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REVIEW ARTICLE

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# Preparing the spinal cord – priming or preconditioning? A systematic review of experimental studies

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**ABSTRACT**

*Objectives.* Paraplegia is devastating complication associated with thoracic and thoracoabdominal aortic aneurysm repair. Vast evidence has been gathered on pre-, peri- and postoperative protective adjuncts aiming to minimize spinal cord ischemia. This review focuses on the pretreatment phase of open surgical or endovascular aortic procedures and gathers the experimental data on the interventional preconditioning and priming methods that increase the spinal cord ischemic tolerance. *Design.* By the start of March 2021, a systematic review was performed in PubMed, Scopus and Web of Science core collection to identify the articles that reported (i) either an ischemic preconditioning, remote ischemic preconditioning or priming method prior to (ii) experimental spinal cord ischemia performed in endovascular or open surgical fashion mimicking either thoracic, abdominal or thoracoabdominal aortic aneurysm procedures. (iii) The outcomes were reported *via* neurological, motor-evoked potential, somatosensory-evoked potential, histopathological, immunohistochemical, physiological analysis, or in different combinations of these measurements. *Results.* The search yielded 7802 articles, and 57 articles were included in the systematic review. The articles were assessed by the evaluated species, the utilized pretreatment, the measured protective effects, and the suggested underlying mechanisms. *Conclusions.* The reviewed articles showed several possible mechanisms in ischemic and remote ischemic preconditioning for prevention of spinal cord ischemia. The main suggested method for priming was arteriogenetic stimulus. Future studies should confirm these hints of arteriogenetic stimulus with more precise quantification of the protective recruitment process.

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## Introduction

Ischemic spinal cord injury (SCI) remains the most devastating setback during and after the repair of thoracic and thoracoabdominal aortic aneurysms (TAAs, TAAAs). In open surgical repair, the reported overall incidence of SCI is up to 32%, and even in experienced centers the pooled spinal cord ischemia rate is 8.3% [1,2]. The most extensive aortic repairs, Crawford type II, managed *via* open surgically or endovascularly, still carry a risk up to 7.7%–12.7% in contemporary series [3–5]. The adverse neurological outcome is not just a personal tragedy for the individual affecting long-term survival and resulting in a socio-economical burden [3,6]. The plasticity of the spinal cord vasculature was recognized in the unintended staged replacement of the aorta in clinical studies. Retrospective data of patients having extensive thoracoabdominal aortic surgery either in single-stage or in two-stage revealed lower permanent paraplegia rates (15% vs. 0%, respectively) between the groups despite a significantly higher number of segmental arteries sacrificed in the two-stage group [7].

However, there exists limited consensus on the development of SCI and its prevention strategies. Some experts rely on the reattachment of the segmental arteries (SAs), extending intraoperative aortic clamp and ischemia times, aiming on elimination of critical hypoperfusion during the peri- and postoperative period. Whereas others sacrifice segmental arteries prior to aneurysm sack opening in order to avoid backbleeding and extensive prolonged intraoperative ischemia. The latter surgical strategy relies on the plasticity of the spinal cord vasculature [8].

Early studies of the spinal cord anatomy date back to the nineteenth century. The concept of one certain prominent artery, so called artery of Adamkiewicz, built the basis of the understanding of the spinal cord perfusion, and thus the surgical strategy later on for decades [9]. Lazorthes et al. broadened our understanding of the spinal cord blood supply with multiple anastomotic pathways outside the spinal canal within nearby tissues [10]. Thereafter, the concept of collateral network (CN) within the paraspinal muscles that situate alongside spinal canal bilaterally, was introduced by Etz et al. after extensive experimental and clinical analysis over the past decades. The features of the CN include

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dynamic alterations of the nutrient flow, axial network of small arteries with multiple anastomoses in the spinal canal, in the perivertebral tissue and in the paraspinous muscles. Inputs into the network involve segmental and extrasegmental, subclavian and hypogastric arteries [11–13].

