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Authors

Zhou, Yingqiu K

Patel, Hemal H

Roth, David M

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Extracellular vesicles: A new paradigm for cellular communication in perioperative medicine, critical care and pain management

Yingqiu K. Zhou, M.D.[1], **Hemal H. Patel, Ph.D.**[1], **David M. Roth, Ph.D., M.D.**[1]

[1]Veterans Administration San Diego Healthcare System, San Diego, CA, USA and Department of Anesthesiology, UCSD School of Medicine, San Diego, CA, USA

Abstract

Extracellular vesicles (EVs) play critical roles in many health and disease states, including ischemia, inflammation and pain, which are major concerns in the perioperative period and in critically ill patients. EVs are functionally active, nanometer-sized, membrane-bound vesicles actively secreted by all cells. Cell signaling is essential to physiological and pathological processes, and recently, EVs have emerged as key players in intercellular communication. Recent studies in EV biology improve our mechanistic knowledge of the pathophysiological processes in perioperative and critical care patients. Studies also show promise in using EVs in novel diagnostic and therapeutic clinical applications. This review considers the current advances and gaps in knowledge of EVs in the areas of ischemia, inflammation, pain, and organ systems that are most relevant to anesthesiology, perioperative medicine, critical care, and pain management. We expect the reader will better understand the relationship between EVs and perioperative and critical care pathophysiological states and their potential use as novel diagnostic and therapeutic modalities.

Introduction

Cell signaling is essential to physiological and pathological processes. It has been long accepted that vesicles secreted by specialized cells carry signaling molecules such as neurotransmitters and hormones. Recently, extracellular vesicles (EVs) have emerged as key players in cell-to-cell communication.[1,2] EVs, first observed in the mid-1900s and considered cellular waste or "dust,"[3] are lipid-bilayer bound nanoparticles now known to be secreted by all cells. Their important signaling functions have been shown in a wide range of physiological and pathological processes including immune function, cancer, organ homeostasis, regeneration[4], and viral spread[5], and are further evidenced by their evolutionary conservation from lower organisms such as bacteria to plants and humans.

Corresponding Author: David M. Roth, Ph.D., M.D., VASDHS (9125), 3350 La Jolla Village Drive, San Diego, California 92161-5085, droth@ucsd.edu, (858) 552-8585, ext. 1091.

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Anesthesiologists face a wide range of pathophysiological processes, and knowledge of the current state of EV research is vital given the critical role that EVs play in pathophysiology. The role of EVs in the perioperative period, critical care and pain management are limited but studies are ongoing. A recent study shows EVs may reveal previously unknown physiological impacts of anesthetic agents,[6] and in the current worldwide coronavirus disease 2019 (COVID-19) pandemic EVs are studied as a novel therapeutic modality.[7] In the rapidly expanding field of EV biology, further research in the perioperative period can impact the understanding and care of perioperative, critical care and pain patients.

Due to the involvement of EVs in a wide range of physiological and pathological processes, the field of EV biology is extremely broad, and the breadth and depth of the subject cannot be covered in one review. This review will focus on the three interconnected areas of ischemia, inflammation, and pain in the organ systems most relevant to anesthesiology, perioperative medicine, and pain management. The review addresses advances in the understanding of EVs in disease mechanisms, potential diagnostic and therapeutic clinical applications.

Extracellular Vesicles: Overview

EVs are a heterogeneous group of membrane bound vesicles differing in size, cargo, membrane composition, and biogenesis. Biogenesis is mainly via two mechanisms. The first mechanism involves fusion of multivesicular bodies (MVBs) with the cell membrane to form exosomes. The second mechanism involves plasma membrane budding to form microvesicles (MVs), ectosomes, or microparticles (Figure 1). Apoptotic bodies, vesicles formed by plasma membrane blebbing during apoptosis, may be co-isolated with EVs but will not be discussed in this review. Extracellular vesicles can also be sorted by size; exosomes are reported mainly in the 50-150 nm size range, MVs in the 100-1000 nm range and apoptotic bodies in the 1000-5000 nm range. Current vesicle isolation and analysis methods cannot clearly distinguish between vesicle subtypes given their overlapping size, density, content, membrane orientation, and surface molecules. A standard nomenclature has yet to be uniformly adopted—we will thus refer to exosomes, MVs, ectosomes, and microparticles collectively as EVs in this review.

EV cargo has functional effects and includes genetic material, proteins, lipids, and soluble mediators. A frequently studied cargo is microRNAs (miRNAs)—small strands (~22 nucleotides) of noncoding RNAs that serve as posttranscriptional gene regulators that bind to target messenger RNAs and impact physiological processes and diseases.[8] Since free miRNAs are degraded in body fluids, EVs function as protective carriers of miRNAs. We discuss the roles of miRNAs and EVs further below. Other than encapsulated cargo, EV membrane proteins and lipids also exert functional effects via autocrine, paracrine, and endocrine signaling. EV surface molecules act as receptors and ligands to target EVs to specific sites, such as the plasma membrane of recipient cells, where EVs activate downstream signaling, endocytosis or fusion with the plasma membrane.[9] The actions of EVs are of critical importance to many health and disease states including but not limited to ischemia, inflammation, pain, malignancy, and metabolism.[10–14]

Extracellular vesicles have been collected and studied in many biofluids including blood, CSF, urine, saliva, tears, and bronchoalveolar lavage (BAL) fluid. The ease of sampling EVs from biofluids to obtain a snapshot of pathophysiological states makes EVs exceptional biomarker candidates.

Compared to soluble mediators, EVs are stable as membrane-bound vesicles and can cross biological membranes such as the blood brain barrier (BBB).[15–17] Thus, EVs have also been the focus of therapeutic development (Figure 2). Studies have shown success in customizing EV cargo and membrane molecules to target and deliver to specific tissues or cells. Their low immunogenicity[18] compared to whole-cell treatments are also a focus of recent studies—the efficacy of stem cell therapy, such as mesenchymal stem cell (MSC) treatments, are mediated by EVs secreted by stem cells.[19–21] Recently, with the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and COVID-19, EVs have been suggested as both mediators of viral spread[5] and as a novel therapeutic in the form of MSC derived EVs,[7] or delivery vehicles for messenger RNA (mRNA) vaccines.[22]

Extracellular vesicles and perioperative ischemia

Acute ischemia and ischemia-reperfusion (IR) injury are common among perioperative and critical care patients. EVs have been shown to play critical roles in ischemia, including promoting angiogenesis, inhibiting apoptosis and reducing inflammation. EVs have also been the focus of many investigations into novel therapeutics for acute ischemia. This section discusses studies in acute ischemia or IR injury in cardiac, CNS and renal systems with relevance to perioperative medicine and critical care.

Cardiac Ischemia

Acute myocardial ischemia and myocardial IR injury are frequently seen in perioperative and critical care patients due to increases in sympathetic tone, myocardial oxygen supply and demand mismatch, and prothrombotic states.[23] Within the last decade, there have been exciting advances in EV research related to the mechanism and treatment of acute cardiac ischemia and IR injury (Table 1).

