

Morphine in the Setting of Acute Heart Failure: Do the Risks Outweigh the Benefits?

Oren Caspi and Doron Aronson

Departments of Cardiology, Rambam Medical Centre and B Rappaport Faculty of Medicine, Technion Medical School, Haifa, Israel

Abstract

The use of opioids in acute pulmonary oedema is considered standard therapy by many physicians. The immediate relieving effect of morphine on the key symptomatic discomfort associated with acute heart failure, dyspnoea, facilitated the categorisation of morphine as a beneficial treatment in this setting. During the last decade, several retrospective studies raised concerns regarding the safety and efficacy of morphine in the setting of acute heart failure. In this article, the physiological effects of morphine on the cardiovascular and respiratory systems are summarised, as well as the potential clinical benefits and risks associated with morphine therapy. Finally, the reported clinical outcomes and adverse event profiles from recent observational studies are discussed, as well as future perspectives and potential alternatives to morphine in the setting of acute heart failure.

Keywords

Acute heart failure, congestion, opiates, morphine, mechanical ventilation

Disclosure: The authors have no conflicts of interest to declare.

Received: 23 December 2019 **Accepted:** 8 March 2020 **Citation:** Cardiac Failure Review 2020;6:e20. **DOI:** <https://doi.org/10.15420/cfr.2019.22>

Correspondence: Doron Aronson, Department of Cardiology, Rambam Medical Center, POB 9602, Haifa 31096, Israel. E: daronson@technion.ac.il

Open Access: This work is open access under the CC-BY-NC 4.0 License which allows users to copy, redistribute and make derivative works for non-commercial purposes, provided the original work is cited correctly.

Heart failure is a growing pandemic worldwide, and it is associated with a high burden of morbidity and mortality. Acute heart failure (AHF) is one of the most prevalent causes of adult patients' hospitalisation. While the treatment of most cardiovascular diseases has significantly improved since the beginning of this century, the outcomes of AHF have not progressed significantly, and AHF still carries a substantial risk for in-hospital mortality, readmission and post-discharge mortality.^{1,2}

The use of opioids to relieve breathlessness in patients with respiratory disease dates back to the late 19th century.³ The immediate relieving effect of morphine on the key symptomatic discomfort associated with AHF, dyspnoea, facilitated the categorisation of morphine as a beneficial treatment in this setting. The rationale for the use of morphine as a decongestive therapy was further supported by animal studies showing a certain shift of volume between central and peripheral circulation, and has been attributed as medical phlebotomy.^{4,5}

Evidence supporting morphine treatment for reducing AHF-associated mortality or morbidity are lacking. Nevertheless, current guidelines and textbooks continue the historical tradition mentioned above, and still accept morphine as a viable option for treating AHF and accordingly it is commonly prescribed.^{6–8} In particular, the relief of dyspnoea and anxiety is generally considered beneficial and serves as a justification for morphine administration.

During the last decade, however, several retrospective studies raised concerns regarding the safety and efficacy of morphine in the setting of AHF.^{9–12} In the current review, the physiological effects of morphine on the cardiovascular and respiratory systems are summarised, as well as the potential clinical benefits and risks. This is followed by a discussion

on the reported clinical outcomes associated with morphine treatment in AHF.

Effects of Morphine on the Cardiovascular System

The effect of morphine on reducing vascular tone has been the key rationale for using the drug in the setting of AHF (*Table 1*). Animal studies have shown that morphine reduces both venous and arterial tone.^{4,5} Morphine exerts the vasodilatory effect mainly by an indirect increase in histamine release and not directly via the mu-opioid receptors.^{13,14} Henney et al. demonstrated that morphine administration at high doses (0.5–1 mg/kg) in dogs results in an immediate decrease in peripheral vascular resistance (46%) and in venous tone (49%). This was accompanied by an increase in venous capacitance of 11 ml/kg.⁴ The resulting increase in venous capacitance was presumed to be beneficial for patients with AHF by facilitating a shift of blood volume from the central to peripheral circulation. Other studies, however, identified only a minor effect on venous tone with a slight reduction in blood pressure.^{15,16}

Zelis et al. studied 69 subjects who were treated with 15 mg of morphine.¹⁶ Venous pressure and tone decreased significantly by 34% and 38%, respectively. Mean systemic arterial pressure remained unchanged, while the authors reported a decrease of 47% in arteriolar constrictor response. A similar evaluation of patients with mild pulmonary oedema revealed a comparable reduction in venous tone that translated into a modest shift of 116 ml of blood to the peripheral circulation.¹⁷ Such a volume shift is too small to explain the presumed beneficial effect on congestion. Timmis et al. examined the effect of morphine in 10 patients with severe LV dysfunction following MI. In this study, morphine was associated with a significant and persistent

