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Review

Bronchodilator administration by pressurized inhaler during invasive mechanical ventilation in adults: A scoping review

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ABSTRACT

Objective: To identify the administration characteristics and connection methods of bronchodilators by pressurized inhalers to the ventilatory circuit of patients under invasive mechanical ventilation.
Methods: A scope review was conducted following the PRISMA for Scoping Review, using the PubMed, Embase Elsevier, Cochrane Library, and Lilacs databases without language restrictions, up to July 2023. Eligible sources included reviews and consensuses (based on clinical studies), experimental and observational studies involving adult patients admitted to the intensive care unit and undergoing invasive mechanical ventilation, regardless of the underlying condition, who used bronchodilator drugs contained in pressurized inhalers. Information regarding inhalation technique, pressurized inhalers connection mode to the circuit, and patient care were collected by 2 researchers independently, with discrepancies resolved by a third reviewer. Studies involving bronchodilators combined with other pharmacological classes in the same device, as well as reviews containing preclinical studies, were excluded.
Results: In total, 23 publications were included, comprising 19 clinical trials and 4 non-randomized experimental studies. Salbutamol (albuterol) was the bronchodilator of study in the majority of the articles ($n = 18$), and the spacer device was the most commonly used to connect the pressurized inhaler to the circuit ($n = 15$), followed by an in-line adapter ($n = 3$), and a direct-acting device without chamber ($n = 3$). Concerning the pressurized inhaler placement in the circuit, 18 studies positioned it in the inspiratory limb, and 19 studies synchronized the jet actuation with the start of the inspiratory phase. Agitation of the pressurized inhaler before each actuation, waiting time between actuations, airway suction before administration, and semi-recumbent patient positioning were the most commonly described measures across the studies.
Conclusions: This review provided insights into the aspects related to inhalation technique in mechanically ventilated patients, as well as the most prevalent findings and the existing gaps in knowledge regarding bronchodilator administration in this context. The evidence indicates the need for further research on this subject.

Administración de broncodilatadores mediante inhalador de dosis medida durante la ventilación mecánica invasiva: Una revisión sistemática exploratoria

Palabras clave:
Respiración Artificial
Unidades de Cuidados Intensivos
Adulto
Inhaladores de Dosis Medida
Administración por Inhalación

RESUMEN

Objetivo: Identificar las características de administración y los métodos de conexión de broncodilatadores mediante inhaladores presurizados al circuito ventilatorio de pacientes sometidos a ventilación mecánica invasiva.
Métodos: Revisión sistemática exploratoria siguiendo las directrices PRISMA *for Scoping Review*, utilizando las bases de datos PubMed, Embase Elsevier, Cochrane Library y Lilacs, sin restricciones de idioma, hasta julio de 2023. Las fuentes elegibles incluyeron revisiones y consensos (basados en estudios clínicos), estudios experimentales y observacionales que involucraron a pacientes adultos ingresados en la Unidad de Cuidados Intensivos y sometidos a ventilación mecánica invasiva, independientemente de la condición subyacente, que utilizaron medicamentos broncodilatadores contenidos en inhaladores de dosis medida. La información sobre la técnica de inhalación, el modo de conexión del inhalador de dosis medida al circuito y la atención al paciente se recopiló de forma independiente por dos investigadores, resolviendo las discrepancias por un tercer revisor.

