Canadian Journal of Cardiology 34 (2018) 1048–1058

Clinical Research

Development and Testing of a Novel Anaesthesia Induction/Ventilation Protocol for Patients With Cardiogenic Shock Complicating Acute Myocardial Infarction

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ABSTRACT

Background: Cardiogenic shock is a life-threatening condition and patients might require rapid sequence induction (RSI) and mechanical ventilation. In this study, we evaluated a new RSI/mechanical ventilation protocol in patients with acute myocardial infarction complicated by cardiogenic shock.

Methods: We included consecutive adult patients who were transferred to the emergency department. The RSI protocol included 5 phases: preoxygenation, pretreatment, induction/paralysis, intubation, and mechanical ventilation (PPIIM). *A posteriori*, we selected historical patients managed with standard RSI as a control group. The primary outcome was hemodynamic derangement or hypoxemia from enrollment until intensive care unit (ICU) admission.

Results: We studied 31 consecutive patients who were intubated using the PPIIM protocol and 22 historical controls. We found significant differences in systolic (85.32 ± 4.23 vs 71.72 ± 7.98 mm Hg; $P < 0.0001$), diastolic (58.84 ± 5.84 vs 39.05 ± 5.63 mm Hg;

RÉSUMÉ

Contexte : Le choc cardiogénique est une affection potentiellement mortelle pouvant nécessiter une intubation en séquence rapide (ISR) et une ventilation mécanique. Dans le cadre de cette étude, nous avons évalué un nouveau protocole d'ISR/de ventilation mécanique chez des patients ayant subi un infarctus aigu du myocarde compliqué par un choc cardiogénique.

Méthodologie : Nous avons inclus des patients adultes consécutifs transférés dans un service d'urgence. Le protocole d'ISR comprenait 5 phases : préoxygénation, prétraitement, induction/paralysie, intubation et ventilation mécanique (PPIIVM). *A posteriori*, nous avons sélectionné des patients historiques pris en charge à l'aide d'une ISR standard à titre de groupe témoin. Le paramètre d'évaluation principal était le dérangement hémodynamique ou l'hypoxémie entre l'inscription et l'admission à l'unité des soins intensifs (USI).

Résultats : Nous avons étudié 31 patients consécutifs intubés selon le protocole PPIIVM et 22 témoins historiques. Nous avons constaté des

Cardiogenic shock is a life-threatening condition characterized by reduced cardiac output and end-organ hypoperfusion in the presence of adequate intravascular volume.[1] The overall incidence of cardiogenic shock is 1.9%-2.7%, whereas its incidence among patients with acute coronary syndrome ranges from 3% to 15%.[2] Cardiac dysfunction is usually caused by a large acute myocardial infarction (AMI) and compensatory mechanisms are activated to increase sympathetic tone and maintain systemic blood pressure.[3,4] Of note, more than half of the AMI patients present with shock on admission, with the prognosis being poor despite the substantial improvements in cardiovascular therapeutics that have occurred over the past decades.[2,5]

In patients with cardiogenic shock, the left ventricular dysfunction decreases stroke volume and coronary perfusion

Received for publication December 9, 2017. Accepted April 15, 2018.

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See page 1056 for disclosure information.

https://doi.org/10.1016/j.cjca.2018.04.015

$P < 0.0001$), and mean arterial pressure (67.71 ± 4.90 vs 49.90 ± 5.66 mm Hg; $P < 0.0001$), as well as in partial pressure of oxygen (85.80 ± 19.82 vs 164.73 ± 43.07 mm Hg; $P < 0.0001$) between the PPIIM and control group at 5 minutes of automated ventilation. Also, statistically significant differences were observed in diastolic (59.74 ± 4.93 vs 47.86 ± 11.47 mm Hg; $P < 0.0001$) and mean arterial pressure (68.65 ± 4.10 vs 60.23 ± 11.67 mm Hg; $P < 0.0001$), as well as in partial pressure of oxygen (119.84 ± 50.57 vs 179.50 ± 42.17 mm Hg; $P < 0.0001$), and partial pressure of carbon dioxide (39.81 ± 10.60 vs 31.00 ± 9.30 mm Hg; $P = 0.003$) between the 2 groups at ICU admission. Compared with the control group, with PPIIM more patients survived to ICU admission (100% vs 77%) and hospital discharge (71% vs 31.8%), as well as at 90 days (51.6% vs 18.2%), and at 180 days (38.7% vs 13.6%).

Conclusions: The PPIIM protocol allows safe intubation of acute myocardial infarction patients with cardiogenic shock and improves hemodynamic and oxygenation parameters.

différences significatives au niveau de la pression systolique (85,32 ± 4,23 vs 71,72 ± 7,98 mm Hg; $p < 0,0001$), de la pression diastolique (58,84 ± 5,84 vs 39,05 ± 5,63 mm Hg; $p < 0,0001$) et de la pression artérielle moyenne (67,71 ± 4,90 vs 49,90 ± 5,66 mm Hg; $p < 0,0001$), mais également au niveau de la pression partielle de l'oxygène (85,80 ± 19,82 vs 164,73 ± 43,07 mm Hg; $p < 0,0001$) entre le groupe PPIIVM et le groupe témoin après 5 minutes de ventilation automatique. Des différences statistiquement significatives ont également été observées au niveau de la pression diastolique (59,74 ± 4,93 vs 47,86 ± 11,47 mm Hg; $p < 0,0001$) et de la pression artérielle moyenne (68,65 ± 4,10 vs 60,23 ± 11,67 mm Hg; $p < 0,0001$), ainsi qu'au niveau de la pression partielle d'oxygène (119,84 ± 50,57 vs 179,50 ± 42,17 mm Hg; $p < 0,0001$) et de la pression partielle de dioxyde de carbone (39,81 ± 10,60 vs 31,00 ± 9,30 mm Hg; $p = 0,003$) entre les deux groupes au moment de l'admission à l'USI. Comparativement au groupe témoin, les patients chez qui un protocole PPIIVM a été réalisé ont été plus nombreux à survivre à l'admission à l'USI (100 % vs 77 %) et à recevoir leur congé de l'hôpital (71 % vs 31,8 %). Ils étaient également plus nombreux à être en vie 90 jours (51,6 % vs 18,2 %) et 180 jours (38,7 % vs 13,6 %) après l'intervention.