Table 1: Effect of Morphine on the Cardiovascular and Respiratory Systems

Cardiovascular System	Respiratory System
Vasodilatory effect, ^{18,19} decrease in peripheral vascular resistance, ^{13,14} hypotension	Diminished chemoreceptor response ^{28,30,31} <ul style="list-style-type: none"> • Reduced hypoxic ventilatory response • Reduced hypercapnic ventilatory response
Decrease in venous tone ^{4,16}	Depression of the brainstem respiratory rhythm–pattern generation ²⁷ <ul style="list-style-type: none"> • Slow and irregular respiration • Reduced minute volume and tidal volume
Attenuation of sympathetic efferent discharge, reduction in heart rate ^{18,19}	Cough suppression

reduction in heart rate and mean arterial pressure, and a small fall in cardiac index with minimal effect on systemic vascular resistance.¹⁸ The fall in cardiac output despite a reduction in systemic vascular resistance may be explained by attenuation of sympathetic efferent discharge from the central nervous system.¹⁶ Interestingly, Timmis et al. also observed a significant reduction in urine output, which was attributed to the stimulation of antidiuretic hormone release.¹⁸ In summary, there is little evidence, based on human studies, that morphine administration, in clinically relevant dosages, can exert a significant increase in venous capacitance that translates to the desired alleviation pulmonary congestion. Additional haemodynamic effects of morphine include decreases in heart rate and blood pressure.¹⁹

Effects of Morphine on the Respiratory System

There are substantial analogies between dyspnoea and pain, as both these subjective experiences involve several common cerebral structures.²⁰ Opioids have powerful effects on respiration and its associated sensations, and their effectiveness in relieving dyspnoea is well-established.²¹ Opioids can also improve dyspnoea by reducing the associated anxiety.²²

Morphine has a direct respiratory depressant effect by activating mu-opioid receptors in a dose-dependent manner.²³ In knockout mice lacking mu-opioid receptors, administration of morphine and other opioids failed to induce respiratory depression.^{24,25} The mu-opioid receptors are expressed in areas of the central nervous system involved in respiratory rhythmogenesis and frequency control, particularly the pre-Bötzinger complex, but also in the cortex and the peripheral chemoreceptors.^{26–28}

The central pattern generator of the respiratory neuron network extends from the facial nucleus to the spinal cord (the ventral respiratory group neuron network).²⁹ The central pattern generator converts tonic excitatory chemo-drive into a respiratory pattern with distinct inspiratory and expiratory phases, and includes the parabrachial and Kölliker-Fuse nuclei in the pons, and the pre-Bötzinger and Bötzing complexes.²⁹ The pre-Bötzinger complex is the main region of respiratory rhythm–pattern generation, and is believed to be the main site of opioid-induced respiratory depression. In addition, opioids have profound effects on the cortical centres that control breathing, thereby augmenting their actions in the brainstem.²⁷

The most opioid-sensitive aspect of respiration is rhythm generation, and changes in the respiratory pattern are observed at lower opioid doses than a change in tidal volume. Opioids cause respiration to slow and progress to become irregular (or cyclic) breathing, and eventually into apnoea.²⁸ The induction of respiratory depression by opioids causes gradual hypercapnia that maintains respiration.

The peripheral chemoreceptors are responsible for 20–30% of the ventilatory drive at rest and for >80% during hypoxia, and express mu-opioid receptors.²⁸ Consequently, opioids profoundly depress the hypoxic ventilatory response and the hypercapnic ventilatory response.^{28,30,31}

Opioid-mediated respiratory depression has been studied mainly in the setting of acute and postoperative pain, with severe respiratory depression and related deaths occurring with an incidence of at least 0.5%.^{32,33} Data from studies conducted with patients experiencing chronic breathlessness demonstrated that opioid therapy (mostly oral) resulted in a small (~2 mmHg) increase in the levels of carbon dioxide without a significant effect on oxygen tension or saturation.³⁴ While the risk for significant respiratory depression may be low in these settings, the associated hypoxia and the increased respiratory effort with pulmonary oedema is a vital compensatory mechanism for the compromised alveolar–capillary diffusion.

Morphine results in a robust and instantaneous anxiolytic effect by activation of the delta and mu-opioid receptors in multiple brain regions, and by reciprocal interaction with the GABAergic system.^{35,36} Morphine administration may also lead to several additional significant adverse events, including over-sedation, delirium, cough depression, nausea and vomiting, and urinary retention.^{37–40}