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Se excluyeron los estudios que involucraban broncodilatadores combinados con otras clases farmacológicas en el mismo dispositivo, así como revisiones que contenían estudios preclínicos.
Resultados: En total, se incluyeron 23 publicaciones, constando de 19 ensayos clínicos y 4 estudios experimentales no aleatorizados. Salbutamol (albuterol) fue el broncodilatador estudiado en la mayoría de los artículos (n = 18), y el dispositivo espaciador fue el más utilizado para conectar el inhalador de dosis medida al circuito (n = 15), seguido de un adaptador en línea (n = 3) y un dispositivo sin cámara con acción directa (n = 3). En relación con la posición del inhalador de dosis medida en el circuito, 18 estudios lo ubicaron en el ramo inspiratorio y 19 sincronizaron la activación del chorro con el inicio de la fase inspiratoria. La agitación del inhalador antes de cada activación, el tiempo de espera entre activaciones, la aspiración de las vías respiratorias antes de la administración y el posicionamiento del paciente en forma semireclinada fueron las medidas más frecuentes descritas en los estudios.
Conclusiones: Esta revisión proporcionó información sobre los aspectos relacionados con la técnica de inhalación en pacientes bajo ventilación mecánica, así como los hallazgos más prevalentes y las lagunas existentes en el conocimiento sobre la administración de broncodilatadores en este contexto. La evidencia indica la necesidad de realizar más investigaciones sobre este tema.

Introduction

Inhaled medications are commonly prescribed in intensive care units (ICUs) for patients undergoing invasive mechanical ventilation (MV). Bronchodilators, anti-inflammatories, and antibiotics are some of the drugs administered through various inhalation methods, such as nebulization, dry powder inhalers, and Pressurized Metered Dose Inhalers (pMDIs).[1,2]

For patients undergoing MV who experience increased airway resistance and expiratory flow obstruction, the administration of bronchodilators can significantly reduce pulmonary resistance and improve respiratory mechanics. In this context, the inhalation route is preferable to other routes due to its rapid onset of action and lower incidence of adverse events.[3]

The pMDIs are aerosols that contain a mixture of propellants and active substances. The use of pMDIs is a routine practice in intensive therapy and is considered preferable to nebulization due to its greater user-friendliness.[4,5] Moreover, in infectious respiratory diseases such as COVID-19, the inhalation method using nebulization is contraindicated due to the risk of viral aerosolization in the environment, leading to contamination. The use of pMDIs is considered safer because they can be administrated in a closed circuit without aerosolization into the external environment.[6]

However, aerosol therapy is affected by a series of factors that directly influence the delivery of aerosol to the airways, including ventilatory parameters, ventilator settings, patient-related factors, medication-related factors, and administration technique according to the employed inhalation method.[2,7–10]

A variety of studies on aerosol therapy during mechanical ventilation are available in the literature. In vitro studies were crucial in initially clarifying the characteristics of aerosol therapy using lung models and different simulations in this context. The profile of pulmonary deposition, particle kinetics, and factors influencing aerosol therapy were better understood through preclinical studies. Subsequently, the bronchodilator effect, dose–response relationship, and comparison of different inhalation methods and devices were extrapolated to clinical practice.

Literature reviews often address aerosol therapy without a specific delineation regarding the device or medication used. Furthermore, they lack methodological descriptions and are generally conducted by experts in the field, incorporating both in vitro and clinical studies. Given this gap and the limitations of such reviews, our study proposes to exclusively focus on clinical trials, centering on a single information: the administration technique.

The objective of this study is to identify the administration characteristics and methods of connecting bronchodilators by pressurized inhalers (pMDIs) to the ventilatory circuit of patients undergoing invasive mechanical ventilation.

Methods

This is a scoping review, developed using the method proposed by the Joanna Briggs Institute (JBI)[11] and structured according to the checklist provided by PRISMA for Scoping Review (PRISMA-ScR).[12] The review protocol was registered on the Open Science Framework (https://osf.io/yd2b4/), DOI identifier doi:10.17605/OSF.IO/YD2B4.

To construct the research question, the Population, Concept, and Context (PCC) strategy was employed: P – adults under invasive mechanical ventilation, C – administration of bronchodilators using pressurized inhalers, C – ICU hospitalization. The research question was defined as follows: "How should the pressurized inhaler be connected to the circuit, and what are the recommendations for administering bronchodilators to adult patients undergoing invasive mechanical ventilation?"

