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Neuroinflammation, neuronal damage or cognitive impairment associated with mechanical ventilation: A systematic review of evidence from animal studies

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ABSTRACT

Purpose: Long-term cognitive impairment is a complication of critical illness survivors. Beside its lifesaving role, mechanical ventilation has potential complications. The aim of this study is to systematically review the evidence collected in animal studies that correlate mechanical ventilation with neuroinflammation, neuronal damage and cognitive impairment.
Methods: We searched MEDLINE and EMBASE databases for studies published from inception until August 31st, 2020, that enrolled mechanically ventilated animals and reported on neuroinflammation or neuronal damage markers changes or cognitive-behavioural impairment.
Results: Of 5583 studies, 11 met inclusion criteria. Mice, rats, pigs were used. Impact of MV: 4 out of 7 studies reported higher neuroinflammation markers in MV-treated animals and 3 studies reported no differences; 7 out of 8 studies reported a higher neuronal damage and 1 reported no differences; 2 out of 2 studies reported cognitive decline up to 3 days after MV. Higher Tidal volumes are associated with higher changes in brain or serum markers.
Conclusion: Preclinical evidence suggests that MV induces neuroinflammation, neuronal damage and cognitive impairment and these are worsened if sub-optimal MV settings are applied. Future studies, with appropriate methodology, are necessary to evaluate for serum monitoring strategies.
Trial registration number: CRD42019148935.

1. Introduction

Different research approaches have been used to define the causal mechanisms involved in post operative cognitive dysfunction (POCD) and possible therapeutic targets, including preclinical research in molecular, cellular and animal models [1,2]. Mechanical ventilation (MV) is a medical intervention which can be accomplished through invasive or non-invasive approaches. It becomes lifesaving when patient's spontaneous breathing is inadequate to ensure appropriate gas exchange -oxygen (O_2) intake and carbon dioxide (CO_2) removal- necessary for survival [3,4]. Clinical use of MV was first described in the '40, and extensively used since the mid '50 during the poliomyelitis epidemic in north Europe and now allows multiple and tailored settings, including: fraction of inspired O2 (FiO2), tidal volume (Vt), peak inspiratory pressure (PIP), respiratory rate (RR), positive end-expiratory pressure (PEEP), etc. [3-5]. Current indications for MV are: respiratory or circulatory failure, coma and general anesthesia with muscle relaxant [4].

Beside the lifesaving role, MV imposes a "price to pay" due to related potential complications: pulmonary damage due to baro- and biotrauma, cardiovascular dysfunction with reduced cardiac output, renal damage and respiratory muscle weakness [4,6,7]. Growing evidence suggest that MV per se might induce or exacerbate neuroinflammation, neuronal damage and cognitive impairment through different mechanisms: alveolar stretching can promote the release of systemic and cerebral mediators (cytokines, chemokines, immune system activation, etc.) that lead to neuroinflammation, abnormal neuronal signaling, and cerebral beta amyloid deposition. [8-11].

In order to develop a validated animal research model of MV-associated neurologic injury and to better understand the spectrum of additional measures that may confound this association (including hypoxia, hyperoxia, hypercapnia, hemodynamic profile, various aspects of mechanical ventilation such as PEEP, driving pressure, etc.) it is necessary to have a wide perspective on available preclinical literature.

Aim of this systematic review (SR) is to report evidence, from animal studies, on the relationship between MV and neuroinflammation, neuronal damage or cognitive impairment.

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2. Methods

2.1. Search strategy

This SR was accomplished according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) principles and registered in the PROSPERO data base on December, 7th, 2019 (identifier: CRD42019148935) [12,13]. The MEDLINE and EMBASE databases were queried and studies published from inception until August 31st, 2020, were screened. In order to retrieve additional relevant articles, reviews from Cochrane Library and references of related articles were also investigated.

2.2. Study selection and data extraction

The query was limited to full-text papers published in English language in peer reviewed journals. The following keywords were used as search terms: "mechanical ventilation" and "neurocognitive impairment" and/or "neuroinflammation" and/or "neuronal damage" and/or "serum" and/or "plasmatic" and/or "cerebral" and/or "inflammatory cytokines" (see detailed search strategy in Appendix A). Studies included in our SR were: randomized controlled trials (RCTs) and non-randomized controlled trials (NRCT). Any type of mammalian animal study, with no gender restriction, was suitable for the present SR. The studied intervention was "mechanical ventilation" and comparators were non-ventilated animals. Different MV settings were considered as well. This SR is intended to report changes in brain (liquor, brain sections or homogenized tissue) or serum markers that correlate MV to neuroinflammation, neuronal damage or cognitive-behavioural impairment. Neuroinflammation is defined as an increase in related brain or serum markers, microglia activation or reduction in blood-brain barrier (BBB) permeability, as shown in Table 1. Neuronal damage is defined as an increase in related brain or serum markers, neuronal pathological activation, downregulation of neuroprotective factors or prosurvival molecular pathways, histological evaluation, as shown in Table 1. Animal studies designed to evaluate cognitive-behavioural function, as fear conditioning or locomotor activity tests, were also considered suitable for the present SR. Primary outcome of this SR is to evaluate the association between MV and the occurrence of neuroinflammation, neuronal damage or cognitive-behavioural impairment. Exclusion criteria were: human studies, preterm or newborn animals, papers published as abstract or letter (not full length manuscript) or published as congress proceeding or other forms of publication that are not evaluated through a peer-reviewed process. After removing duplicates, two authors have independently screened titles and abstracts to identify studies that met the inclusion criteria and, subsequently, the full text versions of selected articles were assessed. A standard form, according the "Cochrane Public Health Group's Data Extraction and Assessment Template" and adapted to be suitable for our SR, was designed in order to extract data from eligible studies, and included: bibliographic source, inclusion criteria, animals, study design, risk of bias, intervention and comparators, study funding and results [14]. The "gold standard publication checklist to improve the quality of animal studies" and the "SYRCLE's risk of bias tool for animal studies" were used to assess risk of bias and quality of the included studies [15,16]. A 3rd opinion has been requested in case of controversies between the 2 authors.