Mesenchymal stem cell (MSC)-derived EVs show promise as a cell-free therapy to treat acute myocardial ischemia. An intravenous bolus of MSC-derived EVs before reperfusion reduces infarct size in a model of myocardial ischemia-reperfusion injury.[24] The effect is also seen with MSC-derived EVs given intramyocardially in a model of cardiac ischemia, with improved systolic and diastolic function compared to controls.[25] MSC EVs also enhance the viability of myocardium after ischemia-reperfusion and improve LV geometry and contractile performance.[26] Possible intracellular processes involved in improving cardiac function with MSC EV administration include increased ATP and NADH levels, decreased oxidative stress,[26] and decreased cellular stress response signaling.[27] MSC EVs are thought to rescue ischemic cells from states of ATP deficit and apoptosis initiation by supplying an abundance of glycolytic enzymes and CD73, which may increase survival signaling in cells by activating reperfusion injury salvage kinases.[28] MSC-derived EV treatments also promote functional myocardial recovery after IR injury by actions on proteins involved in apoptosis and autophagy.[29] Analysis of the miRNA cargo of MSC-

derived EVs revealed that miRNA-181a, which targets a network of inflammation-related genes, could be an important functional component in IR injury treatment—EVs enriched in miR-181a derived from viral transfection of MSCs decreased the inflammatory response, infarct size and improved myocardial function after IR injury compared to non-enriched MSC EVs.[30]

Other stem cell-derived EVs also provide therapeutic benefits. EVs derived from cardiac progenitor cells (CPCs) decreased cardiomyocyte apoptosis by 53% when given intramyocardially during ischemia in a mouse IR model.[31] Surface molecules on EVs may also have beneficial effects. An active protease on the surface of CPC-derived EVs, pregnancy-associated plasma protein-A, released insulin-like growth factor-1 by proteolytic cleavage, reducing myocardial apoptosis. CPC-derived EVs decrease scar size and improve ventricular function when given *in vivo*.[32] Despite being non-cardiac in origin, differentiated neural stem cell (NSC) EVs decreased infarct size after IR.[33] However, non-differentiated NSC EVs did not affect infarct size, indicating not all stem cells possess therapeutic properties.

EVs in blood also are protective in myocardial IR injury. Surface heat shock protein 27 (HSP70) on plasma EVs bind to toll-like receptor 4 and activates downstream pathways involving phosphorylation of ERK1 and 2, culminating in phosphorylation of HSP27[34]. Infarct size is decreased when EVs enriched from plasma are given intravenously before ischemia.[34] The same pathway is involved in a decrease in myocardial apoptosis mediated by serum EVs. An exercise-induced increase of circulating EVs further enhances the protective effects against IR injury.[35] However, serum EVs from type II diabetic patients and animals no longer activated the pathway and did not protect cardiomyocytes from simulated IR *in vitro.* Serum EVs from non-diabetic animals were protective in diabetic animals.[36] The mechanism for the difference between diabetic and non-diabetic EVs is unclear. HSP70 synthesis impairment in hyperglycemic and hyperlipidemic conditions may be a factor,[37] but remains to be experimentally determined. Although cellular and extracellular HSP70 has been known to be a target for cardioprotection and treatment for IR injury,[37] successful delivery to ischemic tissues remains a problem—one that EVs have the potential to solve. Endothelial cell-derived EVs may be partially responsible for the protective effect of blood EVs, as endothelial cell EVs alone when given before reperfusion decrease myocardial damage and apoptosis after IR.[38]

EVs have been modified to exhibit improved therapeutic properties. Injured myocardium overexpresses stromal cell-derived factor 1 (SDF-1α), a member of the CXC chemokine family. SDF1α normally recruits progenitor cells by binding the CXCR4 membrane receptor. EVs collected from engineered CXCR4-overexpressing CPCs are enriched in CXCR4, and when injected intravenously, demonstrate significantly improved myocardial EV uptake and cardiac function after an ischemic insult.[39] MSC EVs modified with platelet membranes better targeted EVs to injured endothelium,[40] while EVs derived from anoxia conditioned MSCs exhibited improved protection against apoptosis in cardiomyocytes due to an increased load of inflammasome-targeting miRNAs.[41]

In addition to developing new therapeutics, EV studies can also elucidate mechanisms of tissue damage or repair after ischemia. One study showed that myocardial ischemia might shift cardiomyocytes to produce pro-angiogenic EVs by modifying cargo.[42] Serum EVs from the coronary blood of patients with myocardial ischemia enhanced endothelial proliferation, migration, and tube formation compared with EVs from healthy patients. The enhanced angiogenesis may be due to downregulation of miR-939-5p in ischemic EVs, resulting in improved iNOS expression and endothelial NO production. Proteins responsible for EV biogenesis were increased in cardiomyocytes after hypoxia but not in fibroblasts or endothelial cells, suggesting the source of EVs may be cardiomyocytes.[42] However, EVs released after cardiac IR may also increase oxidative stress and inflammatory cytokines; blockade of small EV release with GW4869 before IR improved cardiac function, decreased infarct size and myocardial enzyme levels after IR.[43] Stimulating calcium-sensing receptors on polymorphonuclear leukocytes (PMNs) produced EVs that improved cardiac function after cardiac IR, but inhibiting the same receptors produced EVs without protective effects.[44] Further studies are needed to clarify the origins, characteristics, targets, and effects of EVs during various cell and pathophysiological states.

Cerebral and Spinal Cord Ischemia

Cerebral and spinal cord ischemia are also significant complications in perioperative and critical care that lack efficient therapies. EVs are important in communication and signaling between the cerebral endothelium and cells of the brain parenchyma, including neurons, neural precursors, and glial cells.[14] While the clinical significance of EVs in pathophysiology and therapeutics in central nervous system (CNS) ischemia continues to be explored, evidence for the use of EVs as a therapeutic modality has been increasing within the last decade (Table 2).

Stem cell-derived EVs in CNS ischemia have repeatedly demonstrated therapeutic potential. After transient global ischemia, intra-ventricular injection MSC EVs restored basal synaptic transmission, plasticity, and improved learning and memory, possibly due to decreased pathogenic expression of cyclooxygenase-2.[45] MSC EVs also have ability to decrease infarct area, cerebral edema,[46] and apoptosis[47] when given intravenously after cerebral IR. Intrathecal administration of MSC EVs before transient spinal cord ischemia improved lower motor neuron deficits and decreased levels of interleukin-1beta (IL-1β) and tumor necrosis factor alpha (TNFα).[48] NSC-derived EVs given intravenously after transient middle cerebral artery occlusion reduced infarct volumes and preserved astrocyte function.[49] EVs from MSCs that overexpress pigment epithelium-derived factor, a protein that exhibits anti-inflammatory and neuroprotective properties, decreases activation of autophagy, suppressed neuronal apoptosis and ameliorated cerebral IR injury[50].

EVs from sources other than stem cells also mediate positive cerebral responses after ischemia. Microglia can modulate neuronal cell death and recovery via secretion of trophic factors.[51,52] EVs from M2, anti-inflammatory, type microglia injected intravenously after cerebral IR reduced infarct volume and attenuated behavioral deficits in mice.[53,54] Possible mechanisms for the protective effects include encapsulated miR-124,[53] important in neuronal development and brain function,[55] or miR-137, which regulates of adjacent

cell signaling in the brain.[54] Astrocyte derived EVs injected intravenously increased hippocampal neuron organization and improved behavioral deficits after cerebral IR.[56]

Remote ischemic preconditioning (RIPC), produced by transient episodes of ischemia at a remote site, was initially studied in cardiac ischemia but has now demonstrated protective effects in other organs, including the brain.[57] EVs are likely important mediators of RIPC[58] and have important implications in patients in whom cerebral ischemic risk is high, such as those undergoing neurointerventional and neurosurgical procedures. Li et al. showed plasma EVs collected after RIPC attenuated infarct size in a model of cerebral ischemia, possibly due to increased levels of hypoxia-inducible transcription factor-1alpha within RIPC EVs.[59]