Potential Clinical Benefits of Morphine in the Treatment of Acute Heart Failure

The haemodynamic benefits frequently cited as the rationale for using morphine to treat AHF include the reduction of venous tone with pooling of blood in the systemic (in particular, venous) circulation, peripheral arteriolar dilatation and antisympathetic effects (*Table 2*).^{4,5,15,41} Morphine-induced reduction in venous tone is considered advantageous in the setting of pulmonary oedema, as it may result in a volume shift from central to peripheral circulation. The venodilatation results in reduced venous return to the right heart and reduced right ventricular output, allowing the failing left ventricle to operate at a lower filling pressure, but may also lead to decreased cardiac output and hypotension, particularly with concomitant pulmonary hypertension. This negative effect on cardiac output may be mitigated by the mild reduction in systemic vascular resistance, resulting in decreased afterload and preserved stroke index.¹⁸ However, as discussed earlier, there is little compelling evidence that morphine causes either clinically significant venous pooling in the systemic circulation or a meaningful reduction of left or right ventricular filling pressures.^{16–18,42,43}

Potential Clinical Risks of Morphine in the Treatment of Acute Heart Failure

Opioids decrease both hypoxic and hypercapnic respiratory drive, and this effect is directly proportional to the opioid dose and its analgesic potency.⁴⁴ Induction of sedation and respiratory depression are among

Table 2: Summary of Studies Conducted on Morphine in the Setting of Acute Heart Failure

Study	Study Year	Patients (n)	Morphine-treated Patients (n)	PSM Pairs	Primary Outcomes, HR [95% CI]*,†	Secondary Outcomes HR [95% CI]*,†
Peacock et al. ⁹	2008	147,362	20,782	NA	In-hospital mortality 4.84 [4.52–5.18]	
Gray et al. ⁵⁷	2010	1,052	541	NA	7-day mortality 1.2 [0.79–1.81]	
Iakobishvili et al. ¹⁰	2011	2,336	218	218	In-hospital mortality 1.2 [0.6–2.5]	
Miro et al. ⁵⁸	2017	6,516	416	275	30-day mortality: 1.66 [0.97–2.82]	
Caspi et al. ¹²	2019	13,788	761	672	Invasive ventilation: 2.13 [1.30–3.50] In-hospital mortality: 1.43 [1.05–1.96]	Non-invasive ventilation: 2.78 [1.95–3.96] Inotropes use: 3.50 [2.10–5.82] Acute kidney injury: 1.81 [1.39–2.36]

*Outcomes are separated into primary and secondary if predefined, otherwise the outcomes field was merged. †Adjusted values. NA = not available; PSM = propensity score matching.

the most serious complications of morphine therapy. Opioids are second in the classes of medications contributing to adverse event reporting for hospitalised patients, with sedation and respiratory depression being among the most commonly reported adverse effects.⁴⁵

Unfortunately, safety data on morphine use in the setting of AHF have not been systematically collected. Available data suggest that bolus administration of opioids is more likely to cause more severe respiratory depression than gradual administration.^{46,47} Various patient groups may be at higher risk for respiratory compromise, including the morbidly obese, patients who suffer from sleep apnoea, patients with respiratory muscle exhaustion and fatigue, patients with neurological or neuromuscular impairment, and the elderly. In addition, drugs, such as propofol and midazolam, have additive or synergistic effects on respiration when combined with opioids.²⁸ Patients with metabolic alkalosis, which often accompanies diuretic therapy and depresses the respiratory centres, may also be susceptible to morphine.

These deleterious respiratory effects are accompanied by the increased risk for nausea and vomiting, consequently leading to further sympathetic activation, hindering the use of non-invasive ventilation, and augmenting the risk for aspiration and further respiratory compromise.^{48,49} The frequency of these dose-dependent complications were not reported in the setting of pulmonary oedema, but based on surgical series, the expected proportions of vomiting with 5 mg and 10 mg of morphine is 8% and 14%, respectively.⁵⁰ The addition of 10 mg metoclopramide is recommended to counteract nausea if morphine is administered.⁴⁹

Furthermore, morphine may affect the absorption of oral medications and therefore confer indirect harm. A randomised trial in the setting of acute MI recently demonstrated that morphine can delay clopidogrel absorption and decrease the plasma level of its active metabolite.⁵¹ A similar study revealed that the same effect is also relevant for ticagrelor administration.^{52–54} Inhibition of oral drugs absorption may be directly relevant to the treatment of AHF in the setting of MI, but presumably may be also relevant to treatment with oral drugs for AHF (e.g. thiazides and neurohormonal inhibitors). Finally, the haemodynamic effects of morphine can, directly and indirectly, affect urine output and renal function, resulting in decreased urine output in the setting of AHF.^{18,28,55,56}

Morphine Therapy and Clinical Outcomes in Acute Heart Failure

Morphine, together with nitrates and diuretics, is one of the most prescribed drugs for AHF, historically. Retrospective studies from the

last decade raised doubts regarding the efficacy and safety of morphine therapy in AHF. In a large retrospective study including patients from the Acute Decompensated HEart Failure National REgistry (ADHERE), morphine therapy was associated with a marked increase in in-hospital mortality (OR 4.8), a higher rate of mechanical ventilation, intensive care admissions and longer duration of hospital stay.⁹ However, morphine dosage and timing of administration were not reported.

