Letter to the Editor

Morphine in acute heart failure: good in relieving symptoms, bad in improving outcomes

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For centuries, perhaps longer, morphine has been used to palliate the discomfort of human beings. Remarkably, after all the astounding advances in the science of medicine, it is still unbeatable for the relief of pain. It is for this reason alone, it can be found in every emergency department (ED) across the globe. To have an ED without morphine is unthinkable.

Morphine was first isolated between 1803 and 1805 by F. Sertürner, and shortly thereafter, in 1827, Merck Laboratories began marketing it commercially (1). It has been used, sometimes to excess, ever since. Morphine, and its synthetic derivatives, are extensively used in medicine to treat both acute and chronic pain, anxiety, and shortness of breath in a broad variety of circumstances, including cancer, acute myocardial infarction, colic pain, labour, etc. And in terms of acquisition costs, it remains an extremely effective pharmacologic.

But morphine is not without side effects. The most notorious is respiratory depression which, in itself, can be fatal. Additionally, morphine induced hypotension may also occur. This has the potential to decrease myocardial perfusion, which can increase myocardial ischemia, the consequence of which is decreased myocardial contractility that further exacerbates the cardiac output deficit, and ultimately results in death from cardiogenic shock. And while the respiratory depressive effects of narcotics can be reversed by the appropriate use of naloxone, the hypotensive effects of morphine are more challenging and resistant (2,3).

Acute heart failure (AHF) is one of the syndromes in which morphine has been used since long time ago, especially in those patients exhibiting the clinical form of acute pulmonary edema (APE). Every emergency physician knows well how much feelings of imminent death, respiratory distress and anxiety are in any patient suffering from a severe episode of AHF, and how effective and rapid morphine is in relieving these feelings. Nearly all patients (and doctors) feel more comfortable after morphine is given.

However, it is possible that for certain diseases and syndromes, morphine may shorten survival, and this seems to be the case in patients presenting with AHF, who are treated with morphine during the first minutes of medical intervention (4,5). The two main complications commented above, respiratory depression and hypotension, represent concerns for the use of morphine in the setting of AHF and may explain the potential increased mortality shown in large AHF registries associated with its use. These risks are not to say that morphine may not improve a patient's symptom perception. But ultimately the risk of respiratory depression and hypotension must be balanced with the relief from the symptoms of hypoxia-induced anxiety and that of severe dyspnea.

It is important to recognize that palliative care considerations may not share the same objectives when morphine is used in the acute or even chronic setting. The benefits of morphine for palliation may be appropriate, if

the objective is to relieve suffering, even accepting that in some cases it will ultimately impact negatively on outcome.

These considerations notwithstanding, we recently published results from a propensity score-matching analysis based on the Epidemiology of Acute Heart Failure in Emergency department (EAHFE) registry, an extensive prospective database of consecutive patients diagnosed with AHF in Spanish ED. We found consistent data suggesting that the use of morphine in the ED to treat AHF is associated with increased mortality at 30 days (HR, 1.66; 95% CI: 1.09–2.54), and that this risk seems to be even greater in the very short-term, as the 3-day mortality for patients treated with morphine exhibit a HR of 3.33 (1.40–7.93) (6). As some of the accompanying editorials (7-9) published in the previous issue of *Journal of Thoracic Disease* remarks, our data come from a secondary analysis of an observational cohort, and they are not definitive by themselves. Nonetheless, they add evidence to other similar studies where morphine was found to be associated with increased mortality (10) or to consistently point towards to non-significant trends of increased ratios of death in small underpowered studies (11,12).

Additionally, although death is the most important outcome, it is not the only relevant one. It is possible that, although mortality remains unaffected, worse results could occur in terms of increased intensive care admission, need for intubation, prolonged length of hospitalization, or repeated hospitalizations and ED presentations (13-15). In this sense, every effort to prevent patient deterioration may help in improving these outcomes.

Certainly, randomized clinical trials will provide definitive evidence on whether there are harmful effects of morphine. The ongoing MIdazolan versus Morphine in APE (MIMO) Trial will ascertain, in a head to head comparison of morphine versus midazolam, which is superior to treat anxiety and dyspnea accompanying severe forms of AHF, as well as their impact on mortality (16). It is important to note that MIMO's design compares morphine versus midazolam, but without a placebo. This is because, even though that morphine may be associated with increased mortality in patients with AHF, it is felt ethically unacceptable to provide no symptoms relief in these terribly uncomfortably patients.

There are important considerations and limitations to our study. Although our study involved 6,516 patients, it limited to morphine use in the ED during the first 3 hours of patient arrival. Thus, our data do not support any assumption on effects of morphine use in other settings (e.g., general wards or intensive care units). Further, it has been repeatedly demonstrated that the characteristics of ED patients with AHF may differ from those of hospitalized patients, as the former are usually in a more acute and unstable situation, are older, more frequently affected by comorbidities, have higher rates of cardiac failure with preserved left ventricular ejection fraction, and have greater propensity to frailty and functional dependence (17). Therefore, ED patients may represent a challenging management cohort. Our observed negative mortality results associated with the use of morphine minutes after ED presentation may partly be a function of this fact.

And last, but not least, patient opinion is critical (18). Unfortunately, our study did not evaluate patient's perceptions regarding symptom relief as a result of morphine use. It is possible that the relaxing effects of morphine could be preferred by AHF patients, even in the scenario had they been informed about the potential, although unproven, negative impact of morphine over short-term survival rates. In connection with this, morphine may still be the first-choice drug in a patient's "final hours". Heart failure is a terminal condition for which death cannot be avoided. Given that, it is reasonable to identify which AHF patients are at very high risk for short-term mortality and not deprive them of symptom relief for their last hours. Unfortunately, a reliable risk score for ED use in patients with AHF is not routinely applied (19). The very recent development in large population of patients with AHF of two scales, the EHMRG (20) and the MEESSI-AHF (21) scales, for reliable prediction of short-term mortality in patients with AHF to be used in the ED should help emergency physicians to improve detection of this subset of very sick patients.

With all the arguments suggesting that morphine should not be routinely used in AHF, what remains of to treat AHF? New drugs have repeatedly failed in demonstrating benefits for this long-lasting therapeutically challenging syndrome. And, as Stefan Agewall remarks in his editorial (7), the number of drugs classically used in AHF that are under suspicion to negatively impact outcome are increasing. Certainly, it seems that the best emergency physicians can do for these decompensated patients, in therapeutic terms, is to ensure that treatments that have demonstrated to be useful in the chronic phase are maintained if the patient is currently receiving them, and for those patients that are not, start them as soon as possible (22,23). In the meanwhile, we will have to wait for better data for morphine. Indications of the Guidelines of

the European Society of Cardiology (not recommending routine use of opiates and only be cautiously considered in patients with severe dyspnea, mostly with APE) (24) and the American Heart Association/American College of Cardiology (only supporting the use of morphine for palliative care in end-stage heart failure) (25) are likely to stand for a long while. In the end, it would have been nice for us to find that morphine, a substance used by humans to feel better for a very long time, when used in precise doses and well-defined scenarios, provided improvement in outcomes beyond symptom relief. Wine did it (along with other components of Mediterranean diet) (26). Unfortunately, it seems that morphine will not.

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Footnote

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