

NALOXONE IN ACUTE CORONARY SYNDROMES AND CARIOGENIC SHOCK PATIENTS PRETREATED WITH MORPHINE. A CLINICAL AND ECHOCARDIOGRAPHIC STUDY

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ABSTRACT

Purpose: The use of morphine is common in acute heart failure critically ill patients and although it remains indicated in guidelines however now beginning to be controversial. Naloxone could improve hemodynamic status in cardiogenic shock (CS) patients pretreated with morphine. **Objective:** The objectives were to evaluate whether naloxone administration to patients treated with morphine improves haemodynamic and echocardiographic parameters. **Methods:** Intensive Care Unit of Jaén University Hospital. It is an observational prospective study. Only exists an unique cohort treated with naloxone; there is no control group or randomization. Inclusion criteria were 1) acute myocardial infarction with CS and considered "no alternative receiving invasive mechanical ventilation", 2) previous administration of ≥ 10 mg of morphine chloride. Naloxone was used as "compassionate use". The study period was from January 2012 to September 2013. Hemodynamic and echocardiographic variables including speckle tracking techniques were evaluated before and after naloxone administration. Statistical analysis was performed using the Student t test. **Results:** 37 patients were included. They had a mean age 73.08 ± 3.41 years, 54% being male. Clinical parameters improved after naloxone administration, especially systolic blood pressure [82.33 ± 2.27 to 117.35 ± 1.89] mmHg. The respiratory and heart frequencies decreased and GCS were normalized. LVEF [261 ± 01 - 338 ± 01]; left ventricle strain [-9.503 - (-11.91)], and left ventricle SR [$-.48$ - (-1.12)] increased after naloxone. An increase in right ventricular contractility was also observed. **Conclusion:** This study generates the hypothesis that naloxone could improve clinical and echocardiographic parameters in CS patients treated with morphine. The morphine use should be approached with caution.

KEYWORDS: Echocardiography; cardiogenic shock; speckle tracking; morphine; naloxone.

ABBREVIATIONS

PCI: Percutaneous coronary interventions
 ICU: Intensive Care Unit
 S: Strain
 SR: Strain rate
 LVEF: Left ventricular ejection fraction
 RVEF: Right ventricular ejection fraction
 AMI: Acute myocardial infarction
 STEMI: ST elevated myocardial infarction
 n-STEMI: Non-ST elevated myocardial infarction
 GCS: Glasgow Coma Score
 EDLVV: en diastolic left ventricular volume
 VTI: Velocity time integral
 CS: Cardiogenic Shock

INTRODUCTION

The morphine administration has been recommended classically to ischemic heart disease, and acute or chronic heart failure. This is reflected in the European and U.S.

guidelines.^[1-4] Furthermore, it is considered that morphine could be effective as a cardioprotective agent, especially in ischemic heart disease,^[5] against cardiac surgery.^[6] Morphine is currently considered a first-line drug.^[1-4]

Its indication in chronic heart failure patients, especially with palliative effects, is beyond dispute. However, his administration in critically ill patients may have deleterious effects to increase its complications and mortality. This has been shown with n-STEMI patients^[7] and with acute heart failure.^[8]

This controversy in the management of critically ill patients requires us to ask the effect and indication of morphine, and even ask the reversal of this treatment by naloxone. Many patients who are treated with morphine, it is used for "traditional" way and without even coronary pain. Usually administered by the mere fact of heart failure, in order to reduce anxiety. However, this

treatment option could induce a deleterious effect on myocardial performance in both systolic and diastolic function. This effect could worsen heart failure which can convert a hypertensive pulmonary edema in cardiogenic shock (CS).

That possible conversion to CS could occur by mere hemodynamic phenomena, or even worsening biventricular systolic and diastolic function, and may be changed pulmonary capillary wedge pressure (PCWP), the left ventricle ejection fraction (LVEF), and the right ventricle ejection fraction (RVEF). However, these parameters, which are highly charge dependent, could mask the presence of myocardial dysfunction or even a myocardial stunning. The speckle tracking is a powerful tool, especially the left ventricular longitudinal strain. Strain is considered fewer loads dependent and more representative of cardiac function. However, their use is underutilized in intensive care units (ICU).