3. Results

3.1. Study selection

Literature search of listed key words led to retrieve a total of 5583 articles (1097 from PubMed, 4486 from EMBASE) (Fig. 1). After duplicates have been removed and papers screened by titles and abstracts, 21 studies were selected for "full-text" assessment. After the selection process, 11 studies were included in this SR (Table 2) [17-27].

3.2. Study characteristics

Eleven studies were included in this SR: 10 are RCTs and 1 is NRCT. All the studies were accomplished in animals: mice in 5, rats in 3, pigs in 3. In the studies accomplished in mice, wild-type (WT) C57BL/6 strain were investigated in 4 and WT C3H/HeN strain in 1. In all the studies investigating rats "Sprague–Dawley model" were used. In studies run with pigs, "German landrace" type were tested in 1 study, *Sus scrofa domestica* were tested in 1 study and the remaining study provided no details. In 9 of the 11 selected studies the impact of MV has been compared toward non-ventilated controls [17,18,20-25,27]; in 7, various MV settings (i.e. FiO_2, Vt, PIP, RR, PEEP, CPAP, etc.) have been studied [19-21,23-26]; in 5, both non-ventilated controls and various MV settings have been compared [20,21,23-25]. Tested MV protocols varied significantly among different studies: MV duration ranged from 5 min to 8 h; FiO_2 ranged from 0.5% to 1.0%, Vts ranged between 2 and 30 mL/Kg; PIP ranged from 12 to 20 cmH2O; RR varied depending on studies animal type and PEEP ranged between 0 and 7 cmH2O. The brain and serum markers were reported as concentration in mass (pg/mL) or as mRNA expression determined by quantitative real time reverse transcriptase-polymerase chain reaction. The brain tissue sections were prepared for immunofluorescence and transmission electron microscopy; the brain homogenized tissue were prepared for enzyme-linked immunosorbent assay, nuclear protein or mRNA extraction or western blot analysis. The brain samples were extracted from different cerebral areas: hippocampal formation in 6 studies [17,18,21,22,24,26], hindbrain in 1 [18], brainstem in 1 [23], cortex in 1 [26], cerebral tissue in 1 [27]; thalamus, retrosplenial cortex (RS), central amygdala (CeA), hippocampus, paraventricular hypothalamic nuclei (PVN), and supraoptic nucleus (SON) in 2 [20,25]; in 1 study, cerebral microdialysis was used [19]. The reported cognitive-behavioural tests included memory function with fear conditioning tests (expressed as percent of freezing time) and locomotor activity in open field apparatus (expressed as the % of the distance traveled in 5 min in the graph). Duration of follow up

Table 1
Principal brain or serum markers of neuroinflammation or neuronal damage.

Neuroinflammation	b-IFN-γ, b-IL-2, b-IL-4, b-IL-12p70, b-IL-13, b-IL-9, b-IL-33, b-IL-27p28/IL-30, b-IL-15, b-IL-17A/F, b-IP-10, b-IL-1β, b-IL-6, b-IL-5, b-IL-10, b-IL-8, b-TNFα, b-NF-κB, b-KC, b-MCP-1, b-MIP1α, b-MIP-2, b-TLR4, b-E-selectin, b-ICAM-1, b-VCAM-1, b-PECAM-1, b-MPO activity, histological assessment of microglial cells, histological assessment of BBB permeability, assessment of brain number of CD11b-positive cells, assessment of brain number of Iba-1 positive cell, assessment of brain number of anti-GFAP positive cells
Neuronal damage	b-cleaved caspase-3, b-caspase-9, b-cleaved caspase-7, b-LC-3, b-p62, b-HIF1α, b-β-actin, b-PARP1, b-p65, b-cytochrome c, b-PTEN, b-dysbindin-1, b-Th, b-Aβ, b-lactate, b-lactate/pyruvate ratio, b-glucose, s-S-100, s-S-100B, s-neuroflament light and tau, CSF β-amyloid protein/tau ratio, c-Fos immunopositive brain areas, b-TASK1, b-Akt/GSK3b inhibition, ultrastructural changes of synapses, PSD areas, width of synaptic cleft and number of vesicles, histological evaluation of the number of neurons, intraneuronal neurofibrillary tangles

b: brain; BBB: blood brain barrier; CSF: cerebrospinal fluid; GFAP: glial fibrillary acid protein; GSK3b: glycogen synthase kinase-3b; HIF: hypoxia-inducible factor; I-CAM1: intercellular adhesion molecule 1; IFN-γ: interferon γ; IL: interleukin; IP: IFN-γ-induced protein; KC: keratinocyte-derived chemokine; MCP-1: monocyte chemoattractant protein; MIP-2: macrophage inflammatory protein; MPO: myeloperoxidase; NF-κB: nuclear factor κB; PARP-1: cytosolic-cleaved poly ADP-ribose polymerase 1; PECAM-1: platelet endothelial cell adhesion molecule-1; PSD: postsynaptic density; PTEN: phosphatase and tensin homolog; s: serum, TASK1: TWIK-related acid-sensitive potassium channel 1; Th: tyrosine hydroxylase encoding gene; TLR4: Toll-like Receptor 4; TNFα: tumor necrosis factor α; VCAM-1: vascular cell adhesion protein 1.

