

ORIGINAL ARTICLE

Respiratory outcomes and complications in patients with cardiac arrest according to ventilation strategy: subanalysis of the SYMEVECA study

Alberto Hernández-Tejedor¹, Vanesa González Puebla¹, Jorge Duerto Álvarez², Sandra Ofelia Rosillo Rodríguez³, María Jiménez Lapastora⁴, Sara Casanova Prieto⁵, Aaron Blandino Ortiz⁶, Hans Paul Gaebelt Slocker⁷, Manuel Quintana Díaz³, Emilia Rosas Carvajal⁸

Objective. This analysis evaluates respiratory outcomes and the occurrence of respiratory complications during the first 24 hours after hospital admission, according to the ventilatory strategy used during out-of-hospital cardiopulmonary resuscitation, including a group with a ventilatory mode synchronized with chest compressions.

Method. Pragmatic quasi-experimental study including all patients with out of hospital cardiac arrest with persistence of cardiac arrest 3 minutes after early intubation who were transferred to a hospital. Duration: 3.5 years. Patients were grouped according to ventilation strategy: Chest Compression Synchronized Ventilation (CCSV), Intermittent Positive Pressure Ventilation (IPPV), or bag-valve ventilation. Radiological findings (pneumothorax, signs of barotrauma, and pulmonary infiltrates according to the Modified Chest X-ray Scoring System) and arterial blood gas parameters within the first 24 hours after hospital admission were analyzed.

Results. A total of 278 patients transferred to a hospital were included, and 68 were excluded because no radiological study was performed due to immediate certification of death (22.7% women, mean age 61.9 (SD, 16.5) years, 44.3% with shockable rhythm): 41 in the CCSV group, 65 in the IPPV group, and 104 with bag-valve ventilation. PaO₂/FiO₂ values were, respectively, 247 (SD, 162), 200 (SD, 117), and 202 (SD, 118) mmHg ($P < .05$ between CCSV and the other groups). Pneumothorax or subcutaneous emphysema was found in 2.4% of patients ventilated with CCSV, 10.8% with IPPV, and 6.7% with bag-valve ventilation ($P = .26$). The Modified Chest X-ray Score was, respectively, 4.6 (SD, 3.1), 5.7 (SD, 3.3), and 5.1 (SD, 3.1) ($P = .23$).

Conclusions. CCSV is associated with better PaO₂/FiO₂ at 24 hours vs other ventilation strategies. There was no higher incidence rate of pneumothorax with CCSV, and no significant differences were found in the development of radiological infiltrates.

Keywords: Cardiorespiratory arrest. Mechanical ventilation. Emergency medical services.

Evolución respiratoria y complicaciones en pacientes con parada cardiaca según la estrategia ventilatoria: subanálisis del estudio SYMEVECA

Objetivo. Se analiza la evolución y aparición de complicaciones respiratorias en las primeras 24 horas de ingreso de los pacientes que fueron trasladados a un hospital, en función de la estrategia ventilatoria empleada durante la reanimación cardiopulmonar extrahospitalaria, incluyendo un grupo con un modo ventilatorio sincronizado con las compresiones.

Método. Estudio cuasiexperimental pragmático que incluye todos los pacientes en parada cardiaca extrahospitalaria no traumática con persistencia de la parada cardiaca 3 minutos después de intubación precoz que fueron trasladados a un hospital. Durante un periodo de 3,5 años. Los pacientes se agruparon según la estrategia ventilatoria: ventilación sincronizada con la compresión torácica (CCSV), ventilación con presión positiva intermitente (IPPV) o balón de resucitación. Se analizan datos radiológicos (neumotórax, signos de barotrauma e infiltrados pulmonares según la escala Modified Chest X-ray Scoring System) y parámetros gasométricos arteriales de las primeras 24 horas de ingreso hospitalario.

Resultados. Se incluyeron 278 pacientes trasladados a un hospital y se excluyeron 68 sin estudio radiológico por certificación inmediata de fallecimiento (22,7% mujeres, edad media 61,9 (DE 16,5) años, 44,3% con ritmo desfibrilable): 41 en CCSV, 65 en IPPV y 104 con balón. La PaO₂/FiO₂ fue, respectivamente, 247 (DE 162), 200 (DE 117) y 202 (DE 118) mmHg ($p < 0,05$ entre CCSV y los otros grupos). Se encontró neumotórax o enfisema subcutáneo el 2,4% de los ventilados en CCSV, 10,8% en IPPV y 6,7% con balón ($p = 0,26$). El Modified Chest X-ray Score fue, respectivamente, 4,6 (DE 3,1), 5,7 (DE 3,3) y 5,1 (DE 3,1) ($p = 0,23$).

