



Potential Roles of Exercise in Regulating Myoendothelial Feedback in Resistance Arteries

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PURPOSE: Resistance arteries rely on tightly coordinated signaling between vascular smooth muscle cells (SMCs) and endothelial cells (ECs) to regulate vascular tone and ensure appropriate tissue perfusion. Myoendothelial feedback via gap junctions is crucial in limiting excessive vasoconstriction triggered by myogenic and sympathetic stimuli. This review synthesizes current knowledge on second messenger-dependent SMC-to-EC communication and explores how exercise training modulates these heterocellular signaling pathways to influence myoendothelial feedback.

METHODS: Relevant literature was systematically retrieved from major scientific databases (e.g., PubMed and Web of Science), with a primary focus on studies examining vascular myoendothelial feedback regulation and the effect of exercise training on SMC-EC heterocellular communication.

RESULTS: SMC activation by adrenergic or purinergic stimuli generates intracellular Ca^{2+} and IP_3 signals that are transmitted to adjacent ECs via myoendothelial gap junctions. These signals elicit localized endothelial Ca^{2+} events, stimulate nitric oxide production, activate endothelial IK_{Ca} and SK_{Ca} channels, and induce endothelium-dependent hyperpolarization, collectively suppressing SMC contraction. Ca^{2+} diffusion and IP_3 transfer contribute to this negative feedback, with growing evidence supporting $\text{C}^{2+}/\text{IP}_3$ -dependent signaling as a dominant mechanism during physiological sympathetic activation. Exercise training enhances endothelial C^{2+} signaling capacity, improves gap junctional communication, and augments downstream vasodilatory responses.

CONCLUSIONS: Myoendothelial feedback represents a critical protective mechanism against excessive vasoconstriction in resistance arteries. Exercise training reinforces this negative feedback by strengthening endothelial signaling and heterocellular communication, thereby promoting vascular homeostasis during physiological stress.

Key words: Ca^{2+} , Endothelium-dependent hyperpolarization (EDH), Heterocellular communication, Inositol 1,4,5-trisphosphate (IP_3), Myoendothelial gap junctions

INTRODUCTION

In the integrated cardiovascular system, resistance arteries regulate blood flow distribution and blood pressure [1]. Small arteries possess an intrinsic ability to tune their diameter in response to physiological changes - such as fluctuations in intravascular pressure - to control blood flow appropriately [2]. Additionally, perivascular sympathetic and sensory nerves play a crucial role in modulating peripheral vascular resistance by releasing neurotransmitters into the vessel wall [3]. Endothe-

lial cells (ECs) and smooth muscle cells (SMCs) are the primary cellular components of resistance arteries and coordinate intracellular and intercellular signaling pathways to maintain hemodynamic homeostasis. Disruption of this coordinated signaling can contribute to the development of cardiovascular disorders.

For instance, myogenic vasoconstriction of cerebral arteriolar myocytes is restrained by Ca^{2+} release events from ryanodine receptors (RyRs) in the sarcoplasmic reticulum of SMCs, termed “ Ca^{2+} sparks”. These signaling events stimulate large-conductance Ca^{2+} -sensitive K^+

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(BK_{Ca}) channels, which limit Ca²⁺ influx via inhibition of voltage-dependent Ca²⁺ channels (VDCCs) [4,5]. This intracellular negative feedback prevents exaggerated vasoconstriction, cerebral ischemia, and neuronal hypoxia [5,6]. However, some vascular beds, including the skeletal muscle microcirculation, do not possess this intracellular signaling mechanism [7,8] and rely more heavily on intercellular communication between SMCs and ECs to govern vascular reactivity.

The functional integration of SMCs and ECs is critical for controlling blood flow/pressure and limiting excessive contractility; this is mediated by direct cell-to-cell contact and myoendothelial gap junctions (MEGJs) [9,10]. Initial contractile signaling of SMCs evoked by perivascular nerve activation is transmitted to ECs via MEGJs, where it is subsequently attenuated by endothelial-derived vasodilatory pathways. This feedback regulation in myogenically active and sympathetically innervated SMCs plays a vital role in preventing the total cessation of blood flow and maintaining vascular patency.

Exercise training is characterized by repetitive increases in blood flow and intraluminal shear stress. These hemodynamic stimuli act as potent physiological signals that enhance endothelial vasodilatory function [11-13]. In resistance arteries supplying skeletal muscle, exercise training improves endothelium-dependent vasodilation and attenuates excessive vasoconstrictor responses [14,15], suggesting enhanced EC-mediated negative feedback on SMC contractility. Specifically, exercise training increases endothelial Ca²⁺ signaling and reinforces Ca²⁺-dependent activation of endothelial small- and intermediate-conductance Ca²⁺-sensitive potassium channels (SK_{Ca} and IK_{Ca}) [16,17]. These adaptations strengthen endothelium-dependent hyperpolarization (EDH) and the diffusion of EDH factors (EDHF) through MEGJs to SMCs, ultimately improving vasodilatory function.

These mechanisms are particularly relevant during exercise, a state defined by markedly elevated sympathetic nerve activity. During physical activity, α_1 -adrenergic SMC contractile signaling must be precisely counterbalanced by EC-derived vasodilatory mechanisms (including NO- and EDH-dependent pathways) to preserve tissue perfusion. Although direct evidence linking exercise training to altered SMC-derived signals (e.g., Ca²⁺ and IP₃) transfer to ECs through MEGJs is limited, several lines of evidence support this possibility. Given that SMC-derived Ca²⁺ and IP₃ have been identified as critical messengers initiating endothelial Ca²⁺ release and subsequent NO- or EDH-mediated suppression of vasoconstriction [6,18,19], exercise-induced enhancement of endothelial signaling capacity may increase SMC-to-EC heterocellular myoendo-

thelial feedback. This, in turn, contributes to proper blood flow regulation and vascular protection against excessive vasoconstriction. Therefore, this literature review discusses heterocellular communication between SMCs and ECs in resistance arteries, conceptualized as myoendothelial feedback mechanisms, and explores the specific mechanisms by which exercise training modulates myoendothelial negative feedback regulation. A schematic overview summarizing the proposed mechanisms of SMC-EC heterocellular communication and the potential modulatory effects of exercise training on myoendothelial feedback regulation is presented in Fig. 1.

1. Initiators for myoendothelial feedback mechanism

The sympathetic nervous system regulates vascular tone by activating adrenergic and purinergic receptors in SMCs [20]. Propagation of action potentials along the efferent axon triggers Ca²⁺ influx in the depolarized presynaptic membrane, stimulating the release of neurotransmitters such as norepinephrine and adenosine triphosphate (ATP) from sympathetic varicosities [21]. Once released, norepinephrine binds to postsynaptic α_1 -adrenergic receptors (α_1 ARs) on SMCs. As α_1 ARs belong to the G_q protein-coupled receptor (GPCR) subfamily, the binding of norepinephrine to α_1 ARs induces G_q protein-mediated activation of phospholipase C (PLC) activation, yielding diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP₃) through the metabolism of the membrane phospholipid, phosphatidylinositol 4,5-bisphosphate (PIP₂). DAG is linked to the activation of transient receptor potential canonical 6 (TRPC6) channels and facilitates Ca²⁺ entry through a PKC-independent mechanism [22,23]. The released IP₃ leads to intracellular Ca²⁺ release from IP₃ receptors (IP₃Rs) in the sarcoplasmic reticulum of SMCs [24].