EVs can be safe and effective targeted drug delivery vehicles due to their ability to cross the blood-brain barrier, low immunogenicity, stability, and delivery efficiency.[60] They can be enriched in bioactive material that would otherwise be degraded and targeted to ischemic CNS tissues.[61] Zhang et al. labeled and incorporated miR-210, a miRNA that promotes angiogenesis, into EVs. The EVs were also conjugated to a peptide with affinity for integrin $\alpha_v\beta_3$, which is expressed in cerebral vascular endothelial cells after ischemia. EVs delivered intravenously after cerebral IR targeted the lesion, increased miR-210 at the ischemia site, and when administered over 14 days, improved angiogenesis and improved survival.[61] Others showed that IV administration of EVs loaded with miR-124 can target ischemic regions in the brain by using genetically engineered vesicles expressing surface neuron-specific rabies virus glycoprotein, inducing neurogenesis and exerting a protective effect against cerebral ischemia.[62]

Renal Ischemia

Acute kidney injury (AKI) is a major concern in the perioperative and critical care setting. AKI is associated with considerable morbidity and mortality[63] and approximately 30-40% of all AKI cases occur after surgery.[63] Useful biomarkers for AKI are needed in the clinical setting for early diagnosis and successful treatment.[64] Recent work suggests EVs are important in renal ischemia and have potential as biomarkers for diagnosis and therapy (Table 2). Urinary EV aquaporin-1 (AQP1) was decreased from six to 96 hours after renal IR in a rat model.[65] Although the sample size was limited, the same study showed decreased urinary EV AQP1 normalized to creatinine in a renal transplant recipient after transplantation, during which renal IR injury is inevitable. In contrast, there was no change in donor creatinine-normalized EV AQP1. A decrease in both EV AQP1 and AQP2 after IR-induced AKI was also shown in another study.[66] EVs as secreted packets of molecules may reflect the status of their cells of origin than measures of total urine levels. The amount of transcriptional repressor activating transcription factor 3 (ATF3) RNA in urinary EVs were 60 fold greater in patients with AKI, whereas the total ATF3 RNA in urine was not significantly different.[67] Urinary EVs are easily accessible and may serve as biomarkers of renal IR injury.

Studies have also investigated the therapeutic efficacy of EVs in the treatment of AKI (Table 2). EVs derived from hypoxic renal tubular cells can reverse renal IR injury.[68] Renal transcriptome analysis showed a significant deviation post-IR in genes involved in apoptosis, inflammation, angiogenesis, oxidative stress, and fibrosis—changes almost completely

reversed by intravenous injection of EVs derived from hypoxia exposed renal tubular cells.[68] Other than transcriptome shift reversal, EV administration improved renal function and histological appearance. Renal function improvement after IR has also been shown using EVs derived from human renal tubular cells,[69] EVs from ischemic preconditioned right ventricular perfusates, and interestingly, EVs from contralateral kidneys exposed to transient ischemia.[70] Endothelial progenitor cells (EPCs) play roles in endothelial regeneration and recent unpublished data suggest EPC-derived EVs may limit preeclampsia associated glomerular injury by attenuating endothelial cell lysis.[71] Stem cell-derived EVs also have renal protective effects. MSC-derived EVs express surface level C-C motif chemokine receptor-2 (CCR2), which act as decoys to bind to C-C motif chemokine ligand 2 (CCL2), decreasing concentration of free CCL2 and subsequent macrophage recruitment and activation to protect against renal IR injury.[72] Many studies show protective effects of cargo within stem cell-derived EVs against renal IR. MiR-199-3p, transferred to renal cells from MSC EVs, induces functional and histological recovery after renal IR by suppressing apoptosis.[73] The transfer of miR-199-5p from MSC EVs to renal tubular cells reduced endoplasmic reticulum stress and was protective against renal IR injury.[74] Other MSC EV cargo protective in IR injury include MiR-30 via modulation of mitochondrial fission and reduction of apoptosis,[75] and specificity protein via inhibiting inflammatory cell death.[76] EVs can deliver many molecules, which in concert have immense therapeutic value in IR injury. However, the functions of cargo and membrane molecules, differences between EVs of different origins, or EVs from cells in different states, are still unclear.

Extracellular vesicles and inflammatory states in the perioperative period and critical care

Inflammation is an important component of many disease states. In the perioperative setting, inflammation plays a large part in end organ injury, postoperative cognitive dysfunction, cancer metastasis, infection, and wound healing. Inflammation is a system-wide process not limited to the site of disease, trauma or infection; it is thus important to understand the interplay of inflammatory signals, their effects on sites adjacent or distant to the inflammatory stimulus, and mechanisms of transfer. EVs are increasingly recognized as critical mediators and modifiers of the inflammatory response.[77] EVs exert both pro- or anti-inflammatory effects[78] depending on origin and pathophysiological state under which they are secreted. This section focuses on EVs in acute lung injury and sepsis—two common conditions in perioperative medicine and critical care—and studies on diagnostic or therapeutic potential of EVs in these areas (Table 3).

Inflammation in Acute Lung Injury

EVs are implicated in acute lung injury (ALI). Under normal conditions, most EVs isolated from BAL fluid are derived from alveolar macrophages. However, inflammatory stimuli such as hyperoxia[79] or acid exposure[80] increase EVs in BAL fluid and change the proportion of EVs to predominantly epithelial-derived. EV cargo also changes after inflammatory stimulus—after acid exposure, the amount of RNA per EV was increased in BAL fluid.[80] The RNA cargo of these EVs includes miRNAs, which at least in part contribute to macrophage activation and recruitment to lung tissue.[80] Hyperoxia-induced

lung epithelium-derived EVs can activate macrophages and increase macrophage and neutrophil infiltration into lung tissue. Epithelial EVs were also present in serum and activated systemic macrophages. The effects of hyperoxia-induced lung inflammation were largely caused by encapsulated caspase-3, as its levels significantly increase post-hyperoxia, and depletion of caspase-3 from EVs decreases neutrophil infiltration and lung parenchyma inflammation.[79] The EV crosstalk also occurs in the opposite direction, with an anti-inflammatory effect in ALI. EVs ameliorate ventilator- or infection-induced injury by transferring miR-223, a modulator of inflammatory responses, from PMNs to alveolar epithelial cells. The transfer decreases severe lung inflammation by repressing poly (adenosine diphosphate–ribose) polymerase–1, which is involved in inflammation and ischemia-reperfusion injury.[81] miR-223 is also involved in chronic pain and is further discussed below.

Circulating EVs play a large role in ALI. Serum EVs from a model of sepsis-induced ALI were taken up into lung parenchyma of naïve mice and increased the number of total and activated alveolar macrophages. The increase in number and activation of macrophages may be due to delivery of miR-155, a miRNA involved in regulation of inflammatory responses, to macrophages.[82] Plasma EVs from a sepsis model were sufficient to induce endothelial injury, cytokine production, and lung inflammation, indicated by neutrophil infiltration and hyaline membrane formation, when injected intravenously or intratracheally.[83]

EVs are involved in the inflammation and endothelial damage of transfusion-related acute lung injury (TRALI). Platelet-derived EVs in apheresis platelet concentrates promote pulmonary endothelial damage, and their numbers and ability to prime neutrophils' respiratory bursts increase with storage length.[84] Packed red cells (pRBCs) act similarly —in a model of hemorrhage and resuscitation, prolonged storage of pRBCs increases EVs that induce human neutrophil activation and superoxide release. The EVs created during prolonged storage of pRBCs also induced neutrophil accumulation in the lungs of hemorrhaged mice.[85] A proposed mechanism of ALI related to blood product administration describes a two-hit phenomenon, where critical illness leads to neutrophil recruitment into the pulmonary endothelium and activation of recruited neutrophils by EVs leads to destruction of endothelial cells, capillary leakage, and acute respiratory distress syndrome (ARDS).[86] However, ongoing studies are needed to clarify the relative contribution of damaging EVs versus other factors in blood products. Filtering blood products with a 100 nm filter significantly decreased alveolar and endothelial permeability but decreased PMN priming by only 20% and had no effect on pulmonary edema.[86] Whether this difference is due purely to contributions from other factors in blood products or possible inadequate filtering and lingering effects of EVs smaller than 100 nm is unknown. Further studies are needed to clarify the possible benefits of removing EVs from blood products to decrease the risk of TRALI in patients.