The consistent anatomical and physiological studies of the spinal cord, involving spinal cord blood flow, spinal cord perfusion pressure, resin casts and imaging methods, have extended our knowledge of the collateral network anatomy and its physiology both in normal and in simulated aortic repair environments [12,14–21]. The collateral network divides into paraspinal and intraspinal compartments. Paraspinal compartment with immature arterioles serves as reservoir for spinal cord vasculature in long-term when disruption of network inflow is occurred [22]. Whereas the intraspinal compartment includes repetitive epidural arcades and anterior radiculomedullary arteries (ARMAs). Kari et al. have focused on the intraspinal compartment and cleared its contributions to the spinal cord blood supply as an immediate recovery source directly after serial occlusion of the segmental arteries in experimental and clinical studies [23–25]. In acute situations when network inflow is interrupted and crucial intraspinal arcades maintain sufficient blood pressure directing blood through ARMAs and further anterior spinal artery, paraspinal compartment requires blood flow stimulus which between these components is also secured *via* intraspinal epidural arcades to cover long-term changes in spinal cord vasculature [22].

The phenomenon of ischemic preconditioning (IPC), with brief sublethal ischemic periods prior to a more severe ischemic event, was first introduced by Murry et al. over three decades ago [26]. They occluded left circumflex artery in repetitive cycles prior to prolonged occlusion of the same artery reducing myocardial infarct size. In neural tissue the same concept of ischemic tolerance was introduced in a gerbil model [27]. Further studies found ischemic preconditioning to be similarly effective when applied at a distance along with another non-target tissue referring to a method of remote ischemic preconditioning [28,29] (RIPC). Gho et al. reported that short mesenteric artery occlusion contributed equally as effectively to myocardium protection as myocardial preconditioning [29]. In spinal cord protection, the first models were canine and rabbit models with ischemic preconditioning [30,31].

The method of priming, permanently altering the spinal cord vasculature, requires thorough understanding and acceptance of the collateral network concept introduced by Etz et al. It was discovered that the spinal cord vasculature has the ability to adapt to a change in perfusion inflow, by occlusion of selected segmental arteries as stimulus, rearranging the paraspinal CN resulting from the staged repair concept of aneurysms in humans [7]. Thereafter, the concept of minimally invasive staged segmental artery coil- and plug embolization (MISACE) was invented after experimental and first-in-man study on staged segmental artery sacrifice studies [32–36]. This concept was introduced to stimulate the spinal cord vasculature prior to surgery by means of minimally-invasive occlusion of a limited number of SA not resulting in a significant spinal cord ischemia with the consequence of paraparesis or paraplegia, but reducing the spinal cord blood flow enough to stimulate arteriogenesis.

In 2014, experimental pig models were introduced to prove the technical feasibility of endovascular coiling for all segmental arteries and optimize its threshold in spinal cord protection [34,37]. Geisbüsch et al. reported limited number of coiled segmental arteries prior to simulated hybrid TAA repair resulting in reduction of histologic damage in the spinal cord [37]. Interestingly, in the earlier canine studies, Fujimaki et al. and later Kato et al. also considered selective segmental artery sacrifice as beneficial and not harmful action prior to extensive *en bloc* tumor resections in spinal surgery. They studied the risk level of bilateral occlusion of segmental arteries producing spinal cord ischemia in different levels of the spinal cord [38,39].

We performed a systematic literature review to evaluate the experimental data concerning the topic preparing the spinal cord for upcoming ischemia in experimental models simulating thoracic, abdominal or thoracoabdominal aortic procedures in open or endovascular fashion. The articles were analyzed based on the method used to produce ischemic tolerance prior to spinal cord ischemia categorizing it as priming or preconditioning; ischemic or remote ischemic. The main aim was to evaluate the real protective effects of each method by reviewing the outcomes of the experimental studies, and mainly focusing on the final neurological recovery after SCI. Furthermore, the suggested mechanisms behind the protective actions were considered since the exact mechanisms of both pretreatments are still unclear.