Additionally, the neurotransmitter ATP activates two types of purinergic receptors: P2X and P2Y [25]. Specifically, P2X₁ ionotropic receptors are primarily expressed in the SMCs of resistance arteries [26,27]. ATP-mediated activation of P2X₁ receptors evokes Ca²⁺ and/or Na⁺ influx, causing rapid and transient depolarization [28]. When the excitatory junction potential is sufficiently large, sympathetic vasoconstriction is mediated by the activation of VDCCs in SMCs [29-31]. According to previous studies, adrenergic and purinergic receptor activation results in distinguishable Ca²⁺ events in SMCs: 1) P2X₁-mediated rapid and transient Ca²⁺ entry [26,32] and 2) IP₃-mediated slow-onset Ca²⁺ waves [29, 33]. These distinct Ca²⁺ events are associated with SMC contraction [30, 34]. The extracellular and intracellular Ca²⁺ signals and IP₃ generation in

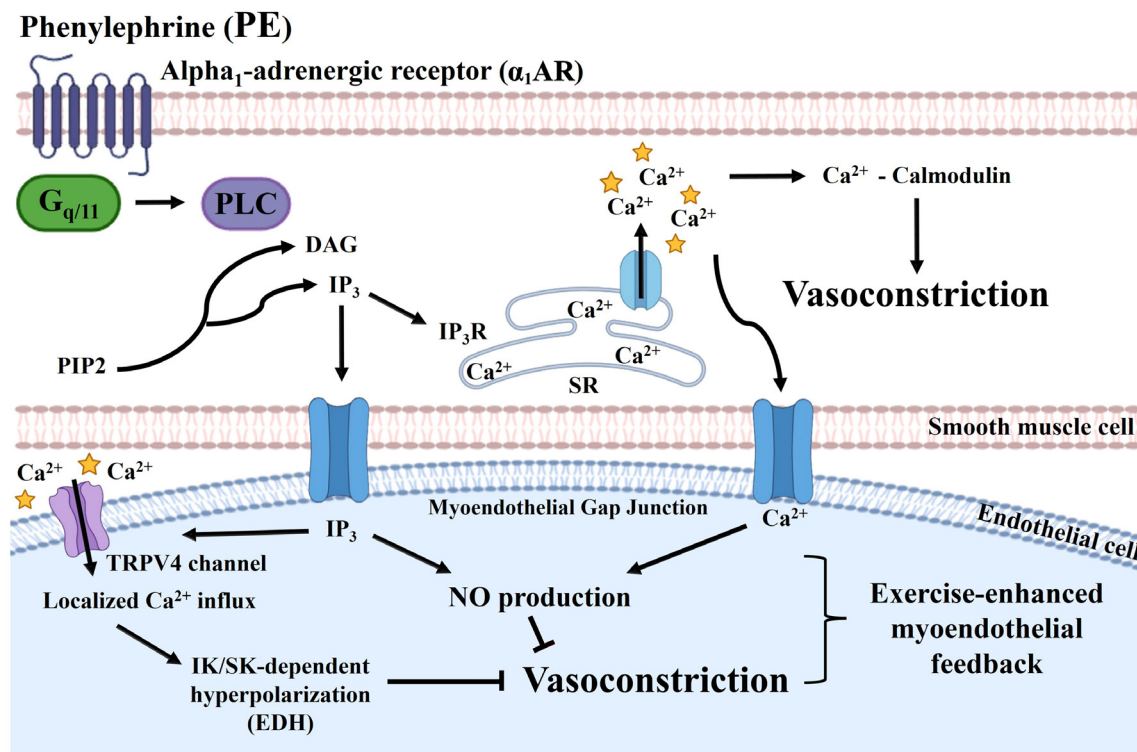


Fig. 1. Schematic illustration of myoendothelial feedback mechanisms and the modulatory effects of exercise training in resistance arteries. Sympathetic or agonist-induced α_1 -adrenergic activation of smooth muscle cells (SMCs) generates Ca^{2+} and IP_3 signals that are transmitted to adjacent endothelial cells (ECs) via myoendothelial gap junctions (MEGJs). These signals evoke localized endothelial Ca^{2+} elevations, activating nitric oxide (NO) production and endothelium-dependent hyperpolarization (EDH) through $\text{IK}_{\text{Ca}}/\text{SK}_{\text{Ca}}$ channels, which collectively suppress SMC contraction. Exercise training is potentially proposed to enhance endothelial Ca^{2+} signaling capacity, gap junctional communication, and downstream vasodilatory pathways. These adaptations strengthen myoendothelial negative feedback, contributing to improved vascular tone regulation and protection against excessive vasoconstriction.

SMCs not only contribute to sympathetic vasoconstriction but are also involved in SMC-to-EC heterocellular communication. Thus, neurally released transmitters required for endogenous agonist-dependent activation of GPCRs in SMCs and the subsequent production of second messengers (Ca^{2+} and IP_3) serve as primary initiators of myoendothelial feedback regulation.

2. Ca^{2+} -dependent SMC-EC communication

The functional cooperation of SMC and EC in resistance arteries is essential for appropriate vasomotor reactivity. Vascular smooth muscle tone is modulated by endothelium-derived relaxing or hyperpolarizing factors [35]. Phenylephrine (PE), a specific $\alpha_1\text{AR}$ agonist, induces SMC depolarization, which is subsequently conducted to adjacent ECs [36]. Moreover, the second messengers Ca^{2+} and IP_3 are permeable through MEGJs [37,38], implying that SMCs and ECs are functionally coupled through these gap junctions [39].

Accordingly, Dora et al. [40] first demonstrated that SMC $\alpha_1\text{AR}$ acti-

vation or membrane depolarization-induced rises in EC Ca^{2+} signals result from the diffusion of SMC Ca^{2+} through MEGJs. In hamster cheek pouch arterioles, the application of PE or KCl augmented Ca^{2+} concentrations in ECs to levels similar to those evoked by acetylcholine (ACh), an agonist of endothelial muscarinic receptors, but these levels were markedly reduced in the presence of nifedipine, a VDCC antagonist. This result suggests that the secondary increase in the EC Ca^{2+} signal following PE or KCl stimulation originates from Ca^{2+} influx through SMC VDCCs. Furthermore, Dora et al. [40] observed enhanced SMC contractile responses to PE or KCl in the presence of L-NAME, a global inhibitor of nitric oxide synthesis (NOS), consistent with previous studies [41,42]. Collectively, these results suggest that Ca^{2+} transfer from SMCs to ECs via MEGJs stimulates nitric oxide (NO) production, thereby suppressing PE- or KCl-mediated vasoconstriction.