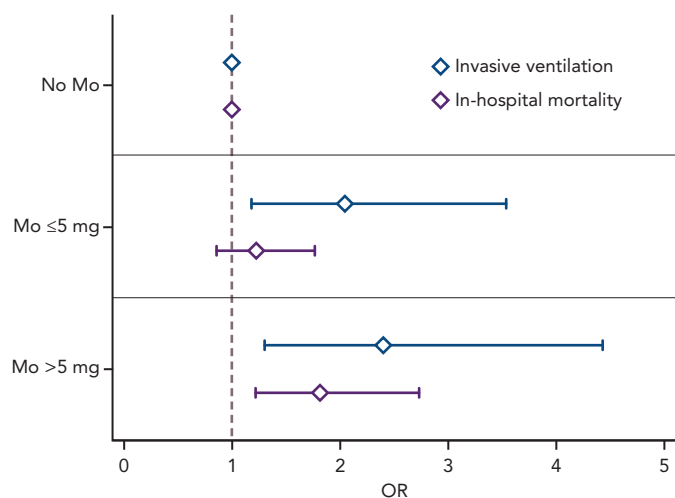
A significant limitation of any non-randomised analysis of the effect of morphine in AHF is that morphine-treated patients represent a cohort with more severe illness and would have been predicted to have greater mortality. Therefore, more recent studies applied propensity score (PS) matching to partially address these limitations.

In contrast, a study based on an Israeli registry of AHF (with two-thirds of morphine-treated patients having an acute coronary syndrome) showed that, in a multivariate analysis, morphine was associated with increased in-hospital mortality, but after PS matching (218 pairs), this effect was rendered insignificant.¹⁰ In addition, an analysis from the Three Interventions in Cardiogenic Pulmonary Oedema (3CPO) trial did not identify a relationship between opiate administration and mortality. However, opiate administration was independently associated with less improvement in arterial pH and did not improve breathlessness.⁵⁷ Recently, a study based on the Spanish Epidemiology of Acute Heart Failure in Emergency Department (EAHFE) registry, which included 275 PS matched pairs, reported that morphine therapy during emergency department stay was associated with increased 30-day mortality (HR 1.66).⁵⁸

We recently studied the association between morphine use within the first 24 hours after admission and in-hospital clinical outcomes in 673 PS matched pairs of patients admitted with the primary diagnosis of AHF.⁵⁸ Morphine therapy was associated with a significant increase in the need for subsequent invasive ventilation (OR 2.13; 95% CI [1.32–3.57], $p=0.007$) and in-hospital mortality (OR 1.43; 95% CI [1.05–1.98], $p=0.024$). Morphine therapy was also associated with a significant increase in the use of inotropes, non-invasive ventilation and acute kidney injury. Furthermore, we observed a significant direct relationship between morphine dose and the endpoints of invasive ventilation and mortality (*Figure 1*).

Importantly, we should approach the results of PS-based studies with caution. A full discussion on the merits and limitations of PS matching is beyond the scope of this review. Although PS matching provides excellent covariate balance, it frequently greatly reduced the sample

Figure 1: ORs and 95% CIs for Invasive Ventilation and In-hospital Mortality According to Morphine Dose



Data from a study using propensity score-matched patients with acute heart failure (672 patient pairs). Invasive ventilation is shown in blue, and in-hospital mortality of shown in purple. The reference group includes patients who did not receive morphine. Mo = morphine. Source: Caspi et al. 2019.¹² Reproduced with permission from Elsevier.

size, resulting in a loss of both precision and generalisability.⁵⁹ The fact that PS methods cannot control for unmeasured confounding is particularly relevant to studies on morphine use in patients with AHF.⁶⁰ Such ‘unobserved confounders’ may be highly unbalanced in the treated and untreated groups, and may arise when clinicians use their expert knowledge (or gut feeling) to make the decision to administer morphine. Such clinical judgement is often based on unmeasured clinical characteristics that introduce significant bias.⁶¹ Finally, under some circumstances, PS matching may actually increase bias.^{60,62}

Conclusion

Morphine administration in the setting of AHF is not currently encouraged by European guidelines (except for palliative and end-of-life care).⁷ Older US guidelines advocated morphine use in acute pulmonary oedema, but it is not mentioned in recent US guidelines.^{63,64} However, it is still frequently used, despite accumulating signals for harm.⁶⁵ The continued use of morphine may be attributed to the desire to rapidly manage dyspnoea and anxiety per se, rather than waiting for these symptoms to improve with the resolution of the pulmonary oedema.

