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Leptomeningeal anastomoses: Mechanisms of pial collateral remodeling in ischemic stroke

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Abstract

Arterial collateralization, as determined by leptomeningeal anastomoses or pial collateral vessels, is a well-established vital player in cerebral blood flow restoration and neurological recovery from ischemic stroke. A secondary network of cerebral collateral circulation apart from the Circle of Willis, exist as remnants of arteriole development that connect the distal arteries in the pia mater. Recent interest lies in understanding the cellular and molecular adaptations that control the growth and remodeling, or arteriogenesis, of these preexisting collateral vessels. New findings from both animal models and human studies of ischemic stroke suggest a multi-factorial and complex, temporospatial interplay of endothelium, immune and vessel-associated cell interactions may work in concert to facilitate or thwart arteriogenesis. These valuable reports may provide critical insight into potential predictors of the pial collateral response in patients with large vessel occlusion and may aid in therapeutics to enhance collateral function and improve recovery from stroke.

This article is categorized under:

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KEYWORDS

arteriogenesis, ischemic stroke, large vessel occlusion, leptomeningeal anastomoses, pial collateral

1 | INTRODUCTION

Stroke is a leading cause of death and long-term disability worldwide, with the majority of these stroke cases being ischemic strokes where a vascular obstruction prevents blood flow to areas of the brain. Globally, ischemic strokes accounted for over 3.3 million deaths in 2019 and in the United States impacts nearly 700,000 individuals annually (Benjamin et al., 2017; Virani et al., 2021). This vast case load creates a major medical and financial burden in the United States, with projected direct and indirect costs of ischemic strokes increasing from the $105.2 billion seen in 2010 to $240.7 billion in 2030 (Ovbiagele et al., 2013). To date, the development of ischemic stroke treatments has been limited to tissue plasmogen activator and mechanical thrombectomy (Powers et al., 2019). Recently, leptomeningeal anastomoses (LMA), also known as pial collateral vessels have garnered attention for their adaptive remodeling process, arteriogenesis, which makes them a critical determinant of stroke outcomes and an attractive therapeutic target.

Observational studies of collateral vessels date back to 1785 when Sir John Hunter, a Scottish anatomist discovered that if the external carotid artery of a male fallow deer was permanently ligated, the ipsilateral antler would become cool. However, a week postligation the antler temperature and pulse would return to normal and was coupled with enlargement of smaller vessels around the ligation site (Murley, 1984). Nearly 100 years passed after Hunters experiments before LMAs were first reported by Heubner in 1874, then more extensively described by Van der Eecken and Adams (Heubner, 1874; Vander Eecken & Adams, 1953). Later, the term *arteriogenesis* was coined by Wolfgang Schaper and colleagues to distinguish the growth of pre-existing collateral vessels from angiogenesis, or the formation of new vessels (W. Schaper & Buschmann, 1999).

LMAs are a network of small arteriole-to-arteriole bypass vessels that connect the anterior, middle, and posterior cerebral arteries (ACA, MCA, PCA) in the pia mater (Liebeskind, 2003). The arteriole collateral vessel wall, is comprised of the tunica intima (endothelial cells, the basement membrane, internal elastic lamina), tunica media (smooth muscle cells, external elastic membrane), and tunica adventitia (connective tissue, nerve endings, and other vessel associated cells) (Martinez-Lemus, 2012). Under healthy conditions, no pressure gradient exists on the luminal side of the collateral vessel wall (Chalothorn & Faber, 2010). However, following vascular obstruction of the main MCA branch, a change in pressure that occurs in the occluded vessel, causes retrograde cerebral blood flow (CBF) through the LMAs into the territory of tissue served by the primary vessel (I. Buschmann & Schaper, 2000). This rescue of CBF can prevent neuronal loss and preserve the penumbra (Aoki et al., 2014). Poor collateral flow is associated with worse outcome and extensive infarct damage in patients with large vessel occlusion (LVO), most often occurring in the MCA (Bang et al., 2008; Bang et al., 2011; Campbell et al., 2013). On the other hand, the enhanced recruitment of these subsidiary networks of vessels can stabilize CBF and improve outcome from stroke (Christoforidis et al., 2005; Mohammad et al., 2008; Roberts et al., 2002). Therefore, understanding both the growth potential and limiting factors that dictate LMA circulation may offer insight into clinical management of these vessels that may provide neuroprotection prior to and/or following mechanical thrombectomy.

