U, Neibaur MT, et al. Comparison of the occurrence of ventricular arrhythmias in patents with acutely decompensated congestive heart failure receiving dobutamine versus nesiritide therapy. Am J Cardiol 2001;88:35-9.

Buseman W, Schupp D. Effect of sublingual nitroglycerin in emergency treatment of severe pulmonary edema. Am J Cardiol 1978;41:931-6.

Colucci WS, Elkayam U, Horton DP. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. N Engl J Med 2000;343:246-53.

Colucci WS, Wright RF, Jaski BE, et al. Milrinone and dobutamine in severe heart failure: differing hemodynamic effects and individual patient responsiveness. Circulation 1986;73: III 175-83.

Cotter G, Metzkor E, Kaluski E, et al. Randomized trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary oedema. Lancet 1998;351:389-93.

Cross AM, Cameron P, Kierce M, et al. Non-invasive ventilation in acute respiratory failure: a randomized comparison of continuous positive airway pressure and bi-level positive airway pressure. Emerg Med J 2003;20:531-4.

Cuffe MS, Califf RM, Adams KF Jr, et al. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. JAMA 2002;287:1541-7.

Dikshit K, Vyden MB, Forrester JS, et al. Renal and extrarenal hemodynamic effects of furosemide in congestive heart failure after acute myocardial infarction. N Engl J Med 1973;288:1087-90.

Dormans TPJ, Pickkers P, Russel FGM, et al. Vascular effects of loop diuretics. Cardiovasc Res 1996;32:988-97.

Dupuis J. Nitrates in congestive heart failure. Cardiovasc Drugs Ther 1994;8:501-7.

Eisenberg PR, Jaffe AS, Schuster DP. Clinical evaluation compared to pulmonary artery catheterization in the hemodynamic assessment of critically ill patients. Crit Care Med 1984;12:549-53.

Felker GM, O'Connor CM. Between Scylla and Charybdis: The choice of inotropic agent for decompensated heart failure. Am Heart J 2001;142:932-3..

Fett DL, Cavero PG, Burnett JC Jr. Low-dose atrial natriuretic factor and furosemide in experimental acute congestive heart failure. J Am Soc Nephrol 1993;4:162-7.

Figueras J, Weil MH. Blood volume prior to and following treatment of acute cardiogenic pulmonary edema. Circulation 1978;57:349-55.

Franciosa JA, Silverstein SR. Hemodynamic effects of nitroprusside and furosemide in left ventricular failure. Clin Pharmacol Ther 1982;32:62-9.

Francis GS, Siegel RM, Goldsmith SR, et al. Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure. Ann Intern Med 1985;103:1-6.

Gagnon RM, Fortin L, Boucher R, et al. Combined hemodynamic effects of dobutamine and IV nitroglycerin in congestive heart failure. Chest 1980;78:694-8.

Gammage M. Treatment of acute pulmonary oedema: diuresis or vasodilatation? Lancet 1998;351:382-3.

Gehm L, Propp DA. Pulmonary edema in the renal failure patient. Am J Emerg Med 1989;7:336-9.

Goldstein RA, Passamani ER, Robets R. A comparison of digoxin and dobutamine in patients with acute infarction and cardiac failure. N Engl J Med 1980;303:846-50.

Grace MP, Greenbaum DM. Cardiac performance and response to PEEP in patients with cardiac dysfunction. Crit Care Med 1982;10:358-60.

Gropper MA, Wiener-Kronish JP, Hashimoto S. Acute cardiogenic pulmonary edema. Clin Chest Med 1994;15:501-15.

Grose R, Strain J, Greenberg M, et al. Systemic and coronary effects of intravenous milrinone and dobutamine in congestive heart failure. J Am Coll Cardiol 1986;7:1107-13.

Hamilton RJ, Carter WA, Gallagher EJ. Rapid improvement of acute pulmonary edema with sublingual captopril. Acad Emerg Med 1996;3:205-12.

Haude M, Steffen W, Erbel R, et al. Sublingual administration of captopril versus nitroglycerin in patients with severe congestive heart failure. Int J Cardiol 1990;27:351-9.

Hoffman JR, Reynolds S. Comparison of nitroglycerin, morphine and furosemide in treatment of presumed pre-hospital pulmonary edema. Chest 1988;92:586-93.

Holt AW, Bersten AD, Fuller S, et al. Intensive care costing methodology: cost benefit analysis of mask continuous positive airway pressure for severe cardiogenic pulmonary oedema. Anaesth Intens Care 1994;22:170-4.

Hsieh M, Auble TE, Yealy DM. Predicting the future: can this patient with acute congestive heart failure be safely discharged from the emergency department? Ann Emerg Med 2002;39:181-9.

Ikram H, Chan W, Espiner EA, et al. Haemodynamic and hormone responses to acute and chronic frusemide therapy in congestive heart failure. Clin Sci 1980;59:443-9.

