Editorial

Harmful impact of morphine use in acute heart failure

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Acute heart failure, frequently observed in the emergency department, could be a life-threatening condition. Most intravenous therapies introduced for the treatment of acute heart failure continue to be used despite very limited studies (loop diuretics, nitrates) or studies showing their possible harmful effects (inotrope) (1). Likewise in the case of opiates—they continue to be used for some patients with acute heart failure, especially in those presenting with acute pulmonary edema. The use of opiates in the treatment of heart failure dates back to the 1960s, and opiates were considered one of the most important agents for treatment of heart failure in the 1970s (2,3). The most reasonable argument for use of morphine in treating acute heart failure is that it possesses some vasodilatory properties, which have been reported in several studies performed between the 1960s and 1980s (4-6), suggesting that morphine is beneficial in acute heart failure by decreasing venous tone and increasing peripheral venous pooling, leading to decreased cardiac filling pressures. Achieving decreased filling pressure is an important goal of therapy in the early phase of acute heart failure; therefore, morphine could prove beneficial in this regard. Additionally, it produces an anxiolytic effect (7), by reducing the activity of the sympathetic nervous system and lowers both preload and afterload. Owing to its anxiolytic and vasodilatory effects, morphine has traditionally been used in patients with acute heart failure for several decades despite lack of sufficient evidence to support its continued use. Intravenous morphine may cause central nervous system suppression and depression of ventilation (8,9), in addition to hypotension, especially in the presence of co-existing volume depletion or when a significantly reduced decrease filling pressure reduces the preload and thereby affects the cardiac output. Therefore, the efficacy of morphine use in patients with heart failure should be considered while remaining mindful of the risk-benefit ratio.

Results obtained from previous retrospective studies evaluating the effects of morphine are controversial. Recently, Ellingsrud *et al.* have reported on a review article through a literature search in MedLine and Embase (7). Convincing evidence regarding the use of opiates in acute heart failure is limited, and Sosnowski *et al.* in their review article published in 2008, mentioned a correlation between the use of morphine and worsening outcomes in patients with acute heart failure, based on several small studies (10). However, in those cases morphine was administered to very serious patients, which is a confounder in this analysis. After 2008, three large retrospective studies have been reported: (I) Peacock *et al.* revealed that the use of morphine for patients with heart failure was an independent predictor of mortality per the Acute Decompensated Heart Failure National Registry (ADHERE), a large multicenter registry that records data from patients hospitalized with acute heart failure (11). This retrospective and largest of the three studies included more than 147,000 patients with typical features of heart failure, and over 20,000 patients (14%) received morphine. After adjusting for confounding factors known to be associated with increased

hospital mortality, including advanced age, renal function, troponin level elevation, hypertension, and heart rate, morphine remained an independent predictor of mortality [odds ratio (OR) 4.84, 95% confidence interval (CI): 4.52–5.18, P<0.001]. Additionally, significant correlations were noted between morphine administration and increased intubation rate, greater number of intensive care unit admissions, and prolonged hospitalization. (II) In a similar but smaller study between 2003 and 2007 reported from the United Kingdom, adjusted analysis showed that opiate treatment was associated with lesser improvement in acidosis. Furthermore, no significant correlation was observed between morphine administration and mortality or improvement in respiratory distress (12). (III) A retrospective study conducted in Israel comprising 2,336 patients showed that morphine administration (n=218, 9.3%) was independently associated with an increased mortality using multivariate analysis (OR 2.0, 95% CI: 1.1–3.5, P=0.02), but not with use of propensity score analysis (OR 1.2, 95% CI: 0.6–2.4, P=0.55) (13). Although some studies have observed no significant difference between morphine administration and clinical outcomes, positive effects associated with use of morphine have not been documented.