Theoretically, both IP_3 and Ca^{2+} in SMCs are potential candidates mediating SMC-EC heterocellular communication through MEGJs. However, due to technical limitations in tracking the real-time move-

ment of SMC IP_3 and Ca^{2+} , identifying a predominant diffusing molecule for myoendothelial feedback regulation remains challenging. While SMC $\alpha_1\text{AR}$ stimulation with PE increases both IP_3 and Ca^{2+} levels, KCl-dependent depolarization in SMCs induces Ca^{2+} elevations exclusively via the opening of VDCCs. Given that the change in EC Ca^{2+} concentration following PE stimulation closely mirrors that elicited by KCl, several studies suggest that Ca^{2+} , rather than IP_3 , may be the primary molecule diffusing from SMC to ECs [40,43].

Beyond NO-mediated myoendothelial feedback [40], subsequent studies investigated novel regulatory mechanisms following the passage of Ca^{2+} from SMCs to ECs. In these studies, SMC $\alpha_1\text{AR}$ activation with PE resulted in simultaneous Ca^{2+} elevations in both cell types and subsequent vasorelaxation following PE-induced vasoconstriction [44]. Pretreatment with L-NAME increased agonist-dependent vasoconstriction in rat mesentery arteries two-fold; remarkably, the subsequent application of apamin (an SK_{Ca} channel antagonist) further increased PE-induced vasoconstriction by more than three-fold. Because PE does not directly affect EC Ca^{2+} signaling and acts exclusively on SMCs [40,44-46], these findings suggest that SMC $\alpha_1\text{AR}$ -mediated vasoconstriction is regulated via negative feedback from EC-dependent signaling, specifically NO production and K^+ efflux-dependent hyperpolarization.

Indeed, the elevation of intracellular EC Ca^{2+} contributes to EDH through the activation of IK_{Ca} and SK_{Ca} channels [35,47,48]. These channels are exclusively expressed in ECs and serve as essential components of myoendothelial feedback regulation of vasoconstriction [49]. These K^+ channels are voltage-insensitive and are activated by nanomolar increases in intracellular Ca^{2+} (e.g., EC_{50} of 300-500 nM) through Ca^{2+} -calmodulin binding at the channel carboxyl terminus [50,51]. Consequently, elevations in endothelial Ca^{2+} concentration promote EDH. This hyperpolarization, transmitted to SMCs via MEGJs, hyperpolarizes the SMC membrane and leads to vasodilation by inhibiting VDCCs. Taken together, the evidence suggests that SMC $\alpha_1\text{AR}$ stimulation increases intracellular Ca^{2+} signals through the direct movement of SMC-derived Ca^{2+} and Ca^{2+} -induced Ca^{2+} release from the endoplasmic reticulum (ER), which activates K^+ channels to trigger an EDH-mediated negative feedback mechanism.

Regarding intercellular communication from SMC to EC, various pharmacological agents have been employed to uncouple MEGJ, including palmitoleic acid, 18α - or 18β -glycyrrhetic acid (18α or $18\beta\text{GA}$), carboxoxolone, and 1-heptanol [19,43,52]. Secondary increases in EC Ca^{2+} signals and EDH/NO production following SMC $\alpha_1\text{AR}$ activation

with PE or membrane depolarization with KCl were markedly diminished after pre-incubation with these gap junction uncouplers [19,43,52]. These observations further support the movement of SMC-derived second messengers toward ECs. However, caution is warranted because these uncouplers have been reported to exert non-specific side effects directly on ECs [53,54].

Given the lack of highly specific uncoupling agents, inherent difficulties remain in studying the interchange of second messengers between SMCs and ECs. To address this, Isakson et al. [52,55] developed an intriguing approach: a vascular cell co-culture system composed of monolayers of ECs and SMCs. Although vasomotor reactivity cannot be directly examined in this system, the SMC-EC co-culture model forms MEGJs similar to those found in intact resistance arteries, facilitates the measurement of Ca^{2+} signaling in both cell types, and allows for the selective pharmacological stimulation of SMCs and ECs [52,55]. Consistently, an increase in EC Ca^{2+} signaling was monitored after SMC stimulation with PE, which was significantly attenuated by $18\alpha\text{GA}$ in the co-culture system [52,55]. Furthermore, PE-induced SMC stimulation still resulted in a secondary rise in EC Ca^{2+} concentration even when IP_3R -mediated Ca^{2+} release in ECs was completely inhibited by thapsigargin, an inhibitor of the SERCA Ca^{2+} pump in the ER. These results from culture studies support findings from vascular studies indicating that Ca^{2+} diffusion from SMCs to ECs plays a critical role in myoendothelial feedback [6,40,43,56].

Technological advances in optical Ca^{2+} imaging techniques and sensitive detectors (e.g., fluo-4 and GCaMP2 biosensors) have enabled investigators to examine Ca^{2+} dynamics involving heterocellular communication. An innovative study in skeletal muscle resistance arteries found that the opening of SMC VDCCs with BayK8644 (a selective VDCC agonist) elicited elementary and localized EC Ca^{2+} transient events, termed vascular endothelial Ca^{2+} transients (VECTors) [6]. These events are distinct from IP_3R -dependent local Ca^{2+} events, such as Ca^{2+} pulsars or wavelets in ECs [18,46].

Under IP_3R inhibition with heparin in both SMCs and ECs, either direct or indirect VDCC-driven Ca^{2+} entry driven by BayK8644, membrane depolarization (using 4-aminopyridine: an antagonist of voltage-dependent K^+ channels), or PE-induced signals transmitted through MEGJs activated IK_{Ca} channels predominantly expressed at myoendothelial projections (MEPs). Functional studies confirmed this, as BayK8644 or PE-induced vasoconstriction was followed by vasodilation toward or beyond baseline, a response that was substantially attenuated

by the IK_{Ca} blocker TRAM-34. Garland and Bagher [6] provided the first optical evidence of Ca^{2+} movement from SMCs to ECs and suggested that SMC depolarization evokes local and transient Ca^{2+} events in ECs to activate negative feedback regulation, thereby suppressing excessive vasoconstriction.

3. Putative effects of exercise training on Ca^{2+} -dependent SMC-EC negative feedback regulation

Exercise training is characterized by repetitive increases in blood flow and intraluminal shear stress, which constitute potent physiological stimuli for endothelial adaptation and the enhancement of Ca^{2+} -dependent signaling pathways [11]. In resistance arteries supplying skeletal muscle, exercise training consistently improves endothelium-dependent vasodilation and attenuates exaggerated vasoconstrictor responsiveness, suggesting that exercise enhances endothelial restraint on SMC contractility [14]. These functional adaptations are particularly relevant to Ca^{2+} -dependent myoendothelial feedback regulation, in which SMC-derived Ca^{2+} signals transferred through MEGJs evoke endothelial Ca^{2+} elevations that activate NO and EDH pathways to suppress excessive vasoconstriction.