By modulation of the inflammatory response, EVs can also be therapeutic in lung injury. One dose of human MSC-derived EVs ameliorates decreased alveolar septation, pulmonary hypertension, and fibrosis and showed long term benefits of improved pulmonary function in a hypoxia-induced lung injury model. EV encapsulated mRNAs were found to contribute via directing pulmonary macrophages toward a more anti-inflammatory, M2-

like phenotype.[87] Other cargo in MSC-derived EVs that play a role in ALI treatment by modulating inflammation include mitochondria[88] in large EVs and miRNAs, which improve oxidative stress injury[89] or decreases apoptosis.[90] EPC-derived EVs have also been shown to ameliorate ALI by improving endothelial cell function via transfer of encapsulated miR-126.[91] COVID-19 caused by SARS-CoV-2 can present with a dysregulated immune response and cytokine storm, similar to the effects of other coronaviruses,[92,93] resulting in lung injury which may progress to severe ARDS and multi-organ failure. Treatment with MSCs have been shown to ameliorate immune dysregulation,[94] and given the immunomodulatory effects of MSC-derived EVs, new studies are investigating the therapeutic potential of MSC EVs in COVID-19. Clinical trials have been planned or started–one registered pilot study with will study inhalational aerosolized MSC-derived EVs in treatment of severe COVID-19 cases.[7]

Inflammation and Sepsis

EVs play a functional role in the system-wide, multi-organ effects of sepsis. When blood-derived EVs from septic patients are injected into healthy animals, pleiotropic and tissue-selective changes were seen in the expression of proinflammatory proteins related to nitrative and oxidative stresses.[95] However, an earlier study showed a protective effect of circulating EVs against vascular hyporeactivity from patients with septic shock.[96] These effects may be due to genetic material within EVs. Plasma EVs from septic patients contain differentially expressed miRNA and mRNA involved in inflammatory response, oxidative stress, and cell cycle regulation compared to non-septic patients at both day 0 and day 7 after ICU admission.[97] Similarly, EVs can act in sepsis-related myocardial depression. Inhibition of small EV biogenesis and release decreased cardiac inflammation and myocardial depression as well as prolonged survival in a model of sepsis.[98] MSC-derived EVs also show therapeutic immunomodulatory properties by improving survival when given intravenously in a model of sepsis.[99]

Peripheral inflammation and CNS lesions greatly increase the transfer of peripheral EVs into the CNS.[17] Genetic material such as miRNA is transferred to and change the miRNA profile of recipient cells in the CNS. This EV spread is either via direct crossing of the BBB or via local spread from hematopoietic cells that have crossed the BBB to neurons.[17] Thus, EVs may be detrimental in or potential treatment vehicles for sepsis-induced encephalopathy. IV administration of MSC-derived EVs attenuated levels of apoptotic and inflammatory cells in blood and inflammatory cytokines (TNFα, IL-6) in blood and CSF after cecal ligation and puncture. Inflammatory cell infiltration in the brain, markers of inflammation, edema, DNA damage, and apoptosis was attenuated as well.[100]

Characterization of EVs could allow for early identification of the host response to infection and early recognition and sepsis management. Pre-clinical biomarker studies have shown miRNAs in EVs could distinguish between septic and non-septic patients[101] and between sepsis and SIRS in patients.[102,103] Lower EVs levels in plasma were also associated with the development of ARDS in critically ill and especially septic patients, but not in non-septic patients.[104]

EVs play a wide variety of roles as system-wide signaling particles in sepsis and related organ dysfunction. However, more information is needed on which EV components exert beneficial and/or detrimental actions, given the diversity of EV cargo and functional effects. Ongoing investigations into the cell or tissue-specific release of EVs, time course of release, composition, uptake, and functional effects will allow us to harness the potential of EVs to diagnose and treat complex pathophysiological states such as sepsis rapidly.

Extracellular vesicles and pain management

Perioperative pain management is complicated by choosing appropriate anesthetic modalities, patient history of previous pain syndromes, and subacute or chronic pain development. Individual patients often exhibit complex pain profiles that cannot be grouped into simple categories. Given these intricacies, there remains much room in improving our understanding of pathophysiology, development of novel biomarkers, and new treatment modalities. EVs have great potential to revolutionize pain management due to their ubiquitous and functional nature—work in this field is growing (Table 4).

Although currently limited, early investigations into EVs as biomarkers for pain diagnosis[105] or treatment stratification purposes show promise. Circulating EV miRNAs are altered in patients with complex regional pain syndrome (CRPS).[106] Plasmapheresis to remove autoantibodies and humoral factors can be utilized in combination with other modalities to treat the etiologically complex and difficult to manage pain in CRPS. To stratify responders and non-responders, a study looked for markers differentiating the two groups. Nine miRNAs in plasma EVs were significantly different before plasmapheresis between responders and non-responders.[107] A future study with a larger cohort and next-generation sequencing to study larger numbers of miRNAs may be able to identify an EV miRNA panel able to accurately predict response to therapy. To predict development of CRPS after trauma, Dietz et al. found that patients with a history of a fracture without CRPS had higher levels of plasma EV miR-223-5p than patients with history of fracture with development of CRPS type I. MiR-223-5p has potential significance to CRPS given its involvement in immune barrier breakdown, a hallmark of neuropathy related to leakage of blood-nerve or blood-spinal cord barrier and reduced expression of tight junction protein.[108] However, the specific mechanisms leading to cell barrier disruption remain to be explored. Other studies of EV cargo are implicating previously unknown mechanisms in the pathophysiology of chronic pain syndromes. Moen et al. showed that miRNA release in EVs is upregulated in nucleus pulposis cells, and higher extracellular miR-223, involved in immunomodulation, in the acute phase after disc herniation is associated with a lower risk of chronic lumbar radicular pain.[109]

EVs are therapeutic in pain disease states. The anti-inflammatory effect of EV cargo in treating pain has recently begun to be explored.[110] When injected intra-articularly in an animal model of temporomandibular joint OA, MSC-derived EVs reduce pain and inflammation and promotes joint regeneration and repair.[111] Intravenously administered MSC EVs also improve low back pain and attenuates cartilage degeneration and enabled subchondral bone remodeling in a lumbar facet osteoarthritis model.[112] In an inflammatory pain model, macrophage-derived EVs can attenuate thermal but not mechanical allodynia

when injected at the site of inflammation.[106] However, the opposite is seen when EVs are administered intrathecally, but only when EVs are derived from lipopolysaccharide (LPS) stimulated macrophages.[113] LPS-stimulated EVs have higher levels of miRNAs that inhibit proinflammatory cytokine transcription and translation.[106] EVs from both stimulated and unstimulated macrophages reduce thermal and mechanical hyperalgesia when given prophylactically, suggesting the possibility of a vaccine-like chronic pain therapy.[113] Changes in route and timing of administration and the state of originating cells have important differing effects. Thus, to fully harness their therapeutic potential, further studies are needed to improve our understanding of EVs.

Conclusions and future directions

Numerous studies have shown that EVs are important mediators of various pathophysiological states. The study of EVs in perioperative medicine, critical care, and pain management is in its infancy, but it is important to be aware of and understand the biology and potential of EVs to affect the practice of anesthesia. EVs are key players in ischemia-reperfusion, and the potential of EV based therapeutics is demonstrated in pre-clinical studies that have successfully modified EVs to target specific ischemic tissues and deliver customized cargo. EVs are known to play important roles in inflammation, and future studies to improve understanding of these roles will create new therapies for or prevent TRALI, ARDS, aspiration pneumonia, or sepsis-induced organ dysfunction. In contrast to cell-based therapies such as MSC therapy, the use of EVs are advantageous due to their ease of storage, low immunogenicity, and low thrombogenic risk. Modified, autologous EVs have been proposed as non-immunogenic drug vehicles. Despite the physiologically complex and diverse etiologies in pain disease states, the potential of EV-based biomarkers and therapies for pain management are emerging.