## Materials and methods

By the start of March 2021, systematic literature searches in the PubMed, in the Scopus and in the Web of Science core collection were performed according to the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guideline [40] and its newly updated version [41] to identify full-length, English-language articles with the following search term: '(spinal cord protection OR spinal cord ischemia) AND (preconditioning OR remote ischemic preconditioning OR MISACE OR coiling OR staging OR segmental artery occlusion OR segmental artery ligation OR segmental artery sacrifice OR collateral network OR staged repair OR staged approach OR priming)'.

Studies with the following criteria were included: (i) experimental animal models were used; (ii) the preparing method was interventionally produced: clamped, coiled, covered altering the systemic or spinal cord blood flow balance prior to spinal cord ischemia; (iii) the spinal cord ischemia set-up simulated thoracic, abdominal or thoracoabdominal aortic procedure in open or endovascular fashion; (iv) the results were reported with neurological outcome; histopathological analysis; immunohistochemical analysis; physiological characteristics i.e. direct spinal cord perfusion pressure, cerebrospinal fluid pressure, regional spinal cord

blood flow; motor-evoked potential (MEP) or somatosensory-evoked potential (SSEP) monitoring.

Only original articles, English-written articles, articles studying experimental animal model, interventional pretreatments and studies simulating aortic procedures were included. In addition, reference list screening was performed to search eligible articles according to the defined criteria. The defined terms of paraplegia were borrowed from the authors and any variables or terms were not defined additionally.

## Results

The results are summarized in Supplementary Tables 1–4. This systematic review included 57 articles (Figure 1). Two articles published results of the same study population [42,43]. The additional information of the second article was evaluated and clearly marked in the Supplementary Tables 2 and 4. The included articles studied the following species: pig (18 articles; 16 articles of the original study population), dog (three articles), rabbit (19 articles), rat (16 articles) and mouse (one article) models. The articles included pretreatment methods as ischemic preconditioning in 32 articles [30,31,44–73], remote ischemic preconditioning in 11 articles [74–83] or compared the protective actions of ischemic preconditioning, remote ischemic preconditioning, ischemic postconditioning or different combinations of the aforementioned methods in five articles [84–88]. The rest nine articles [20,32,33,36,37,43,89–91] involved the method of priming as pretreatment. There were varieties of ways providing spinal cord ischemia, preconditioning: ischemic and remote ischemic and priming, as well as reporting neurological outcome and these are summarized in Supplementary Tables 1–4.

### *Ischemic preconditioning*

The suggested mechanisms underlying ischemic preconditioning protection were heat shock proteins alone or

