

A critical appraisal of the morphine in the acute pulmonary edema: real or real uncertain?

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Acute heart failure (AHF) is the leading cause of hospitalization and consultation in hospital emergency department (ED) in industrialized nations (1,2), and its prevalence increases with age (1). For many physicians, acute pulmonary edema (APE) is the real clinical presentation of AHF; typically, signs and symptoms develop rapidly and patients demonstrate severe respiratory distress with tachypnea, orthopnea, and pulmonary congestion (3).

Interestingly, despite the tremendous burden of AHF on the medical system, few prospective randomized trials have been conducted to establish best care. Given the lack of good evidence to guide their practice, it is not surprising that many clinicians base their treatment decisions on their own experience, as well as the anecdotal reports provided by colleagues and instructors during their training (4). Often treatment must be administered in parallel with the diagnostic work-up. Systolic blood pressure, heart rhythm and rate, saturation of peripheral oxygen using a pulse oximeter, and urine output should be monitored on a regular and frequent basis until the patient is stabilized. Although not 'evidence based' in the same way as treatments for chronic heart failure, the key drugs are oxygen, diuretics (furosemide, torasemide, hydrochlorothiazide, indapamide, spironolactone, eplerenone, amiloride and triamterene), and vasodilators (nitroglycerine and nitroprusside) (1,4).

Most often, APE is thought to be caused by an ischaemic

event on the background of more chronic myocardial dysfunction. The overall effect is a feeling of suffocation, causing a state of anxiety, panic and impending doom. This further raises the work of breathing. The endogenous catecholamine release increases peripheral vasoconstriction, resulting in an even greater workload demand from the myocardium (5). The treatment of APE therefore is primarily aimed at reducing pulmonary capillary pressure, redistributing pulmonary fluid and improving the forward flow (1). Traditionally, treatment of anxiety is thought to be also important in the acute stages of an attack (6).

For several decades, morphine has been used in cases of APE due to the anxiolytic and vasodilatory properties of the drug. Up to date, the use of intravenous morphine in the treatment of APE remains controversial (7). There are no large randomised controlled trials supporting the use of morphine in the treatment of patients with APE (8,9). The evidence to support their use is essentially non-existent, but clear 'practice changing' evidence for alternate agents is not much better. As a result, a therapeutic approach that includes this potentially harmful class of medications continues to be handed down from one medical generation to the next.

It is well known that opiate receptors exist outside the central nervous system. Pugsley (10) summarizes their effects as:

- ❖ On vasculature—direct and indirect vasodilatory effects;
- ❖ Heart failure—fluid offload;
- ❖ Cardiac arrhythmogenesis—both pro- and antiarrhythmogenic;
- ❖ Ischaemic preconditioning;
- ❖ Heart function directly.

The European Society of Cardiology does not recommend routine use of morphine, suggesting that it should only cautiously be used in patients with severe dyspnoea, and predominately in those with APE (recommendation class IIB; level of evidence B) (1). In contrast, the American Heart Association/American College of Cardiology Heart Failure guidelines does not mention morphine in their guidelines from 2013, which reserve this therapy only for palliative care of end-stage heart failure patients (11).

In a recent report, Miró and colleagues (12) demonstrated in a study carried out in patients included in the EAHFE (Epidemiology of Acute Heart Failure in Emergency Department) Registry (2), that the use of morphine in ED patients diagnosed with AHF is associated with an increased 30-day mortality, and that this increased risk is especially higher during the first 3 days. This registry is a multicenter, observational, multipurpose, cohort-designed database that includes consecutive patients diagnosed with AHF in 34 Spanish EDs in both university and community hospitals from all areas of the country.