Mechanistic studies of the release, transport, and effects of EVs and their subtypes will undoubtedly continue to greatly improve our understanding of physiology, pathophysiological processes, diagnosis, patient stratification, and development of novel therapeutics. EV research is not without obstacles, especially given the technical difficulties of studying nanoparticles of varying and continuously changing composition mixed with other particles of similar density and size *in vitro*.[114,115] Fortunately, new data, guidelines, and techniques are standardizing and improving EV research.[116] Despite the challenges, EV research continues to provide exciting new insight into patient care. Perioperative and anesthesiology sub-specialty based EV research is presently limited compared to more developed EV fields such as cancer biology. However, Buschmann et al. recently showed the feasibility of studying EVs in patients in the intraoperative period by correlating the effects of different anesthetic agents on EV miRNA content. This paradigm shifting-work used EV's to reveal previously unknown physiological impacts of commonly used anesthetic agents.[6] Future developments in EV research and integration into perioperative medicine will likely change management of perioperative disease states and hold significant promise to improve the perioperative outcomes of patients.

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Glossary of Terms

AKI	acute kidney injury
ALI	acute lung injury
AQP1	aquaporin-1
ARDS	acute respiratory distress syndrome
ATF3	activating transcription factor 3
BAL	bronchoalveolar lavage
BBB	blood brain barrier
CCL2	C-C motif chemokine ligand 2
CCR2	C-C motif chemokine receptor-2
CNS	central nervous system
CSF	cerebral spinal fluid
COVID-19	coronavirus disease 2019
CPC	cardiac progenitor cell
CRPS	complex regional pain syndrome
EPC	endothelial progenitor cell
EV	extracellular vesicle
IL-1β	interleukin 1 beta
IR	ischemia-reperfusion
LPS	lipopolysaccharide
miRNA	microRNA
mRNA	messenger RNA
MSC	mesenchymal stem cell
MVB	multivesicular body
MV	microvesicle
NSC	neural stem cell

pRBCs	packed red blood cells
RIPC	remote ischemic preconditioning
PMN	polymorphonuclear leukocytes
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
TNFα	tumor necrosis factor alpha
TRALI	transfusion-related acute lung injury

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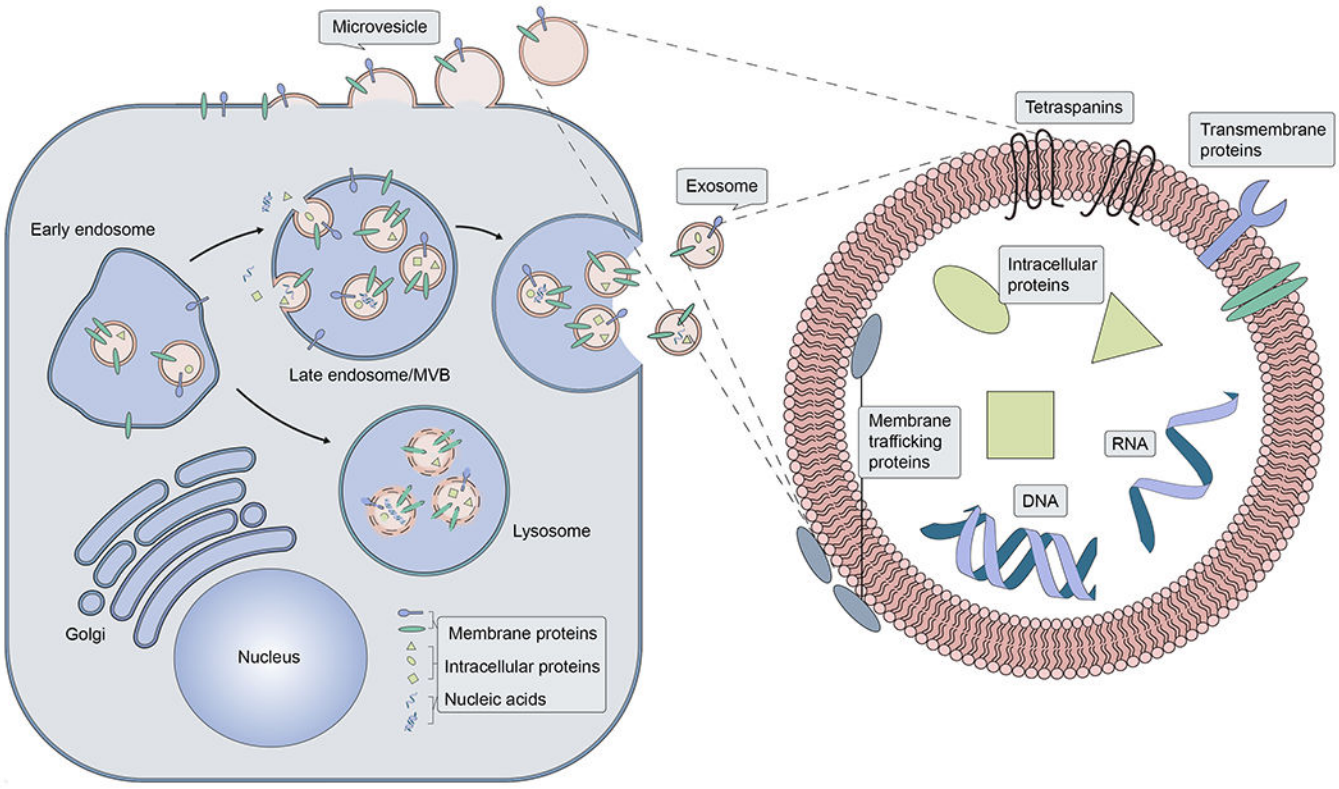

Figure 1:

Left. Extracellular vesicles (EVs) are formed via budding from the plasma membrane, (microvesicles), or via fusion of multivesicular bodies (MVBs) with the plasma membrane (exosomes). MVBs, also termed late endosomes, are part of the endolysosomal pathway. Right. EV characteristics include transmembrane proteins, key EV markers such as tetraspanins and membrane trafficking proteins involved in EV biogenesis, proteins, and nucleic acids such as DNA and RNA (microRNAs, messenger RNAs, small nucleolar RNAs, ribosomal RNAs[117]).