Conclusiones. CCSV se asocia a mejor PaO₂/FiO₂ a las 24 horas que las otras estrategias. No existe una mayor incidencia de neumotórax con CCSV ni se encuentran diferencias significativas en la aparición de infiltrados radiológicos.

Palabras clave: Parada cardiorrespiratoria. Ventilación mecánica. Servicios médicos de emergencia.

Author Affiliations:

¹SAMUR-Protección Civil, Madrid, Spain.

²Hospital Universitario Clínico San Carlos, Madrid, Spain.

³Hospital Universitario La Paz, Instituto de Investigación IdIPAZ, Madrid, Spain.

⁴Hospital Universitario 12 de Octubre, Madrid, Spain.

⁵Hospital General Universitario Gregorio Marañón, Madrid, Spain.

⁶Hospital Universitario Ramón y Cajal, Madrid, Spain.

⁷Fundación Jiménez Díaz, Madrid, Spain.

⁸Hospital Universitario La Princesa, Madrid, Spain.

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Corresponding Author:

Alberto Hernández-Tejedor. SAMUR-Protección Civil. Madrid.

Email:

hernandeztal@madrid.es

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Introduction

Out-of-hospital treatment of nontraumatic cardiac arrest (OHCA) remains a challenge. Scientific evidence regarding how to ventilate patients in this setting is very limited. In this context, we conducted the SYMEVECA study (SYnchronized MEchanical VEntilation in CARDiac arrest) to compare different ventilatory strategies during cardiopulmonary resuscitation (CPR). The study demonstrated improved ventilation (documented by analytical data) in OHCA patients on mechanical ventilation (chest compression synchronized ventilation –CCSV–, intermittent positive pressure ventilation –IPPV–) vs those on bag-valve ventilation.^{1,2} Similarly, a favorable clinical outcome (survival with CPC 1-2) was achieved in 16% of patients ventilated with CCSV, 12.4% of those ventilated with IPPV, and 9.4% of those ventilated with a bag-valve device in the overall sample, and in 41.9%, 29.8%, and 20.5%, respectively, among patients with shockable rhythm. In binary logistic regression, among all collected variables, those showing the strongest association with CPC 1-2 were initial shockable rhythm [OR 15.46 (95% CI, 6.21-38.49); $P < .001$], age with a cutoff point of 62.5 years [OR 0.14 (95% CI, 0.06-0.34); $P < .001$], and the use of the CCSV mode [OR 1.91 (95% CI, 0.80-4.58), $P = .15$]. CCSV is a ventilatory mode in which ventilations are synchronized with chest compressions by delivering a small tidal volume at the moment of compression.³

Phase 2 of the SYMEVECA study had not been published at the time the available evidence was analyzed for the development of the latest clinical practice guidelines; therefore, only phase 1, comparing IPPV and bag-valve ventilation, could be referenced.⁴ These guidelines provide a weak recommendation regarding the general criteria for ventilating patients during cardiovascular resuscitation (CPR), without suggesting the use of mechanical ventilators over other strategies. One must go back to 2010 to find previous international recommendations mentioning ventilation, in which the use of mechanical ventilators over bag-valve ventilation was suggested with a low level of evidence. The reasons supporting those recommendations were that personnel could focus on other tasks, a constant tidal volume was facilitated, and possible hyperventilation and high peak pressures associated with manual ventilation were avoided, thereby improving venous return.⁵ However, the use of mechanical ventilators has not become widespread in cardiac arrest care.⁶ Along with initial rhythm, metabolic status could be another important prognostic factor in patients with OHCA.^{7,8}

One of the objectives of the SYMEVECA study was to evaluate the respiratory evolution of patients according to the ventilatory strategy used during CPR. This article addresses this aspect, which had not been covered in previous publications, and is especially relevant for CCSV, since insufflations are always performed simultaneously with external chest compressions, generating an increase in airway pressure from both causes at the same time. The duration of insufflation is short

(205 ms), and therefore the probability of this pressure reaching the alveolus is lower; nevertheless, it is important to understand its potential impact on oxygenation as well as on the development of complications.