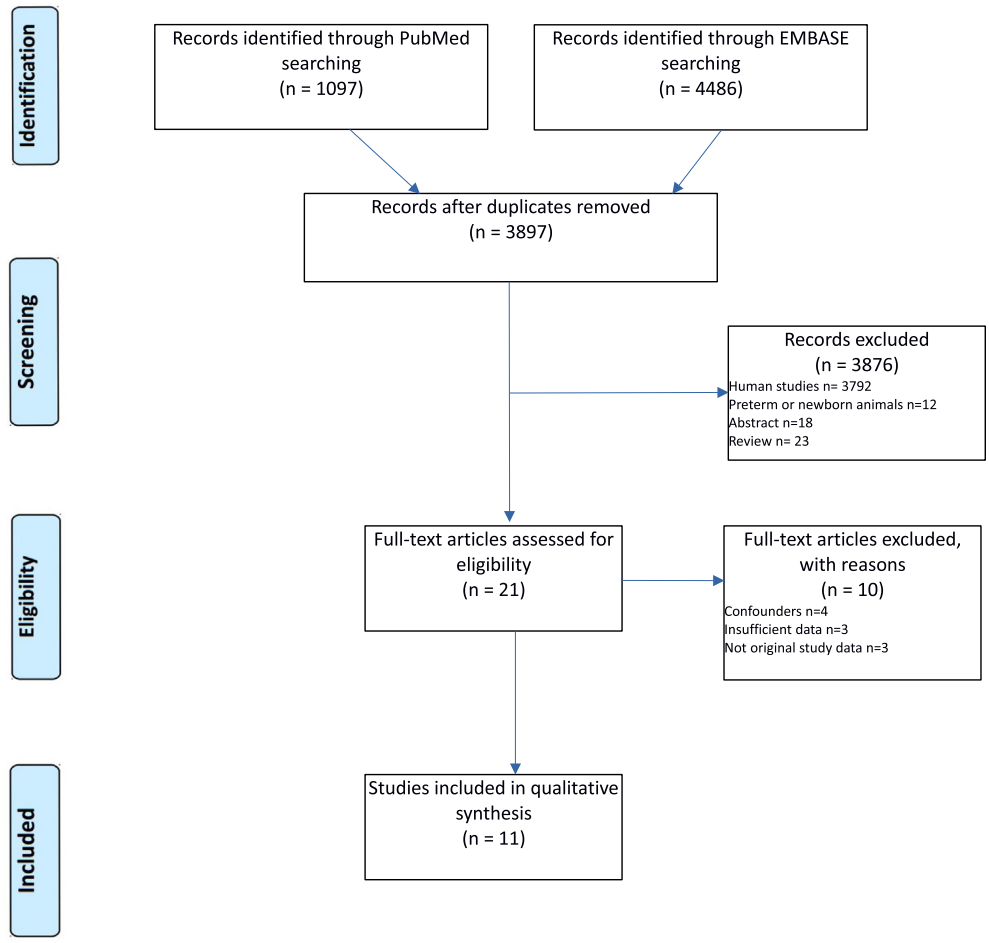

Figure 1. PRISMA 2009 flow diagram. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:https://doi.org/10.1371/journal.pmed1000097.

for neuroinflammation or neuronal damage markers changed depending on the sample and type of marker: for brain markers measurement, the follow-up coincided with animal's euthanasia timing after the end of the experiment; for serum markers measurements, the follow up depended on the experimental protocol (Table 2). Animals were euthanized immediately at the end of the experiment in 7 studies [20,21,23-27], after 6 h in 1 study [18], after 8 h in 1 study [19], after 3 days in 2 studies [17,22]. Duration of follow up in studies that investigated cognitive-behavioural outcome was 6 h, 1 and 3 days in 1 study [17] and 1 and 3 days in the other study [22].

Of the 11 selected studies, 8 reported on neuroinflammation; 8 reported on neuronal damage; and 2 reported on cognitive-behavioural performance (Tables 1, 2).

3.3. Neuroinflammation

Of the 8 studies that investigated neuroinflammation markers release [17,18,21-24,26,27], 7 compared MV-treated animals to non-ventilated controls [17,18,21-24,27] and 4 compared the effect of different Vts (low vs. high vs. control) on severity of MV-induced neuroinflammation [21,23,24,26]. Impact of MV on neuroinflammation led to controversial evidence: of the 7 studies that compared MV-treated animals to non-ventilated controls, 4 reported higher neuroinflammation markers in MV-treated animals than in those non-ventilated [17,18,21,22]; while 3 studies reported no differences between the 2 study groups [23,24,27]. The impact of different Vt settings on neuroinflammation also led to controversial results: 2 studies reported higher neuroinflammation when higher Vts are applied [21,26], 1 reported lower neuroinflammation when higher Vt is applied [23] and 1 reported no differences between groups [24].