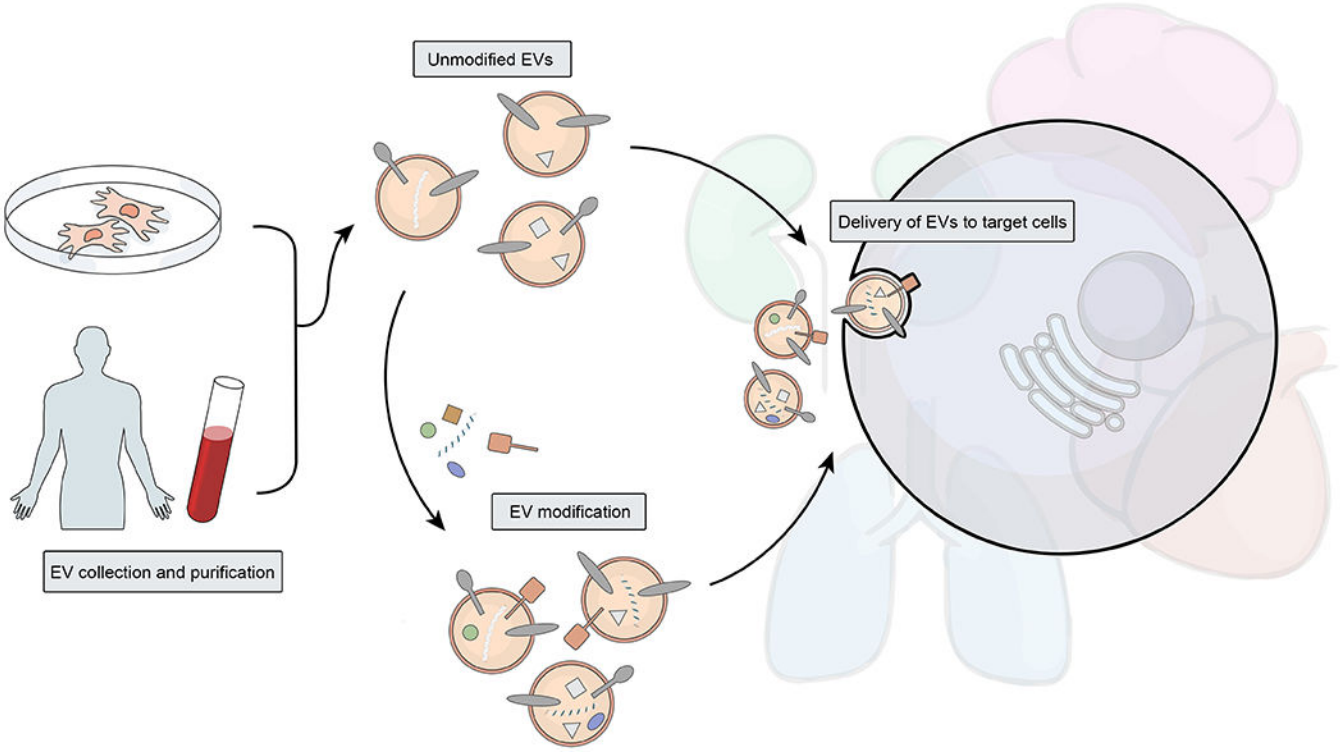

Figure 2:

Extracellular vesicles (EVs) can be collected and purified from cells such as mesenchymal stem cells (MSC), or animals for autologous or allogenic use. After collection and purification, EVs can be administered in an unmodified form or enriched with cargo or membrane proteins that exert an improved therapeutic effect. Unmodified or modified EVs exert therapeutic effects by interacting with cells in the tissues of many organ systems, including the brain, heart, lungs and kidneys.

Table 1.

EV Studies Described in the Extracellular Vesicles and Perioperative Ischemia Section – Cardiac Ischemia Subsection

Reference	Topic	EV Type/Treatment	Species	Route	Timing of EV/ Treatment	Effect	Proposed Mechanism
24	cardiac IR	MSC EVs	mouse	IV	before reperfusion	reduced infarct size	delivery of functional proteins, RNA
25	cardiac ischemia	MSC EVs	rat	intramyocardial	after ischemia	improved systolic and diastolic function	angiogenesis, inflammation modulation
26	cardiac IR	MSC EVs	mouse	IV	before reperfusion	reduced infarct size, improved myocardium viability, LV geometry, contractile performance	increased ATP, NADH levels, decreased oxidative stress
27	cardiac IR	MSC EVs	rat	intracoronary	before reperfusion	reduced infarct size, collagen deposition, fibrotic area, increased LVEF	decreased oxidative stress and inflammatory response signaling
30	cardiac IR	MSC EVs, miR-181a enriched	mouse	intramyocardial	after IR	decreased inflammatory response, infarct size, improved myocardial function	modulation of inflammation; mir-181a targets inflammation related genes
31	cardiac IR	CPC EVs	mouse	intramyocardial	before reperfusion	inhibition of apoptosis	modulation of gene expression by miR-451
32	cardiac IR	human CPC EVs	rat	intramyocardial	after IR	decreased scar size, apoptosis, improved ventricular function	PAPP-A activates IGF-1 receptor, intracellular AKT and ERK1/2 phosphorylation, decreased caspase activation
33	cardiac IR	human NSC EVs	mouse	IV	before IR	decreased infarct size	delayed cardiomyocyte mitochondrial permeability
34	cardiac IR	blood EVs	rat	IV	before IR	decreased infarct size	HSP70 activates pro-survival signaling pathway, binds TLR4, phosphorylation of ERK1/2 and HSP27
35	cardiac IR	blood EVs	mouse	intramyocardial	before IR	decrease myocardial apoptosis	phosphorylation of ERK1/2, HSP27, but not in diabetic EVs
36	cardiac IR, type II diabetes	blood EVs	rat, human	N/A	N/A	diabetic human, rat blood EVs not protective against hypoxia/ reoxygenation in vitro	HSP70 synthesis impairment in hyperglycemia and hyperlipidemia
38	cardiac IR	endothelial cell EVs	mouse	IV	before reperfusion	decreased myocardial damage, apoptosis, vacuolation, autophagy	lncRNA LINC00174 suppressed p53, decreased activation of AKT/AMPK autophagy pathway
39	cardiac IR	CPC EVs, CXCR4 enriched	rat	IV	after IR	improved cardia EV uptake and function, decreased scarring, apoptosis	ERK1/2 phosphorylation, CXCR4 binds to SDF1alpha, overexpressed on injured myocardium
40	cardiac IR	MSC EVs modified with platelet membranes	mouse	IV	after IR	Platelet-EVs improved cardiac function after IR versus unmodified EVs	platelet-EV accumulation in injured endothelium, improved angiogenesis

Reference	Topic	EV Type/Treatment	Species	Route	Timing of EV/ Treatment	Effect	Proposed Mechanism
41	cardiac IR	MSC EVs anoxic preconditioned	mouse	IV	before IR	improves MSCs cardioprotective properties	higher load of inflammasome-targeting miRNAs, apoptosis protection via sustained Bcl-2 expression
42	cardiac ischemia	coronary serum EVs, human, after ischemia	mouse	IM	after ischemia	enhanced angiogenesis compared to non-ischemic EVs	miRNA cargo modification; downregulation of miR-939-5p, improved iNOS expression and endothelial NO production
43	cardiac IR	GW4869 (small EV inhibitor)	mouse	intraperitoneal	before IR	improved cardiac function, decreased infarct size, myocardial enzyme levels	decreased NOS2 expression and inflammatory cytokines
44	cardiac ischemia, IR	PMN EVs, stimulated	rat	IV	continuous, 7 days after AMI/IR	improved cardiac function	AKT signaling pathway

Abbreviations. IR: ischemia-reperfusion, MSC: mesenchymal stem cell, EV: extracellular vesicle, LV: left ventricle, LVEF: LV ejection fraction, CPC: cardiac progenitor cell, PAPP-A: pregnancy-associated plasma protein A, IGF-1: insulin-like growth factor 1, Akt: protein kinase B, ERK1/2: extracellular signal-regulated protein kinase 1/2, HSP: heat shock protein, TLR4: Toll-like receptor 4, NSC: neural stem cell, AMPK: AMP-activated protein kinase, Bcl-2: B-cell lymphoma 2, lncRNA: long noncoding RNA, COX2: cyclooxygenase 2, TNFα: tumor necrosis factor alpha, NOX4: NADPH oxidase 4, PEDF: pigment epithelium-derived factor, USP14: ubiquitin specific peptidase 14, HITF1α: hypoxia inducible factor 1 alpha, AQP: aquaporin, ATF: activating transcription factor, CCR2: C-C motif chemokine receptor-2, CCL2: chemokine ligand 2, ER: endoplasmic reticulum, EPC: endothelial progenitor cell, SP1: specificity protein-1, X: times given, N/A: not applicable, where route, timing or mechanism not discussed

Anesth Analg. Author manuscript; available in PMC 2022 November 01.