Exercise training has been shown to enhance endothelial Ca^{2+} signaling capacity and to potentiate Ca^{2+} -dependent activation of endothelial IK_{Ca} and SK_{Ca} channels, which are critical effectors of EDH-mediated vasodilation [16,17]. Because IK_{Ca} and SK_{Ca} channels are activated by submicromolar increases in endothelial intracellular Ca^{2+} , exercise-induced improvements in endothelial Ca^{2+} handling are postulated to amplify the sensitivity and gain of EDH-dependent negative feedback on SMC membrane potential and Ca^{2+} influx. Indeed, in conditions such as aging and metabolic disease, exercise training restores EDH-mediated vasodilatory function by normalizing signaling through endothelial Ca^{2+} -sensitive potassium channels, supporting the concept that exercise training enhances Ca^{2+} -dependent endothelial restraint of SMC tone [16,17].

During exercise, sympathetic nerve activity is markedly elevated, yet blood flow to active skeletal muscle is preserved through functional sympatholysis, a process requiring precise local counterbalancing of α_1 -adrenergic SMC contractile signaling by endothelial vasodilatory mechanisms [57,58]. Exercise training enhances sympatholysis in both humans and experimental models, largely through NO- and EDH-dependent pathways [59,60]. Given that SMC-derived Ca^{2+} signals transmitted via MEGJs have been identified as initiators of this feedback [6, 18], these findings provide indirect support for the hypothesis that exercise train-

ing strengthens Ca^{2+} -dependent SMC-EC heterocellular feedback regulation.

Collectively, current evidence supports the concept that exercise training enhances Ca^{2+} -dependent SMC-EC heterocellular communication primarily by augmenting endothelial Ca^{2+} signaling capacity, EDH/NO effector pathways, and potentially MEGJ coupling efficiency. These adaptations increase the effectiveness of myoendothelial negative feedback regulation, thereby protecting resistance arteries from excessive sympathetic vasoconstriction and ensuring adequate tissue perfusion during conditions of heightened neural and myogenic drive.

4. IP_3 -dependent SMC-EC communication

Although the concept of SMC Ca^{2+} diffusion-mediated myoendothelial feedback regulation was first introduced and has been continually suggested in small arteries [6,40,56], SMC IP_3 is also considered a key determinant of SMC-EC intercellular communication [18,19,46,52,61]. IP_3 is generated by phospholipase C (PLC)-induced cleavage of PIP_2 once GPCRs are activated. Initial studies found that the blockade of PLC with U-73122 or the inhibition of IP_3 -induced Ca^{2+} release from the ER with 2-aminoethoxydiphenylborate (2-APB) suppressed the increase in EC Ca^{2+} concentration following PE stimulation [62]. In contrast, a high extracellular K^+ solution used to induce membrane depolarization augmented only SMC Ca^{2+} signals through VDCC-mediated Ca^{2+} entry without altering EC Ca^{2+} levels; this implies that agonist-induced SMC-to-EC communication may be mediated by IP_3 [62].

Isakson et al. [52] also attempted to examine the influence of SMC-derived IP_3 on EC Ca^{2+} signals using an SMC-EC co-culture model and pharmacological approaches. Even when Ca^{2+} signals in ECs were selectively buffered by BAPTA (a cell-permeable Ca^{2+} chelator) treatment, a secondary rise in EC Ca^{2+} concentration was not abolished following PE-dependent SMC stimulation. When SMC and EC monolayers were loaded with BAPTA and xestospongin C (an IP_3 R inhibitor), respectively, SMC α_1 AR activation with PE did not alter Ca^{2+} signals in either cell type. These data support the movement of SMC-derived IP_3 toward ECs [52].

Research has revealed a novel signaling mechanism in which IP_3 generated by SMC α_1 AR stimulation induces eNOS phosphorylation at serine 1177. This phosphorylation event occurs specifically at MEPs and is notably absent in the global EC population [63]. MEJ eNOS phosphorylation following PE treatment was significantly inhibited by pre-treatment with 18 α GA, a gap junction uncoupler, or Gö-6983, a pan-PKC in-

hibitor. Furthermore, the loading of thapsigargin, xestospongin C, or BAPTA consistently reduced eNOS phosphorylation at the MEJ after PE treatment.

These findings suggest that IP₃ traveling from SMCs to ECs triggers IP₃R-mediated Ca²⁺ release from the ER, which locally activates the PKC-Akt-eNOS pathway at MEPs [63]. This mechanism was further confirmed by observations that SMC α_1 AR activation with PE increased cyclic guanosine monophosphate (cGMP) levels within the SMCs [63]. Collectively, the transfer of SMC IP₃ to ECs appears to attenuate SMC α_1 AR activation-induced vasoconstriction by generating NO in ECs and subsequently increasing cGMP in the adjacent SMCs.

The discovery of elementary and spatially restricted Ca²⁺ events has broadened the understanding of myoendothelial feedback mechanisms in intact resistance arteries. Ledoux et al. [50] identified localized Ca²⁺ release events from the ER at MEPs, termed “Ca²⁺ pulsars”, in *en face* mesentery artery preparations. These events were demonstrated to be distinct from RyR-mediated Ca²⁺ sparks in SMCs and IP₃-mediated Ca²⁺ puffs observed in *Xenopus* oocytes [50]. This local increase in EC Ca²⁺ signaling is sufficient to activate IK_{Ca} and/or SK_{Ca} channels and subsequently induce EDH [64].

Research by Tran et al. [46] further elucidated that these fundamental Ca²⁺ signals participate in SMC-to-EC intercellular communication. Using confocal Ca²⁺ imaging, they observed IP₃R-dependent Ca²⁺ pulsars (referred to as “Ca²⁺ wavelets”) occurring in response to PE application. Furthermore, PE-induced SMC depolarization and vasoconstriction were enhanced in the presence of TRAM-34 and apamin (IK_{Ca} and SK_{Ca} channel blockers, respectively). Interrupting IP₃R-mediated Ca²⁺ release in ECs via luminal infusion of BAPTA-AM, thapsigargin, 2-APB, or xestospongin C increased agonist-induced vasoconstriction in pressurized retractor muscle feed arteries. These results indicate that the diffusion of IP₃ across MEGJs following PE-induced α_1 AR activation evokes Ca²⁺ pulsars/wavelets and EDH at MEPs, thereby attenuating agonist-induced vasoconstriction.

While many studies rely on pharmacological application (e.g., PE) to explore EC Ca²⁺ signaling response to SMC activation, electrical field stimulation of sympathetic nerves has confirmed that unitary Ca²⁺ pulsar events are increased by endogenous sympathetic nerve activation [18]. Sympathetic nerve activation releases norepinephrine and ATP, activating SMC α_1 AR and P2X₁ receptors, respectively [20]. While an α_1 AR antagonist (prazosin) or PLC inhibitor (U-73122) significantly diminished EC Ca²⁺ signaling in response to electrical stimulation of sympathetic

nerves, a P2X₁ receptor antagonist ($\alpha\beta$ -meATP) had a negligible effect [18]. Additionally, pre-treatment with the VDCC blocker nifedipine did not suppress rises in EC Ca²⁺ pulsar events following sympathetic nerve stimulation. These data support the concept that IP₃, rather than Ca²⁺, plays a vital role in increasing EC Ca²⁺ signaling after SMC α_1 AR activation by nerve-released norepinephrine [18]. Prior studies indicate that SMCs communicate with ECs via MEGJs to limit agonist/nerve-evoked vasoconstriction in an IP₃ flux-dependent manner.