3.4. Neuronal damage

Of the 9 studies that investigated neuronal damage markers release [17-25], 8 compared MV-treated animals to non-ventilated controls [17,18,20-23,25], 5 compared the effect of different Vts (low vs. high vs. control) [19-21,23,24] and 1 compared the effect of different PEEPs on severity of MV-induced neuronal damage (low vs. high vs. control) [25]. Available evidence suggest a possible association between MV and neuronal damage: of the 8 studies that compared MV-treated animals to non-ventilated controls, 7 reported an higher neuronal damage in MV-treated animals than in those non-ventilated [17,18,20,22-25]; 1 reported no differences between the 2 study groups [21]. The impact of different Vt settings on neuronal damage also led to possible association between high Vt and neuronal damage: 4 studies reported higher neuronal damage when higher Vts are applied [19,20,23,24] and 1 reported no differences between groups [21]. The study that investigated the effect of different PEEPs reported higher pathological neuronal activation when higher PEEP is applied [25].

3.5. Cognitive-behavioural outcomes

The 2 studies that reported cognitive-behavioural tests, investigated memory function with fear conditioning tests (expressed as percent of

Table 2
Studies included in this SR.

Reference	Type of study	Sample	Study groups	MV settings	Measurements	Follow up	Findings
Chen et al. [17]	RCT	Male C57BL/6 mice, n = 84, 6 to 8 weeks old, weighing 20 to 25 g	Control (spontaneous breathing under anesthesia) Surgery (spontaneous breathing under anesthesia after surgery) MV (MV under anesthesia after surgery)	PIP 12 to 15 cmH2O; FiO2 = 0.5; RR = 100/min; MV duration 1, 3, 6 h	Fear conditioning test	6 h, 1 d and 3 d	After 6 h exposure to MV, mice showed significantly reduced memory at 6 h, 1 d and 3 d post-MV when compared to controls ($P < 0.05$)
					Plasma and hippocampal IL-1β, IL-6 and TNFα		After 6 h exposure to MV after surgery increased the levels of IL-1β, IL-6 and TNFα in the hippocampus and plasma at 6 h and 1 d post-MV compared with the surgery-only group ($P < 0.05$)
					Microglial activation using CD11b Ab		Degenerating presynaptic elements with a typical dark appearance and a curved PSD were observed, and these impairments of the synaptic cleft were aggravated in the MV 3 h and MV 6 h groups. Mitochondrial swelling and vacuolation were particularly conspicuous, and the degree of rough endoplasmic reticulum degranulation in the hippocampal CA1 region was more severe in the MV 3 h and MV 6 h groups. The number of vesicles was greater in MV6h animals than in S6h mice ($P < 0.05$)
					Ultrastructure changes of synapses by TEM		The amoeboid hypertrophy of cell bodies and clumping of processes in the MV6h group seen in the entire hippocampus were more severe on day 1 than S6h group. CD11b immunoreactivity was enhanced in the hippocampus of operated animals treated with MV6h at 6 h and 1 day post-MV ($P < 0.05$)
					Brain NF-κB p65, cytochrome c, PARP-1 activation		NF-κB p65 was increased compared with the surgery group at any time point examined. The levels of IL-6 and TNFα in the hippocampus and plasma were not different between the MV and surgery groups on day 3 post-MV
Lahiri et al. [18]	NRCT	Male and female B6Cg-Tg (APPSWE, PSEN1DE9) 85Dbo/J and wild type mice, n = 41, 4 to 6.5 months old, weighing 24.1 to 29.7 g	MV-treated ADtg Non MV-treated ADtg	15 mL/Kg; PEEP = 0; RR = 70/min; MV duration 4 h	Cerebral Aβ quantification	6 h	Significant increase in cerebral soluble amyloid-β1–40 in MV mice ($P = 0.007$)
					Systemic and cerebral inflammatory		MV mice demonstrated significant increases in cerebral IL-6 and TNF-α in both mice strains. Significant increase in IL-5 in MV WT and a significant increase in IL-10 in MV ADtg mice; plasma IL-1β increased significantly in the MV WT mice only
			MV-treated WT Non MV-treated WT		Biomarkers quantification Blood-brain barrier permeability		Significant decrease in blood-brain barrier permeability in MV ADtg mice
Bickenbach et al. [19]	RCT	Female pigs, n = 10, weighing 30.2 ± 2.0 kg (mean ± sd)	LVt HVt	6 mL/Kg (LVt) or 12 mL/Kg (HVt); PEEP = 5 cmH2O; MV duration 8 h	Serum inflammatory cytokines	Baseline, after induction of ALI, and 2, 4, and 8 h afterward	Serum IL-6: after 2 h, significantly higher levels could be demonstrated in the HVt group
					Serum S-100		After 2 h, a decrease of S-100 was noted in the LVt group, whereas the levels in the HVt group remained unchanged. Continuing higher levels for S-100 were found in the HVt group after 4 h and 8 h
					Cerebral lactate		Cerebral lactate was significantly higher in the HVt group after 2 h, 4 h and 8 h
Quilez et al. [20]	RCT	Male Sprague Dawley rats, n = 24, weighing 350 to 370 g	Basal	8 mL/Kg (LVt) or 30 mL/Kg (HVt); PEEP = 0 cmH2O; MV duration 3 h	Serum inflammatory	At the end of the experiment	MV increased plasma levels of IL-6, IL-10, IL-1b, MCP-1, and MIP-2, irrespective of the Vt level (LVt or HVt) (P < 0.05).