Conclusions : Le protocole PPIIVM permet d'intuber en toute sécurité les patients ayant subi un infarctus aigu du myocarde qui présentent un choc cardiogénique, tout en améliorant les paramètres hémodynamiques et d'oxygénation.

pressure, while the increased diastolic stiffness and left atrial pressure lead to pulmonary congestion, hypoxia, and worsening ischemia, which is further aggravated by hypotension and its associated inflammatory response.[1] One of the initial goals in the management of these patients is to prevent the consequences of prolonged end-organ hypoperfusion and death. However, some of them might require invasive ventilation because of decreased level of consciousness, severe hypoxemia, etc, and rapid sequence induction (RSI) and mechanical ventilation (MV) might be required. Resuscitation efforts should be commenced without inactivating the compensatory mechanisms, causing further injury, and RSI has to be performed within a short time frame, after which the consequences of prolonged end-organ insult will be deleterious. However, blunted hypertensive responses during RSI might increase afterload and oxygen demand, further aggravating myocardial injury, cardiac output, and coronary perfusion pressure.[1,5]

Until now, very few studies have addressed the ideal RSI/MV mode in these patients. In addition, although emerging evidence highlights the potential deleterious effect of hyperoxia,[6-9] the ideal oxygenation targets remain undefined. As a result, there is insufficient evidence to recommend specific ventilation modes or strategies in this population. In the absence of high-quality data, the American Heart Association suggests that MV modes and settings be adjusted to prevent hypoxemia and hyperoxia, to minimize patient discomfort and ventilator dyssynchrony, and to optimize hemodynamics.[10] In this context, we created an RSI/MV protocol in our institution. Our experience has shown that optimization of oxygenation and RSI using small drug quantities might prevent deterioration and hemodynamic collapse in this fragile population. In this study, we assessed our protocol in a cohort of patients with AMI complicated by cardiogenic shock.

Methods

Study design and setting

This before-and-after cohort study included patients with AMI complicated by cardiogenic shock. The study design complies with the Declaration of Helsinki,[11,12] and ethical approval for this study was provided by the Ethical Committee of the Hospital (number 2856). The study was undertaken in a large tertiary hospital in Attica, Greece, covering an area of 50.4 km^2 with a population of 448,997 residents. In this hospital, patients are transferred to the emergency department (ED) by the National Emergency Medical Service.

Population

We performed a before-and-after cohort study including consecutive adult patients (18 years of age or older) with AMI complicated by cardiogenic shock who were intubated in the ED between September 2014 and September 2016. Cardiogenic shock was confirmed after documentation of AMI, shock, echocardiographic evidence of cardiac dysfunction (AMI-related left ventricular failure [large infarction, small/moderate infarction with preexisting dysfunction and/or extensive ischemia] and/or right ventricular failure [large infarction, small/moderate infarction with preexisting dysfunction and/or extensive ischemia] and/or global ischemia and/or mechanical complications), and exclusion of alternative causes of hypotension. Shock was defined as severe hypotension (systolic arterial pressure < 90 mm Hg or mean arterial pressure [MAP] 30 mm Hg lower than baseline for more than 30 minutes despite adequate fluid resuscitation) within 6 hours of first AMI symptoms, end-organ hypoperfusion (defined as cool extremities, oliguria with urine output of < 30 mL/h, altered mental status, serum lactate > 2.0 mmol/L, and clinical signs of pulmonary congestion), low mixed venous oxygen saturation, low

inferior vena cava collapsibility index, and high central venous pressure.[1,13,14] The patients were required to have all of the criteria to be eligible for the study.

Patients with decreased level of consciousness, severe dyspnea with use of accessory muscles and paradoxical abdominal motion, respiratory rate > 35 breaths per minute, life-threatening hypoxemia (arterial partial pressure of oxygen [PaO_2] < 40 mm Hg or PaO_2/fraction of inspired oxygen [FiO_2] < 200 mm Hg), severe acidosis (pH < 7.25), and/or hypercapnia (arterial partial pressure of carbon dioxide [$PaCO_2$] > 60 mm Hg) were intubated using our RSI/MV protocol. All patients received the standard of care recommended for patients with AMI and cardiogenic shock, whereas the decision to intubate a patient was taken considering the clinical indication (unconsciousness, increased work of breathing, airway protection, hemodynamic or electric instability) and also the risk-benefit ratio. Patients with incomplete data, prehospital intubation attempt, obstructed airway, mechanical or other cause of shock, prehospital vasopressor/inotrope use, dilated cardiomyopathy, allergy to any of the RSI drugs, air transport, and out-of-hospital cardiac arrest were excluded from the study.

Twenty-two historical patients with AMI complicated by cardiogenic shock were *a posteriori* selected as comparative controls. Control patients were included if they were admitted to the ED within 6 hours of first AMI symptoms and had the same (as much as possible) demographic characteristics, organ function/failure, comorbidities, and available data (including RSI and survival rates) to the study group. All of them were intubated in the ED between January 2008 and January 2012 and were managed by experienced anaesthesiologists using an RSI with standard doses of midazolam, propofol or etomidate, and succinylcholine. Although we were not able to collect all of the data or end points, we could extract several hemodynamics and metabolic parameters and were able to compare mortality rates. The methods section only refers to the study group, because we are unable to describe such phases in the historical group.

Rapid sequence intubation and MV protocol

An RSI/MV protocol was developed and approved by a committee including experts in resuscitation. The protocol included 5 phases: preoxygenation, pretreatment, induction/paralysis, intubation, and MV (PPIIM).