A study recently published in pigs suggested a higher incidence rate of pneumothorax in animals ventilated with CCSV compared with IPPV, a finding not previously described in earlier studies.⁹ These findings may be due to anatomical differences in this species, but in any case they should be investigated in humans. Moreover, better oxygenation outcomes with CCSV compared with IPPV have also been described in both animal studies and a recent clinical trial with a small number of patients.^{10,11}

The primary endpoint of this study was to analyze respiratory evolution within the first 24 hours of hospital admission and the development of complications among SYMEVECA study patients who were transferred to hospital according to the ventilatory strategy used.

Method

The SYMEVECA study is a pragmatic quasi-experimental clinical study conducted in OHCA patients with 3 allocation groups according to the ventilatory strategy used during CPR (CCSV, IPPV, or bag-valve ventilation), comparing their clinical and analytical outcomes.^{1,2} The study population included all patients older than 18 years with OHCA and persistence of cardiac arrest 3 minutes after early intubation attended by an emergency medical service in a large city from April 2021 through October 2024. Exclusion criteria were patients in whom airway isolation (tracheal intubation) was not achieved early, within the first 8 minutes of care; OHCA occurring during medical assistance; patients achieving return of spontaneous circulation (ROSC) before intubation or within the first 3 minutes thereafter; patients declared dead on arrival or with a decision to limit life-support treatments; and patients ventilated with more than one different method after tracheal intubation.

Despite the lack of former human studies with blood gas analyses according to ventilatory strategy in OHCA, a sample size estimation was performed based on animal results and standard deviations from previous studies conducted by our group.¹²⁻¹⁴ In the absence of robust human data from former studies and considering a combination of arterial and venous samples, the aim was to include at least 100 patients in each group. The investigation was conducted according to practical criteria, following standard field procedures. Groups were created according to clinical decisions made by the responsible team and available resources.

The CCSV group used the following parameters: inspiratory time of 205 ms, initial PEEP of 3 mbar, FiO_2 of 1, and an upper airway pressure limit of 60 mbar. The IPPV group used a tidal volume of 7 mL/kg of estimated ideal body weight, PEEP of 5 mbar, FiO_2 of 1, a respiratory rate of 10-12 breaths per minute, and an up-

per airway pressure limit of 50 mbar. In both cases, the Weinmann® Medumat Standard² ventilator (Hamburg, Germany) was used. The bag-valve group used an Ambu® bag with reservoir and without PEEP valve, at 10-12 breaths per minute and an oxygen flow of 15 L/min.

For the study of respiratory evolution and complications, hospital data from all transferred patients were used. Arterial blood gas parameters closest to 24 hours after admission and chest radiographs at hospital admission and at 24 hours, when available, were analyzed, specifically searching for pneumothorax, other signs of barotrauma, and pulmonary infiltrates according to the Modified Chest X-ray Scoring System. Analysis of these data was performed by personnel not involved in the development of the study, one per center.

Continuous variables are expressed as mean and standard deviation (SD), and categorical variables as their relative frequency as a percentage of included patients (n). Analytical values and radiological findings were considered dependent variables. A bivariable analysis (Student's *t* test for quantitative variables and Pearson's chi-square test for categorical variables, including Bonferroni correction for multiple comparisons) was performed using parametric techniques. Furthermore, we conducted a multivariable analysis with binary logistic regression to estimate the role of different variables in the development of respiratory complications. Given the low number of events, all collected variables that could have an influence were included (Intro method). The study was approved by the Research Ethics Committee of *Hospital Clínico San Carlos* (Madrid, Spain) code (19/560-E). Full waiver of informed consent was requested and granted.

Results

Of the 773 OHCA recorded during the study period (of which 63.9% achieved pulse recovery and 24.3% achieved CPC 1-2), 521 met inclusion criteria and were incorporated into the SYMEVECA study. Of these, 278 were transferred to hospital and constitute the sample for this subanalysis. There was no loss of cases. Women represented 22.7% of patients, mean age was 62 (SD, 16) years, 44.3% had a shockable rhythm, and mean response time was 7.1 (SD, 3.1) minutes. There was a first responder in 72.3% of cases. The flowchart is shown in Figure 1, and the distribution of baseline characteristics by group is presented in Table 1.