Some previous investigations have suggested that direct diffusion of SMC Ca²⁺ to ECs mediates the myoendothelial feedback of SMC α_1 AR activation-induced vasoconstriction [40,56,65]. However, other studies [18,19,46,52,61-63] indicate that the diffusion of SMC-derived IP₃ via MEGJs is essential for SMC-EC heterocellular communication. This is supported by evidence that SMC Ca²⁺ depolarization or VDCC opening, which elevates SMC Ca²⁺ but not IP₃, fails to alter EC Ca²⁺ signaling, whereas PLC inhibition significantly abrogates the secondary EC Ca²⁺ responses to PE or nerve stimulation. In line with these observations, Ca²⁺ diffusion-independent myoendothelial feedback is further supported by the distinct kinetic properties of IP₃ [66]. IP₃ was discovered in 1983 and has been considered a “global” or highly mobile cellular messenger because it can diffuse significantly faster than Ca²⁺ (280 vs. 38 μ m/sec), making it suitable for rapid, long-distance biological signaling [67]. In contrast, free Ca²⁺ exhibits slower mobility because its interactions with Ca²⁺-binding proteins (e.g., calmodulin) effectively increase its molecular weight and reduce the diffusion rate [68].

While IP₃ is a strong candidate for SMC to EC communication, research by Dickinson et al. [69] has recently suggested that its diffusion rate may vary significantly based on the density of functionally inactive IP₃Rs in mammalian cells, which can act as molecular buffers [69]. For instance, while IP₃ diffusion is relatively fast in cardiomyocytes with low IP₃R density, it appears diminished in Purkinje cells where IP₃R density is high [69]. Furthermore, an IP₃ diffusion rate of 280 μ m/sec was first discovered in *Xenopus* oocytes [68], and neuroblastoma cells displayed a much slower diffusion coefficient of IP₃ (5–10 μ m/sec, approximately 30-fold slower) [69]. As IP₃ mobilization varies across different cell types, further research on myoendothelial feedback mechanisms is required to explore IP₃R buffering capacity and IP₃ diffusion rates in SMCs and ECs, particularly at MEPs. In addition, the impact of IP₃ on SMC-EC heterocellular communication has been debated because IP₃ may be easily metabolized by type-I 5-phosphatases [70]. However, prior studies have demonstrated that IP₃ is sufficiently stable to survive and diffuse to

neighboring cells through gap junctions [71,72]. Collectively, SMC-EC communication for myoendothelial feedback predominantly occurs in an IP₃-dependent manner.

Unitary, spatially restricted Ca²⁺ influx events through endothelial transient receptor potential vanilloid 4 (TRPV4) channels, termed “TRPV4 Ca²⁺ sparklets,” regulate endothelium-dependent vasodilation in resistance arteries [73]. These TRPV4 sparklets activate nearby IK_{Ca} and SK_{Ca} channels at MEPs to cause membrane hyperpolarization and subsequent vasodilation. While endothelial TRPV4 channels are known to be crucial sources of localized Ca²⁺ influx in resistance arteries, recent findings have reported that these Ca²⁺-selective cation channels are also involved in heterocellular communication and myoendothelial feedback [19]. Specifically, research has revealed that IP₃ generated from SMC GPCR activation stimulates endothelial TRPV4 channels.

In the presence of cyclopiazonic acid (CPA, a SERCA pump inhibitor) to eliminate IP₃R-mediated Ca²⁺ events, the application of GPCR agonists, including PE or U46619 (a thromboxane A₂ receptor agonist), significantly increased TRPV4 Ca²⁺ sparklet activity predominantly at MEPs in intact systemic arteries. These events were markedly diminished by PLC inhibitors (U-73122) or gap junction uncouplers (18β-GA and 1-heptanol). While TRPV4 sparklet activity remained unaltered by VDCC activators (BayK 8644) or inhibitors (nifedipine), the photorelease of IP₃ using ultraviolet light augmented TRPV4 sparklet activity. This indicates that SMC-derived IP₃, rather than Ca²⁺, serves as the endogenous/physiological activator stimulating endothelial TRPV4 channels expressed at MEPs. These findings are further supported by previous reports that the binding of IP₃ to the ankyrin repeat domain of TRPV4 channels increases channel activity [74].

Furthermore, the pharmacological or genetic ablation of TRPV4 channels, the use of gap junction uncoupling agents, endothelium denudation, or IK_{Ca}/SK_{Ca} channel inhibition profoundly abolished vasodilation following PE-induced vasoconstriction. PE injection into global TRPV4 knockout mice also substantially elevated mean arterial pressure. Taken together, these findings suggest that heterocellular communication between SMC IP₃ and EC TRPV4 channels contributes significantly to preventing excessive vasoconstriction and the development of hypertension.

5. Putative effects of exercise on IP₃-dependent SMC-EC negative feedback regulation

Exercise training has not yet been shown directly to augment SMC-

derived IP₃ transfer across MEGJs in intact resistance arteries; specifically, quantitative studies comparing IP₃ flux from SMC to EC via MEGJs before and after exercise training are currently lacking. However, there is a high likelihood that regular exercise can strengthen IP₃-dependent myoendothelial negative feedback that restrains excessive vasoconstriction. Repetitive exercise bouts may increase MEGJ communication capacity by altering the abundance or distribution of connexins (e.g., Cx37/Cx40/Cx43) in ways that facilitate heterocellular signaling at MEJs [75, 76]. In parallel, enhanced endothelial IP₃R-dependent Ca²⁺ release is postulated to promote vasodilator restraint of tone [77].

Consistent with this, exercise training could conceivably contribute to sensitizing endothelial Ca²⁺-dependent effector pathways that are typically engaged by GPCR-PLC-IP₃ signaling [78]. Since IP₃-dependent myoendothelial feedback relies on SMC GPCR activation, IP₃ diffusion to ECs, and EC Ca²⁺ release-mediated activation of NO and/or EDH pathways [77], an exercise-induced enhancement in endothelial Ca²⁺ responsiveness provides a robust biological mechanism. Through this mechanism, the same quantity of SMC-derived IP₃ could presumably elicit larger EC effector output (NO/EDH), thereby enhancing negative feedback against α₁-adrenergic vasoconstriction.