Interestingly, recent findings describe a phenomenon known as Willisian collateral failure (S. J. Lee et al., 2020). Willisian collateral vessels are primary collaterals that exist between major arteries of the Circle of Willis. Failure of these blood vessels to move adequate quantities of blood can contribute to increased speed of infarct growth and may be due to an incomplete Circle of Willis, with absent or hypoplastic communicating arteries (S. U. Lee et al., 2016). Willisian collateral failure can also result as a consequence of thrombus embolization, or detachment and movement of the original blood clot, to the ACA (Kurre et al., 2013) or distal embolization in the same territory (Mazur et al., 2016) during mechanical thrombectomy. Patients with collateral failure showed worse outcome under these conditions compared to those with collateral sparing (S. J. Lee et al., 2020). However, these are considered minor cases (~11%) that occur during endovascular recanalization of M1 occlusion resulting in ACA emboli and infarct that limit poststroke motor recovery (Kurre et al., 2013). These studies further highlight the importance of pial collateral circulation.

The time from onset of ischemic stroke to hospital entry and admission to treatment greatly influences infarct growth, with the majority of patients arriving at the hospital more than 3 h after symptoms for large vessel occlusion begin (E. J. Lee et al., 2021; Lees et al., 2010; Man et al., 2020; Tong et al., 2012). However, recent evidence has shown that greater penumbra salvaging is just as critical as time to treatment for effecting disability outcome after stroke (Kawano et al., 2017). LMAs are vital for maintaining the penumbra region, especially in the first 24-h after stroke onset (Agarwal et al., 2018; Cheng-Ching et al., 2015; Cheripelli et al., 2016; Christoforidis et al., 2017; Jung et al., 2013). Upon admission to the hospital, patients undergo imaging to determine their eligibility for revascularization therapy, as well as establish penumbra volume and collateral grade. Computed tomography angiography (CTA) is the most popular method for evaluating collateral status due to its wide availability and sensitivity, with dynamic CTA assessing extent and filling time of LMAs (Raymond & Schaefer, 2017). Analysis of penumbra volume, as well as collateral scoring, was the main outcome assessment used when extending the mechanical thrombectomy therapeutic window from 6 to 24 h after symptom onset, and may indicate extending this window further for eligible patients (Campbell et al., 2015; Casetta et al., 2020; Goyal et al., 2015). This shift toward using penumbra volume with support from collateral scoring assessments instead of time from symptom onset highlights the importance of LMAs and the critical need to improve our understanding of the mechanisms underlying their remodeling to therapeutically target this niche and improve treatment outcome.

2 | THE UNIQUE PIAL COLLATERAL VESSEL NICHE

Unlike adjacent distal arterioles, LMAs display near-zero net flow, with slow oscillations toward either end of the main artery branch from which they anastomose (Chalothorn & Faber, 2010; Toriumi et al., 2009; Traupe et al., 2013).

Additional factors contribute to the increased disturbed flow compared to other arteriole beds, including the non-physiological angles of insertion of the collateral into the anastomosed trees and their hallmark tortuosity, which increases from in utero development through adulthood (Chalothorn & Faber, 2010). Recent findings suggest that although LMAs are exposed to continuous low flow/shear stress, which normally results in a cobble-stoned morphology of endothelial cells (ECs) elsewhere in the vasculature, LMA ECs remain tightly aligned with the vessel axis, have continuous coverage of smooth muscle cells and are less abundant in shear stress sensing cilia (Zhang, Chalothorn, & Faber, 2019). Thus, LMAs represent a specialized vascular niche that may respond differently to aberrant hemodynamic changes that occur following vascular obstruction including unidirectional high-speed flow, increased hematocrit, and perfusion pressure (van Royen et al., 2009; Zhang et al., 2020).During postnatal development, LMAs undergo pruning, where their numbers decrease as brain size increases, which reaches steady-state at postnatal (P) day 21. Additionally, the absolute diameter of LMAs increases during postnatal pruning (Chalothorn & Faber, 2010). Aging has been linked to collateral rarefaction, with regards to both LMA number and diameter. Rodent studies show that collateral reduction was found to occur in an age-dependent manner, with aged animals having significantly fewer LMAs than younger animals of the same strain (Faber et al., 2011; Hecht et al., 2012; Sonntag et al., 1997). Additionally, collateral rarefaction can be further exacerbated by cardiovascular risk factors, including hypertension, metabolic syndrome, diabetes mellitus, and obesity (Moore et al., 2015). The extent of pre-existing collateral rarefaction, and the acute LMA arteriogenic response to occlusion, contribute to patient prognosis. Those patients with poor collateral grade, such as elderly patients with collateral rarefaction, correlate with increased stroke severity, especially when coupled with failed or incomplete recanalization (Faber et al., 2011; Seker et al., 2020). Rarefaction of LMAs, in AD murine models, is suggested to be associated with increased markers of oxidative stress and inflammation in the aged endothelium (Zhang, Jin, & Faber, 2019). Although additional direct cellular analysis of the LMA vessel wall during aging is needed to elucidate changes in shear stress, EC alignment, immune cell recruitment, and smooth muscle cell coverage.