We read with interest Dr. Miró's article, "*Morphine use in the emergency department and outcomes of patients with acute heart failure*: *A propensity score-matching analysis based on the EAHFE Registry*" published in April 2017 in the *Chest* (14). This study was designed to address a lack of sufficient knowledge regarding the efficacy and safety pertaining to the use of morphine, which continues to be used in the real-world clinical setting for patients with acute heart failure in the emergency department. Their study included 6,516 patients with a mean age of 81 years and 56% women. Subjects were classified as those with (n=416, 6.4%) and without (n=6,100, 93.6%) intravenous morphine treatment. Using propensity score matching, 275 paired patients constituted each group. They found the use of intravenous morphine in acute heart failure patients in the emergency department is associated with a greater risk of 30-day mortality based on a propensity score matched analysis [20.0% *vs.* 12.7% deaths; hazard ratio (HR): 1.66, 95% CI: 1.09–2.54, P=0.017]. They mentioned mortality was increased at every time point, especially high at the shortest time points (8.0% *vs.* 2.5% deaths, OR: 3.33, 95% CI: 1.40–7.93, P=0.014) of 3 days. In-hospital mortality in the morphine treatment group tended to be higher than in the group without morphine treatment (14.2% *vs.* 9.1%, OR: 1.65, P=0.083), but the length of hospitalization did not differ between the two groups (P=0.79). Current guidelines for heart failure established by the European Society of Cardiology (ESC) do not recommend routine use of opiates for heart failure (class IIb recommendation, level of evidence B). This guideline states, "opiates may only be cautiously considered in patients with severe dyspnea" (15). Guidelines issued in 2009 by the American Heart Association (AHA)/American College of Cardiology (ACC) mention the use of opiates as palliatives at the end of life (16). However, guidelines issued in 2013 do not touch upon opiates (17). Miró's report (14) has expanded our knowledge of the harmful impact of morphine use in acute heart failure, and is supportive of the current international guidelines.

Previous reports evaluating the effect of morphine use in heart failure are obtained from retrospective studies (10-14). Thus, the relationship between its use and high mortality is not proof of a causal relationship. Recently, a multicenter, prospective, open-label, and randomized study, the MIdazolan versus MOrphine in APE trial (MIMO) was designed to address gaps in our knowledge pertaining to efficacy and safety of morphine in patients with acute heart failure (18). 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 include use of mechanical ventilation, cardiopulmonary resuscitation, intensive care unit admission rate, duration of intensive care unit stay, and length of hospitalization. It may not be reasonable to consider the safety and efficacy of morphine treatment in acute heart failure in view of the concerning results noted with its use, based on previous retrospective studies, and benzodiazepines could be evaluated as a viable alternative treatment option. Data from the MIMO trial will add to our knowledge on the adverse effects and/or risks associated with morphine use in patients with acute heart failure in the future.

The prevalence of heart failure among elderly patients has increased over the decades with better management of various cardiac conditions such as coronary artery disease. Based on the contemporary heart failure registry survey, the mean age of patients admitted with a primary diagnosis of heart failure ranges between 70 and 75 years (19). Miró's article (14) reported mean age was 81, therefore their cohort might have represented a super-elderly population. Interestingly, their pre-planned subgroup analyses demonstrated that the increased risk of short-term

mortality differed with respect to age—a higher mortality was associated with morphine use in patients ≤80 years of age, although after morphine administration, advanced age and frailty are factors related to higher mortality. Recently, there is growing evidence that medication effects could differ between younger and elderly patients (20-22). Although mechanisms that explain the difference in effects of morphine between young and elderly patients in Miró's article (14) remain unknown, it is necessary to remain aware that their conclusion should be applied in patients individually in terms of age or frailty.

Despite increasing interest in the field of palliative care for heart failure, limited data are available concerning management including morphine use (23). Recent ESC guidelines support the use of morphine for palliative care in end-stage heart failure (15). This guideline states, "morphine (with an antiemetic when high doses are needed) can be used to reduce breathlessness, pain and anxiety". However, so far, most of our experience with morphine use is based on symptoms in cancer patients, and our knowledge is limited pertaining to its use for symptoms in advanced heart failure in the setting of palliative care. Based on previous reports, opioids have shown inconsistent effects in patients with chronic heart failure (24,25). Double-blinded, placebo-controlled, cross-over pilot studies have demonstrated that oral morphine produced clinically significant improvement in breathlessness in ten patients with advanced heart failure, with few adverse effects and good tolerability of chronic dosing with low doses of morphine (24). However, a recent randomized controlled double-blind cross-over trial demonstrated no benefit over a placebo for relief of breathlessness with short-term low-dose oral opioids for chronic heart failure patients (25). Limitations of these studies include a small sample size, a short treatment period, and not adequate evaluation in terms of the amount and administration route of opioids. Advanced heart failure patients often cannot be administered medication orally in the setting of palliative care, therefore intravenous administration needs to be considered. Despite the concerning results noted with morphine use mentioned in Miró's article (14), its use could be markedly different in those who are administered morphine as boluses as needed, for example in the emergency department, compared to admitted patients who receive a fixed dose of morphine orally or intravenously, suggesting that their results cannot be applied in the setting of palliative care. Though evidence for care of patients with heart failure in the field of palliative care is difficult to establish, this matter requires consideration because of an increasing geriatric population in the near future.

In conclusion, morphine treatment for acute heart failure is disputable and cannot be recommended with an increasing body of evidence opposed to the use of morphine for the initial management of acute heart failure especially in emergency departments.

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Footnote

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

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