In the present study, 6,516 patients were included for the analysis. Overall 416 patients (6%) were included in the morphine and 6,100 (94%) in the without morphine groups (12). The authors investigated if there were any differences in the distribution of the 46 independent variables collected. After this first approach, they used propensity score (PS) matching analysis in order to analyse two comparable cohorts: with or without the use of morphine. The PS was estimated for each of the patients using multivariate logistic regression. With an exhaustive statistical analysis, they demonstrated that the survival analysis of the PS-matched patients showed a significant increase in 30-day mortality in the morphine group (HR 1.66, 95% CI: 1.09–2.54; $P=0.017$). Mortality was increased at 3, 7, and 14 days, with the greatest OR being found at the shortest post-ED time (8.0% *vs.* 2.5%, OR 3.33, 95% CI: 1.40–7.93, $P=0.007$) of 3 days. In hospital mortality in the morphine group was higher than in the without morphine group, although without statistical significance (14.2% *vs.*

9.1%, OR 1.65, 95% CI: 0.97–2.82, $P=0.083$) (12).

The study of Miró and colleagues are in line with previous reports about of the use of opiates in AHF. Peacock *et al.*, reported data from the ADHERE registry, including 147,632 patients admitted to US acute care hospitals for AHF. They demonstrated that morphine given in AHF was an independent predictor of increased hospital mortality (OR 4.8, 95% CI: 4.52–5.18) (13). This study is limited by its retrospective and observational nature, and moreover the authors not performing PS analysis. Gray *et al.*, performed a secondary analysis of 1,052 patients included in the UK 3CPO trial carried out from 2003 to 2007. The authors not find any relationship between morphine and 7-day mortality (14). In another study from 2011 conducted in Israel, of the 2,336 AHF patients, 9.3% received intravenous morphine (15). The authors demonstrated that the use of intravenous morphine was independently associated with increases in-hospital death in the multivariable analysis (OR 2, 95% CI: 1.1–3.5), but after performing PS analysis, intravenous morphine use was no longer associated with increased mortality (OR 1.2, 95% CI: 0.6–2.5) (15). Finally, in a retrospective analysis of 991 Spanish patients with AHF in the ED of an university hospital, which 16.2% received intravenous morphine, Dominguez *et al.* found an increased risk of in-hospital death (OR 1.8, 95% CI: 1.1–3.1). However, one limitation of this study was that the authors did not perform a PS analysis (16).

All studies above mentioned, are retrospective uncontrolled evaluations, insight into the conclusions must be limited to the generation of hypotheses. Moreover, one important limitation in these studies cited is the total dose of morphine administered to each patient was not quantified. Although morphine is used in the ED for APE, it is necessary to evaluate risks and benefits of this therapy. Indeed, a current ongoing randomised clinical trial could eventually answer this question (17).

The Midazolam versus Morphine in APE trial (MIMO) is a multicenter, prospective, open-label, randomized study designed to evaluate the efficacy and safety of morphine in patients with APE (17). The MIMO trial will evaluate as a primary endpoint whether intravenous morphine administration improves clinical outcomes defined as in-hospital mortality. Secondary endpoint evaluation will be: mechanical ventilation, cardiopulmonary resuscitation, intensive care unit admission rate, intensive care unit length of stay and hospitalisation length. Subjects will be

randomly assigned to 1 of 2 treatment groups in a 1:1 ratio of morphine or midazolam. Morphine will be administered intravenously in dosages of 2–4 mg that may be repeated given if the patient continues suffering from severe anxiety or distress caused by APE until a total dose of 8 mg has been given. By the contrary, midazolam will be administered intravenously in dosages of 1 mg that may be repeated given if the patient continues suffering from severe anxiety or distress caused by APE until a total dose of 3 mg has been given (17).

In summary, the use of morphine in APE is something of a metaphor for the limitations of our current approach in AHF. There appears to be a strong association between morphine administration and a worsening outcome. The causality is difficult to prove because of the poor research methodology. The quality of the evidence makes it impossible to conclude that it definitely has no use in this setting. Its main effect appears to be anxiolytic but, even so, some authors advocate the use of benzodiazepines as they are much more potent and cause less respiratory depression. So, the MIMO trial is willing to answer any open questions on the subject.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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