3 | INFLUENCE OF FLUID SHEER STRESS ON COLLATERAL VESSELS

Unlike angiogenesis, where hypoxic/ischemic conditions trigger sprouting of new capillaries, arteriogenesis is not driven by low oxygen (I. Buschmann et al., 2010; H. T. Yang et al., 1994). In fact, the LMA niche lies in an oxygen-rich environment separate from the ischemic tissue (Gray et al., 2007). Arteriogenesis is triggered by an increase in the mechanical forces on the collateral vessel wall (Heil & Schaper, 2004). Following the loss of pressure gradient after arterial occlusion, unidirectional blood flow from the nonoccluded artery flows at an accelerated rate through the nascent collateral vessel, which provides retrograde CBF to the blocked artery. This increase in unidirectional blood flow is directly proportional to increased fluid shear stress (FSS), the viscous drag exerted by the blood on the endothelium of the vessel (Roux et al., 2020). Due to the small size of the collateral vessels, FSS is very difficult to directly measure. As a result, it is often calculated using the blood flow (Q) and radius (r) of the vessel which are both more easily measured, and the equation $\tau = \frac{4\eta Q}{\pi r^3}$ where τ is FSS and η is blood viscosity (assumes Newtonian fluid dynamics; Helisch & Schaper, 2003). In preclinical models, collateral flow can be directly measured using two-photon laser scanning microscopy or laser speckle contrast imaging and indirectly through laser Doppler imaging (J. Ma et al., 2017; Okyere et al., 2020). In the clinical setting, collateral flow and grade is most commonly determined using computed tomographic angiography, but can also be measured indirectly using computed tomography perfusion or magnetic resonance imaging (Piedade et al., 2019).

Since FSS is inversely related to vessel diameter, as the collateral vessel wall undergoes outward expansion, FSS decreases. For this reason, collateral vessels are limited in growth to restore up to 35%–40% of the blood flow originally provided by occluded parent artery (Hoefer et al., 2001; W. Schaper et al., 1976). However, studies investigating the administration of growth factors and cytokines, including FGF-1, FGF-2, vascular endothelial growth factor (VEGF), and MCP-1, show increased collateral conductance to 50% of that provided by the original occluded artery (Arras et al., 1998; Henry et al., 2003; Lazarous et al., 1995; Unger et al., 1993). To date, increasing FSS on the collateral vessel wall, by utilizing an arteriovenous shunt, has been the only effective way to fully restore and surpass the maximum conductance of the occluded parent vessel (Eitenmüller et al., 2006; Pipp et al., 2004). This inherent shortfall highlights the need to fully elucidate the mechanisms that govern arteriogenesis in the LMA niche to maximize their therapeutic potential to restore CBF following ischemic stroke and to overcome additional challenges that may exist as a consequence of age and chronic inflammatory conditions.