Table 2.

EV Studies Described in the Extracellular Vesicles and Perioperative Ischemia Section – Cerebral and Spinal Cord Ischemia and Renal Ischemia Subsections

Reference	Topic	EV Type/Treatment	Species	Route	Timing of EV/ Treatment	Effect	Proposed Mechanism
Cerebral and Spinal Cord Ischemia							
45	cerebral IR	MSC EVs	mouse	intraventricular	before IR	restored basal synaptic transmission, plasticity, improved spatial learning and memory	decreased COX2 expression, improved synaptic transmission, neuron plasticity in hippocampus
46	cerebral IR	MSC EVs	rat	IV	before IR	improved neurological function, decreased edema, infarct area	Downregulated inflammasome- and pyroptosis-related proteins, microglia shift towards M2 phenotype
47	cerebral IR	MSC EVs	rat	intraventricular	3 X daily after IR	reduced infarct volume, apoptosis, increased mature neurons	miR-22-3p downregulation of an apoptotic activator BMF
48	spinal cord IR	MSC EVs, miR-25 enriched	rat	intrathecal	before IR	decreased lower motor neuron deficits, increased motor neuron survival in spinal cord	decreased IL1Beta and TNFα, miRNA-25 abolishes NOX4 enhancement after IR, decreases ROS
49	cerebral IR	NSC EVs	mouse	IV	after IR	reduced infarct volumes, preserved motor function	preservation of astrocyte function
50	cerebral IR	MSC EVs, PEDF enriched		intraventricular	3 X daily, 3 days before IR	decreased ischemic volume, increased autophagy, decreased apoptosis	PEDF mediated autophagy activation, caspase-9 and -3 apoptotic pathway inhibition
53	cerebral IR	microglia M2 type EVs	mouse	IV	after IR	reduced infarct volume, attenuated behavioral deficits	miR-124, targets and inhibits USP14
54	cerebral IR	M2 type microglial EVs	mouse	IV	3 X after IR	attenuated neuronal apoptosis, decreased infarct volume and behavioral deficits	miR-137 targets Notch1, effects adjacent cell signaling
56	cerebral IR	astrocyte EVs	rat	IV	before IR	improved balance and motor function, hippocampal neuron organization, decreased infarct area, apoptosis	possible miR-29a mediated inhibition of inflammation
59	cerebral ischemia	RIPC plasma EVs	mouse	IV	after ischemia	decreased infarct size	increased HITF1α delivery to brain increases tolerance to hypoxia
61	cerebral IR	MSC EVs, miR-210 enriched, surface peptide with affinity for integrin αvβ3	mouse	IV	7 X; after IR, every other day for 14 days	EVs targeted lesion, increased miR-210 at ischemia site, improved angiogenesis, survival	EVs bind integrin αvβ3 expressed in cerebral vascular endothelial cells after ischemia, miR210 promotes angiogenesis
62	cerebral ischemia	MSC EVs, miR-124 enriched, surface neuron-specific rabies virus glycoprotein	mouse	IV	after ischemia	target ischemic regions in brain, promotes neurogenesis in cortex	miR-124 promotes differentiation of neural progenitors

Reference	Topic	EV Type/Treatment	Species	Route	Timing of EV/ Treatment	Effect	Proposed Mechanism
Renal Ischemia							
65	renal IR	urine EVs	rat	N/A	N/A	urine EV AQP1 decreased from 6-96 hours after renal IR, without decrease in creatinine	N/A
66	renal IR induced AKI	urine EVs	rat	N/A	N/A	urine EV AQP1, AQP2 is reduced in IR induced AKI, before development of renal fibrosis	N/A
67	renal IR induced AKI	urine EVs	mouse	N/A	N/A	urine EV ATF3 60 fold higher in urinary EVs than in urine, EV ATF3 improves renal dysfunction induced by IR	ATF3 RNA inhibits potent endothelial cell produced chemokine, decreases recruitment of inflammatory cells
68	renal IR	renal tubular EVs, rat, normoxic and hypoxic	rat	IV	2 X, 1 and 2 days after IR	improved renal function, decreased fibrosis, tubular damage, oxidative damage	transcriptome shift reverses post-IR changes transcription of genes involved in apoptosis, inflammation, angiogenesis, oxidative stress, fibrosis
69	renal IR	renal tubular EVs, human, normoxic and hypoxic	rat	IV	2 X, 1 and 2 days after IR	improved renal function, decreased fibrosis, tubular damage, apoptosis, reversal of post-ischemic proteome shift	limit proteomic alterations or improve nutrient delivery, oxygenation
70	renal IR, RIPC	blood EVs, post-RIPC	rat	IV	after IR	improved renal function, histological appearance	N/A
72	renal IR	MSC EVs, CCR2 enriched	mouse	renal capsular	after IR	improved renal function, decreased monocyte infiltration, decreased tubular lesions	Surface CCR2 act as decoys, binds CCL2, decreasing extracellular CCL2 concentration, decreasing macrophage recruitment and activation in IR injury
73	renal IR	MSC EVs	mouse	IV	before IR	improved renal function, histological improvement	miR-199-3p suppresses apoptosis
74	renal IR	MSC EVs	mouse	IV	before IR	improved renal function	miR-199-5p decreases ER stress
75	renal IR	MSC EVs	rat	IV	after IR	improved renal function, decreased apoptosis, mitochondrial fragmentation	miR-30b/c/d modulates mitochondrial fission and reduces apoptosis in renal tubular cells
76	renal IR	MSC EVs	rat	IV	before IR	improved renal function, histological improvement, decreased oxidative stress	SP1 activates pathways that inhibits necroptosis

Abbreviations. IR: ischemia-reperfusion, MSC: mesenchymal stem cell, EV: extracellular vesicle, COX2: cyclooxygenase 2, BMF: B cell lymphoma-2 modifying factor, IL1β: interleukin 1 beta, TNFα: tumor necrosis factor alpha, NOX4: NADPH oxidase 4, PEDF: pigment epithelium-derived factor, USP14: ubiquitin specific peptidase 14, HITF1α: hypoxia inducible factor 1 alpha, AQP: aquaporin, ATF: activating transcription factor, CCR2: C-C motif chemokine receptor-2, CCL2: chemokine ligand 2, ER: endoplasmic reticulum, EPC: endothelial progenitor cell, SP1: specificity protein-1, X: times given, N/A: not applicable, where route, timing or mechanism not discussed

Table 3.