TRPV4 sparklet activity and downstream K_{Ca}2.3 activation provide a potent hyperpolarizing brake on SMC contraction [79]. Importantly, research has shown that exercise training restores impaired EDH/EDHF-mediated vasodilation in aged arteries via the TRPV4-K_{Ca}2.3 signaling complex. This indicates that exercise training improves the integrity or coupling efficiency of this endothelial microdomain, which is central to local vasodilator feedback [16]. In resistance-artery paradigms of heterocellular signaling, SMC-derived IP₃ acts as an endothelial activator capable of engaging TRPV4-dependent microdomain Ca²⁺ influx at myoendothelial projections (MEPs). This links the SMC IP₃-EC TRPV4 sparklets-IK/SK_{Ca} channel activation-EDH sequence, which subsequently spreads to SMCs as a negative-feedback loop that limits excessive vasoconstriction and hypertension [19,74].

Therefore, even without direct measurements of increased SMC-to-EC IP₃ transfer following exercise training, existing evidence supports the interpretation that exercise can amplify the endothelial component of IP₃-dependent myoendothelial feedback by: 1) increasing gap-junctional signaling capacity through shear-sensitive connexin regulation; 2) enhancing IP₃R-dependent endothelial Ca²⁺ release and NO signaling; and 3) improving TRPV4-K_{Ca}2.3 microdomain function that translates local Ca²⁺ events into EDH-mediated suppression of vasoconstriction.

CONCLUSIONS

Myoendothelial feedback mechanisms represent a fundamental regulatory system that prevents resistance arteries from exaggerated vasoconstriction induced by myogenic activity and sympathetic nerve stimulation. Second messengers generated in SMCs, specifically Ca^{2+} and IP_3 , are transmitted to ECs through MEGJs, where they initiate localized endothelial Ca^{2+} signaling and activate NO and EDH(F)-dependent vasodilation. These heterocellular interactions ensure precise, site-specific regulation of vascular tone. Meanwhile, exercise training emerges as a potent physiological stimulus capable of enhancing these feedback processes. Exercise training reinforces myoendothelial negative feedback on SMC contractility. This effect is likely mediated by improvements in endothelial Ca^{2+} handling, preservation of IP_3 -dependent signaling microdomains, and enhanced gap junctional coupling. Such adaptations may be especially important under conditions of elevated sympathetic activity, contributing to improved blood flow regulation and vascular protection. Further experimental studies are required to directly elucidate exercise-induced alterations in SMC-EC heterocellular communication.

CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest with the contents of this study.

AUTHOR CONTRIBUTIONS

Conceptualization: YM Park, KS Hong; Data curation: KS Hong; Formal analysis: KS Hong; Funding acquisition: YM Park, KS Hong; Methodology: YM Park, KS Hong; Project administration: KS Hong; Visualization: YM Park, KS Hong; Writing original draft: YM Park, KS Hong; Writing-review & editing: YM Park, KS Hong.

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REFERENCES

1. Sandow SL, Tare M, Coleman HA, Hill CE, Parkinson HC. Involvement of myoendothelial gap junctions in the actions of endothelium-derived hyperpolarizing factor. *Circ Res.* 2002;90(10):1108-13.

2. Bayliss WM. On the local reactions of the arterial wall to changes of internal pressure. *J Physiol.* 1902;28(3):220-31.
3. Westcott EB, Segal SS. Perivascular innervation: a multiplicity of roles in vasomotor control and myoendothelial signaling. *Microcirculation.* 2013;20(3):217-38.
4. Nourian Z, Li M, Leo MD, Jagger JH, Braun AP, et al. Large conductance Ca^{2+} -activated K^{+} channel (BKCa) α -subunit splice variants in resistance arteries from rat cerebral and skeletal muscle vasculature. *PLoS One.* 2014;9(6):e98863.
5. Hill MA, Yang Y, Ella SR, Davis MJ, Braun AP. Large conductance, Ca^{2+} -activated K^{+} channels (BKCa) and arteriolar myogenic signaling. *FEBS Lett.* 2010;584(10):2033-42.
6. Garland CJ, Bagher P, Powell C, Ye X, Lemmey HAL, et al. Voltage-dependent Ca^{2+} entry into smooth muscle during contraction promotes endothelium-mediated feedback vasodilation in arterioles. *Sci Signal.* 2017;10(486):eaal3806.
7. Westcott EB, Jackson WF. Heterogeneous function of ryanodine receptors, but not IP_3 receptors, in hamster cremaster muscle feed arteries and arterioles. *Am J Physiol Heart Circ Physiol.* 2011;300(5):H1616-30.
8. Westcott EB, Goodwin EL, Segal SS, Jackson WF. Function and expression of ryanodine receptors and inositol 1,4,5-trisphosphate receptors in smooth muscle cells of murine feed arteries and arterioles. *J Physiol.* 2012;590(8):1849-69.
9. Sandow SL, Hill CE. Incidence of myoendothelial gap junctions in the proximal and distal mesenteric arteries of the rat is suggestive of a role in endothelium-derived hyperpolarizing factor-mediated responses. *Circ Res.* 2000;86(3):341-6.
10. Figueroa XF, Isakson BE, Duling BR. Vascular gap junctions in hypertension. *Hypertension.* 2006;48(5):804-11.
11. Tinken TM, Thijssen DHJ, Hopkins N, Dawson EA, Cable NT, et al. Shear stress mediates endothelial adaptations to exercise training in humans. *Hypertension.* 2010;55(2):312-8.
12. Casey DP, Ueda K, Wegman-Points L, Pierce GL. Muscle contraction induced arterial shear stress increases endothelial nitric oxide synthase phosphorylation in humans. *Am J Physiol Heart Circ Physiol.* 2017;313(4):H854-9.
13. Kim JS, Baek KW, Kim SJ, Lee J, Johnston CA, et al. Exercise-induced laminar blood flow maintains vascular function by enhanced endothelium-derived hyperpolarizing factor-mediated responses.