To identify potentially relevant documents, the PubMed, Embase Elsevier, Cochrane Library, and Lilacs databases were consulted, using the descriptors "Respiration, artificial" and "Metered Dose Inhalers" connected by the boolean operator "AND," followed by their respective synonyms and keywords contained in titles and abstracts. The main search strategy for PubMed (Table 1) was developed by researchers with the support of an experienced librarian in the field. The search key was translated for each database according to their specificities.

The eligibility criteria were as follows: adult patients admitted to the ICU, undergoing invasive mechanical ventilation (regardless of the underlying disease), and using bronchodilator medication contained in an pMDI. Both experimental and observational studies without language restrictions were included, until July 31, 2023. Literature reviews (of any kind) and expert consensus were also included, as long as they discussed the theme based on clinical study literature. Studies involving bronchodilators combined with another pharmacological class (e.g., corticosteroids) in the same device and reviews containing preclinical studies were excluded.

Table 1
Main search strategy.

Database	Search strategy
PubMed	("Respiration, artificial"[mh] OR "Mechanical Ventilation"[tiab] OR "Artificial respiration"[tiab]) AND ("Metered Dose Inhalers"[mh] OR "Metered Dose Inhaler*"[tiab] OR MDI[tiab] OR "Spacer Inhaler*"[tiab] OR "Spacer-Inhaler*"[tiab] OR Spinhaler*[tiab]) AND (1000/1/1:2023/07/31[pdat])

After searching the databases, the studies were imported into the web application Rayyan IA© 2022,[13] and duplicates were removed. The inclusion and exclusion criteria were applied by reading titles and abstracts independently by 2 researchers, and disagreements were resolved by a third reviewer.

A pilot data extraction form was developed, tested by the researchers, and then data extraction was carried out by 2 independent reviewers. In case of discrepancies in the collected data, a third review of the document was conducted. The reference lists of the included studies were examined for possible inclusion of additional studies.

The collected data included: patient preparation before medication administration, type of device used for pMDI connection, pMDI placement in the circuit, distance between pMDI and endotracheal tube (ETT), ventilator circuit preparation, and medication-related care. The presence of figures or images depicting the medication connection to the circuit was also evaluated. The data were summarized using Excel® software.

Results

A total of 510 publications were identified from the databases. After removing duplicates, 429 had their titles and abstracts read. Sixty-seven publications were selected from the initial analysis, and 21 studies met the inclusion criteria. Two studies were included from the reference lists of the previously selected studies, as shown in Fig. 1, resulting in a total of 23 studies included in this review.

All 23 studies were experimental: 19 randomized controlled trials (82.60%) and 4 non-randomized intervention studies (17.39%). None of the studies tested the inhalation technique as an intervention. Therefore, the data of interest were collected from the provided administration protocol. Albuterol, also known as salbutamol, was the bronchodilator medication in the majority of trials (78.26%). Fourteen studies (60.86%) included only patients with chronic obstructive pulmonary disease (COPD); 8 studies (34.78%) inclueded any ICU-admitted patient with bronchoconstriction and need for bronchodilator therapy; and 1 study (4.34%) included patients with either COPD or asthma.

Regarding patient preparation before medication administration, 8 studies (34.78%) performed airway aspiration if the patient presented secretion in the respiratory tract or in ETT.[15–22] Eleven studies (47.82%) positioned the patient in a semi-recumbent position (upright positioning of the head and torso at an angle between 30 and 45°),[16,18–21,23–28] one study positioned the patient in a dorsal decubitus position,[15] and one study maintained the patient in the original position they were in.[29]

The device used to connect the pMDI to the mechanical ventilation circuit was described in 22 studies (95.65%). The spacer device (aerochamber) was the most commonly employed device ($n = 15$), followed by an in-line adapter ($n = 3$) and direct-acting device without chamber in endotracheal tube ($n = 3$). Additionally, 3 studies compared the use of a spacer device versus another type of connection device,[30–32] one study used an elbow adapter,[33] and one study did not specify the type of device used,[16] as shown in Table 2.