The naloxone administration is indicated as a therapeutic option in these guidelines.^[1,2] Naloxone to reverse the morphine effects could improve heart failure in critically ill patients. Their use could induce recovery of myocardial contractility and diastolic dysfunction, could improve hemodynamic and respiratory status and may even prevent intubation avoid CS or prevent its progression. In this case, it would be possible to assess and quantify the improvement in myocardial performance by echocardiography, especially by highly specific parameters such as speckle tracking. Therefore our aim was to evaluate the response of naloxone to patients with CS after a coronary event, undergoing invasive coronary revascularization by percutaneous coronary intervention (PCI), and pretreated with cumulative doses in the last 12 hours by more of 10 mg of morphine chloride. We evaluate that response by cardiac image, especially speckle tracking, and clinical changes suffered immediately.

OBJECTIVES

To assess whether hemodynamic and echocardiographic parameters improved after administration of naloxone. Particularly we studied whether the reversal effect of morphine produces an increase in systemic blood pressure and an increase in the longitudinal biventricular fibers, strain (S), rate (SR), and velocities.

METHODS

Study Design

Prospective cohort subjected to assessment and intervention with prospective inclusion. This is not a clinical trial and therefore there is no randomization, neither a group of untreated patients nor a control group was included. Just another group of healthy people was used to view the values considered normal for our group. The inclusion period was from January 2012 to September 2013.

Study was carried in the Intensive Care Unit of the Hospital Medical Surgical Hospital of Jaén. It belongs to PAIDI CTS 606 Andalusian Health Service Project No. PI-0585-2012, approved by the local ethics committee, and funded by the Consejería of Health of the Government of Andalusia, Government Andalusia, Spain.

Intervention and Clinical Cohort

The study cohort consisted of patients who met the following criteria: 1) Patient with acute myocardial infarction (n-STEMI and STEMI), 2) previous administration of ≥ 10 mg of morphine into the last 12 hours, 3) PCI optimized, 4) CS status, 5) patient considered "no alternative receiving invasive mechanical ventilation", or other invasive measures such as renal replacement, or ventricular assist device (Impella catheter®) or intraortic bombe pump, and 6) and naloxone therapy was accepted. Therefore naloxone was performed as a measure of "compassionate use" for recovering and treatment.

The decision not to intubate was according to the "Andalusian Law 2 /2010 of 8 April of Rights Dignity of Persons in the Process of Death", in which there is agreement of two doctors, and the patient or his legal guardian. CS was defined according to the criteria defined in the shock trial.^[9] Optimized PCI was considered when the patient was subjected to the maximum possible reperfusion.

Patient management was as usual considered by the intensivist responsible for the patient care. All patients were managed with norepinephrine,^[10] invasive blood pressure monitored via the femoral artery, after completion of PCI. The intervention consisted in administration of a single intravenous dose of 0.4 mg naloxone for patient, if the last dose of morphine was administered within the last 12 hours.

It was introduced a control group consisting of 30 healthy patients (50% men), with a median age 70 years, without cardiovascular disease, to set parameters considered normal in our unit.

Clinic parameters

The hemodynamic and echocardiographic parameters evolution was evaluated. Hemodynamic data were taken in the first 30 minutes after administration of naloxone. The following parameters were evaluated: 1) invasive systemic blood pressure, 2) heart rate, 3) respiratory rate, 4) SpO₂ by continuous oximetry, 5) level of consciousness by Glasgow Coma Score (GCS), 6) dose of norepinephrine. In addition an echocardiogram was performed at the patient's bedside in the ICU prior to the administration of naloxone, and another one after 5-10 minutes of being administered naloxone.