(continued on next page)

Table 2 (*continued*)

Reference	Type of study	Sample	Study groups	MV settings	Measurements	Follow up	Findings
					cytokines		However, plasma TNFα levels increased significantly after three hours of HVt ventilation ($P = 0.005$) but remained unaltered in the LVt group
			LVt HVt		c-Fos immunopositive brain areas		Increased number of c-Fos immunopositive cells was observed in the RS and thalamus of HVt rats, but not in LVt or basal rats. c-Fos expression was observed in the CeA, PVN, and SON of MV rats, although activation did not differ between HVt and LVt animals. No differences in c-Fos activation in other cortical areas or in the hippocampus were observed between the experimental groups. Animals breathing spontaneously showed similar levels of activation in CeA and PVN than those observed in the basal group. Conversely, the c-Fos signal in RS and Thalamus was higher than those found in basal and LVt groups
Kamuf et al. [21]	RCT	Male pigs (*Sus scrofa domestica*), n = 20, weighing 24 to 31 Kg	Lung injury by central venous injection of oleic acid (OAI)	7 mL/Kg (+ 15 mL/Kg); FiO2 and PEEP according to the dedicated table with an intended SpO2 of 94–98%; MV duration 6 h (+1 h)	Brain inflammatory cytokines	At the end of the experiment	Higher IL-6 expression in the hippocampus samples of the LAV group compared to native tissue ($P = 0.02$); TNFα was significantly increased in the hippocampus of all three groups receiving ventilation in comparison to the native group (LAV vs. native $P = 0.004$; OAI vs. native $P = 0.029$; Ctr vs. native $P = 0.011$). In the cortex TNFα expression showed a similar overall trend ($P = 0.028$)
			Lung injury by bronchoalveolar lavage (LAV)		Absolute number of neurons		No difference in the number of dyed neurons
			Control (Ctr) Native animals		Microgliosis using Iba-1 Ab		No difference in microgliosis
Chen et al. [22]	RCT	Male C57BL/6 (WT) and C57BL/10ScNJNju mice (TLR4 KO), n = 72, 8 to 12 weeks, weighing 20 to 25 g	Control group (spontaneous breathing) Anesthesia group (spontaneous breathing under anesthesia) MV group	PIP 15 cmH2O; RR 100/min; FiO2 = 0.5; MV duration 6 h	Fear conditioning test Locomotor activity Serum and hippocampal IL-1β, IL-6 and TNFα Microglial activation using anti CD11b Ab Anti GFAP Ab Microglia and astrocytes TLR-4 positive Brain histology for neuronal damage	1 and 3 d for cognitive behavioural tests. Blood was collected at 2 h, 6 h, 1 d and 3 d after treatment	WT mice exhibited reduced memory 1 and 3 days after MV or after anesthesia alone compared with control group and this effect was alleviated in TLR4 KO mice. Locomotor activity was not different MV increased the levels of IL-1β, IL-6, and TNFα in the serum and hippocampus of WT mice at 2 h, 6 h, 1 d, and 3 d after treatment compared with controls ($P < 0.05$) In WT mice, the number of TLR4-positive microglia and the number of TLR4-positive astrocytes in group MV were significantly increased compared with others. TLR4 KO mice exhibited fewer activated microglia after MV and anesthesia. TLR4-positive microglia were completely absent in TLR4 KO mice. MV mice exhibited mild neuron damage in the hippocampal CA1 and CA3 region one day after treatment. WT mice exhibited more obvious shrunken neurons with nuclei pyknosis compared with TLR4 KO mice
Na et al. [23]	RCT	Male Sprague-Dawley rats, n = 24, weighing 350 to 400 g	Basal	5 mL/Kg (LVt) or 10 mL/Kg (HVt); PEEP = 0 cmH2O; MV duration 4 h	Serum and hippocampal IL-6	Blood was collected baseline, at 2 h, and at 4	MV increased the plasma levels of IL-6 ($P = 0.001$) and TNFα (HVt versus BAS $P = 0.01$, LVt versus basal $P = 0.001$).