The oxygenation technique included the placement of a nasal cannula together with a nonrebreather face mask (NRFM), both at 15 L/min, 5 minutes before induction (preoxygenation phase).[15] Three minutes before induction (pretreatment phase), fentanyl 0.7 μg/kg intravenous (I.V.) was administered over 30 seconds to mitigate the physiologic increase in sympathetic tone associated with direct laryngoscopy and prevent further myocardial injury. After 5 minutes of oxygenation, RSI drugs were administered (induction phase); induction agents included midazolam 0.02 mg/kg I.V., ketamine 0.35 mg/kg I.V., and 1% propofol 0.5 mg/kg slow I.V., whereas neuromuscular blockade was provided by succinylcholine at 0.8 mg/kg I.V. All RSI drugs were prepared in labelled syringes and induction was achieved by administration of a predetermined I.V. bolus dose on the basis of the patient's weight. When paralysis ensued the NRFM was removed and laryngoscopy was performed with the nasal cannula kept in place to facilitate passive (apneic) oxygenation (intubation phase; Fig. 1). Laryngoscopy and intubation proceeded in a standard fashion. We defined each insertion of the laryngoscope blade into a patient's mouth as an intubation attempt, regardless of the outcome of the attempt.

The position of the endotracheal tube was confirmed by auscultation and capnography/capnometry. End-tidal carbon dioxide was measured using a mainstream method (N-LCM option) using Mainstream CO_2 (Datex Ohmeda S/5 Anaesthesia Monitor; Datex-Ohmeda Inc, Madison, WI). The patients were then connected to an automated ventilator (Draeger Oxylog 2000 portable ventilator; Draeger Medical, Luebeck, Germany). Ventilator settings were FiO_2 60%, tidal volume 6 mL/kg, inspiratory:ixpiratory ratio (I:E) = 1:2, plateau pressures < 30 cm H_2O, and no positive end-expiratory pressure. We do not include positive end-expiratory pressure in the initial settings because the type and cause of shock might not be obvious from the medical history, physical examination, or clinical investigations, and several shock types might coexist.[13] Respiratory rate was adjusted according to arterial blood gas analysis to maintain an end-tidal carbon dioxide of 30-35 mm Hg or 3-5 mm Hg lower than the initial $PaCO_2$ in patients with known asthma/chronic obstructive pulmonary disease, to prevent hypocapnia and abrupt hemodynamic changes. The remaining ventilator settings were not changed until intensive care unit (ICU) admission. Midazolam 0.35 mg/kg/h was initiated and an I.V. bolus dose of cisatracurium 0.15 mg/kg was administered when succinylcholine was metabolized. Low dose noradrenalin infusion (1 μg/kg/min) was initiated when necessary and adjusted on the basis of clinical data, history, and baseline hemodynamics to maintain a MAP of 60-70 mm Hg. All patients were transferred to the ICU.

Data collection

Data analysis was on the basis of predefined data points on a prospective data collection form. The authors for the study group were blinded to measurements until the end of the study and all data were analyzed. An independent Data and Safety Monitoring research staff monitored safety, ethical, and scientific aspects of the study, while an independent enrollment research staff was responsible for obtaining data collection from the emergency medical services field medical record, as well as for exclusion of all patients not meeting inclusion criteria for the study group.

The study was divided in 9 distinct time points: ED admission, before preoxygenation, at 2 minutes of preoxygenation, at 1 minute after induction of anaesthesia, before intubation, immediately after intubation, at 1 minute of MV, at 5 minutes of MV, and ICU admission. Hemodynamics were measured invasively from an indwelling catheter placed in the radial or femoral artery immediately after diagnosis of cardiogenic shock, whereas arterial blood gases were collected at each predefined time point and before respiratory rate adjustment. Arterial blood samples were analyzed immediately using an analysis machine (Radiometer ABL800 Flex Blood Gas Analyzer; Radiometer Medical A/S, Brønshøj, Denmark).

Study end points and ethical considerations

The primary outcome was hemodynamic derangement or hypoxemia from enrollment until ICU admission. Secondary outcomes were peri-intubation cardiac arrest, defined as