Image Acquisition and Processing

A standard transthoracic echocardiogram was performed with Sequoia 512. We use the probes 3VC and 4VC. A digital recording studio was done. Echocardiography was performed using acoustic catches a frame rate greater than 60 Hz, and the analysis was performed off-line in a blinded fashion. We evaluated the usual echocardiographic parameters quantification of biventricular systolic function (LVEF and RVEF), E/E' ratio quantification estimating the PCWP and parameters derived from speckle tracking, such as strain, strain rate, displacement radial, longitudinal and radial velocity, in both ventricles. Of line analysis was performed by Syngo software, U.S. Siemens®. 2013.

Speckle tracking Analysis intra-Observer Variability

Two evaluations in all patients in two different times were performed in a blinded way, to establish their intra-Observer Variability. In each study, each parameter was evaluated at least three times and finally, average values of these parameters were collected. There is only one speckle tracking evaluator in our unit, because we have only one person, with an 8 years' experience, driving this technology, We had the support of a Siemens application engineer.

Statistical Analysis

A study for quantitative variables was performed using Student Test. Univariate analysis was performed using the χ^2 test. The concordance analysis was performed with the Bland and Altman method. Their results are presented using means and standard deviations. Qualitative variables are presented as absolute and relative frequencies. It was regarded a p value <0.05 as statistically significant.

RESULTS

37 patients were included into the study period who met the inclusion criteria. The mean age was 73.08 ± 3.41 . 20 patients were male (54%). 21 patients had a three-vessel disease and 16 a two-vessel (especially left circumflex artery). Only 8 patients had severe lesion of the right coronary artery. Morphine was administered, by indication of the attending physician, at all times during

outpatient medical and/or emergency department (83.73%), during ICP the performance (51.23 %), during the ICU admission (91, 89%), and after the PCI completion (75.76 %); $p < 0.001$. After naloxone administration there was an improvement of hemodynamic and ventilatory parameters in all patients. Table 1. In 18 patients BiPAP was used, and CPAP in 12 patients (with a positive end- expiratory pressure of 5 to 7.5 cmH₂O); 7 patients did not tolerate such therapies. After naloxone administration CPAP was removed in the next 2 days in 9 patients, and in 14 patients treated with BiPAP. Before naloxone administration 17 patients (44.7 %) had a normal GCS , other 17 had 14 points, two patients (5.3 %) had 13 points and only one had 12 points in GCS ($p=0,0043$). Also subsequently naloxone all patients recovered 15 points of GCS. Similarly, all patients initially improved oxygenation with naloxone use. Table 2.

28 patients responded to treatment (75.67 %), the rest died. Intraobserver variability on these patients was good with $r = 0.78$ for strain ($p = 0.0022$), $r = 0.81$ for strain rate ($p = 0.0004$), and $r = 0,562$ for ejection fraction ($p=0.005$). Echocardiography showed improvement of LVEF, RVEF, as well as values of longitudinal velocity, radial, longitudinal strain, longitudinal strain rate, and radial displacement of the two ventricles. Similarly, estimated PCWP showed a clearly decrease. Table 2.

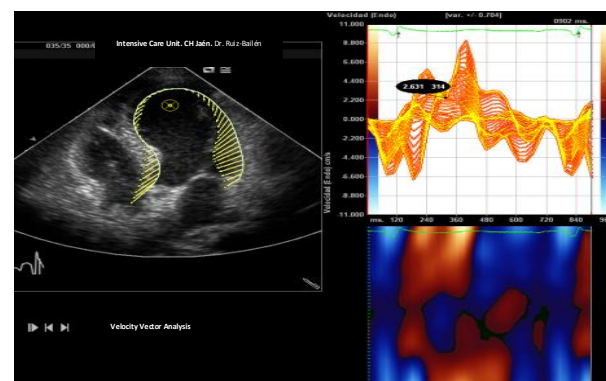


Figure 1: Velocity Vector Analysis. Hybrid Speckle tracking.



Figure 2: Left image are displayed by use of naloxone and right result after administration of naloxone. Segmental changes of left ventricular contractility.