- thelial homeostasis. *Exerc Sci.* 2024;33(2):234-42.
14. Donato AJ, Lesniewski LA, Delp MD. Ageing and exercise training alter adrenergic vasomotor responses of rat skeletal muscle arterioles. *J Physiol.* 2007;579(Pt 1):115-25.
15. Trott DW, Gunduz F, Laughlin MH, Woodman CR. Exercise training reverses age-related decrements in endothelium-dependent dilation in skeletal muscle feed arteries. *J Appl Physiol* (1985). 2009;106(6):1925-34.
16. Huang J, Zhang H, Tan X, Hu M, Shen B. Exercise restores impaired endothelium-derived hyperpolarizing factor-mediated vasodilation in aged rat aortic arteries via the TRPV4-KCa2.3 signaling complex. *Clin Interv Aging.* 2019;14:1579-87.
17. Sonobe T, Tsuchimochi H, Maeda H, Pearson JT. Increased contribution of KCa channels to muscle contraction induced vascular and blood flow responses in sedentary and exercise trained ZFDM rats. *J Physiol.* 2022;600(12):2919-38.
18. Nausch LWM, Bonev AD, Heppner TJ, Tallini Y, Kotlikoff MI, et al. Sympathetic nerve stimulation induces local endothelial Ca²⁺ signals to oppose vasoconstriction of mouse mesenteric arteries. *Am J Physiol Heart Circ Physiol.* 2012;302(3):H594-602.
19. Hong K, Cope EL, DeLalio LJ, Marziano C, Isakson BE, et al. TRPV4 (transient receptor potential vanilloid 4) channel-dependent negative feedback mechanism regulates Gq protein-coupled receptor-induced vasoconstriction. *Arterioscler Thromb Vasc Biol.* 2018;38(3):542-54.
20. Todorov LD, Mihaylova-Todorova ST, Bjur RA, Westfall DP. Differential cotransmission in sympathetic nerves: role of frequency of stimulation and prejunctional autoreceptors. *J Pharmacol Exp Ther.* 1999; 290(1):241-6.
21. Luff SE. Ultrastructure of sympathetic axons and their structural relationship with vascular smooth muscle. *Anat Embryol (Berl).* 1996; 193(6):515-31.
22. Saleh SN, Albert AP, Peppiatt CM, Large WA. Angiotensin II activates two cation conductances with distinct TRPC1 and TRPC6 channel properties in rabbit mesenteric artery myocytes. *J Physiol.* 2006;577 (Pt 2):479-95.
23. Large WA, Saleh SN, Albert AP. Role of phosphoinositol 4,5-bisphosphate and diacylglycerol in regulating native TRPC channel proteins in vascular smooth muscle. *Cell Calcium.* 2009;45(6):574-82.
24. Minneman KP. Alpha 1-adrenergic receptor subtypes, inositol phosphates, and sources of cell Ca²⁺. *Pharmacol Rev.* 1988;40(2):87-119.
25. Burnstock G. Physiology and pathophysiology of purinergic neurotransmission. *Physiol Rev.* 2007;87(2):659-797.
26. Lamont C, Vial C, Evans RJ, Wier WG. P2X1 receptors mediate sympathetic postjunctional Ca²⁺ transients in mesenteric small arteries. *Am J Physiol Heart Circ Physiol.* 2006;291(6):H3106-13.
27. Burnstock G. Purinergic regulation of vascular tone and remodelling. *Auton Autacoid Pharmacol.* 2009;29(3):63-72.
28. Burnstock G. Purinergic signalling: its unpopular beginning, its acceptance and its exciting future. *Bioessays.* 2012;34(3):218-25.
29. Lamont C, Vainorius E, Wier WG. Purinergic and adrenergic Ca²⁺ transients during neurogenic contractions of rat mesenteric small arteries. *J Physiol.* 2003;549(Pt 3):801-8.
30. Zang W, Zacharia J, Lamont C, Wier WG. Sympathetically evoked Ca²⁺ signaling in arterial smooth muscle. *Acta Pharmacol Sin.* 2006;27(12):1515-25.
31. Rummery NM, Brock JA, Pakdeechote P, Ralevic V, Dunn WR. ATP is the predominant sympathetic neurotransmitter in rat mesenteric arteries at high pressure. *J Physiol.* 2007;582(Pt 2):745-54.
32. Hill-Eubanks DC, Werner ME, Nelson MT. Local elementary purinergic-induced Ca²⁺ transients: from optical mapping of nerve activity to local Ca²⁺ signaling networks. *J Gen Physiol.* 2010;136(2):149-54.
33. Hill-Eubanks DC, Werner ME, Heppner TJ, Nelson MT. Calcium signaling in smooth muscle. *Cold Spring Harb Perspect Biol.* 2011; 3(9):a004549.
34. Mauban JR, Lamont C, Balke CW, Wier WG. Adrenergic stimulation of rat resistance arteries affects Ca(2+) sparks, Ca(2+) waves, and Ca(2+) oscillations. *Am J Physiol Heart Circ Physiol.* 2001;280(5): H2399-405.
35. Garland CJ, Dora KA. EDH: endothelium-dependent hyperpolarization and microvascular signalling. *Acta Physiol (Oxf).* 2017;219(1): 152-61.
36. Xia J, Little TL, Duling BR. Cellular pathways of the conducted electrical response in arterioles of hamster cheek pouch in vitro. *Am J Physiol.* 1995;269(6 Pt 2):H2031-8.
37. Rooney TA, Thomas AP. Intracellular calcium waves generated by Ins(1,4,5)P₃-dependent mechanisms. *Cell Calcium.* 1993;14(10):674-90.
38. Sanderson MJ, Charles AC, Boitano S, Dirksen ER. Mechanisms and function of intercellular calcium signaling. *Mol Cell Endocrinol.* 1994; 98(2):173-87.
39. Little TL, Beyer EC, Duling BR. Connexin 43 and connexin 40 gap