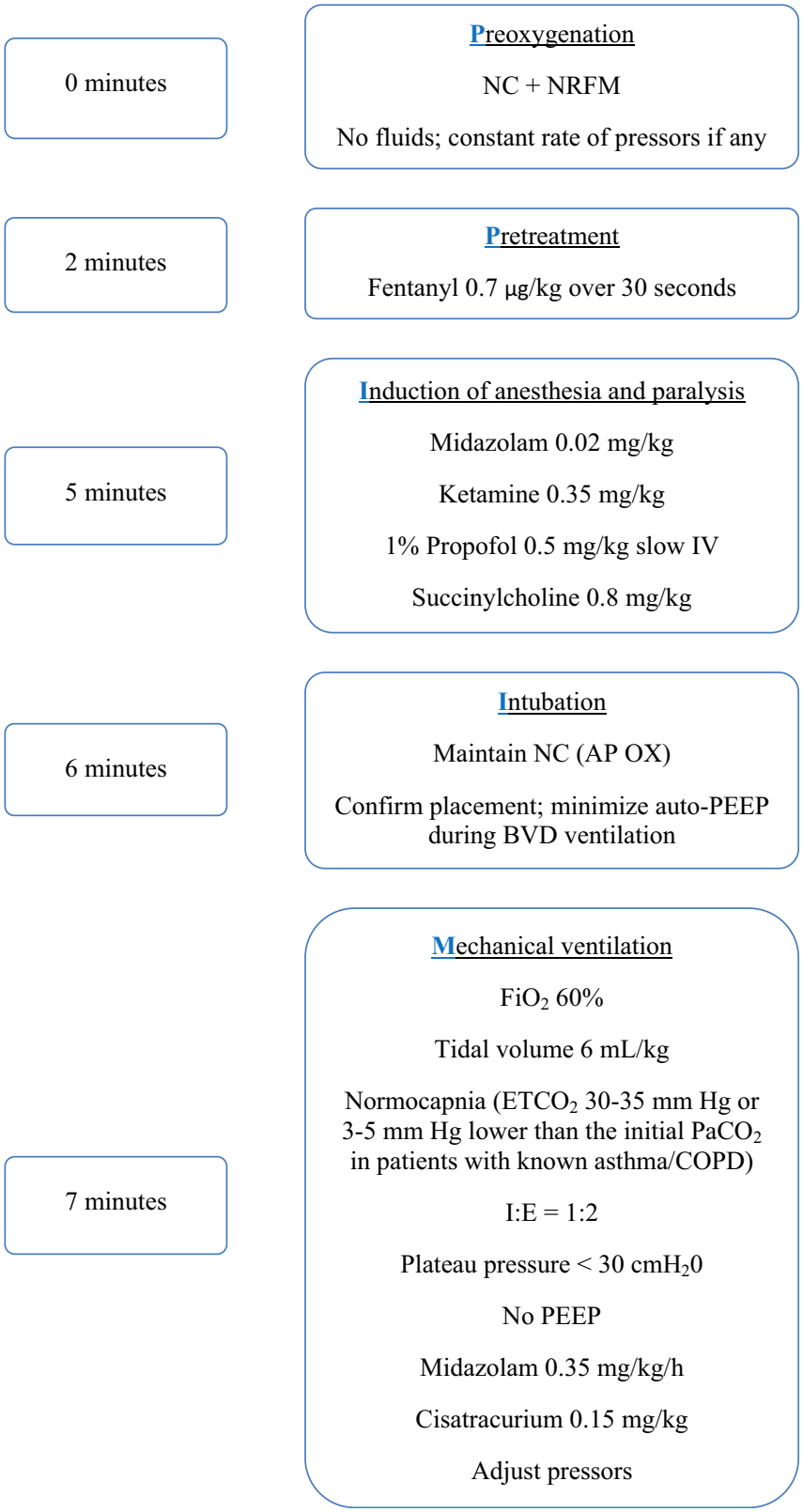

Figure 1. The preoxygenation, pretreatment, induction/paralysis, intubation, and mechanical ventilation (PPIIM) protocol. After the onset of mechanical ventilation, adjust pressors on the basis of clinical data, history, and baseline hemodynamics. AP OX, apneic oxygenation; BVD, bag-valve device; $ETCO_2$, end-tidal carbon dioxide; I:E, inspiratory:expiratory ratio; IV, intravenous; NC, nasal cannula at 15 L/min; NRFM, nonrebreather face mask at 15 L/min; $PaCO_2$, arterial partial pressure of carbon dioxide; PEEP, positive end-expiratory pressure.

Table 1. Patient characteristics

Characteristic	PPIIM group	Historical control group	*P*
N (%)	31 (100)	22 (100)	NA
Male sex, n (%)	20 (64.5)	14 (63.6)	0.392
Mean age ± SD, years	66.55 ± 12.43	67.41 ± 12.60	0.806
Mean BMI ± SD	26.39 ± 4.14	26.68 ± 3.67	0.790
STEMI diagnosis, n (%)	22 (71)	15 (68.2)	0.324
Active smoker, n (%)	22 (71)	12 (54.5)	0.121
Diabetes mellitus, n (%)	10 (32.3)	7 (31.8)	0.148
Hypertension, n (%)	19 (61.3)	14 (63.6)	0.487
Kidney disease, n (%)	10 (32.3)	8 (36.4)	0.815
Previous stroke/TIA, n (%)	10 (32.3)	4 (18.2)	0.180
History of angina, n (%)	17 (54.8)	15 (68.2)	0.860
Heart failure, n (%)	9 (29)	6 (27.3)	0.607
Previous myocardial infarction, n (%)	8 (25.8)	10 (45.5)	0.815
Previous PCI, n (%)	7 (22.6)	9 (40.9)	0.804
Previous CABG, n (%)	8 (25.8)	6 (27.3)	0.791
Asthma/COPD, n (%)	14 (45.2)	6 (27.3)	0.115
Mean Hb ± SD, g/dL	10.00 ± 1.83	10.18 ± 1.71	0.715
Mean hsTnI ± SD, ng/L	2507.42 ± 2933.01	3798.86 ± 2882.04	0.118
Mean Killip score ± SD	2.74 ± 0.73	2.36 ± 0.49	0.039
Mean noradrenaline ± SD, mg	3.11 ± 0.33	3.11 ± 0.34	0.661
Mean time from ED arrival to intubation ± SD, minutes	19.87 ± 7.39	19.14 ± 6.17	0.735
Mean intubation attempts ± SD	1.10 ± 0.31	2.09 ± 1.23	< 0.0001
Mean intubation time ± SD, seconds	3.84 ± 0.90	8.23 ± 4.74	< 0.0001
Stage 1 mean ± SD	65.87 ± 19.45	59.73 ± 17.40	0.242
Peri-intubation cardiac arrest, n (%)	5 (16.1)	9 (40.9)	0.065
Survival to ICU admission, n (%)	31 (100)	17 (77)	0.059
Mean ICU length ± SD, days	7.94 ± 3.63	15.00 ± 15.07	0.016
Survival to hospital discharge, n (%)	22 (71)	7 (31.8)	0.008
Survival at 90 days, n (%)	16 (51.6)	4 (18.2)	0.012
Survival at 180 days, n (%)	12 (38.7)	3 (13.6)	0.035

BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; ED, Emergency Department; Hb, hemoglobin; hsTnI, high-sensitive troponin I; ICU, intensive care unit; NA, nonapplicable; PCI, percutaneous coronary intervention; PPIIM, preoxygenation, pretreatment, induction/paralysis, intubation, and mechanical ventilation; STEMI, ST-elevation myocardial infarction; TIA, transient ischemic attack.

cardiac arrest within 1 hour of induction, ICU length of stay, survival to hospital discharge, and survival at 90 and 180 days. The stage 1 risk score was used for assessing in-hospital mortality risk.[16] This score has been devised on the basis of data from the **Sh**ould We Emergently Revascularize **O**ccluded **C**oronaries for Cardiogenic Sho**k** (SHOCK) trial and includes clinical risk factors as predictors of in-hospital mortality: anoxic brain damage, shock on admission, left ventricular ejection fraction, age, clinical evidence of end-organ hypoperfusion, previous coronary artery bypass grafting surgery, creatinine levels > 1.9 mg/dL, and systolic arterial pressure. Written consent was obtained from patients or next of kin. Surviving patients or their next of kin were also contacted via telephone at 90 and 180 days after hospital discharge. For patients who were unable to be contacted via telephone, attempts were made to contact relatives who might have contact with the patient. Patients who were unable to be contacted after this time were considered lost to follow-up.