EV Studies Described in the Extracellular Vesicles and Inflammatory States in the Perioperative Period and Critical Care Section

Reference	Topic	EV Type /Treatment	Species	Route	Timing of EV /Treatment	Effect	Mechanism
Inflammation in Acute Lung Injury							
79	ALI, ARDS, hyperoxia induced	BAL EVs, lung epithelium derived	mouse	intranasal	N/A	ALI mice EVs increased neutrophil infiltration, inflammatory cytokine bursts, lung inflammation	caspase-3 transfer to alveolar macrophages
80	ALI, ARDS, acid exposure induced	BAL EVs, lung epithelium derived	mouse	intratracheal	N/A	ALI mice EVs increased macrophage recruitment into lung	miR-17, miR-122 modulation of macrophage β1 integrin recycling, promoting recruitment
81	ALI, ARDS, ventilator and infection induced	PMN EVs, synthetic miR-223 in nanoparticles	mouse	intratracheal	3 and 2 days before ventilator induced ALI	decreased acute lung inflammation	miR-223 transfer from activated PMNs to epithelial cells repress of PARP-1, enzyme involved in inflammation
82	ALI, sepsis induced	blood EVs	mouse	IV	N/A	ALI mice EVs taken up by alveolar macrophages, cause lung injury	miR-155 delivery to macrophages increases number of total and activated alveolar macrophages in lung
83	ALI, ARDS, sepsis induced	blood EVs	rat	IV intratracheal	N/A	ALI rat EVs induce interstitial and alveolar edema, diffuse alveolar destruction, hyaline membrane formation, neutrophil and red cell infiltration	EVs induced high myeloperoxidase levels, TNF-α, IL-1β, and IL-10 in BAL fluid and plasma
84	TRALI	apheresis platelet EVs	human	N/A	N/A	endothelial cell damage in vitro	EV CD40 Ligand-PMN CD40 interaction, induces respiratory burst
85	TRALI, hemorrhage resuscitation	pRBC EVs	mouse	IV	N/A	EVs increased with prolonged storage; pRBC EVs increase lung neutrophil infiltration after resuscitation, prime neutrophils, promote respiratory burst and phagocytosis	direct contact of EVs and neutrophils or transfer of a soluble mediator
86	TRALI	pRBC EVs	mouse	IV	N/A	EVs increased with prolonged storage; EV transfusion into LPS-treated mice induced ALI	critical illness leads to neutrophil recruitment into pulmonary endothelium, EVs and other soluble factors activate recruited neutrophils
87	ALI, hyperoxia induced	MSC EVs, human	mouse	IV	during hyperoxia	improves pulmonary function, alveolar septation, pulmonary hypertension, fibrosis and vascular remodeling	EV mRNAs direct pulmonary macrophages toward anti-inflammatory (M2) phenotype
89	ALI, trauma induced	MSC EVs	rat	IV	before trauma	improves oxidative injury, inhibits inflammatory response	miR-124-3p transfer inhibits upregulation of P2X7, purinergic receptor involved in human inflammatory and stress response

Anesth Analg. Author manuscript; available in PMC 2022 November 01.

Reference	Topic	EV Type /Treatment	Species	Route	Timing of EV /Treatment	Effect	Mechanism
90	ALI, LPS induced	MSC EVs	rat	IV	before intratracheal LPS	improved edema, hemorrhage, alveolar collapse, apoptosis, decreased NF-kB expression	miR-22-3p represses FZD6, which has known functions in tumorigenesis
91	ALI, LPS induced	EPC EVs	rat	IV	during intratracheal LPS	decreased pulmonary edema, hemorrhage, alveolar wall thickness, neutrophil infiltration, improved arterial PaO2, endothelial barrier function	miR-126 transfer to endothelial cells promote RAF/ERK pathways, increases proliferation, migration and angiogenesis
Inflammation and Sepsis							
95	sepsis, septic shock	blood EVs from septic patients	mouse	IV	N/A	circulating EVs in sepsis cause organ-specific changes in proinflammatory nitrative, oxidative stress protein expression	EVs in sepsis exert tissue-selective effects
96	sepsis, septic shock	blood EVs from septic patients	mouse	IV	N/A	increased sensitivity to serotonin mediated vasoconstriction	increased thromboxane A2
97	sepsis, septic shock	blood EVs	human	N/A	N/A	EVs contain differentially expressed miRNA and mRNA involved in inflammatory response, oxidative stress, cell cycle regulation	N/A
98	sepsis, myocardial depression	GW4869 (small EV inhibitor)	mouse	IV	before sepsis induction	decreased cardiac inflammation, improved cardiac function, prolonged survival	decrease in septic exosome induction of macrophage inflammatory cytokine release
99	sepsis	IL1B pre-treated MSC EVs	mouse	IV	after sepsis induction	more effective in inducing M2-like macrophage polarization, improved survival rate	miR-21 upregulated in IL1β stimulated MSC EVs, targets PDCD4, a tumor suppressor involved in apoptosis
100	sepsis, encephalopathy	MSC EVs	rats	IV	after sepsis induction	decreased blood apoptotic and inflammatory cells, decreased markers of inflammation, edema, DNA damage, apoptosis in brain	decreased blood and CSF inflammatory cytokines
101	sepsis, SIRS	blood	human	N/A	N/A	serum miR-15a and miR-16 levels distinguishes between sepsis/SIRS and non-septic/SIRS patients	N/A
102	sepsis, SIRS	blood	human	N/A	N/A	miRNA are differentially expressed in critically ill sepsis and non-infective SIRS patients	N/A
103	sepsis, septic shock	blood	human	N/A	N/A	miR-499-5p levels may distinguish between mild sepsis, severe sepsis, and septic shock	N/A
104	sepsis, ARDS	blood EVs	human	N/A	N/A	lower levels of EVs in critically ill, especially septic patients independently associated with ARDS development	N/A

Abbreviations. ALI: acute lung injury, ARDS: acute respiratory distress syndrome, BAL: bronchoalveolar lavage, PMN: polymorphonuclear leukocyte, TNF-α: tumor necrosis factor alpha, IL-1β: interleukin 1 beta, pRBCs: packed red blood cells, PARP-1: poly (adenosine diphosphate–ribose) polymerase–1, P2X7: purinergic receptor P2X ligand gated ion channel 7, FZD6: frizzled class receptor 6,

RAF: rapidly accelerated fibrosarcoma, ERK: extracellular signal-regulated protein kinases, PDCD4L: programmed cell death protein 4, CSF: cerebral spinal fluid, SIRS: systemic inflammatory response syndrome, N/A: not applicable, where route, timing or mechanism not discussed

Table 4.

EV Studies Described in the Extracellular vesicles and Pain Management Section

Reference	Topic	EV Type /Treatment	Species	Route	Timing of EV /Treatment	Effect	Mechanism
106	CRPS, inflammatory pain	macrophage EVs, LPS-stimulated or unstimulated	mouse	intraplantar	after inflammation induction	EVs resolved inflammation, improved thermal but not mechanical hypersensitivity. EV miRNAs are altered in CRPS patients	stimulated or unstimulated macrophage EVs may carry cargo that restores homeostasis in an inflammatory state
107	CRPS	blood EVs	human	N/A	N/A	lower exosomal miR338-5p in plasmapheresis non-responders	Mir-338-5p interacts with *Il6* mRNA. High IL-6 levels in responders may increase miR-338-5p to resolve inflammation
108	CRPS	blood EVs	human	N/A	N/A	miR-223-5p may protective against CRPS, edema formation, and a potential biomarker for CRPS	N/A
109	chronic lumbar radicular pain	nucleus pulposus EVs	rat	N/A	N/A	miR-223 is released in EVs from nucleus pulposus, decreases neuron activity in pain pathways, lower levels may predict chronic radicular pain	N/A
111	osteoarthritis, TMJ	MSC EVs	rat	intraarticular	2, 4, 8 X weekly after inflammation induction	improves pain, promote osteoarthritic and TMJ joint repair and regeneration	reduced inflammation, sustained proliferation, improvements in matrix expression
112	osteoarthritis, lumbar facet	MSC EVs	mouse	IV	4 X weekly after induction of spine instability	improves low back pain, attenuates cartilage degeneration, enables subchondral bone remodeling	decreases abnormal nerve and vessel formation in subchondral bone, inhibits osteoclastogenesis
113	inflammatory pain	macrophage EVs, LPS-stimulated or unstimulated	mouse	intrathecal	immediately after or 14 days before inflammatory pain induction	if given immediately after, attenuates mechanical allodynia; if given before, attenuates mechanical and thermal allodynia	modulation of immune regulatory pathways in spinal cord

Abbreviations. LPS: lipopolysaccharide, IL-6: interleukin 6, CRPS: complex regional pain syndrome, TMJ: temporomandibular joint, X: times given, N/A: not applicable, where route, timing or mechanism not discussed