- junctional proteins are present in arteriolar smooth muscle and endothelium in vivo. *Am J Physiol*. 1995;268(2 Pt 2):H729-39.
40. Dora KA, Doyle MP, Duling BR. Elevation of intracellular calcium in smooth muscle causes endothelial cell generation of NO in arterioles. *Proc Natl Acad Sci USA*. 1997;94(12):6529-34.
41. Jones CJ, DeFily DV, Patterson JL, Chilian WM. Endothelium-dependent relaxation competes with alpha 1- and alpha 2-adrenergic constriction in the canine epicardial coronary microcirculation. *Circulation*. 1993;87(4):1264-74.
42. Pohl U, de Wit C. Interaction of nitric oxide with myogenic and adrenergic vasoconstrictor processes in the control of microcirculatory blood flow. *Pflugers Arch*. 1996;432(3 Suppl):R107-10.
43. Kansui Y, Garland CJ, Dora KA. Enhanced spontaneous Ca²⁺ events in endothelial cells reflect signalling through myoendothelial gap junctions in pressurized mesenteric arteries. *Cell Calcium*. 2008;44(2):135-46.
44. Dora KA, Hinton JM, Walker SD, Garland CJ. An indirect influence of phenylephrine on the release of endothelium-derived vasodilators in rat small mesenteric artery. *Br J Pharmacol* 2000;129(2):381-7.
45. Jackson WF, Boerman EM, Lange EJ, Lundback SS, Cohen KD. Smooth muscle alpha1D-adrenoceptors mediate phenylephrine-induced vasoconstriction and increases in endothelial cell Ca²⁺ in hamster cremaster arterioles. *Br J Pharmacol*. 2008;155(4):514-24.
46. Tran CHT, Taylor MS, Plane F, Nagaraja S, Tsoukias NM, et al. Endothelial Ca²⁺ wavelets and the induction of myoendothelial feedback. *Am J Physiol Cell Physiol*. 2012;302(8):C1226-42.
47. Féletou M. Endothelium-dependent hyperpolarization and endothelial dysfunction. *J Cardiovasc Pharmacol*. 2016;67(5):373-87.
48. Goto K, Ohtsubo T, Kitazono T. Endothelium-dependent hyperpolarization (EDH) in hypertension: the role of endothelial ion channels. *Int J Mol Sci*. 2018;19(1):315.
49. Sandow SL, Neylon CB, Chen MX, Garland CJ. Spatial separation of endothelial small- and intermediate-conductance calcium-activated potassium channels (K(Ca)) and connexins: possible relationship to vasodilator function? *J Anat*. 2006;209(5):689-98.
50. Ledoux J, Taylor MS, Bonev AD, Hannah RM, Solodushko V, et al. Functional architecture of inositol 1,4,5-trisphosphate signaling in restricted spaces of myoendothelial projections. *Proc Natl Acad Sci USA*. 2008;105(28):9627-32.
51. Schumacher MA, Rivard AF, Bächinger HP, Adelman JP. Structure of the gating domain of a Ca²⁺-activated K⁺ channel complexed with Ca²⁺/calmodulin. *Nature*. 2001;410(6832):1120-4.
52. Isakson BE, Ramos SI, Duling BR. Ca²⁺ and inositol 1,4,5-trisphosphate-mediated signaling across the myoendothelial junction. *Circ Res*. 2007;100(2):246-54.
53. Coleman HA, Tare M, Parkington HC. K⁺ currents underlying the action of endothelium-derived hyperpolarizing factor in guinea-pig, rat and human blood vessels. *J Physiol*. 2001;531(Pt 2):359-73.
54. Tare M, Coleman HA, Parkington HC. Glycyrrhetic derivatives inhibit hyperpolarization in endothelial cells of guinea pig and rat arteries. *Am J Physiol Heart Circ Physiol*. 2002;282(1):H335-41.
55. Isakson BE. Localized expression of an Ins(1,4,5)P₃ receptor at the myoendothelial junction selectively regulates heterocellular Ca²⁺ communication. *J Cell Sci*. 2008;121(Pt 21):3664-73.
56. Yashiro Y, Duling BR. Participation of intracellular Ca²⁺ stores in arteriolar conducted responses. *Am J Physiol Heart Circ Physiol*. 2003;285(1):H65-73.
57. Joyner MJ, Casey DP. Regulation of increased blood flow (hyperemia) to muscles during exercise: a hierarchy of competing physiological needs. *Physiol Rev*. 2015;95(2):549-601.
58. Han JM, Baek KW, Won JH, Kim JS. Effects of respiratory muscle exercise on blood pressure response by sympathetic nervous system activation. *Exerc Sci*. 2023;32(3):266-74.
59. Jendzjowsky NG, Delorey DS. Short-term exercise training enhances functional sympatholysis through a nitric oxide-dependent mechanism. *J Physiol*. 2013;591(6):1535-49.
60. Mortensen SP, Nyberg M, Gliemann L, Thaning P, Saltin B, et al. Exercise training modulates functional sympatholysis and α-adrenergic vasoconstrictor responsiveness in hypertensive and normotensive individuals. *J Physiol*. 2014;592(14):3063-73.
61. Biwer LA, Good ME, Hong K, Patel RK, Agrawal N, et al. Non-endoplasmic reticulum-based Calr (calreticulin) can coordinate heterocellular calcium signaling and vascular function. *Arterioscler Thromb Vasc Biol*. 2018;38(1):120-30.
62. Lamboley M, Pittet P, Koenigsberger M, Sauser R, Bény JL, et al. Evidence for signaling via gap junctions from smooth muscle to endothelial cells in rat mesenteric arteries: possible implication of a second messenger. *Cell Calcium*. 2005;37(4):311-20.
63. Biwer LA, Taddeo EP, Kenwood BM, Hoehn KL, Straub AC, et al. Two functionally distinct pools of eNOS in endothelium are facilitated by myoendothelial junction lipid composition. *Biochim Biophys Acta*. 2016;1861(7):671-9.

64. Hong KS, Lee MG. Endothelial Ca²⁺ signaling-dependent vasodilation through transient receptor potential channels. *Korean J Physiol Pharmacol*. 2020;24(4):287-98.
65. Bagher P, Garland CJ. Scaffolding builds to reduce blood pressure. *Sci Signal*. 2014;7(333):pe16.
66. Streb H, Irvine RF, Berridge MJ, Schulz I. Release of Ca²⁺ from a nonmitochondrial intracellular store in pancreatic acinar cells by inositol-1,4,5-trisphosphate. *Nature*. 1983;306(5938):67-9.
67. Leybaert L. IP₃, still on the move but now in the slow lane. *Sci Signal*. 2016;9(453):fs17.
68. Allbritton NL, Meyer T, Stryer L. Range of messenger action of calcium ion and inositol 1,4,5-trisphosphate. *Science*. 1992;258(5089):1812-5.
69. Dickinson GD, Ellefsen KL, Dawson SP, Pearson JE, Parker I. Hindered cytoplasmic diffusion of inositol trisphosphate restricts its cellular range of action. *Sci Signal*. 2016;9(453):ra108.
70. Gaspers LD, Thomas AP. Calcium signaling in liver. *Cell Calcium*. 2005;38(3-4):329-42.
71. Boitano S, Dirksen ER, Sanderson MJ. Intercellular propagation of calcium waves mediated by inositol trisphosphate. *Science*. 1992;258(5080):292-5.
72. Carter TD, Chen XY, Carlile G, Kalapothakis E, Ogden D, et al. Porcine aortic endothelial gap junctions: identification and permeation by caged InsP₃. *J Cell Sci*. 1996;109(Pt 7):1765-73.
73. Ottolini M, Hong K, Cope EL, Daneva Z, DeLalio LJ, et al. Local peroxynitrite impairs endothelial transient receptor potential vanilloid 4 channels and elevates blood pressure in obesity. *Circulation*. 2020;141(16):1318-33.
74. Takahashi N, Hamada-Nakahara S, Itoh Y, Takemura K, Shimada A, et al. TRPV4 channel activity is modulated by direct interaction of the ankyrin domain to PI(4,5)P₂. *Nat Commun*. 2014;5:4994.
75. Johnson TL, Nerem RM. Endothelial connexin 37, connexin 40, and connexin 43 respond uniquely to substrate and shear stress. *Endothelium*. 2007;14(4-5):215-26.
76. Vorderwülbecke BJ, Maroski J, Fiedorowicz K, Da Silva-Azevedo L, Marki A, et al. Regulation of endothelial connexin40 expression by shear stress. *Am J Physiol Heart Circ Physiol*. 2012;302(1):H143-52.
77. Lin Q, Zhao L, Jing R, Trexler C, Wang H, et al. Inositol 1,4,5-trisphosphate receptors in endothelial cells play an essential role in vasodilation and blood pressure regulation. *J Am Heart Assoc*. 2019;8(4):e011704.
78. Sun MY, Geyer M, Komarova YA. IP₃ receptor signaling and endothelial barrier function. *Cell Mol Life Sci*. 2017;74(22):4189-207.
79. Ma X, Du J, Zhang P, Deng J, Liu J, et al. Functional role of TRPV4-KCa2.3 signaling in vascular endothelial cells in normal and streptozotocin-induced diabetic rats. *Hypertension*. 2013;62(1):134-9.