Some physicians believe that morphine-associated harmful effects may be restricted only to specific high-risk groups, such as those with hypoperfusion, low left ventricular ejection fraction or CO₂ retention. However, the heterogeneity of treatment effect has not been shown in the above-mentioned studies.^{12,58} The association between morphine therapy and adverse events in AHF is complex, and likely requires the coexistence of several risk factors/patient susceptibilities to progress to a clinical event. Given the inability to acquire all the relevant patient data at the appropriate temporal resolution, causality remains to be established. However, there is little evidence that morphine is beneficial in the setting of AHF, and accumulating observational data demonstrating harm.

Clinicians encountering a distressed dyspnoeic AHF patient have no doubt that there is a compelling need for anxiolytic therapy, especially if this may be beneficial in alternative ways for the patient. Randomised controlled trials are required to assess the efficacy and safety of morphine in patients with AHF. In addition, the use of substituting agents, such as midazolam, may be explored. The ongoing Midazolam Versus Morphine in Acute Pulmonary Oedema (MIMO) randomised trial may provide this essential information.⁶⁶ Alternative approaches focusing on agents with instantaneous anxiolytic effect and minimal respiratory depression (e.g. dexmedetomidine) may also be useful.⁶⁷ ■

- Ambrosy AP, Fonarow GC, Butler J, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. *J Am Coll Cardiol* 2014;63:1123–33. <https://doi.org/10.1016/j.jacc.2013.11.053>; PMID: 24491689.
- Shiraishi Y, Kohsaka S, Sato N, et al. 9-year trend in the management of acute heart failure in Japan: a report from the National Consortium of Acute Heart Failure Registries. *J Am Heart Assoc* 2018;7:e008687. <https://doi.org/10.1161/JAHA.118.008687>; PMID: 30371201.
- Powell D, Hartley P. *Diseases of the Lungs and Pleurae*. London: HK Lewis, 1911.
- Henney RP, Vasko JS, Brawley RK, Oldham HN and Morrow AG. The effects of morphine on the resistance and capacitance vessels of the peripheral circulation. *Am Heart J* 1966;72:242–50. [https://doi.org/10.1016/0002-8703\(66\)90448-0](https://doi.org/10.1016/0002-8703(66)90448-0); PMID: 5915559.
- Vasko JS, Henney RP, Brawley RK, et al. Effects of morphine on ventricular function and myocardial contractile force. *Am J Physiol* 1966;210:329–34. <https://doi.org/10.1152/ajplegacy.1966.210.2.329>; PMID: 5901471.
- Mebazaa A, Yilmaz MB, Levy P, et al. Recommendations on pre-hospital and early hospital management of acute heart failure: a consensus paper from the Heart Failure Association of the European Society of Cardiology, the European Society of Emergency Medicine and the Society of Academic Emergency Medicine – short version. *Eur Heart J* 2015;36:1958–66. <https://doi.org/10.1093/eurheartj/ehv066>; PMID: 25998514.
- Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). *Eur Heart J* 2016;37:2129–200. <https://doi.org/10.1093/eurheartj/ehw128>; PMID: 27206819.
- Zipes DP, Libby P, Bonow RO, et al, eds. *Braunwald's Heart Disease*. Amsterdam: Elsevier, 2018.
- Peacock WF, Hollander JE, Diercks DB, et al. Morphine and outcomes in acute decompensated heart failure: an ADHERE analysis. *Emerg Med J* 2008;25:205–9. <https://doi.org/10.1136/emj.2007.050419>; PMID: 18356349.
- Iakobishvili Z, Cohen E, Garty M, et al. Use of intravenous morphine for acute decompensated heart failure in patients with and without acute coronary syndromes. *Acute Card Care* 2011;13:76–80. <https://doi.org/10.3109/17482941.2011.575165>; PMID: 21627393.
- García Garmendia JL, Fernández Sosbilla JM, Gallego Lara SL. Morphine use in acute heart failure and limitation of therapeutic effort. *Chest* 2018;153:756–9. <https://doi.org/10.1016/j.chest.2017.10.047>; PMID: 29519305.