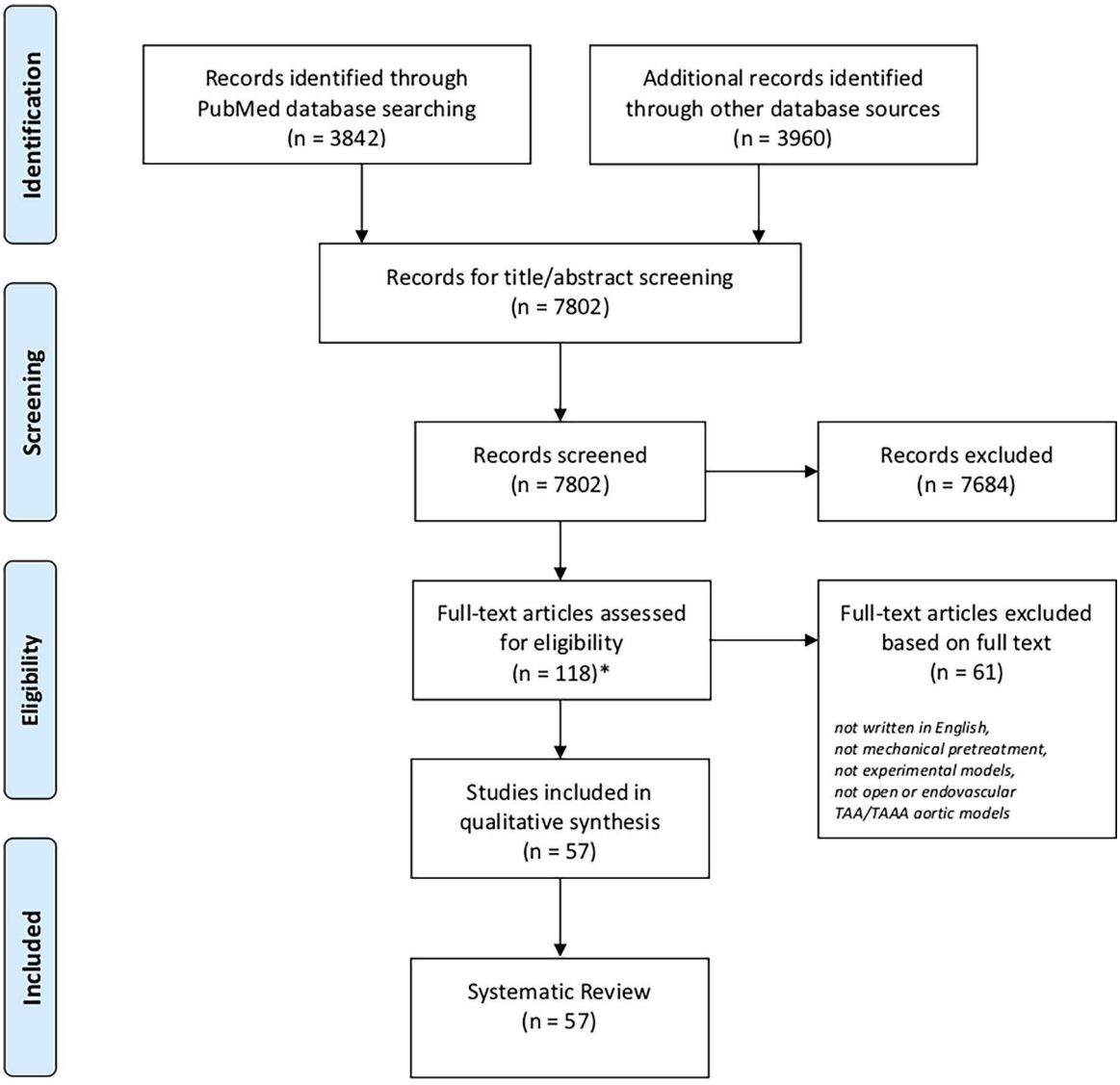


Figure 1. Flow chart of the systematic review process. Studies not written in English, not studying experimental animals, not using mechanical pretreatment, and not using simulated endovascular or open surgical aortic models for spinal cord ischemia were excluded. In total, 57 studies were included. Flow-chart modified after Moher et al. [40]. *Three articles were included in the analysis through reference list search.

together with cytoskeleton elements and their signaling pathways or tissue architecture elements [27,44,48,49,57,68,69]. Catecholamine and its metabolites by Fan et al. [46], as well as, copper, calcium, magnesium, zinc by Yu et al. [61], oxidative stress by Lee et al. [63], proliferative, degenerating and ependymal cells by Orendáčová et al. [55,59] were also evaluated as possible mechanisms. Spinal cord blood flow and autoregulation, as physiological changes were also suggested mechanisms in the studies by Ueno et al. and Zvara et al. [50,56]. Tight junction protein marker, vascular permeability and inflammation were also studied mechanisms by Fang et al. [70]. The study interest was focused on apoptosis by Yang et al. and Li et al. [64,73], autophagosomes by Fan et al. [71] and endoplasmic reticulum stress by Li et al. [73] and their downstream actions. Whereas by Uento et al. the recent study focused on microRNA-analyses and contribution of vascular endothelial growth factor (VEGF), growth/differentiation factor 15 (GDF15) and CD34-positive bone marrow cells (CD34 cells) [72].