					and TNFα	h. Animals were euthanized at the end of the experiment	The HVt group showed reduced levels of IL-6 ($P = 0.001$) and TNFα ($P = 0.05$) compared with the baseline level. IL-6 and TNFα levels were similar in the LVt and basal groups
			LVt		Brainstem TASK-1		Compared with basal rats, TASK-1 channel levels were significantly lower in the HVt and LVt groups (both $P = 0.002$)
			HVt		Serum and brain S-100B		In the serum, S-100B increased significantly in the HVt group ($p = 0.001$). In brain, S-100B decreased in HVt and increased in LVt group.
Gonzàlez-Lòpez et al. [24]	RCT	C57BL6 mice, n = 127, 8–12 weeks old	Sham (spontaneous breathing)	PIP 12 cm H2O (low-pressure ventilation); PEEP = 2 cm H2O; RR 100/min	Hippocampal malondialdehyde levels and IL-1β or IL-6	At the end of the experiment	No differences among groups in malondialdehyde levels or in IL-1β or IL-6 expression in hippocampal formation
			Low-pressure ventilation	PIP 20 cm H2O (high-pressure ventilation); PEEP = 0 cm H2O; RR 50/min;	Brain PARP-1		Mice ventilated with either a low or high tidal volume strategy showed elevated immunoreactivity for cleaved PARP-1 in the hippocampal area after 90 min compared with sham mice. No other brain areas showed positive staining for cleaved PARP-1
			High-pressure ventilation	MV duration 90 m (or 330 m for prolonged MV group)	Brain Akt survival pathway		Hippocampal formation from MV mice showed decreased Akt pS473 and the corresponding decrease in GSK3b pS9 compared with sham mice. Phosphorylation of PTEN was also decreased in ventilated animals
					Brain Dysbindin		High pressure MV induced an increase in the expression of the specific variant 1C. There was a slight increase in dysbindin-1 protein after high-pressure ventilation. In the prolonged MV group, there was a significant increase in dysbindin-1C
Quilez et al. [25]	RCT	Male Sprague-Dawley rats, n = 38, 348 ± 32 g (mean ± sd)	Basal group (no LPS or MV) Low-PEEP-saline group (SAL-2)	7 mL/Kg Vt; PEEP 2 cmH2O (low-PEEP) or PEEP 7 cmH2O (moderate-PEEP); RR 46/min, FiO2 = 0.4; inspiratory-to-expiratory ratio 1:2; MV duration 3 h	Serum inflammatory cytokines	At the end of the experiment	In LPS-instilled animals, TNFα ($P = 0.048$), IL-1β ($P = 0.08$), IL-6 ($P = 0.09$), MCP-1 ($P = 0.038$), and IL-10 ($P = 0.09$) levels were higher in PEEP-2 than in PEEP-7. In saline-instilled animals, IL-6 ($P = 0.03$) and IL-10 ($P = 0.09$) plasma levels were higher in PEEP-2 than in PEEP-7.
			Low-PEEP-LPS group (LPS-2) Moderate-PEEP-saline group (SAL-7) Moderate-PEEP-LPS group (LPS-7)		c-Fos immunopositive brain areas		PEEP level had no effect on neuronal activation in LPS-instilled rats. In saline-instilled rats, neuronal activation in the CeA (P = 0.09) and NTS ($P = 0.01$) was higher in animals receiving PEEP-7 than in those receiving PEEP-2. In the PVN, no differences in neuronal activation were found between groups. LPS-7 rats had more c-Fos-immunopositive cells than LPS-2 rats in the RS ($P = 0.012$), SON ($P = 0.049$), and thalamus ($P = 0.049$), but there were no differences between SAL-7 and SAL-2 rats.
Ruemmler et al. [26]	RCT	Male German landrace pigs, n = 30, 12–16 weeks old, weighing 30 to 35 Kg	IPPV	Vt 8–9 mL/Kg (IPPV) or Vt 2–3 mL/Kg (ULTVV) PEEP = 5 mbar; RR: 10/min (IPPV) or 50/min (ULTVV)	Brain IL-6 and TNFα	At the end of the experiment	IL-6 and TNFα was increased in hippocampal samples of the animals receiving IPPV, when compared with ULTVV and CPAP
			ULTVV CPAP	Continuous oxygen flow of 10 L/min with an applied positive pressure of 5 mbar (CPAP); MV duration 5 m			
Hegeman et al. [27]	RCT	Male C3H/HeN mice, n = 42, weighing 25 to 30 g	MV non-ventilated controls	PIP 20 cmH2O; PEEP = 0 cmH20; inspiration to expiration ratio 1:2; RR 20 to 30/min; FiO2 = 1.0; MV duration 1, 2 or 4 h	Brain inflammatory cytokines	At the end of the experiment	No differences between groups

Ab: antibodies; ADtg: Alzheimer's disease; CD: cluster of differentiation; CeA: central amygdala; CPAP: continuous positive airway pressure; GFAP: glial fibrillary acid protein; HVt: High Vt; IL: interleukin; IPPV: intermittent positive pressure ventilation; LVt: Low Vt; MCP: monocyte chemoattractant protein; MIP: macrophage inflammatory protein; MV: mechanical ventilation; NRCT: non-randomized controlled trial; PARP: cleaved caspase-3 and cleaved poly(ADP-ribose) polymerase; PEEP: positive end-expiratory pressure; PIP: peak inspiratory pressure; PSD: postsynaptic density; PVN: paraventricular hypothalamic nuclei; RCT: randomized controlled trial; RR: respiratory rate; RS: retrosplenial cortex; SON: supraoptic nucleus; SpO2: peripheral oxygen saturation; TASK: TWIK-related acid-sensitive potassium channel; TEM: transmission electron microscopy; TNF: tumor necrosis factor; ULTVV: ultra low tidal volume ventilation; Vt: Tidal volume; WT: wild type.

Table 3
Quality of reporting and risk of bias.