Twenty-one studies specified the pMDI position in the circuit, evaluating whether it was placed in the inspiratory limb, expiratory limb, or directly connected to the ETT. In 16 studies,[17–28,32,34–36] the pMDI was positioned in the inspiratory limb, and in 3 studies (13.04%), the pMDI was directly connected to the ETT.[15,29,33] In Fuller et al.,[30] the pMDI was positioned in the inspiratory limb (when using a spacer device or in-line adapter) and placed directly into the ETT (when using a device without a chamber that acted directly on the tube). In Marik et al.,[31] the pMDI was positioned in the inspiratory limb (when using a spacer device) and directly connected to the ETT (when using an in-line adapter).

The distance, in centimeters (cm), between the pMDI and the start of the ETT was evaluated, with 12 studies not specifying this measurement (52.17%). Three studies connected the pMDI directly to the ETT,[15,29,33] 1 study positioned it at a distance of 10 cm[22], and 5 studies positioned it at a distance of 15 cm.[18–21,34] In Fuller et al.,[30] the pMDI was positioned directly into the ETT (when using direct-acting device without chamber) and positioned at a distance of 22 cm from the ETT (when using a spacer device or in-line adapter). In Marik et al.,[31] it was positioned directly into the ETT (when using an in-line adapter), but the distance was not specified when using a spacer device.

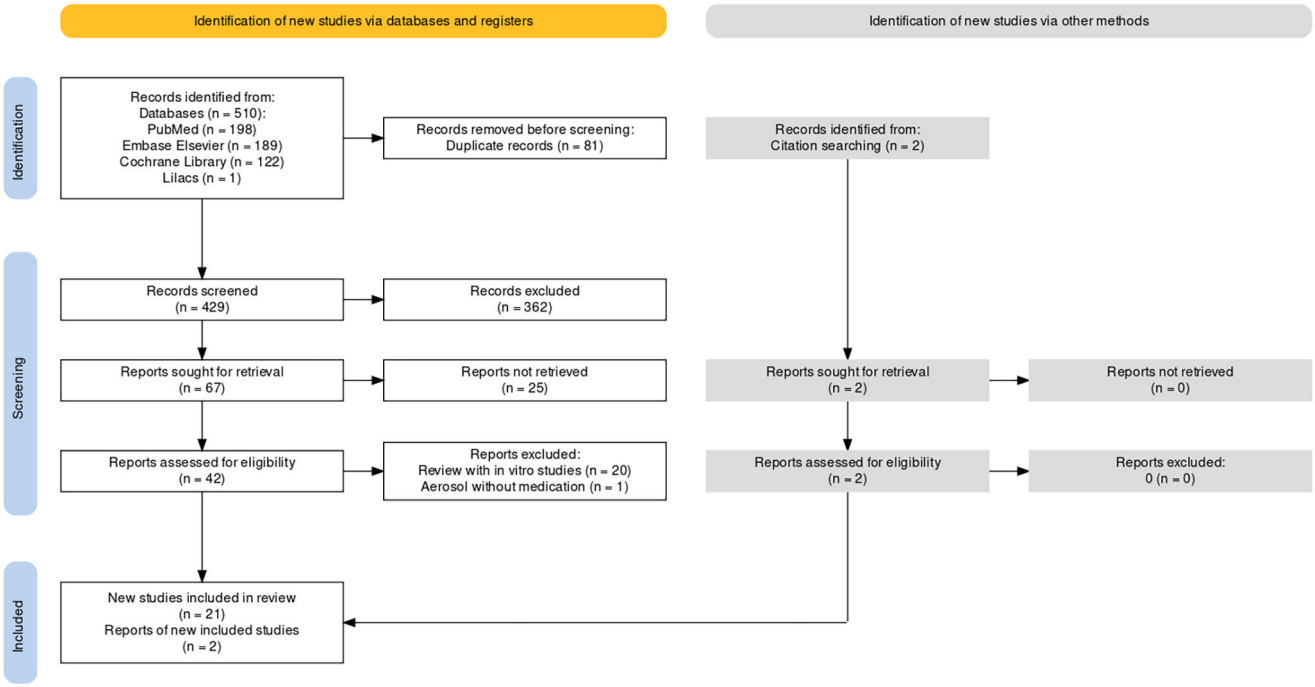

Fig. 1. Flow diagram of the study selection process according to the PRISMA flow diagram.[14]

Table 2
Characteristics of included studies.