- Caspi O, Naami R, Halfin E, Aronson D. Adverse dose-dependent effects of morphine therapy in acute heart failure. *Int J Cardiol* 2019;15:131–6. <https://doi.org/10.1016/j.ijcard.2019.06.015>; PMID: 31239212.
- Grossmann M, Abiose A, Tangphao O, et al. Morphine-induced venodilation in humans. *Clin Pharmacol Ther* 1996;60:554–60. [https://doi.org/10.1016/S0009-9236\(96\)90151-4](https://doi.org/10.1016/S0009-9236(96)90151-4); PMID: 8941028.
- Rosow CE, Moss J, Philbin DM, Savarese JJ. Histamine release during morphine and fentanyl anesthesia. *Anesthesiology* 1982;56:93–6. <https://doi.org/10.1097/0000542-198202000-00003>; PMID: 6172999.
- Ward JM, McGrath RL, Weil JV. Effects of morphine on the peripheral vascular response to sympathetic stimulation. *Am J Cardiol* 1972;29:659–66. [https://doi.org/10.1016/0002-9149\(72\)90167-1](https://doi.org/10.1016/0002-9149(72)90167-1); PMID: 5021495.
- Zelis R, Mansour EJ, Capone RJ, Mason DT. The cardiovascular effects of morphine. The peripheral capacitance and resistance vessels in human subjects. *J Clin Invest* 1974;54:1247–58. <https://doi.org/10.1172/JCI107869>; PMID: 4612057.
- Vismara LA, Leaman DM, Zelis R. The effects of morphine on venous tone in patients with acute pulmonary edema. *Circulation* 1976;54:335–7. <https://doi.org/10.1161/01.CIR.54.2.335>; PMID: 939031.
- Timmis AD, Rothman MT, Henderson MA, et al. Haemodynamic effects of intravenous morphine in patients with acute myocardial infarction complicated by severe left ventricular failure. *Br Med J* 1980;280:980–2. <https://doi.org/10.1136/bmj.280.6219.980>; PMID: 7417767.
- Rouby JJ, Eurin B, Glaser P, et al. Hemodynamic and metabolic effects of morphine in the critically ill. *Circulation* 1981;64:53–9. <https://doi.org/10.1161/01.CIR.64.1.53>; PMID: 7237725.
- von Leupoldt A, Sommer T, Kegat S, et al. Dyspnea and pain share emotion-related brain network. *Neuroimage* 2009;48:200–6. <https://doi.org/10.1016/j.neuroimage.2009.06.015>; PMID: 19527787.
- Jennings AL, Davies AN, Higgins JP, et al. A systematic review of the use of opioids in the management of dyspnoea. *Thorax* 2002;57:939–44. <https://doi.org/10.1136/thorax.57.11.939>; PMID: 12403875.
- Banzett RB, Adams L, O'Donnell CR, et al. Using laboratory models to test treatment: morphine reduces dyspnea and hypercapnic ventilatory response. *Am J Respir Crit Care Med* 2011;184:920–7. <https://doi.org/10.1164/rccm.201101-0005OC>; PMID: 21778294.
- Mahler DA. Opioids for refractory dyspnea. *Expert Rev Respir Med* 2013;7:123–34; quiz 135. <https://doi.org/10.1586/ers.13.5>; PMID: 23547989.
- Sora I, Takahashi N, Funada M, et al. Opiate receptor knockout mice define mu receptor roles in endogenous nociceptive responses and morphine-induced analgesia. *Proc Natl Acad Sci U S A* 1997;94:1544–9. <https://doi.org/10.1073/pnas.94.4.1544>; PMID: 9037090.
- Matthes HW, Maldonado R, Simonin F, et al. Loss of morphine-induced analgesia, reward effect and withdrawal symptoms in mice lacking the mu-opioid-receptor gene. *Nature* 1996;383:819–23. <https://doi.org/10.1038/383819a0>; PMID: 8893006.
- Gray PA, Rekling JC, Bocchiaro CM, Feldman JL. Modulation of respiratory frequency by peptidergic input to rhythmic neurons in the preBotzinger complex. *Science* 1999;286:1566–8. <https://doi.org/10.1126/science.286.5444.1566>; PMID: 10567264.
- Pattinson KT, Governo RJ, Macintosh BJ, et al. Opioids depress cortical centers responsible for the volitional control of respiration. *J Neurosci* 2009;29:8177–86. <https://doi.org/10.1523/JNEUROSCI.1375-09.2009>; PMID: 19553457.
- Pattinson KT. Opioids and the control of respiration. *Br J Anaesth* 2008;100:747–58. <https://doi.org/10.1093/bja/aen094>; PMID: 18456641.