Statistical analysis

Study variables were analyzed using the Statistical Package for Social Sciences version 24.0 (IBM Corp; Armonk, NY). The assumption of normal distribution of the collected data was tested using the Kolmogorov–Smirnov test and are presented as mean ± SD. For normally distributed variables the intertime point differences were tested using repeated measures analysis of variance (ANOVA). In case of significant differences, the use of Bonferroni post hoc test allowed us to discover which specific means differed. For the non-normally distributed variables differences were assessed using the Friedman test, the nonparametric alternative to the 1-way ANOVA with repeated measures. The independent samples *t* test and proportions binomial were used to compare hemodynamics and metabolic parameters between the PPIIM and control group patients for continuous and categorical variables, respectively. Significance was accepted at $P < 0.05$.

Results

Study population

All PPIIM patients were admitted to the ED within 6 hours of first AMI symptoms. Of the initial 34 patients with cardiogenic shock, 5 (14.7%) suffered a monitored ventricular fibrillation cardiac arrest. Of them, 2 patients restored spontaneous circulation after immediate defibrillation and were included in the study. We analyzed 31 patients with a mean age (± SD) of 66.55 (± 12.43) years (Supplemental Fig. S1); 20 (64.5%) were male, whereas 22 (71%) and 9 (29%) were diagnosed with ST- and non–ST-segment elevation myocardial infarction, respectively. In addition, we analyzed 22 historical control patients. Mean age (± SD) was 67.4

Table 2. Hemodynamic and metabolic parameters of the PPIIM patients

Parameter	ED admission	Preoxygenation		Postinduction	Intubation		Receiving automated ventilator support		ICU admission
		Previous	2 minutes	1 minute	Previous	Post	1 minute	5 minutes	
Respiratory rate, minute^{-1}	30 ± 8	30 ± 7.2	29 ± 6	29 ± 6	NA	NA	NA	NA	NA
SpO_2, %	87 ± 4.5	84 ± 4.9	87 ± 4.2	88 ± 4.3	87 ± 4.1	87 ± 4	89 ± 4	91 ± 4.1	92 ± 3.1
Heart rate, bpm	110 ± 31.2	110 ± 31	110 ± 31	108 ± 30	109 ± 30	108 ± 29	106 ± 27.5	106 ± 27.5	104 ± 26.2
SAP, mm Hg	80 ± 8	80 ± 7.8	80 ± 7.8	80 ± 7.8	84 ± 4.9	84 ± 5.2	84 ± 4.9	85 ± 4.2	86 ± 3.6
DAP, mm Hg	47 ± 9	49 ± 7.8	49 ± 7.9	48 ± 7.5	53 ± 6.4	53 ± 5.9	54 ± 5.3	59 ± 5.8	60 ± 4.9
MAP, mm Hg	58 ± 8.2	59 ± 7.2	59 ± 7.2	59 ± 6.9	64 ± 5.3	64 ± 4.9	64 ± 4.7	68 ± 4.9	69 ± 4.1
CRT, seconds	6 ± 1.3	6 ± 1.3	6 ± 1.3	6 ± 1.3	6 ± 1.3	6 ± 1.3	6 ± 1.3	5.3 ± 1	5.2 ± 1
CVP, mm Hg	12 ± 1.4	12 ± 1.4	12 ± 1.4	12 ± 1.4	12 ± 1.4	12 ± 1.4	12 ± 1.3	12 ± 1.3	13 ± 1.2
pH	7.20 ± 0.1	7.20 ± 0.1	7.20 ± 0.1	7.20 ± 0.1	7.20 ± 0.1	7.20 ± 0.1	7.20 ± 0.1	7.21 ± 0.1	7.21 ± 0.9
PaO_2, mm Hg	67 ± 12	67 ± 11.6	68 ± 11.5	69 ± 11.6	69 ± 11.4	69 ± 11.4	70 ± 11	86 ± 20	120 ± 50.5
$PaCO_2$, mm Hg	40 ± 14.7	40 ± 14.7	40 ± 14.8	40 ± 14.7	40 ± 14.7	40 ± 14.7	40 ± 13.4	40 ± 11.4	40 ± 10.6
SaO_2, %	88 ± 4.4	88 ± 4.2	89 ± 3.9	90 ± 4.1	89 ± 3.5	89 ± 3.5	91 ± 3.7	91 ± 3.8	94 ± 4.6
Lactate, mmol/L	4.2 ± 1.2	4.2 ± 1.2	4.2 ± 1.2	4.2 ± 1.2	4.2 ± 1.2	4.2 ± 1.2	4.2 ± 1.2	4.2 ± 1.2	4.3 ± 1.2
Base deficit, mmol/L	−5.6 ± 3	−10 ± 4.3	−10 ± 4.3	−10 ± 4.3	−10 ± 4.3	−10 ± 4.3	−9.9 ± 4.2	−9.8 ± 3.8	−9.5 ± 3.4
HCO_3, mmol/L	16 ± 5.2	16 ± 5.2	16 ± 5.2	16 ± 5.2	16 ± 5.2	16 ± 5.2	16 ± 5.2	16 ± 4.9	15 ± 4.6
LVEF, %	30 ± 4.8	30 ± 4.8	30 ± 4.8	30 ± 4.8	30 ± 4.8	32 ± 3.3	30 ± 4.7	30 ± 4.4	30 ± 4.4

bpm, beats per minute; CRT, capillary refill time; CVP, central venous pressure; DAP, diastolic arterial pressure; ED, Emergency Department; ICU, Intensive Care Unit; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; NA, not available; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; PPIIM, preoxygenation, pretreatment, induction/paralysis, intubation, and mechanical ventilation; SaO_2, oxygen saturation of arterial blood; SAP, systolic arterial pressure; SpO_2, peripheral capillary oxygen saturation.

(± 12.6) years and 14 (64%) were male. Of them, 15 (68%) and 7 (32%) were diagnosed with ST- and non−ST-segment elevation myocardial infarction, respectively (Table 1). In both groups, all patients underwent successful primary percutaneous coronary intervention within 12 hours of first symptom onset and 90 minutes after ED admission.