### Remote ischemic preconditioning

Following effects of RIPC in association with SCI were suggested: heat shock proteins by Selimoglu et al. [74], Cannabinoid-1 and Cannabinoid-2 by Su et al. and Jing et al. [75,79], endocannabinoids by Su et al. [75], oxygen free radicals and antioxidants [42,76,78,80–82] in several articles, apoptosis by Haapanen et al. and Herajärvi et al. [42,78] and tight junction protein, endothelial cell markers by Jing et al. [79]. Inflammatory markers, nitrate/nitrite levels, activity of iNOS were studied mechanisms of RIPC by Bashir et al. [81] together with diminished glutamate concentrations and suppressed N-methyl-D-aspartate receptor 2B subunit expression by Mukai et al. [82].

### Combined conditioning

The studied markers and mechanisms included neuron specific enolase and nitric oxide by Gurcun et al. [84], oxygen free radicals suggested by several groups: Gurcun et al. Jiang et al. and Fukui et al. [84,86,88], amyloid precursor protein by Jiang et al. [86] and apoptosis by Sapmaz et al. [87]. Fukui et al. focused on several mechanisms including ERK/Akt(2), adenosine A1 receptor, and mitochondrial ATP sensitive potassium channel [88].

### Priming

The suggested mechanisms of priming's protective effects included increase in perfusion *via* collateral circulation by Vacanti et al. [89], stabilization of hemodynamics by Etz et al. [20] and vascular remodeling by Zoli et al. and Bischoff et al. [32,33]. Increased angiogenetic response was suggested by Geisbüsch et al. and Lewis et al. [37,43], whereas increased arteriogenetic stimulus was widely suggested mechanism by several groups: von Aspern et al. Geisbüsch et al. and Honkanen et al. [36,37,43,90]. The articles that reported the early protective window, suggested that intraspinal compartment serves as an acute backup in spinal cord protection studied by Kari et al. [91] or priming could effect on post-translational modifications and inhibiting steal phenomenon speculated by Honkanen et al. [90].

## Discussion

This systematic review gathers current literature concerning the topic of preparing the spinal cord for upcoming severe ischemic insult with pretreatments defined as preconditioning or priming. In other organs, the method of preconditioning is characterized by early and late protective windows. In neural tissue, the early window lasting 30–60 min focuses on the posttranslational modifications, whereas the late window of 24–72 h targets gene expression and protein synthesis [92]. In the spinal cord, protective effects of ischemic preconditioning were observed both in early and late settings. Whereas remote ischemic preconditioning studies focused only on the early protective window in the current review.

Despite the vast body of literature available on the topic of preconditioning, no clear understanding of its mechanisms and efficacy has been gained. In the spinal cord, the early studies on heat shock proteins (HSP) reported mainly positive results [48,49,68,69,73]. Heat shock proteins are chaperons taking part in the process of protein folding. The cellular distribution of HSPs was evaluated by Matsumoto et al. their presence in the nucleus was detected in conditioned animals suggesting participation in the mechanism of preconditioning [49]. In contrary, Selimoglu et al. have reported increased HSP expression in both preconditioned and control animals [74]. In addition, Kyrou et al. found no relationship between HSPs and β-catenin which is a protein maintaining tissue architecture and cell polarity in adherent junctions, and thus HSP lacks its regulatory role on β-catenin during early ischemic preconditioning [69]. They concluded that β-catenin showed increased levels, as well as translocation between cytoplasm and nucleus suggesting its role in Akt regulation resulting in antiapoptotic and cytoprotective effects [69].