Karlsberg RP, DeWood MA, DeMaria AN, et al. Comparative efficacy of short-term intravenous infusions of milrinone and dobutamine in acute congestive heart failure following acute myocardial infarction. Milrinone-Dobutamine Study Group. Clin Cardiol 1996;19:21-30.

Kawamura A, Yoshikawa T, Takahashi T, et al. Randomized trial of phosphodiesterase inhibitors versus catecholamines in patients with acutely decompensated heart failure. Jpn Circ J 2001;65:858-62.

Keung EC, Siskind SJ, Senneblick EH, et al. Dobutamine therapy for acute myocardial infarction. JAMA 1981;245:144-6.

Kiely J, Kelly DT, Taylor DR, et al. The role of furosemide in the treatment of left ventricular dysfunction associated with acute myocardial infarction. Circulation 1973;48:581-7.

Kosowsky JM, Stephanides SL, Branson RD, et al. Prehospital use of continuous positive airway pressure (CPAP) for presumed pulmonary edema: a preliminary case series. Prehosp Emerg Care 2001;5:190-6.

Kosowsky JM, Storrow AB, Carleton SC. Continuous bilevel positive airway pressure in the treatment of acute cardiogenic pulmonary edema. Am J Emerg Med 2000;18:91-5.

Kraus PA, Lipman J, Becker PJ. Acute preload effects of furosemide. Chest 1990;98:124-8.

Lal S, Murtagh JG, Pollock AM, et al. Acute haemodynamic effects of frusemide in patients with normal and raised left atrial pressures. Br Hear J 1969;31:711-7.

Langes K, Siebels J, Kuck KH. Efficacy and safety of intravenous captopril in congestive heart failure. Curr Ther Res 1993;53:167-76.

Lappas DG, Geha D, Fischer JE, et al. Filling pressures of the heart and pulmonary circulation of the patient with coronary artery disease after large intravenous doses of morphine. Anesthesiology 1975;42:153-9.

Le Conte P, Coutant V, N'Guyen JM, et al. Prognostic factors in acute cardiogenic pulmonary edema. Am J Emerg Med 1999;17:329-32.

Levitt MA. A prospective, randomized trial of BiPAP in severe acute congestive heart failure. J Emerg Med 2001;21:363-9.

Lin M, Yang YF, Chiang HT, et al. Reappraisal of continuous positive airway pressure therapy in acute cardiogenic pulmonary edema: short-term results and long-term follow-up. Chest 1995;107:1379-86.

Mager G, Klocke RK, Kux A, et al. Phosphodiesterase III inhibition or adrenoreceptor stimulation: milrinone as an alternative to dobutamine in the treatment of severe heart failure. Am Heart J 1991;121:1974-83.

Masip J, Betbese AJ, Paez J, et al. Non-invasive pressure support ventilation versus conventional oxygen therapy in acute cardiogenic pulmonary oedema: a randomised trial. Lancet 2000;356:2126-32.

Mattu A. Cardiogenic pulmonary edema. Current Opinion in Cardiovascular, Pulmonary, and Renal Investigational Drugs 2000; 2:9-16.

Mattu A, Sharma S, Perkins AM, Zevitz ME: Pulmonary edema, cardiogenic. eMedicine Journal 2002;3(2): http://www.emedicine.com/med/topic1955.htm

Mattu A. Pulmonary edema. Emergency Physicians Monthly 2002;9(9):1,4-8,12,16,22.

Mehta S, Jay GD, Woolard RH, et al. Randomized, prospective trial of bilevel versus continuous positive airway pressure in acute pulmonary edema. Crit Care Med 1997;25:620-8.

Melandri G, Semprini F, Branzi A, et al. Comparative haemodynamic effects of transdermal vs. intravenous nitroglycerin in acute myocardial infarction with elevated pulmonary artery wedge pressure. Eur Heart J 1990;11:649-55.

Mills RM, LeJemtel TH, Horton DP, et al. Sustained hemodynamic effects of an infusion of nesiritide (human b-type natriuretic peptide) in heart failure: a randomized, double-blind, placebo-controlled clinical trial. Natrecor Study Group. J Am Coll Cardiol 1999;34:155-62.

Mojoli F, Mondi L, Zanierato M, et al. Respiratory fatigue in patients with acute cardiogenic pulmonary edema. Eur Hear J 2004;6(Supplement F):F74-F80.

Mond H, Hunt D, Sloman G. Haemodynamic effects of frusemide in patients suspected of having acute myocardial infarction. Br Heart J 1974;36:44-53.

Mukherjee SK, Katz MA, Michael UF, et al. Mechanisms of hemodynamic actions of furosemide: differentiation of vascular and renal effects on blood pressure in functionally anephric hypertensive patients. Am Heart J 1981;101:313-18.

Nelson GI, Ahuja RC, Silke B, et al. Haemodynamic effects of frusemide and its influence on repetitive rapid volume loading in acute myocardial infarction. Eur Heart J 1983;4:706-11.