First author, year	Methodological design	Medicine	Patients	N	Device
Wegener, 1987[29]	RCT	Ipratropium	CPOD	20	Direct-acting device without chamber
Fernandez, 1990[15]	NRSI	Albuterol, Ipratropium	CPOD	20	Direct-acting device without chamber
Fuller, 1990[34]	RCT	Fenoterol	AO	21	Aerochamber
Gay, 1991[16]	RCT	Albuterol	AO	18	Not specified
Manthous, 1993[33]	RCT	Albuterol	AO	10	Elbow adapter
Fuller, 1994[30]	RCT	Fenoterol	AO	48	In-line adapter vs aerochamber *vs* direct-acting device without chamber
Manthous, 1995[17]	NRSI	Albuterol	AO	10	Aerochamber
Dhand, 1995[18]	NRSI	Albuterol	CPOD	7	Aerochamber
Dhand, 1996[19]	NRSI	Albuterol	CPOD	19	Aerochamber
Duarte, 1996[20]	RCT	Albuterol	AO	20	Aerochamber
Mouloudi, 1998[24]	RCT	Albuterol	CPOD	12	Aerochamber
Mouloudi, 1999[25]	RCT	Albuterol	CPOD	9	Aerochamber
Marik, 1999[31]	RCT	Albuterol	AO	30	In-line adapter *vs* Aerochamber
Guerin, 1999[21]	RCT	Fenoterol-Ipratropium (associate)	CPOD	18	In-line adapter
Mouloudi, 2000[26]	RCT	Albuterol	CPOD	18	Aerochamber
Duarte, 2000[22]	RCT	Albuterol	CPOD	13	Aerochamber
Mouloudi, 2001[27]	RCT	Albuterol	CPOD	10	Aerochamber
Malliotakis, 2007[28]	RCT	Albuterol	CPOD	10	Aerochamber
Malliotakis, 2008[23]	RCT	Albuterol	CPOD	10	Aerochamber
Gowan, 2016[37]	RCT	Albuterol	AO	353	Aerochamber
ElHansy, 2017[35]	RCT	Albuterol	CPOD	60	Aerochamber
Moustafa, 2017[36]	RCT	Albuterol	Asthma or CPOD	36	Aerochamber
Seif, 2021[32]	RCT	Albuterol	CPOD	24	Aerochamber *vs* T-piece
Total: 23 studies				796	

Randomized Clinical Trial (RCT), Non-randomized studies of interventions (NRSI), Chronic Obstructive Pulmonary Disease (COPD), Airway obstruction/bronchoconstriction regardless of underlying disease (AO), Sample size (N), Versus (vs).

About the preparation of the mechanical ventilation circuit, 10 studies (43.47%) positioned the pMDI before the Y-piece of the ventilator; one study positioned it after the Y-piece[29]; one study positioned the Y-piece directly on the ETT, and the pMDI was 10 cm away from the Y-piece[17]; and one study positioned the pMDI along with the Y-piece.[37] Additionally, 2 studies removed or disconnected the Heat and Moisture Exchangers (HME) filter,[23,35] and 1 study kept the filter in place.[32] In the studies by Dhand et al., water condensation drainage was performed if present in the circuit.[18,19]

About medication-related care, 16 studies (69.56%) performed vigorous shaking of the pMDI before each puff, 1 study shook the pMDI every 10 breaths and also when the puff did not come out properly,[17] and 2 studies vigorously shook only at the beginning of the technique without repetition between puffs.[18,31] Nineteen studies triggered the puffs immediately at the start of the inspiratory phase, and 4 studies did not specify how the synchronization of puffs occurred.[15–17,21]

The time between aerosol puff shots was assessed in 17 studies (73.91%). In 8 studies (34.78%), a wait time of 30 s (seconds) or more was observed between puffs[16,20–22,30,31,34,36]; in 7 studies (30.43%), a wait time between 20 and 30 s between puffs was noted.[19,23–28] In Seif et al.,[32] there were 15 s between puffs, and in Dhand et al.,[18] the interval was 20 s.