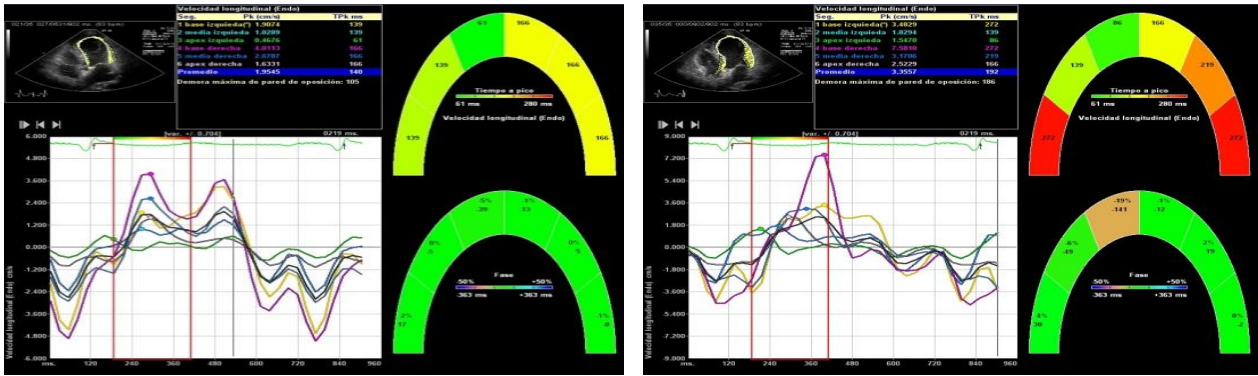


Figure 3: Longitudinal velocity changes in left ventricle. The picture on the right shows an improvement of the longitudinal velocity after naloxone administration.

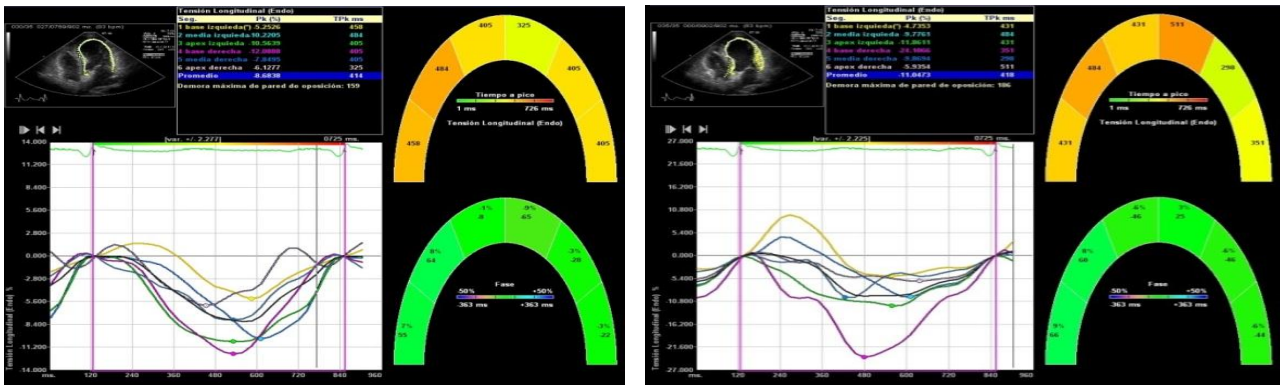


Figure 4: Left images are displayed by use of naloxone and right result after administration of naloxone. Changes in left ventricular strain.