Preconditioning with modified balance between oxidative stress and antioxidants such as catalase and superoxide dismutase has also been excessively studied in different experimental setups [42,63,76,78,80–82,84,86]. Dong et al. suggested positive relationship between initial oxidative stress produced in RIPC and spinal cord protection *via* upregulating antioxidant enzyme activity i.e. small amount of reactive oxygen species (ROS) serves as a trigger for protective actions [76]. Additionally, it has been shown that RIPC, in its early protective window, increased levels of antioxidant regulator nuclear factor erythroid 2-related factor (Nrf2) expression and thus induced positive antioxidant response to oxidative stress [78]. However, no Nrf2 expression was detected after the 24-h follow-up [42]. Interestingly, experimental studies of pharmacological preconditioning of the spinal cord have also reported diminished oxidative stress [93,94].

Nevertheless, according to Fukui et al. it is not the free radicals, adenosine, mitochondrial ATP sensitive potassium channel that play the primary role in preconditioning, but phosphorylation of Akt2 which is one isoform of Akt and thus potential promoter of neuronal survival as seen in cultured neuronal cells. The study set-up focused on early window of IPC and thus phosphorylation of 43 proteins were further analyzed to detect key enzymes, and thus an increase in phosphorylation of Akt2 was detected by immunoblotting [88].

The cell death processes, involving necrosis, apoptosis and autophagy, and their role in neural tissue damage has also been an important topic of research. Reduced apoptosis was found in several studies in conditioned animals [64,87]. Activation of apoptosis signal-regulating kinase 1 (ASK1), which has a role in the apoptotic signaling mechanisms, and the protein 14-3-3, which regulates cell proliferation and survival, cause binding together suppression of the ability of ASK1 to induce apoptosis. Thus, Yang et al. showed that IPC has protective effects against ASK1/14-3-3 dissociation-induced spinal cord injuries [64]. Fan et al. showed that IPC was associated with prolonged and enhanced post-ischemic autophagic response. It has also been suggested that autophagy could promote the survival of spinal neurons following ischemia and therefore a molecular link between apoptosis and autophagic cell death should be studied [71].

The most recent study of gene expression regulator microRNA reported that IPC resulted in downregulation of 13 microRNAs, and downregulation of seven microRNAs was even further confirmed by RIPC pretreatment. Additionally, IPC increased VEGF levels by downregulating microRNA-762, microRNA-3072-5p in CD34-positive bone marrow cells [72].

In clinical perspective, remote ischemic preconditioning provides feasibility with its easily applicable, low-cost, safety features performed in anesthesia induction compared with ischemic preconditioning requiring additional actions during the surgery. Therefore, when relying on early protective window of preconditioning no additional treatment days are required. In recent systematic reviews and meta-analysis, RIPC has not been proven to be efficient in association with open surgical or endovascular abdominal aneurysm repair when considering renal and cardioprotective perspectives or perioperative survival rates [95,96]. To our knowledge, there are no studies focusing on spinal cord preconditioning and thoracoabdominal aortic procedures in clinical settings.

Spinal cord and collateral network priming aim to stimulate the collateral blood flow to spinal cord by means of permanent altering of its neighboring vasculature, however not leading to ischemic tissue injury. A recent extensive review by Simon et al. introduced different signaling pathways such as phosphoinositide 3 kinase, the antiapoptotic kinase, the endothelial nitric oxide synthase, the Erk1, the delta-like ligand, the jagged NOTCH and the midkine regulatory cytokine in association with priming and its potential underlying mechanism of arteriogenesis [22]. Their conclusions of networks were extrapolated from lower limb ischemia studies i.e. occluding femoral artery, and thus no direct spinal cord priming studies were included [22]. After stress stimulus several cascades are initiated, and these key pathways involve with coordination and remodeling of the collaterals, metabolism, apoptosis, cell survival, proliferation and growth and inflammatory response [22]. The hints and suggestions of arteriogenetic stimulus base on experimental imaging and resin cast studies with segmental artery sacrifice showing increased density of intramuscular paraspinous vessels, a shift of size distribution from small to larger arterioles, parallel realignment of arterioles, dilatation of anterior spinal artery (ASA) and proliferation of small collateral vessels [15,21]. Recently, Lewis et al. reported that in a microarray analysis and gene expression profiling study, several modified cell-signaling cascades were detected in the biopsies of paraspinal muscles after selective segmental artery occlusion in a pig model [43].