Oxygenation and intubation

The PPIIM protocol resulted in fewer intubation attempts and less time to intubation; all patients were intubated at first attempt, with the mean time (± SD) to intubation being 3.84 (± 0.90) seconds. The oxygenation technique improved initial PaO_2, whereas after the onset of MV, PaO_2 significantly increased until ICU admission. A repeated measures ANOVA with a Greenhouse−Geisser correction and post hoc tests using the Bonferroni correction revealed that mean PaO_2 differed statistically significantly between the study phases ($F_{1.23,37.128} = 28.169$; $P < 0.0001$; Table 2, Supplemental Fig. S2). $PaCO_2$ did not differ statistically significantly between time points ($F_{1.405,42.139} = 0.589$; $P = 0.502$; Table 2, Supplemental Fig. S2). The analysis of arterial oxygen saturation, peripheral capillary oxygen saturation, and respiratory rate is shown in the Supplementary Materials.

In the control group, oxygenation was improved after the onset of MV. Despite the worst oxygenation indices in the PPIIM group at ED admission, we found significant differences in PaO_2 (85.80 ± 19.82 vs 164.73 ± 43.07 mm Hg; $P < 0.0001$) between the PPIIM and control group at 5 minutes of automated ventilation. Also, statistically significant differences were observed in PaO_2 (119.84 ± 50.57 vs 179.50 ± 42.17 mm Hg; $P < 0.0001$) and $PaCO_2$ (39.81 ± 10.60 vs 31.00 ± 9.30 mm Hg; $P = 0.003$) between the 2 groups at ICU admission (Table 3).

Hemodynamics

In the PPIIM group, we found no statistically significant changes in heart rate from ED admission until the onset of MV, whereas statistically significant changes were subsequently observed until ICU admission ($P < 0.0001$; Supplemental Fig. S4). Systolic arterial pressure was maintained constant from ED admission until 1 minute postinduction, after which a statistically significant increase was observed until ICU admission ($F_{1.213,39.404} = 20.818$; $P < 0.0001$; Supplemental Fig. S4). Diastolic arterial pressure was maintained constant from ED admission until 1 minute postinduction, after which a statistically significant increase was observed until ICU admission ($F_{2.588,77.635} = 34.678$; $P < 0.0001$; Supplemental Fig. S5). MAP was maintained constant from ED admission until at 1 minute postinduction, after which a statistically significant increase was observed until ICU admission ($F_{2.136,64.07} = 36.126$; $P < 0.0001$; Supplemental Fig. S5).

In the control group, heart rate increased from ED to ICU admission, but no statistically significant differences were observed between the 2 groups. In addition, systolic arterial pressure was slightly improved, whereas diastolic arterial pressure and MAP decreased after RSI/MV in the control group. We found significant differences in systolic (85.32 ± 4.23 vs 71.72 ± 7.98 mm Hg; $P < 0.0001$), diastolic (58.84 ± 5.84 vs 39.05 ± 5.63 mm Hg; $P < 0.0001$),

Table 3. Hemodynamic and metabolic differences between the PPIIM and control patients

	ED admission			Five minutes receiving automated ventilator support			ICU admission		
	PPIIM	Control group	*P*	PPIIM	Control group	*P*	PPIIM	Control group	*P*
Respiratory rate, minutes^{-1}	30 ± 8	29 ± 5	0.397	NA	NA	–	NA	NA	–
SpO_2, %	86 ± 4.5	89 ± 3.7	0.033	91 ± 4.1	89 ± 2.5	0.075	92 ± 3.1	91 ± 3.2	0.132
Heart rate, bpm	110 ± 31.2	101 ± 22	0.258	106 ± 27.5	114 ± 12.5	0.248	104 ± 26.2	113 ± 14.5	0.147
SAP, mm Hg	80 ± 8	85 ± 6.6	0.033	85 ± 4.2	72 ± 7.9	< 0.0001	86 ± 3.6	85 ± 14.7	0.778
DAP, mm Hg	47 ± 9	47 ± 6.9	0.823	59 ± 5.8	39 ± 5.6	< 0.0001	60 ± 4.9	48 ± 11.4	< 0.0001
MAP, mm Hg	58 ± 8.2	62 ± 12.8	0.116	68 ± 4.9	50 ± 5.6	< 0.0001	69 ± 4.1	60 ± 11.6	< 0.0001
CRT, seconds	6 ± 1.3	4.7 ± 1.3	0.001	NA	NA	–	5.2 ± 1	4.7 ± 1.3	0.098
CVP, mm Hg	12 ± 1.4	12 ± 2.6	0.858	NA	NA	–	13 ± 1.2	13 ± 2.3	0.814
pH	7.20 ± 0.1	7.38 ± 0.8	<0.0001	7.21 ± 0.1	7.30 ± 0.6	< 0.0001	7.21 ± 0.9	7.31 ± 0.1	< 0.0001
PaO_2, mm Hg	67 ± 12	76 ± 11.7	0.009	86 ± 20	165 ± 43	< 0.0001	120 ± 50.5	180 ± 42.1	< 0.0001
$PaCO_2$, mm Hg	40 ± 14.7	40 ± 11.6	0.950	40 ± 11.4	36 ± 11.5	0.178	40 ± 10.6	31 ± 9.3	0.003
Lactate, mmol/L	4.2 ± 1.2	2.9 ± 1.3	0.001	4.2 ± 1.2	2.9 ± 1.3	0.001	4.3 ± 1.2	2.9 ± 1.3	< 0.0001
Base deficit, mmol/L	−5.6 ± 3	−9.3 ± 3.2	0.497	−9.8 ± 3.8	−10.3 ± 3.2	0.656	−9.5 ± 3.4	−10.2 ± 3	0.464

bpm, beats per minute; CRT, capillary refill time; CVP, central venous pressure; DAP, diastolic arterial pressure; ED, Emergency Department; ICU, Intensive Care Unit; MAP, mean arterial pressure; NA, not available; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; PPIIM, preoxygenation, pretreatment, induction/paralysis, intubation, and mechanical ventilation; SAP, systolic arterial pressure; SpO_2, peripheral capillary oxygen saturation.

and MAP (67.71 ± 4.90 vs 49.90 ± 5.66 mm Hg; $P < 0.0001$) between the PPIIM and control group at 5 minutes of automated ventilation. Also, statistically significant differences were observed in diastolic (59.74 ± 4.93 vs 47.86 ± 11.47 mm Hg; $P < 0.0001$) and MAP (68.65 ± 4.10 vs 60.23 ± 11.67 mm Hg; $P < 0.0001$) between the 2 groups at ICU admission. The administered amount of noradrenaline until ICU admission did not differ between the PPIIM and control group (3.11 ± 0.33 vs 3.11 ± 0.34 mg; $P = 0.661$). In addition, statistically significant differences were observed in hemodynamic and metabolic parameters between the PPIIM and control patients at ED admission, after 5 minutes of automated ventilator, and ICU admission (Table 3). The analysis of the remaining parameters of the PPIIM patients is shown in the Supplementary Materials.