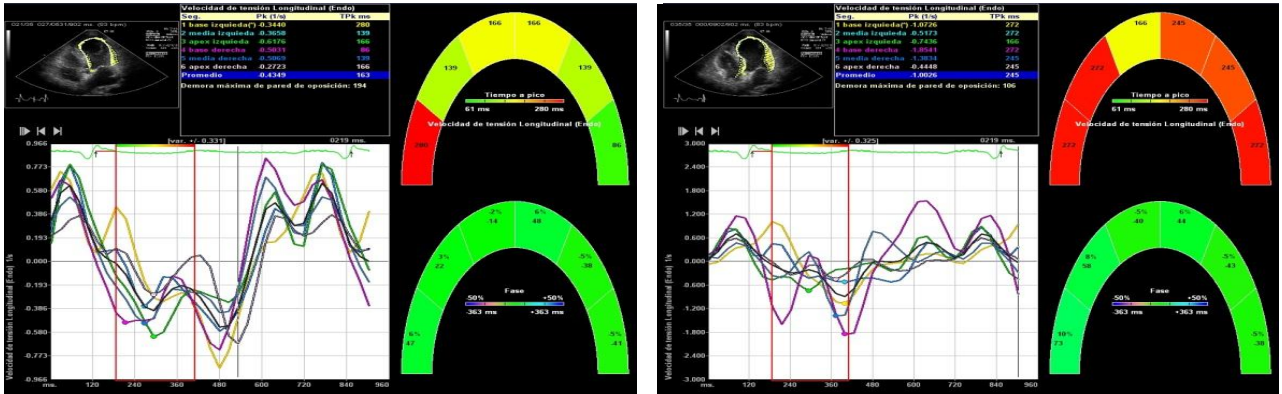


Figure 5: Increasing the strain rate of the right ventricle (right image), after administration of naloxone.

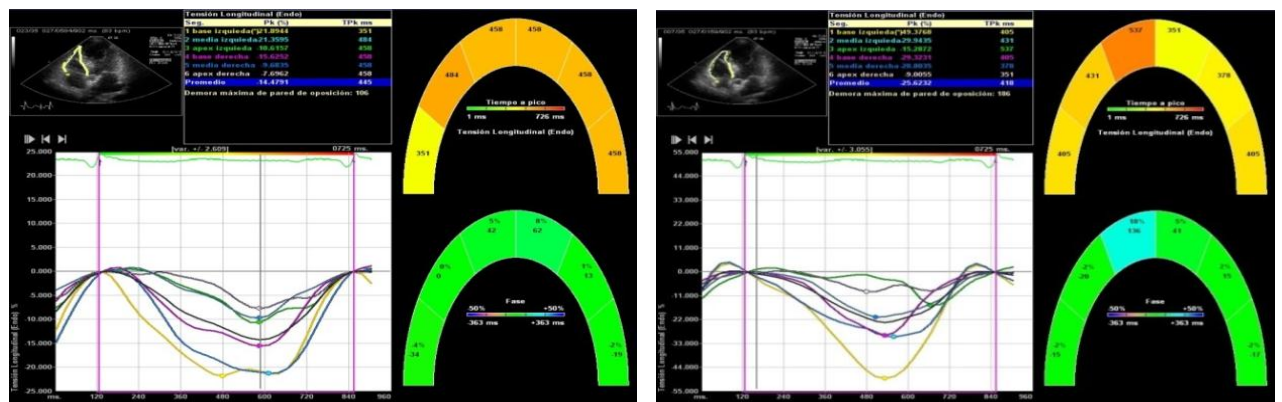


Figure 6: In the right image is observed the increases of the right ventricular strain above the normal level after administration of naloxone.

Table 1: Clinical parameters.

	Before administering naloxone	After administration of Naloxone	P
systolic blood pressure	82,33±2,277	117,35±1,899	0,001
Dyastolic blood pressure	56,37 ± 2,849	78,24 ± 1,339	0,001
Heart frequency	105,72±3,532	85,92d±2,274	0,001
respiratory rate	26,53±1,221	21,3±4,975	0,001
SpO2	92,32±2,248	95,87±,837	0,001
Glasgow Coma Score	14,3514±,71555[12-15]	15,00±0,00	0,001
norepinephrine dose	0.057 □ g /kg/min	0.032 □ g /kg/min	0,001

Table 2: Echocardiographic parameters.