Three studies performed an end inspiratory pause at the final of each dose: in Fernandez et al.'s study,[15] an end inspiratory pause of 10 s was conducted; in Guerin et al.'s study,[21] the pause was 4 s; and in Mouloudi et al.'s study,[24] it was 5 s.

In 6 studies (26.08%), a figure or image illustrating the type of device used to connect the pMDI (spacer device, adapter, etc.) and the position of the pMDI in the circuit was identified.[15,25,29,30,32,34] Only one study included a figure illustrating the pMDI position in the circuit.[35] A summary of the most prevalent results is shown in Table 3.

Discussion

Our review is the first to be conducted with the aim of mapping information exclusively related to bronchodilator administration by pMDI for mechanically ventilated patients. A wide range of techniques and

Table 3
Most prevalent results in included studies.

Variables of interest	Measure	Number of cited articles
Device	Aerochamber	18
Position of pMDI in the circuit	Inspiratory limb	18
Distance between pMDI and ETT	15 cm of distance	5
	Directly connected to the ETT	5
Time interval between puffs	≥30 s	8
Patient care	Airway suctioning	8
	Semi-recumbent position	11
Circuit care	pMDI before the Y-piece	10
pMDI care	Shaking before each puff	16
	Synchronization between puff and the start of inhalation	19

Pressurized Metered dose inhaler (pMDI); endotracheal tube (ETT); connector used as an intermediary in dual-limb respiratory circuits with inspiratory limb and expiratory limb (Y-piece); greater than (≥).

connection methods were identified across the studies, highlighting some existing gaps that still remain.

The delivery of aerosolized medications to the lower airways depends on numerous factors related to the medication formulation, the aerosol-generating device, and the administration technique employed.[4] Particularly in mechanical ventilation, in addition to the factors mentioned, aerosol delivery is influenced by the patient's clinical condition and the ventilator settings, considering the complex circuitry for delivering oxygen to the lower respiratory tract.[2,4,5,8,38,39]

Airway suctioning was a measure adopted in 8 studies and is related to patient care before medication administration. The purpose of respiratory tract suctioning is to remove bronchial secretions generated during the course of mechanical ventilation.[40] The presence of secretions can lead to increased airway resistance and subsequent patient–ventilator asynchrony. Therefore, prior suctioning can improve aerosol delivery. Regarding patient positioning, the semi-recumbent position was adopted in 47.82% of the studies. Although the bronchodilator effect was significant, there are not studies comparing the difference in aerosol delivery while adopting different reclining positions for mechanically ventilated patients.

The pMDI is a device containing a pressurized mixture with propellants, surfactants, preservatives, flavorings, and an active substance.[41] The pMDIs have standard actuators designed for use in an intact airway and are not specifically designed for use during MV. As a result, commercial adapters are used to connect the pMDI to the circuit.[42] In our review, the majority of the studies used a spacer device as the connecting device. A spacer device, also known as a chamber, is typically cylindrical in shape, with the goal of reducing the speed of the aerosol jet. This allows the propellant to evaporate and the particle size to stabilize, minimizing medication deposition on circuit walls and enhancing aerosol delivery to the lower airways.[4,5] Studies demonstrate that using a spacer device in a ventilation circuit results in 4–6 times more aerosol delivery compared to other adapters like elbow adapters or in-line adapters.[4,5,8]