3.1 | Mechanisms of mechanosensing

A simple and eloquent explanation for transduction of mechanical signals is Ingber's "tensegrity" model. Tensegrity is a building principle first coined by Richard Buckminster Fuller in the 1980s, in which a structure is supported by continuous tension (Swanson 2nd, 2013). This principle also applies to the structure of a living cell. In Ingber's model, a cell is shaped by the cytoskeleton, which undergoes tensional forces generated by contractile microfilaments. Those tensional forces are balanced by tethers to the extracellular matrix through focal adhesions, such as integrins (Ingber, 2003). Not only does this design provide structural stabilization for the cell, but it allows for the transduction of external mechanical forces along integrins and load bearing cytoskeletal elements (Ingber, 2008).

In addition to mechanical signals entering the cell through integrins, there are numerous mechanoreceptors (Chatzizisis et al., 2007). One of the most commonly noted mechanoreceptor in arteriogenesis is a complex comprised of platelet endothelial cell adhesion molecule 1 (PECAM-1), vascular endothelial cadherin (VE-Cadherin), and VEGFR2 (T. Ma & Bai, 2020). PECAM-1 serves as the mechanosensor, forming a heparan sulfate stabilized complex with the Gq/G11 protein and couples with the adaptor protein VE-Cadherin to activate VEGFR2 and its subsequent signaling cascade (dela Paz et al., 2014). VEGFR2 activation is vital for EC proliferation and the release of von Willebrand Factor (vWF) from platelets in response to FSS induced extracellular RNA (Lasch et al., 2019). Studies using a hind limb occlusion model showed that reduction in VEGFR2 activity, vWF, or extracellular RNA through RNase treatment all interfered with arteriogenesis by impeding formation of platelet–neutrophil aggregates (Lasch et al., 2019). This complex also activates nuclear factor κB (NFκB) and protein kinase B (Akt), which are essential for expression of adhesion molecules, cytokines expression, and EC survival, respectively (Tzima et al., 2005).

Primary cilia are an immobile organelle that exist on the surface of almost all cell types, including LMA endothelial cells, and are well established for their role as mechanosensors in vascular beds. The primary cilia function through PC1/2 mechanosensitive ion channel complex to regulate nitric oxide production (Kathem et al., 2014; Nauli et al., 2008). In models of atherosclerosis, primary cilia are found in higher abundance on ECs exposed to low shear stress, and areas with more primary cilia tend to be prone to atherosclerotic plaque development (Van der Heiden et al., 2008). The increased concentration is thought to be a mechanism of sensitizing these vessels to mechanical changes (Hierck et al., 2008). Interestingly, LMAs which are normally exposed to low, oscillatory shear stress, have fewer primary cilia than distal arterioles (Zhang, Chalothorn, & Faber, 2019). This raises the questions of why LMA ECs have fewer primary cilia, how this phenotype may contribute to or limit the growth of LMAs in response to changes in shear stress and if they can be therapeutically sensitized following ischemic stroke.

Recent evidence suggests that ECs, from different vessel types, have a preferred level of FSS that determines remodeling. This "shear stress set point", where flow-induced stress is maintained through feedback mechanisms at an optimal point, ensures that aberrant inward or outward remodeling does not occur. Moreover, ECs that highly express VEGFR3, as part of a mechanoreceptor complex, tend to be more sensitive to shear stress, and therefore have a lower set point than those cells that express reduced VEGFR3 levels (Baeyens et al., 2015). Given that collateral ECs are morphologically distinct (Zhang, Chalothorn, & Faber, 2019), it may be postulated that their unique phenotype and by extension ability to remodel, may be governed by the density and properties of select mechanoreceptors. Interestingly, recent findings propose an alternative, flow-independent model to describe the growth of a small diameter vessel into large caliber arteries, involving endothelial cell enlargement. This mechanism proposes that soluble Flt1 controls precise titration of VEGF signaling at the arterial wall to influence the GEF trio in zebrafish and cell models (Klems et al., 2020). These studies highlight the potential level of influence on LMAs that will need further investigation in animal models of ischemic stroke.