	Control group values	Before administering naloxone	After administration of Naloxone	P
LVEF (%)	0.54±0.072	.261±.0124	.338±.0121	0.001
VTI in TSVI (cm)	21±1.16	9.87± 3.24	12.94 ± 5.27	0.001
RVEF (%)	.56±.094	.431±.221	.68±.185	0.001
E/E' ratio	4.03±.14	19.32±5.93	11.382±.54	0.001
PCWP by Nagueh formula*	3.89±2.34	24.6±3.65	15.11±2.12	0.001
Systolic Filling Fraction pulmonary veins	0.59±0.082	.271±.156	.427±.285	0.001
PCWP by Kuecherer**	11.60±.33	24.47±.91	16.87±2.34	0.001
EDLVV (mL)	98.28±0.78	132.887±1.146	111.98±.386	0.001
Average longitudinal velocity LV (cm/s)	6.581±.721	1.983±0.341	3.474±0.329	0.001
Average radial velocity LV(cm/s)	4.386±.351	1.038±.785	2.673±1.015	0.001
Left ventricular Strain	-17.941±(-.721)	-9.503± (-2.483)	-11.91± (-0.947)	0.001
Left SR	-1.513±(-.178)	-.483± (-0.284)	-1.128± (-0.089)	0.001
Left radial displacement (mm)	5.575±.769	2.035± 1.117	2.791± 0.935	0.001
Average longitudinal velocity RV (cm/s)	6.328±.115	2.530±.995	4.731±0.574	0.001
Average radial velocity RV (cm/s)	4.178±.839	1.992±1.021	6.547±0.8474	0.001
Right Strain	-21.034±(-.11)	-14.739±(-2.221)	-25.991±(-3.078)	0.001
Right SR	-1.551±(-.498)	-0.7465± (-0.533)	-1.579±(-.927)	0.001
Right radial displacement(mm)	3.892±.222	1.862±0.873	2.583±0.832	0.001

*Nagueh et al. JACC 1997;15:1527-1533

PCWP = 1.24(E/E') + 1.9

**Kuecherer H et al. Circulation 1990;82:1127-1139.

DISCUSSION

Morphine is recommended for myocardial ischemia since the early twentieth century. In the decade of the 70s is recognized indications as first-line weapon against heart disease, especially against ischemic heart disease; indication that persists until now. While there are experimental animal studies,^[5] and even in humans^[6] that confer a cardioprotective effect of morphine, there is no clinical evidence to support the use of morphine. In 2005, Maine et al.^[7] (CRUSADE register) in 57039 patients with NSTEMI ACS, where 17003 patients received morphine in the first 24 hours, they found increased mortality, with a odds ratio (OR) of 1.5 (95% CI: 1.26-1.78) by logistic regression, and OR=1.41 (95% CI: 1.26-1.57) in propensity score matching method. An important finding is that this group of patients, who received morphine, had a better therapeutic management, nevertheless their mortality was higher. Moreover, in the

morphine group the rate of stroke and combined end point of death / infarction increased.

In Adhere study 147362 acute heart failure patients were included.^[8] Patients on morphine received more inotropes and vasodilators, were more likely to require mechanical ventilation (15.4% vs 2.8%), had a longer median hospitalization (5.6 vs 4.2 days), more ICU admissions (38.7% vs 14.4%), and had a greater mortality (13.0% vs 2.4%) (All p<0.001). Even after risk adjustment and exclusion of ventilated patients, morphine was an independent predictor of mortality (OR 4.84 (95% CI 4.52 to 5.18), p<0.001).

Recently, a new study^[11] carried the same findings by multivariate analysis, however no causality was observed by propensity analysis. Morphine was used in 9.3%. However, this study probably lacks power for the propensity analysis.

The last three studies were performed on clinical registers and therefore are retrospective cohort studies, so it is difficult to establish causality. All these works are based on records, and therefore subject to their limitations, but are the only existing for establishing the safety of morphine.