Criteria	Chen et al. [17]	Lahiri et al. [18]	Bickenbach et al. [19]	Quilez et al. [20]	Kamuf et al. [21]	Chen et al. [22]	Na et al. [23]	Gonzàlez-Lòpez et al. [24]	Quilez et al. [25]	Ruemmler et al. [26]	Hegeman et al. [27]
Quality of reporting											
Any randomization	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Any blinding	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
Sample size calculation	N	N	N	Y	N	N	N	N	N	N	N
Conflict of interest statement	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y
Ethical approval	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Overall (Y)	4	3	2	5	4	3	4	4	4	4	4
Risk of bias											
Random group allocation (selection)	?	n.a.	?	?	H	?	?	?	?	L	?
Groups similar at baseline (selection)	L	L	L	L	L	L	L	L	L	L	L
Blinded group allocation (selection)	?	n.a.	?	?	H	?	?	?	?	L	?
Random housing (performance)	L	L	?	L	H	L	?	?	L	?	?
Random interventions (performance)	L	n.a.	L	L	H	L	L	L	L	L	?
Random outcome assessment (detection)	L	n.a.	L	L	?	L	L	L	L	L	L
Blinded outcome assessment (detection)	L	L	n.a.	L	L	L	L	L	L	L	L
Reporting of drop-outs (attrition)	L	L	L	L	L	L	?	L	L	L	L
Free of selective outcome reporting (reporting)	?	L	H	H	L	?	L	L	L	L	?
Other biases	H	?	H	?	L	H	H	?	L	H	H
Overall (L)	6	5	4	6	5	6	5	6	8	8	4

Y: reported, N: not reported; L: low risk of bias; H: high risk of bias;?: unclear risk of bias; n.a.: not applicable.

freezing time): both reported cognitive decline up to 3 days after MV when compared to non-ventilated controls [17,22]. In 1 study, locomotor activity (expressed as the % of the distance traveled in 5 min in the graph) was tested in open field apparatus: no changes between MV-treated animals and controls were reported [22].

3.6. Quality and risk of bias

The quality assessment of the included studies included: randomization, blinding, sample size calculation, conflict of interest statement and ethical approval (Table 3). Randomization, as well as blinding, were reported in 10 out of the 11 included studies. Only 1 of the studies reported on a sample size calculation for the analysis of statistical power. The risk of bias of the included studies was assessed using SYRCLE's risk of bias tool, that includes 10 items related to 6 types of bias (selection, performance, detection, attrition, reporting and other biases) [16]. On average, the included studies reported 7 out of 10 characteristics. However, 2 out of the 11 included studies reported randomization of the animals across treatment groups and blinding of the group allocation. Ten of the 11 studies selected, reported blinding of the outcome assessment.

4. Discussion

This SR originally reports evidence from animal studies designed to evaluate the relationship between MV and neuroinflammation, neuronal damage or cognitive impairment. The majority of selected studies report that MV associates with an increase of neuroinflammation and neuronal damage markers and some report no differences between ventilated and non-ventilated controls. The MV settings resulted to be relevant in the extent of neuroinflammation and neuronal damage and more "protective" settings (lower Vts and PEEP) associated with less severity in brain or serum markers changes or in modulation of activated brain areas. Of interest, MV was found to associate also with worse cognitive-behavioural performance, but since these results are supported by a very limited number of studies and short-term assessment, a cautious interpretation is imperative.

In humans, cognitive impairment has been reported as a long term outcome complication after critical illness and in acute respiratory distress syndrome (ARDS) survivors, with an important impact on patients' life, relatives and society as well [28-32]. Its incidence widely ranges in different studies (4%–64%), depending on clinical subgroup, and in 1 study it has been reported up to 100% of patients at hospital discharge, up to 36% at 6 months and 30% at 1 year, and can persist for years [31,33-35]. Several possible etiologies and pathophysiological mechanisms of perioperative neurocognitive disorder have been described and these include: neuroinflammation, neuronal damage, general anesthetic use, surgery, MV, etc. [1,36]. Of note, the type of anesthetic has been implicated in both neuroinflammation and neuronal injury: propofol for example, due to potential emulsion instability, can develop droplet enlargement that can lead to microvascular occlusion [37]. Brain atrophy has been reported to be the anatomical correlation of cognitive impairment in ARDS survivors [38-40]. Several risk factors have been proposed, including: age, comorbidities, preexisting cognitive impairment, acute severity of illness, prolonged delirium, hypoxia, dysglycemia, hypotension, use of sedatives, acute brain dysfunction, severe sepsis, use of renal replacement therapy, etc. [32,40–44]. Among these, MV and MV duration have also been mentioned as risk factors [11,41,45,46]. The link between MV and the brain has been addressed by preclinical and clinical studies and several mechanisms have been identified but clinical studies on this topic are strongly limited by safety issues and ethical considerations [46–49]. Of note, despite no human studies have been designed to assess MV-induced neuroinflammation, neuronal damage or cognitive impairment, a retrospective study in survivors after out of hospital cardiac arrest (OHCA) reported that *"[…] lower Vt was independently associated with favorable neurocognitive outcome among patients hospitalized after nontraumatic OHCA"* [10].