Arteriogenesis and angiogenesis are the two mechanisms of new blood vessel formation after embryonic phases sharing some growth features, but also differing in many aspects [97]. In spinal cord priming studies these two mechanisms are speculated without clear consensus and detailed studies [32,33,36,37,43,89,90]. Angiogenesis is characterized by a formation of new blood vessels from preexisting capillaries with local hypoxia/ischemia being the main initiator of the process. Among the factors stimulating angiogenesis are vascular endothelial growth factor, hypoxia inducible factor (HIF-1), placental and fibroblast growth factor (PIGF and FGF-2), angiopoietins and many others [97,98]. During angiogenesis the steps of endothelial migration and proliferation, extracellular proteolysis, endothelial differentiation and vascular wall remodeling are followed by [97]. In these blood vessel tubes the wall structure, and adventitial stabilizing structures are undeveloped for example lacking smooth muscle cells, hence these capillaries are not fully functioning collateral arteries adapting to physiological changes in blood supply. Their growth is characterized by intussusception or sprouting i.e. an increase in their density and thus functioning *via* effective diffusion with short distances [97,98]. Noteworthy, the actions of angiogenesis take usually days compared to days to weeks in arteriogenesis [97].

Arteriogenesis is defined as rapid local recruitment of the capillary bad leading to its differentiation into new collateral arteries [97]. The main trigger of arteriogenesis is not ischemia but increased arterial shear stress in combination with local inflammation (monocytes, lymphocytes, intracellular adhesion molecules and other inflammatory agents) [97,99,100]. The multifactorial process of arteriogenesis involves activation of endothelium, attraction and invasion of circulating cells, creation of inflammatory environment, proliferation and remodeling phases, changes of basal membrane and extracellular matrix resulting in replacement of the old structures [97,100]. Notably, arteriogenesis depends on the organ or vascular region involved, since metabolic needs, oxygen availability, oxygen radicals and shear stress have species-dependent differences [22,100]. In hind limb artery occlusion studies of rabbits and rats the time span for vascular remodeling has been suggested to occur in 7 days and up to 3 weeks. In neural tissue some capillary