Survival

Mean (± SD) stage 1 risk score was 65.87 (± 19.45). In the PPIIM group, survival to ICU admission, survival to hospital discharge, survival at 90 days, and survival at 180 days was 100%, 71%, 51.6%, and 38.7%, respectively. In the historical control group, survival to ICU admission, survival to hospital discharge, survival at 90 days, and survival at 180 days was 77%, 31%, 18%, and 13.6%, respectively.

Discussion

The current management of patients with cardiogenic shock complicating AMI is associated with a high rate of mortality, despite widespread regional implementation of rapid transfer to percutaneous coronary intervention-capable centres.[17] Specifically, endotracheal intubation and MV in these patients is challenging and must be performed under particular pathophysiological disturbances. Our study is the first that evaluates a new RSI/MV protocol in AMI patients with cardiogenic shock. In our cohort, the PPIIM protocol proved safe and effective; it improved oxygenation and hemodynamics compared with historical controls, and was not associated with any procedure-related complication.

In 2015, Weingart et al. described a delayed sequence intubation technique that has some similarities with the PPIIM protocol.[15] In the delayed approach, however, preoxygenation is initiated after administration of ketamine. Also, the administration of the induction agent is temporarily separated from the administration of the muscle relaxant, to allow adequate preparation. In contrast, the PPIIM technique does not separate these agents and allows preparation for a longer time. Considering that the delayed-sequence intubation should proceed to standard RSI when complications arise,[15] the PPIIM might prove an optimal RSI/MV method in all critically ill patients.

The decision to incorporate apneic oxygenation into our protocol was on the basis of extensive literature searching.[15,18-22] Apneic oxygenation is the passive flow of oxygen into the alveoli during apnea, occurring because of the differential rate between alveolar oxygen absorption and carbon dioxide excretion. This produces a mass flow of gas from the upper respiratory tract into the lungs. In the delayed approach of Weingart et al., the patients receive a muscle relaxant at 3 minutes of denitrogenation and then apneic oxygenation is initiated, with intubation following after 45-60

seconds.[15] In our study, the simultaneous application of a standard nasal cannula together with a NRFM, both at 15 L/min, during the preoxygenation phase and the maintenance of the first during intubation provided an oxygen reservoir for use during induction and paralysis.[15,23] This resulted in significant differences in oxygenation at 5 minutes of automated ventilator use and ICU admission compared with the historical control group. Sakles et al. reported that a starting oxygen saturation $> 93\%$ was associated with an almost fivefold increase in first pass success without hypoxemia,[20] whereas Davis et al. reported that patients who had a starting oxygen saturation of $\leq 93\%$ during prehospital RSI universally desaturated during the intubation attempt.[24] In the control group, uncontrolled MV (various tidal volumes, respiratory rate, and/or higher FiO_2) led to hyperoxemia at 5 minutes of automated ventilator use and at ICU admission. However, hyperoxemia has been associated with adverse events.[1,6,8-10] Considering the lower arterial PaO_2 in the PPIIM group before intubation, our protocol significantly improves oxygenation while minimizing adverse events and especially hyperoxia, which induces vasoconstriction and reduces cardiac output.[20,21,25]

Patients with cardiogenic shock are characterized by a fragile cardiovascular physiology, which is maintained by compensatory mechanisms. Consequently, the choice and dose of RSI medications are paramount to preserve or improve hemodynamics.[26] In our study, drug administration started 3 minutes before induction with fentanyl 0.7 μg/kg over 30 seconds, to blunt the sympathetic surge that occurs with intubation. We chose this agent because of its high degree of lipophilicity, lack of histamine release, fast onset, short duration of action, and minimal respiratory depression if administered over 30-60 seconds.[26] In addition, fentanyl enhances cardioprotection via its antiarrhythmic activity, especially in arrhythmias associated with ischemia-reperfusion injury, and by inducing pharmacologic preconditioning of the myocardium.[27] As expected, administration of fentanyl neither aggravated hemodynamics nor hampered the favourable effects of nasal cannula and NRFM on oxygenation.[28]

For the induction and paralysis, we administered midazolam 0.02 mg/kg, ketamine 0.35 mg/kg, 1% propofol 0.5 mg/kg slow I.V., and succinylcholine 0.8 mg/kg. Midazolam was used as the first induction agent at a 10-fold reduced dose than recommended followed by a subanaesthetic dose of ketamine. Ketamine causes brain dissociation, is associated with limited suppression of ventilatory drive, increases pulmonary blood flow and produces airway relaxation, provides analgesia, exerts sympathomimetic effects, and lessens the reuptake of catecholamines.[29] Although ketamine can worsen hypotension and exacerbate myocardial depression in catecholamine-depleted patients, we did not observe such an effect.[26] On the contrary, ketamine increased MAP and prevented exogenous vasopressor administration and their potential adverse effects, therefore improving outcome.[30,31] Of note, the classical notion of cardiogenic shock with decreased cardiac output and increased systemic vascular resistance is currently debated and many patients die with a normalized cardiac output, which suggests other shock types, in the absence of infection.[32,33] In our study, the ketamine-induced sympathetic stimulation modified circulatory shock and combatted the unwanted side effects of the other drugs, enhancing hemodynamic stability.[34,35] The favourable effects of ketamine might not be limited to the early postinduction period, but might be prolonged much after this time point, improving outcome and survival rates. Research has shown that ketamine might precondition the myocardium, enhance recovery of force after hypoxia-reoxygenation, and inhibit tumour necrosis factor-α and interleukin-6 gene expression in macrophages, therefore preventing further myocardial injury via anti-inflammatory effects.[36,37] In the delayed approach, Weingart et al. used a dose of 1-1.5 mg/kg to dissociate patients requiring emergency airway management, which is approximately 3 times as much as ours. In our study, we did not observe any ketamine-related complications, such as hypersalivation or laryngospasm, before succinylcholine administration.[15]