Available literature suggests that there might be a relationship between neuroinflammation, neuronal damage and cognitive

impairment; nevertheless it is important to acknowledge that there are several important differences: inflammation can flair, but also subside while neuronal damage and cognitive impairment are final results that likely will not improve [47,50,51]. Moreover, the presence of neuroinflammation does not necessarily lead to neuronal injury. Brain cytokines, chemokines, endothelial activation molecules are reliable neuroinflammation markers and therefore studies based on these variables were considered suitable for this SR [50,51]. Marker on neuronal damage reported in the studies described in this SR, include: S-100, C-Fos, cleavage of PARP-1, TASK-1, etc. The S-100 (and the brain specific variant S—100B) protein is an astroglial cell-derived marker that is released as consequence of neuronal damage and disintegration of the BBB and there is evidence that MV, per se, could lead to its release in the blood circulation [52-56]. The C-Fos is a marker of neuronal activation and is involved in gene transcription, apoptosis or proliferation: its cerebral basal expression is low, but pathological activation has been related to metabolic stress, ischemia, and inflammation [20,56–59]. The detection of the cleavage of PARP-1 and of the caspases cascade is considered to be a marker of neuronal damage and apoptosis and was included in this SR [24]. The TASK-1 is a potassium channel, involved in the regulation of cell membrane potential and in respiratory rhythm generation and its down-regulation might cause damage to the respiratory center by increasing neuronal excitability [23,60,61]. Histological analysis and immunohistochemical assays of brain tissue sections were used in some of the studies included in this SR to asses MV-related microgliosis and neuronal death or apoptosis. Microgliosis has been defined as an increment in the absolute number of microglia cells or as a change in their status of activation [62,63]. Microglial cells are "activated" when showing a significant increase in size of microglia or if there is a significant increase in expression of a microglial marker at immunohistochemical investigation [62]. Different markers for microglia cell have been considered suitable for this SR, with slightly different meaning: anti CD11b antibodies are markers of microglia activation and anti Iba-1 antibodies are used to evaluate the number or microglia cells [17,21]. Cognitive-behavioural tests such as fear conditioning tests and locomotor activity tests are indicators of cognitive performance and were considered suitable for this SR. Of note, there is consistently high heterogeneity across the methodological design of the studies included in this SR: different MV protocols and brain and serum markers have been included. Moreover, the contemporary presence of neuroinflammation and neuronal damage brain and serum markers was assessed only in 6 of the 11 studies included in this SR [17,18,21-24]; of these, only 2 reported also on cognitive-behavioural tests [17,22].

Given these premises, there is room to proceed in this research field that could unveil important clinical implications. Therefore, considering available preclinical evidence, it is appropriate to design dedicated human clinical trials aimed to investigate the possible relationship between the number of serum markers that have been identified and the cognitive decline after MV in critical illness survivors. Moreover, it could be valuable to confirm neuronal and brain damage in MV-treated patients through histopathological examination during autopsies. Of note, particular attention must be paid in order to discriminate through possible confounding factors existing in the complex pathophysiology of critical illness. To confirm MV-associated neuroinflammation, neuronal damage or cognitive impairment in humans should prompt developing appropriate monitoring and therapeutic strategies and included in informed consent approval [8,46,47,64-66].

This SR demonstrates several limitations associated with heterogeneity of the methodological design of the original selected studies. Such heterogeneity, together with the relatively small amount of studies included in this SR, might limit the association of MV with the investigated outcomes: first, MV protocols varied significantly among different studies and in some there was no comparison of different MV settings; second, the use of MV has been tested in different therapeutic contexts (i.e. ARDS and surgery, etc); third general anesthetics have been used in all of the studies; fourth, in one study [18], the use of a control group of unventilated animals, that were simply left alone in their cages instead of having undergone anesthesia, intubation and MV, could represent a confounding factor and it is not clear which could be the role of the stress induced by the procedure surrounding MV in generating the reported differences. All of these factors are proven to induce cognitive impairment thus introducing confounding elements [1,66,67]. Nevertheless, in each study the groups were homogeneous enough and – in our opinion – these variables have not affected the overall validity of reported results. Furthermore, different animal models have been used and different brain regions were examined in the studies suitable for this SR, and the interspecies differences might limit immediate translation of the results to humans, especially for complex and multifactorial diseases as the study of cognitive functions [68,69]. Whether the size of the animal model has an impact on the strength of the inference in human pathophysiology, is controversial [70-72]. It is important to highlight that there is no particular model that can be considered the gold standard in investigating the relationship between MV, lung injury and systemic-inflammation and that it is not clear how to translate the MV settings into what would be the equivalent settings in a human [70]. While anatomy and respiratory mechanics are more similar to humans in large-size animal models (e.g. pigs), some inflammatory patterns (including differences in TLR, pulmonary intravascular macrophages, lipopolysaccharide sensitivity and nitric oxide production) are best described by small-size animals (e.g. rodents) [70,72]. Lastly, it would be of great value to distinguish between immediate and long term consequences of MV. Unfortunately, the maximum follow up time in the reported articles was 3 days. Moreover, evidence suggests that is not possible to compare "timing" in animal models with human time, also in consideration of large differences in size, metabolic rate and life history [73,74].

5. Conclusions

Ample preclinical evidence in animal studies suggests that MV associates with neuroinflammation, neuronal damage and cognitive impairment. Sub-optimal setting of MV, beyond the criteria of "protective" ventilation, associates with more severe signs of brain damage. Future preclinical and clinical studies designed along standardized methodological criteria are necessary to provide reproducible and comparable results. Should consistent evidence of MV-induced neuroinflammation, neuronal damage and cognitive impairment be proven, it will prompt the implementation of appropriate monitoring and dedicated therapeutic strategies into clinical practice.

Authors' contribution

Giovanni Giordano: Conceptualization; Data curation; Methodology; Investigation; Writing – original draft. Francesco Pugliese: Data curation; Investigation; Writing - original draft. Federico Bilotta: Conceptualization; Supervision; Writing - original draft; Writing - review & editing.

Declaration of Competing Interest

GG, FP, FB declare to have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2020.12.017.

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