A total of 41 patients were declared dead at the time of admission, and another 40 died in the emergency department without hospital radiography (27) or blood gas analysis (13). Patients with radiographic studies were distributed as follows: 41 patients ventilated with CCSV, 65 with IPPV, and 104 with bag-valve ventilation, on whom the present statistical analysis was performed. CPR duration was not significantly different among groups: 25.7 minutes (SD, 13.3) in the CCSV group, 25.4 minutes (SD, 10.8) in the IPPV group, and

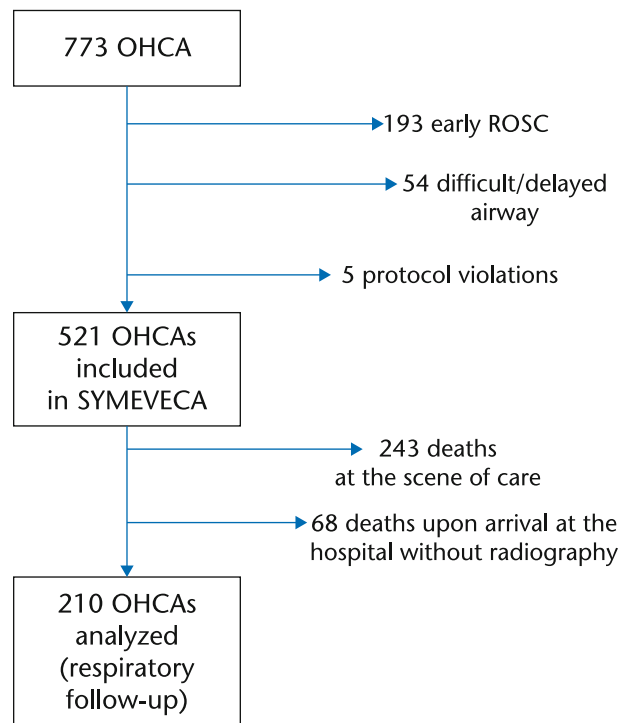


Figure 1. Flowchart of included patients.

OHCA: nontraumatic out-of-hospital cardiac arrest; ROSC: return of spontaneous circulation.

21.7 minutes (SD, 10.3) in the bag-valve group ($P = .13$).

The most relevant results are shown in Table 2. In patients with arterial blood gas analysis, the $\text{PaO}_2/\text{FiO}_2$ was 247 mmHg (SD, 162) in CCSV, 200 mmHg (SD, 117) in IPPV, and 202 mmHg (SD, 118) with bag-valve ventilation ($P < .05$ between CCSV and the other 2). Regarding the development of complications, pneumothorax or subcutaneous emphysema was found in 15 patients: 1 among patients ventilated with CCSV, 7 with IPPV, and 7 with bag-valve ventilation (2.4%, 10.8%, and 6.7%, respectively; $P = .26$). Of the 15 patients with pneumothorax, only 2 survived, both from the bag-valve group.

Table 1. Demographic and baseline characteristics

	CCSV N = 41	IPPV N = 65	Bag-valve ventilation N = 104	P
Age, years [mean (SD)]	58 (13)	61 (15)	60 (18)	.75
Female sex (%)	12.2	20.0	26.9	.07
First responder (%)	84.2	71.0	75.3	.32
Initial rhythm (%)				.53
Ventricular fibrillation	48.8	56.9	42.3	
Pulseless ventricular tachycardia	0.0	1.5	1.0	
Asystole	39.0	33.8	48.5	
Pulseless electrical activity	12.2	7.7	8.2	
Response time, minutes [mean (SD)]	6.9 (2.3)	7.1 (3.0)	6.8 (3.5)	.76
Time to intubation, minutes [mean (SD)]	6.1 (5.2)	6.6 (4.0)	6.3 (7.8)	.90

CCSV: chest compression synchronized ventilation; IPPV: intermittent positive pressure ventilation; SD: standard deviation.

Table 2. Evolution of respiratory data during the first 24 hours of hospital admission

	CCSV N = 41	IPPV N = 65	Bag-valve ventilation N = 104	P
Pneumothorax [n (%)]	1 (2.4)	7 (10.8)	7 (6.7)	.26
Modified Chest X-ray Scoring System [mean (SD)]	4.6 (3.1)	5.7 (3.3)	5.1 (3.1)	.23
PaO₂/FiO₂, mmHg [mean (SD)]	247 (162)	200 (117)	202 (108)	< .05

CCSV: chest compression synchronized ventilation; IPPV: intermittent positive pressure ventilation; SD: standard deviation.
Values in bold denote statistical significance ($P < .05$).

Binary logistic regression (Table 3) shows the role of different variables in the development of pneumothorax or subcutaneous emphysema. Age showed a statistically significant association. Ventilatory strategy was not associated with a statistically significant increase or decrease in complications in the collected sample, nor were sex or the presence of first responders.

The Modified Chest X-ray Score was 4.6 (SD, 3.1), 5.7 (SD, 3.3), and 5.1 (SD, 3.1), respectively ($P = .09$ between CCSV and IPPV, $P = .38$ between CCSV and bag-valve ventilation, $P = .23$ between IPPV and bag-valve ventilation).