Two studies included in our review compared the difference between using a spacer device and other devices. In Fuller et al., the delivery of radiolabeled fenoterol was compared using 4 different devices: a large-volume spacer device, a small-volume spacer device, an in-line adapter, and a device with direct action on the ETT. The study demonstrated that aerosol delivery was significantly higher when administered with a spacer device (regardless of volume) compared to the in-line adapter or direct-acting device ($p = .004$).[30] Marik et al. compared 3 aerosol delivery methods (spacer device, in-line adapter, nebulizer) and found that the spacer device showed higher delivery efficiency among the devices ($p = .02$).[31]

The majority of studies specified the pMDI position in the circuit ($n = 21$; 91.30%). The inspiratory limb was the most prevalent choice, followed by direct connection to the ETT. This recommendation aligns with preclinical studies, because the positioning in the expiratory limb would completely alter aerosol delivery, directing it in the opposite direction of the patient's airway.[43] The same applies to the synchronization of puff shots. The most studies specified this recommendation and triggered the puffs immediately at the start of the inspiratory phase ($n = 19$; 82.60%), which is a crucial measure to ensure aerosol is directed to the patient's airway.

The position of the pMDI in relation to the Y-piece varied among the studies, but among those that specified it, the majority positioned the pMDI before the Y-piece. Disagreement also occurred when analyzing the distance between the pMDI and the ETT. How the circuit can be visualized from 2 directions (patient–ventilator or ventilator–patient) and contains different connectors and specificities, including variations among commercial brands and institutional availability, the presence of images, figures, or representative schematics becomes essential to comprehend the arrangement of items and medication in — the circuit. The majority of studies ($n = 16$; 69.56%) did not include images or figures demonstrating the bronchodilator administration protocol.

The time interval between puff shots varied among the studies, but waiting for 30 s or more was the prevalent time interval between puffs. According to preclinical studies,[43–45] consecutive puff shots without pauses negatively impact aerosol delivery. If all puffs are released simultaneously, synchronization will be affected, and medication particles may be directed away from the patient's airway.[46]

The effect of the end inspiratory pause was compared in the study by Mouloudi et al. in a group of 12 COPD patients randomized to receive 6 puffs of albuterol with a 5-s pause and without an end pause. Bronchodilation was satisfactory regardless of the application of the end pause ($p > .05$).[24]

In addition to the mentioned factors, the ventilator settings can also influence medication delivery. Tidal volume, airflow rate, circuit humidity, and ventilatory mode are parameters that directly impact the drug's delivery to the lower airways.[42,46] However, our study did not aim to collect data on these parameters.

The absence of certain information, a small number of studies found (considering a 35-year period between the oldest and most recent), and the non-inclusion of studies with bronchodilators associated with other classes of medications are limitations of this review. Additionally, the inhalation technique information was obtained through the administration protocols provided in the trials, and these studies did not evaluate outcomes or results related to the technique or different connections.

The complexity of drug administration in this context and the variety of ventilator settings make it challenging to measure parameters and clinical implications in patients. Despite the existing knowledge gaps, bronchodilators by pMDI are routinely prescribed and administered in clinical practice for mechanically ventilated patients. Our review can help in understanding the key characteristics and precautions to be taken during medication administration, contributing to the optimization of the technique.

The use of bronchodilators by pressurized metered dose inhaler for mechanically ventilated patients requires careful attention to the inhalation technique to ensure effective delivery of the medication to the lower airways. The use of a specific device for pMDI connection to the circuit (preferably a spacer device), positioning of the pMDI in the inspiratory limb, shaking the pMDI, timing between puff shots, and synchronization with the start of the inspiratory phase are factors that should be observed when administering the medication.

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Ethical considerations

As this is a review, our work did not use primary data and is not research involving human subjects.

Responsibility and release of rights

All authors accept the responsibility defined by the International Committee of Medical Journal Editors (available at http://www.icmje.org/).

CRediT authorship contribution statement

Kathleen Asturian: Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Mariana Balhego-Rocha: Writing – review & editing, Methodology, Investigation, Data curation, Conceptualization. **Diogo Pilger:** Validation, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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