Nelson GI, Silke B, Ahuja RC, et al. Haemodynamic advantages of isosorbide dinitrate over frusemide in acute heart-failure following myocardial infarction. Lancet 1983 Apr 2;1(8327):730-3.

Nishimura N, Kanbe N. The renal and hemodynamic effects of furosemide in acute myocardial infarction. Crit Care Med 1981;9:829-32.

Northridge D. Frusemide or nitrates for acute heart failure? Lancet 1996;347:667-8.

Noviasky JA, Kelberman M, Whalen KM, et al. Science or fiction: use of nesiritide as a first-line agent? Pharmacotherapy 2003;23:1081-3.

Pang D, Keenan SP, Cook DJ, et al. The effect of positive pressure airway support on mortality and the need for intubation in cardiogenic pulmonary edema. Chest 1998;114: 1185-92.

Pickkers P, Dormans TPJ, Smits P. Direct vasoactivity of frusemide. Lancet 1996;347:1338-9.

Pickkers P, Dormans TP, Russel FG, et al. Direct vascular effects of furosemide in humans. Circulation 1997;96:1847-52.

Poole-Wilson PA. Treatment of acute heart failure: out with the old, in with the new. JAMA 2002;287:1578-80.

Publication Committee for the VMAC Investigators. Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. JAMA 2002;287:1531-40.

Rasanen J, Heikklia J, Downs J, et al. Continuous positive airway pressure by face mask in acute cardiogenic pulmonary edema. Am J Cardiol 1985;55:296-300.

Sacchetti A, McCabe J, Torres M, et al. ED management of acute congestive heart failure in renal dialysis patients. Am J Emerg Med 1993;11:644-7.

Sacchetti AD, Harris RH, Paston C, et al. Bi-level positive airway pressure support system use in acute congestive heart failure: preliminary case series. Acad Emerg Med 1995;2:714-8.

Sacchetti A, Ramoska E, Moakes ME, et al. Effect of ED management on ICU use in acute pulmonary edema. Am J Emerg Med 1999;17:571-4.

Sackner-Bernstein JD, Skopicki HA, Aaronson KD. Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. Circulation 2005;111:1487-91.

Shipley JB, Tolman D, Hastillo A, et al. Milrinone: basic and clinical pharmacology and acute and chronic management. Am J Med Sci 1996;311:286-91.

Southall JC, Bissell DM, Burton JH, et al. ACE inhibitors in acutely decompensated congestive heart failure. Acad Emerg Med 2004;11:503.

Tei C, Horikiri Y, Park JC, et al. Acute hemodynamic improvement by thermal vasodilation in congestive heart failure. Circulation 1995;91:2582-90.

Timmis AD, Rothman MT, Henderson MA, et al. Haemodynamic effect of intravenous morphine in patients with acute myocardial infarction complicated by severe left ventricular failure. Br Med J 1980;280:980-2.

Tohmo H, Karanko M, Korpilahti K. Haemodynamic effects of enalaprilat and preload in acute severe heart failure complicating myocardial infarction. Eur Heart J 1994;15:523-7.

Travill CM, Pugh S, Noble MI. The inotropic and hemodynamic effects of intravenous milrinone when reflex adrenergic stimulation is suppressed by beta-adrenergic blockade. Clin Ther 1994;16:783-92.

Varriale P, David W, Chryssos BE. Hemodynamic response to intravenous enalaprilat in patients with severe congestive heart failure and mitral regurgitation. Clin Cardiol 1993;16:235-8.

Varriale P, Ramaprasad S. Short-term intravenous milrinone for severe congestive heart failure: the good, bad, and not so good. Pharmacotherapy 1997;17:371-4.

Vismara LA, Leaman DM, Zelis R. The effects of morphine on venous tone in patients with acute pulmonary edema. Circulation 1976;54:335-7.

Wigder HN, Hoffmann P, Mazzolini D, et al. Pressure support noninvasive positive pressure ventilation treatment of acute cardiogenic pulmonary edema. Am J Emerg Med 2001;19:179-81.

Wuerz RC, Meador SA. Effects of prehospital medications on mortality and length of stay in congestive heart failure. Ann Emerg Med 1992;21:669-74.

Yamani MH, Haji SA, Starling RC, et al. Comparison of dobutamine-based and milrinone-based therapy for advanced decompensated congestive heart failure: Hemodynamic efficacy, clinical outcome, and economic impact. Am Heart J 2001;142:998-1002.

Zelis R, Mansour EJ, Capone RJ, et al. The cardiovascular effects of morphine. The peripheral capacitance and resistance vessels in human subjects. J Clin Invest 1974;54:1247-58.

Questions or comments? Please contact me:
Amal Mattu, MD, FAAEM, FACEP
Department of Emergency Medicine
419 West Redwood St., Suite 280
Baltimore, MD 21201
amalmattu@comcast.net