Propofol protects the myocardium against ischemia and reperfusion injury, at least in part because of its antioxidant and free radical-scavenging properties.[27] However, it causes hypotension in 25%-67.5% of patients independent of the presence of cardiovascular disease because of venous and arterial vasodilation, impaired baroreflex mechanism, and myocardial depression.[38] The PPIIM protocol includes 1% propofol at a dose of 0.5 mg/kg slow I.V., which is much lower than currently recommended.[26] Our experience has shown that patients with cardiogenic shock are largely relying on their compensatory mechanisms and propofol might aggravate hemodynamics despite its rapid clearance and short duration of action. Although in one study the choice of RSI induction agents was not related to outcome for ED patients who were subsequently admitted to the ICU,[39] RSI-induced hypotension might increase mortality and morbidity rates.[40] Of note, the PPIIM protocol improved hemodynamics compared with standard RSI, which is very important considering the worse hemodynamic status of the PPIIM patients at ED admission. Our results show that the synergistic action of the PPIIM agents enhanced their favourable actions and diminished their adverse effects, stabilizing and improving hemodynamics in our study.[26]

Despite substantial improvements in the treatment of AMI, the prognosis for patients who deteriorate into cardiogenic shock remains poor.[2,5,41,42] In a recent retrospective analysis, there was an increase in the prevalence and the adjusted odds of mortality in patients with early cardiac arrest/intubation on presentation (odds ratio, 3.1).[43] In another analysis, multivariable adjustment revealed an odds ratio for in-hospital mortality of 3.4 for patients with a cardiac arrest/intubation delay.[44] Also, Zuin et al. investigated the incidence of postintubation hypotension in hemodynamically stable patients with ST-elevation AMI requiring RSI using 1 mg/kg ketamine or 0.3 mg/kg midazolam and 1.5 mg/kg succinylcholine.[45] The authors reported that hypotension was observed in 27.9% of their patients, with administration of midazolam resulting in a significantly lower systolic blood pressure at 5 as well as at 10 minutes after induction compared with ketamine (97.75 ± 8.06 vs 100.81 ± 8.08; $P = 0.029$ and 92.83 ± 7.53 vs 101.58 ± 7.29; $P < 0.0001$, respectively). In addition, a significant higher heart rate frequency was present at each time observation in the midazolam cohort compared with the ketamine ones ($P = 0.001$ and $P < 0.0001$, respectively), whereas no bradycardic responses were observed. Of note, the authors evaluated RSI in stable

AMI patients after primary percutaneous coronary intervention and therefore, our patients were sicker than those in the study by Zuin et al.[45]

Despite the nonsignificant difference in stage 1 risk score, outcomes were markedly different between the PPIIM and control group, which might be because of downstream management. However, the careful selection of the control group ensured that both groups received the same standard therapy after admission to the ICU. Considering that the mean stage 1 risk score in the PPIIM group implies that in-hospital mortality was expected to be $> 60\%$,[16,46] the improved survival in PPIIM is of major importance, especially if we take into account that the mortality from cardiogenic shock complicating AMI has been reported to be 45.4%-81%.[1] Also, the most common cause of death after cardiogenic shock is pump failure, which often occurs within days after the event.[47] Although evidence suggests that supplementary oxygen might be harmful after AMI,[6,7] we may hypothesize that our protocol had a favourable effect on patient outcome and survival rates by improving oxygenation and hemodynamics and preventing further end-organ damage.[48,49] Of note, the PPIIM protocol improved hemodynamics at 5 minutes of automated ventilator use and at ICU admission. Although we did not observe a statistically significant difference in systolic arterial pressure at ICU admission between the PPIIM and control group, the most impressive difference at this time point was the increase in diastolic arterial pressure, which not only drove the improvement in MAP but likely enhanced coronary perfusion in the PPIIM patients. These results might possibly indicate that short-term hyperoxemia until ICU admission might not be harmful, especially if hemodynamic optimization is preceded. Nevertheless, we plan a large prospective, randomized double-blind, multicentre controlled trial to assess the effectiveness of our protocol.

Our study has several limitations. Although we included a small number of patients from a highly selected population, it was an observational pragmatic cohort from the ED in a tertiary centre. Also, our patients were monitored via invasive blood pressure assessment, which minimized the possibility of undetected postintubation hemodynamic changes. To minimize bias, the attending physicians were blinded to measurements until the end of the study and all data were analyzed. Also, an independent enrollment research staff was responsible for obtaining data collection from the emergency medical services field medical record, as well as for exclusion of all patients not meeting inclusion criteria. All of these, together with the study's careful design minimize the effect of other influential factors and enhance the potential generalizability of our findings. Furthermore, the hemodynamic data might have been influenced by the administration of low-dose noradrenaline. However, this is a common practice in mechanically ventilated patients and depriving vasopressors when indicated would be unethical. Nevertheless, the cumulative dose of noradrenaline did not differ between the 2 groups. In addition, the significant improvements in AMI care, cardiogenic shock strategies, and general critical care so far might have contributed to the improved outcomes in our study. Because patients with cardiogenic shock are a difficult population to study, we had to include all consecutive patients who fulfilled the inclusion criteria during the study period. In the control group, we were not able to collect all of the data or end points, but we could extract several hemodynamics and metabolic parameters and were able to compare mortality rates. Also, the selection of the control group ensured that both groups received the appropriate therapy after admission to the ICU.

In conclusion, RSI with the PPIIM protocol allows safe intubation of AMI patients with cardiogenic shock and improves hemodynamic and oxygenation parameters. Our results must be evaluated in a multicentre trial investigating superiority over standard of care.

Funding Sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2018.04.015.