Necropsy data were not obtained; therefore, it was not possible to analyze the occurrence of respiratory complications in patients without radiographic studies.

Discussion

The present study demonstrates a comparative advantage of the CCSV ventilatory mode over the other strategies, with better oxygenation and without increasing the number of respiratory complications in the analyzed sample. Together with the possible hemodynamic advantages, not analyzed in this study but reported in the initial pig studies,¹⁵ this could be one of the reasons for the clinical improvement demonstrated in phase 2 of the SYMEVECA study,² in which no statistically significant difference was found in the complete sample but was observed in the subgroup of patients with shockable rhythms.

Regarding oxygenation, these data are consistent with previous animal studies^{10,15,16} and with human studies, both in the in-hospital setting¹¹ and in the out-of-hospital setting with preliminary data presented by the Austrian group (data presented by Brock R, Veigl C, Kornfehl A, Grassmann D, Krammel M, and Schaubelt at the ERC Congress 2024 entitled "CCSV post marketing clinical follow-up trial").

The number of complications does not provide sufficient statistical power. Nevertheless, multivariable analysis showed that age is a risk factor and CPR duration, although not reaching statistical significance, demonstrated a clear trend. There was no clear protective factor; however, the CCSV ventilatory strategy, despite not reaching statistical significance, resulted in a lower inci-

Table 3. Binary logistic regression. Effect of different variables on the risk of developing respiratory complications

	Odds ratio	95% CI	P
Age (per each year)	1.08	1.03-1.14	< .01
CPR duration (per each minute)	1.04	1.00-1.09	.08
Sex (male vs. female)	1.54	0.31-7.77	.60
Presence of first responder	0.81	0.22-2.97	.75
CCSV versus other ventilatory strategies	0.31	0.03-2.72	.29

95% CI: confidence interval of the odds ratio; CPR: cardiopulmonary resuscitation; CCSV: chest compression synchronized ventilation.
Values in bold denote statistical significance ($P < .05$).

dence of respiratory complications in the collected sample. Regarding this aspect, we are unaware of previous human studies with which to compare these findings. Contradictory findings have been described in animals: on one hand, a recent Finnish study described, with some limitations, a higher incidence of pneumothorax in cases ventilated with CCSV compared with IPPV⁹; on the other hand, a study including histological analyses did not detect an increase in inflammatory markers such as tumor necrosis factor alpha.¹⁷

This study has clear clinical implications and confirms the clinical results of the previously published study with intermediate outcomes. Particularly important is ruling out a higher incidence rate of complications with the CCSV mode. All these findings support the use of mechanical ventilators during OHCA care, a practice that is not widespread (nor is it in the hospital setting), but is common and undoubtedly feasible, with the added advantage of avoiding the variability associated with the use of resuscitation bags, as already suggested by the 2010 ERC guidelines.

Additionally, the study has the following strengths: 1) it is the prospective study with the largest number of patients ventilated with the CCSV mode to date; 2) it is a pragmatic study, with intervention groups but without randomization, linked to routine working conditions in the out-of-hospital setting, with limited resources during the initial stages; and 3) the analytical data obtained 24 hours after hospital admission are consistent with those described in the control analysis obtained 15 minutes after intubation during OHCA.

The study also has limitations, the most important being the impossibility of including patients who died without hospital transfer or without radiological studies, which prevents determining the true incidence of respiratory complications in the total study population and in each group, due to the lack of available necropsy data, which may affect the comparative analysis of the groups. This limitation is important for the analysis of complications and intermediate outcomes, but it does not interfere with the primary objective, which is overall survival in each group. On the other hand, patients were not randomized, which may have led to undetected selection bias, although the groups showed no differences in baseline characteristics. Furthermore, the PaO₂/FiO₂ ratio showed wide dispersion, which could affect statistical analysis. Finally, although involving several receiving hospitals, this study was conducted with-

in a single out-of-hospital emergency medical service in a large city, responsible for care in public places (the number of cases at home was minimal), with short response times and high availability of support resources (a second physician and second nurse on site in more than 95% of cases).

In conclusion, CCSV was associated with better blood gas status at 24 hours than the other strategies. Similarly, there was no higher incidence of pneumothorax with CCSV compared with other strategies and, although the data were not statistically significant, they represented a lower percentage of cases among OHCA patients transferred to hospital. No significant differences were found in the development of radiological infiltrates either.

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