29. Rubin JE, Shevtsova NA, Ermentrout GB, et al. Multiple rhythmic states in a model of the respiratory central pattern generator. *J Neurophysiol* 2009;101:2146–65. <https://doi.org/10.1152/jn.90958.2008>; PMID: 19193773.
30. Algera MH, Kamp J, van der Schrier R, et al. Opioid-induced respiratory depression in humans: a review of pharmacokinetic-pharmacodynamic modelling of reversal. *Br J Anaesth* 2019;122:e168–79. <https://doi.org/10.1016/j.bja.2018.12.023>; PMID: 30915997.
31. Dahan A. Respiratory depression with opioids. *J Pain Palliat Care Pharmacother* 2009;21:63–6. https://doi.org/10.1080/J354v21n01_15; PMID: 17430835.
32. Dahan A, Aarts L, Smith TW. Incidence, reversal, and prevention of opioid-induced respiratory depression. *Anesthesiology* 2010;112:226–38. <https://doi.org/10.1097/ALN.0b013e3181c38c25>; PMID: 20010421.
33. Gupta K, Prasad A, Nagappa M, et al. Risk factors for opioid-induced respiratory depression and failure to rescue: a review. *Curr Opin Anaesthesiol* 2018;31:110–119. <https://doi.org/10.1097/ACO.0000000000000541>; PMID: 29120929.
34. Verberk CA, van den Beuken-van Everdingen MHJ, Schols J, et al. Respiratory adverse effects of opioids for breathlessness: a systematic review and meta-analysis. *Eur Respir J* 2017;50. <https://doi.org/10.1183/13993003.01153-2017>; PMID: 29167300.
35. Colasanti A, Rabiner EA, Lingford-Hughes A, Nutt DJ. Opioids and anxiety. *J Psychopharmacol* 2011;25:1415–33. <https://doi.org/10.1177/0269881110367726>; PMID: 20530588.
36. Johnson MJ, McDonagh TA, Harkness A, et al. Morphine for the relief of breathlessness in patients with chronic heart failure – a pilot study. *Eur J Heart Fail* 2002;4:753–6. [https://doi.org/10.1016/S1388-9842\(02\)00158-7](https://doi.org/10.1016/S1388-9842(02)00158-7); PMID: 12453546.
37. Nicholson BD. Economic and clinical burden of opioid-induced nausea and vomiting. *Postgrad Med* 2017;129:111–7. <https://doi.org/10.1080/00325481.2017.1243004>; PMID: 27690715.
38. de Boer HD, Detrich O, Forget P. Opioid-related side effects: Postoperative ileus, urinary retention, nausea and vomiting and shivering. A review of the literature. *Best Pract Res Clin Anaesthesiol* 2017;31:499–504. <https://doi.org/10.1016/j.bpa.2017.07.002>; PMID: 29739538.
39. Pandharipande P, Cotton BA, Shintani A, et al. Prevalence and risk factors for development of delirium in surgical and trauma intensive care unit patients. *J Trauma* 2008;65:34–41. <https://doi.org/10.1097/TA.0b013e31814b2c4d>; PMID: 18580517.
40. Martyn JAJ, Mao J, Bittner EA. Opioid tolerance in critical illness. *N Engl J Med* 2019;380:365–78. <https://doi.org/10.1056/NEJMr1800222>; PMID: 30673555.
41. Opie LH. Drugs and the heart. VII. Which drug for which disease? *Lancet* 1980;1:1011–7. [https://doi.org/10.1016/S0140-6736\(80\)91448-8](https://doi.org/10.1016/S0140-6736(80)91448-8); PMID: 6103335.
42. Lee G, DeMaria AN, Amsterdam EA, et al. Comparative effects of morphine, meperidine and pentazocine on cardiocirculatory dynamics in patients with acute myocardial infarction. *Am J Med* 1976;60:949–55. [https://doi.org/10.1016/0002-9343\(76\)90565-9](https://doi.org/10.1016/0002-9343(76)90565-9); PMID: 937355.
43. Leaman DM, Levenson L, Zelis R, Shiroff R. Effect of morphine on splanchnic blood flow. *Br Heart J* 1978;40:569–71. <https://doi.org/10.1136/hrt.40.5.569>; PMID: 656226.
44. Weil JV, McCullough RE, Kline JS, Sodal IE. Diminished ventilatory response to hypoxia and hypercapnia after morphine in normal man. *N Engl J Med* 1975;292:1103–6. <https://doi.org/10.1056/NEJM197505222922106>; PMID: 1128555.
45. Davies EC, Green CF, Taylor S, et al. Adverse drug reactions in hospital in-patients: a prospective analysis of 3695 patient-episodes. *PLoS One* 2009;4:e4439. <https://doi.org/10.1371/journal.pone.0004439>; PMID: 19209224.
46. Gross JB. When you breathe IN you inspire, when you DON'T breathe, you... expire: new insights regarding opioid-induced ventilatory depression. *Anesthesiology* 2003;99:767–70. PMID: 14508302.
47. Bouillon T, Bruhn J, Radu-Radulescu L, et al. A model of the ventilatory depressant potency of remifentanyl in the non-steady state. *Anesthesiology* 2003;99:779–87. <https://doi.org/10.1097/0000542-200310000-00007>; PMID: 14508307.