Naloxone is a drug used in the guidelines to reverse the effects of too much morphine.^[12,13]

There is pre-clinical evidence, involving several animal species, suggesting that opioid peptides play a role in the pathophysiology of shock. Many case reports have suggested that naloxone might be an effective therapy for humans shock. In a meta-analysis including six studies involving 126 shock patients, naloxone therapy was associated with statistically significant hemodynamic improvement (odds ratio 0.24; 95% confidence interval [95%CI] 0.09-0.68). The mean arterial pressure was significantly higher in the naloxone groups than in the placebo groups (weighted mean difference: +9.33 mmHg; 95%CI 7.07-11.59). No heterogeneity was found for this outcome. The death rate was lower in the naloxone group.^[14]

Our study, despite its limitations, detects in an uncontrolled population that naloxone improves cardiorespiratory status and this results in a clear improvement in systolic and diastolic function. While ejection fraction is a variable parameter and load dependent, the strain, the SR, the radial or longitudinal displacement and radial velocities of the two ventricles rise, like their ejection fractions do. This creates the hypothesis that morphine alters the myocardial performance. Interestingly, the heart rate is lower with naloxone, a fact already detected in the ADHERE study. Despite the possibility of assessing cardiac output by echocardiography, given the extent attributable to LVOT radius mistake, we did not evaluate it. We only quantified the VTI LVOT, and we notice that becomes greater than 11 cm, consistent with the CS output. Before the administration of naloxone, the right ventricle maintains a moderate dysfunction and speckle tracking parameters supported it. RVEF and the parameters obtained by speckle tracking were normalized after administration of naloxone. This effect leads us to consider the existence of a pre-existing myocardial stunning that was normalized after administration of naloxone. Another fact was the low frequency of patients with involvement of the right coronary artery, probably prior choice to give less morphine to these patients.

Another effect associated with morphine is the possible over-sedation, which contributes to hemodynamic and cerebral dysfunction. It is associated with ventilatory impairment, excessive vasodilation, and even may be accompanied with transient myocardial dysfunction which could induce CS.^[15] This study found that these patients had a cognitive impairment, probably due to the association of multiple causes such as hypoperfusion,

excessive sedation, old age, and unquestionably morphine can only worsen this situation.^[16,17]

Our study, despite its limitations, shows that the morphine reversal with naloxone in these patients generates a clear beneficial effect preventing significantly the CS progression both analytically as clinically. Besides, a clear improvement in echocardiographic parameters of contractility and compliance was obtained.

Despite being studies with a low evidence level, they are the only ones that there are, and make us thinking that administration of morphine could be harmful. One possible explanation for this adverse effect of morphine is its damping effect of angina without improving the underlying pathology and the ability to cause hypotension, bradycardia, decreased chronotropism, lusitropism and respiratory depression, which might condition adverse events, and induce a CS.^[11-18] There is no "free drug delivery", because although short term can lead to an improvement or mask a poor clinical condition), and, in the specific case of morphine, this could alter the hemodynamic status which prevents use of proven drugs such as vasodilators. So, maybe we should "break with tradition without scientific evidence" and avoid morphine in heart failure. Especially in the absence of pain, or if there is pain use the lowest dose as possible or use other sedative drugs. We know about the safety of drugs such as benzodiazepines in this context.^[19] In recent years it seems that this idea is settling and morphine is being used less frequently than in the past (7, 8, and 11). This therapeutic approach should be taken in these patients until a clinical trial could be conducted. However conducting this trial would seem complicated because the low cost of the drug. Therapy with intravenous morphine administered an acute patient, could represent a marker of suboptimal care. However, his administration would be a marker of adequate medical attention if it applies to chronic patients with palliative care. Furthermore, our study supports that show that speckle tracking is useful for the management of critically ill patients.^[20-21]

Limitations

Main limitation of this study is its methodology. It is not a controlled study and there is no control group. Only a population of subjects, mainly elderly, with high morbidity and mortality, and a cumulative dose of 10 mg of chloride morphine were evaluated. In this study it is impossible to assume causal effect; however, it does allow us to generate the hypothesis that administration of naloxone could be beneficial in patients with CS. The main advantage of this study is that, in addition to clinical, the analysis performed by echocardiography and speckle tracking gives strength to the hypothesis of the beneficial effect of the reversal of morphine with naloxone. Besides, the possible effect of naloxone reversal would be first visible and measurable by echocardiography.

CONCLUSIONS

This study generates the hypothesis that reversal of morphine by naloxone in the CS could improve clinical and echocardiographic parameters. Probably, morphine should be cautiously administered in these patients.

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