4 | ACTIVATION AND GROWTH OF COLLATERALS VESSELS

4.1 | Activation of the endothelium

In response to increases in FSS, one of the first signs of endothelial cell activation is cell swelling. It has been observed in human coronary collaterals that flat endothelial cells lining the vessel become longitudinal bulges in response to the heightened FSS (Seiler, 2010). In an attempt to counteract this swelling, the endothelial cells activate ion channels, including the volume-regulated anion channel (VRAC). These channels allow for the efflux mainly of chloride ions, and permit entry of Ca^{2+} ions and movement of organic osmolytes, which drives a secondary efflux of water from the

cell thereby decreasing its volume (Hoffmann et al., 2009). Blockade of these channels using mibefradil, which inhibits both VRACs and T-type calcium channels, resulting in decreased collateral growth in a hind limb occlusion model (Manolopoulos et al., 2000; Ziegelhoeffer et al., 2003). Therefore, shear stress-induced activation of ion channels is one of the first signs of endothelial cell activation. Although most RTKs are activated by shear stress (Chen et al., 1999), the Tie2 receptor, expressed predominately on endothelial cells, shows rapid and sustained, velocity-dependent phosphorylation that is correlated with Akt phosphorylation (H. J. Lee & Koh, 2003). These findings support recent studies that demonstrate the EphA4 RTK negatively regulates LMAs in ischemic stroke by suppressing Tie2/pAkt function and cell proliferation in the vessel wall (Okyere et al., 2020). Additionally, in models of hind limb and myocardial ischemia, both angiopoietin ligands have been implicated in supporting collateral growth and improving perfusion although the exact mechanisms of action have not been fully elucidated (Chae et al., 2000; Gluzman et al., 2007; Siddiqui et al., 2003; Tressel et al., 2008).

4.1.1 | Vasodilation

To date, the role of NO in arteriogenesis has remained paradoxical. When activated by shear stress, endothelial cells increase expression of eNOS, elevating the release of NO, a potent vasodilatory agent. However, as collateral vessels vasodilate and therefore increase in diameter, FSS is reduced, potentially serving as a negative regulator for arteriogenesis. In a mouse model of hind limb occlusion, mice overexpressing eNOS (eNOStg mice) had significantly improved blood flow immediately flowing occlusion compared to wild-type controls. Conversely, eNOS deficient mice had sustained decreases in blood flow. Interestingly, no difference was seen in collateral artery diameter between the groups after 3 weeks (Mees et al., 2007). This implies that NO is indispensable for initial vasodilation of collateral vessels, perhaps through increased dilation of arteries feeding the collateral upstream, but does not significantly impact arteriogenesis (Dai & Faber, 2010). Furthermore, inhaled NO (iNO) is being investigated for clinical applications to reduce ischemic brain damage and increase collateral flow through vasodilation. Studies in rodent and large animal models have shown the iNO treatment at moderate (10–40 ppm) but not high (80 ppm) concentrations following either transient or permanent models of ischemic stroke reduces tissue damage and increases collateral dilation and flow (Charriaut-Marlangue et al., 2012; Terpolilli et al., 2012). Although this treatment is beneficial when given during the ischemic period, when administered later it can cause negative effects by exacerbating oxidative stress and the formation of harmful nitrogen species (Charriaut-Marlangue et al., 2012; Joriot-Chekaf et al., 2010).

To combat the increase in oxidative stress that accompanies iNO, prostaglandins have emerged as an attractive target for improving acute vasodilation in collateral vessels following stroke due to their more delayed and moderate vasodilatory effects. Treatment with prostaglandin E1 in neonatal rats showed improvements in blood flow back to basal levels and significant reductions in lesion volume 2 days following injury in treated mice. The restoration in blood flow was thought to be due to increases in recruitment and blood flow through primary collaterals in the circle of Willis or through pial collaterals, although no direct analysis of the collateral vessels was performed (Bonnin et al., 2018). While this work sets the stage to solidify prostaglandin E1 as a potential therapy for stroke aimed at improving collateral vasodilation, more direct studies of LMAs are necessary.

Other pharmacological agents for enhancing vasodilation of collaterals have been found, such as leptin. Leptin increases collateral flow but does not impact cellular proliferation or collateral conductance when tested under maximum dilation, indicating no changes in vessel diameter occurred (Busch et al., 2011; Schirmer et al., 2004). Therefore, initial studies have shown the importance of taking advantage of collateral vessels for acute vasodilation and subsequent arteriogenesis to improve blood flow restoration in ischemic stroke. From a clinical perspective, pharmacologically increasing vasodilation of collaterals could provide short-term improvements in tissue perfusion prior to recanalization. It could also help complement the on-going process of arteriogenesis, which may take additional time to allow for maximum vessel growth. The field would benefit from additional studies within the acute phase of ischemic stroke to determine the extent of vasodilation following occlusion and its relationship to early stages of arteriogenesis.