48. Hårdemark Cedborg AI, Sundman E, Bodén K, et al. Effects of morphine and midazolam on pharyngeal function, airway protection, and coordination of breathing and swallowing in healthy adults. *Anesthesiology* 2015;122:1253–67. <https://doi.org/10.1097/ALN.0000000000000657>; PMID: 25853450.
49. Ellingsrud C and Agewall S. Morphine in the treatment of acute pulmonary oedema—Why? *Int J Cardiol* 2016;202:870–3. <https://doi.org/10.1016/j.ijcard.2015.10.014>; PMID: 26476045.
50. Roberts GW, Bekker TB, Carlsen HH, et al. Postoperative nausea and vomiting are strongly influenced by postoperative opioid use in a dose-related manner. *Anesth Analg* 2005;101:1343–8. <https://doi.org/10.1213/01.ANE.0000180204.64588.EC>; PMID: 16243992.
51. Hobi E-L, Stimpfl T, Ebner J, et al. Morphine decreases clopidogrel concentrations and effects: a randomized, double-blind, placebo-controlled trial. *Am J Coll Cardiol* 2014;63:630–5. <https://doi.org/10.1016/j.jacc.2013.10.068>; PMID: 24315907.
52. Farag M, Spinthakis N, Srinivasan M, Gorog DA. Should STEMI patients receive opiate analgesia? The morphine paradox. *Curr Vasc Pharmacol* 2018;16:477–83. <https://doi.org/10.2174/1570161116666180117145704>; PMID: 29345594.
53. Giannopoulos G, Deffereros S, Kolokathis F, et al. P2Y12 receptor antagonists and morphine: a dangerous liaison? *Circ Cardiovasc Interv* 2016;9:e004229. <https://doi.org/10.1161/CIRCINTERVENTIONS.116.004229>; PMID: 27586412.
54. Kubica J, Adamski P, Ostrowska M, et al. Morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction: the randomized, double-blind, placebo-controlled IMPRESSION trial. *Eur Heart J* 2016;37:245–52. <https://doi.org/10.1093/eurheartj/ehv547>; PMID: 26491112.
55. Anderson MK, Day TK. Effects of morphine and fentanyl constant rate infusion on urine output in healthy and traumatized dogs. *Vet Anaesth Analg* 2008;35:528–36. <https://doi.org/10.1111/j.1467-2995.2008.00413.x>; PMID: 18565200.
56. Agewall S. Morphine in acute heart failure. *J Thorac Dis* 2017;9:1851–4. <https://doi.org/10.21037/jtd.2017.06.129>; PMID: 28839982.
57. Gray A, Goodacre S, Seah M, Tilley S. Diuretic, opiate and nitrate use in severe acidotic acute cardiogenic pulmonary oedema: analysis from the 3CPO trial. *QJM* 2010;103:573–81. <https://doi.org/10.1093/qjmed/hcq077>; PMID: 20511258.
58. Miro O, Gil V, Martin-Sanchez FJ, et al. Morphine use in the ED and outcomes of patients with acute heart failure: a propensity score-matching analysis based on the EAHF registry. *Chest* 2017;152:821–32. <https://doi.org/10.1016/j.chest.2017.03.037>; PMID: 28411112.
59. Elze MC, Gregson J, Baber U, et al. Comparison of propensity score methods and covariate adjustment: evaluation in 4 cardiovascular studies. *Am Coll Cardiol* 2017;69:345–57. <https://doi.org/10.1016/j.jacc.2016.10.060>; PMID: 28104076.
60. Pearl J. Remarks on the method of propensity score. *Stat Med* 2009;28:1415–6; author reply 1420–3. <https://doi.org/10.1002/sim.3521>; PMID: 19340847.
61. Fu EL, Groenwold RHH, Zoccali C, et al. Merits and caveats of propensity scores to adjust for confounding. *Nephrol Dial Transplant* 2019;34:1629–1635. <https://doi.org/10.1093/ndt/gyf283>; PMID: 30215791.
62. Pearl J. Causal inference in statistics: an overview. *Statist Surv* 2009;3:96–146. <https://doi.org/10.1214/09-SS057>.
63. Guidelines for the evaluation and management of heart failure. Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Evaluation and Management of Heart Failure). *Circulation* 1995;92:2764–84. <https://doi.org/10.1161/01.CIR.92.9.2764>; PMID: 7586389.
64. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013;128:1810–52. <https://doi.org/10.1161/CIR.0b013e31829e8807>; PMID: 23741057.
65. Miro O, Hazlitt M, Escalada X, et al. Effects of the intensity of prehospital treatment on short-term outcomes in patients with acute heart failure: the SEMICA-2 study. *Clin Res Cardiol* 2018;107:347–61. <https://doi.org/10.1007/s00392-017-1190-2>; PMID: 29285622.
66. Dominguez-Rodriguez A, Burillo-Putze G, Garcia-Saiz MDM, et al. Study design and rationale of “a multicenter, open-labeled, randomized controlled trial comparing Midazolam versus Morphine in acute pulmonary edema”: MIMO trial. *Cardiovasc Drugs Ther* 2017;31:209–13. <https://doi.org/10.1007/s10557-017-6722-5>; PMID: 28265880.
67. Jun JH, Kim KN, Kim JY, Song SM. The effects of intranasal dexmedetomidine premedication in children: a systematic review and meta-analysis. *Can J Anaesth* 2017;64:947–61. <https://doi.org/10.1007/s12630-017-0917-x>; PMID: 28639236.