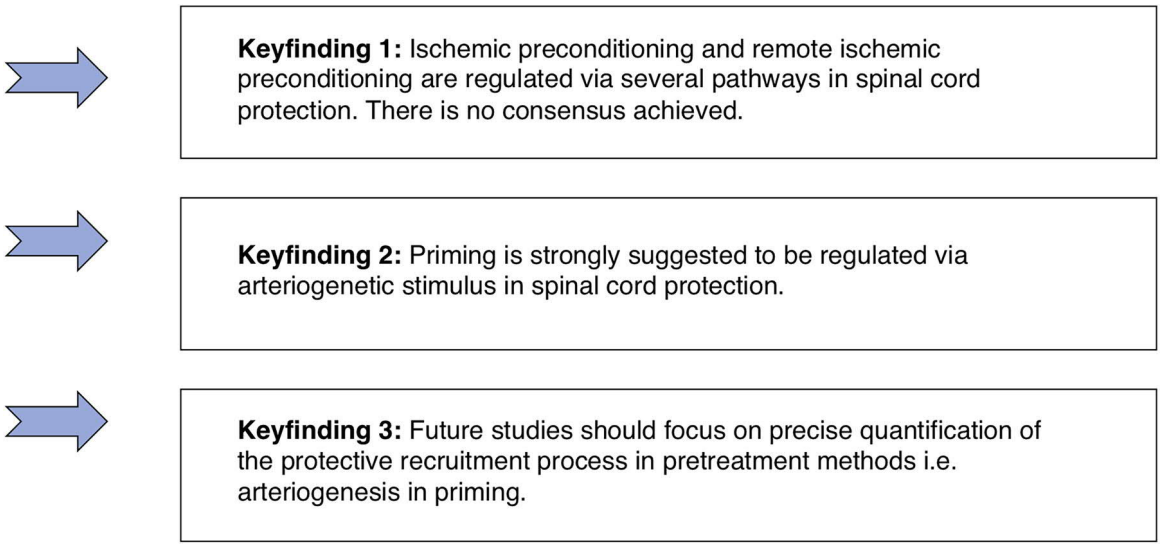


Figure 2. Summarized key findings of the systematic review.

proliferation occurs 5–7 days after ligation and doubling of diameter in collateral arterioles is detected 30 days later [100]. In a rat model of triggering cerebral arteriogenesis 7–14 days showed clear changes in cerebral collaterals *via* magnetic resonance imaging assessing blood flow and vessel length and diameter in addition to immunohistochemistry findings [101]. The cell types involved in arteriogenesis derive from at least two signaling pathways: bone marrow-derived cells for remodeling and another signaling pathway causing endothelial and smooth muscle cells to enter the cell cycle leading to proliferation [99].

For the first time endovascular priming, MISACE, was reported in two clinical cases in 2014 [34]. With a cohort of 57 patients, Branzan et al. reported the results of MISACE as a pretreatment strategy prior to endovascular aortic repair. The retrospectively derived data reported zero paraplegia rate in pre-treated patients. However, in 13 patients backpain was observed after MISACE. This complication should be kept in mind and interpreted as a sign of muscle ischemia [102]. The suggested mechanisms of arteriogenetic stimulus should also be clarified thoroughly. It is possible that in the near future, the extent of triggered by MISACE arteriogenesis could be evaluated *via* blood or cerebrospinal fluid samples in order to insure adequate acquired spinal cord protection. In clinical settings this could potentially optimize the pretreatment strategy. Moreover, patients with known aortic aneurysms under surveillance, not reaching the treatment threshold yet could be primed in advance and thus be prepared for the unfavorable emergent complication of dissection, thus, the treatment profile of MISACE could be later extended to acute settings too. Noteworthy pretreatment would cause extra costs but since MISACE is easily applicable with local anesthesia and thus no recovery from general anesthesia is required limiting its feasibility. Additionally, radiation amounts can be kept reasonable with upfront planning.

Considering the heterogeneity and lack of standardization of different species, study definitions including preconditioning or priming protocol, discrepancies in spinal cord ischemia definition, and study endpoints, no meta-analysis could be performed setting limitations of the study. There are studies settling time limits for induced irreversible spinal cord ischemia in different species [32,103]. However, some study protocols went beyond these limits when inducing SCI, others used alternative models to produce paraplegia, for example using endovascular stent grafts in the study of Geisbüsch et al. [37]. One could suppose that these extreme ischemia durations diminished the protective effects of pretreatments. On the other hand, possible different underlying pathophysiology of the spinal cord ischemia in endovascular and surgical repairs could be speculated effecting the results [104]. Therefore, especially endovascular repair studies should focus on gathering precise understanding of the mechanisms in spinal cord ischemia in which pretreatment strategies should target in future settings.

In conclusion, several underlying mechanisms in ischemic and remote ischemic preconditioning against the spinal cord ischemia were studied focusing on different cellular processes and lacking clear consensus. The main suggested method for priming was arteriogenetic stimulus recruiting the reservoir of collateral network and especially its paraspinal compartments in the fight against permanent paraplegia. Future studies should evaluate the mechanisms of arteriogenetic stimulus with more precise quantification of the protective recruitment process (Figure 2). The first ongoing prospective, controlled, randomized, multicenter, publicly funded, clinical trial of minimally invasive staged segmental artery coil embolization in aortic repair, shortly named PAPAartis will define the role of the MISACE as priming method in clinical practice [105].

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