4.1.2 | Increased vascular permeability

Increases in vascular permeability during ischemic conditions have been described since the 1970s, when Schaper and colleagues found increased leakage of erythrocytes and plasma proteins in the wall of collateral vessels, as well as

increased monocyte recruitment following induced cardiac ischemia (J. Schaper et al., 1972). Work by Yang et al reveals that NO and VE-Cadherin play a major role in regulating endothelial cell permeability and therefore likely contribute to the invasion of immune cells (B. Yang, Cai, et al., 2015). VE-cadherin is the transmembrane component of adherens junctions that are involved in cell–cell contacts. It is expressed in all vascular endothelial cells, with its function and organization controlled by numerous molecules, including NO. In endothelial cells exposed to laminar flow or in collaterals subjected to sham hind limb occlusion, endothelial cells highly express VE-cadherin with continuous expression along the junctions between endothelial cells (Miao et al., 2005; B. Yang, Cai, et al., 2015). However, in collateral vessels following occlusion of the femoral artery, VE-cadherin becomes significantly downregulated on collateral endothelial cells and form a broken, punctate pattern (B. Yang, Cai, et al., 2015). This is associated with disassembly of adherens junctions, increased vascular permeability, and modulates immune cell infiltration (Miyazaki et al., 2011; Zhao et al., 2021). This stark downregulation could be inhibited using L-NAME, a NO synthase inhibitor, or even further reduced using DETA NONOate, a NO donor (B. Yang, Cai, et al., 2015). This work indicates an important crosstalk between NO and VE-cadherin in regulating the permeability of the endothelium. This also suggests that permeability may allow for recruitment of key immune cells that participate and are required for the remodeling process.

Another contributor to vascular permeability is one of the hallmark regulators of collateral vessels, VEGF, with roles both in vascular development and in arteriogenesis after ischemic stroke. Following femoral artery ligation VEGF is upregulated in the FSS exposed endothelium, with isoform expression differing between mouse strains, potentially contributing to differences seen in arteriogenic capacity (Chalothorn et al., 2007). When disruption of VEGF signaling is performed using gene manipulation, inhibitors, anti-VEGF-A neutralizing antibodies, or soluble VEGFR traps, arteriogenesis is reduced (Clayton et al., 2008; Jacobi et al., 2004; Lloyd et al., 2005; Toyota et al., 2005). Downstream of VEGFR2, the guanine exchange factor Trio, activates RhoG and Rac1 inducing focal adhesions, F-actin remodeling, and actomyosin activity (Klems et al., 2020). Signaling through Trio has been shown to stabilize junctions between endothelial cells and prevent leakage during vascular remodeling (Timmerman et al., 2015).

4.2 | Collateral vessel growth and remodeling

In order for collateral vessels to enlarge into conductance arteries, the endothelium may expand through cellular proliferation, the mechanisms of which remain under investigation and may be organ specific. Following activation of mechanoreceptors, endothelial cells upregulate expression of matrix metalloproteinase (MMP)-2, MMP-9, tissue plasminogen activator (tPA), and urokinase plasminogen activator (uPA), which assist in the breakdown of extracellular matrix. The endothelium also upregulates the expression of chemoattractants and integrins to recruit leukocytes. These events are required for the remodeling of the vessel and monocyte invasion has been found to proceed vascular proliferation (Arras et al., 1998; Heil & Schaper, 2004). Under healthy conditions, ECs are quiescent, but following ischemic stroke must transition into a proliferative phenotype, allowing them to multiply and migrate as needed to grow the pial collaterals (Jin et al., 2017; Tzima et al., 2005). Intracellular signaling cascades involved in endothelial cell migration are also upregulated following activation, including focal adhesion kinase (FAK), integrin α5β1, integrin αvβ3, and Erk1/2.

Activation and proliferation of the endothelium were first reported in the 1970s in canine coronary collaterals. DNA synthesis peaked in the canine collaterals 3 weeks following constriction of the coronary artery (W. Schaper et al., 1971). However, when proliferation was evaluated at more acute time points following occlusion, it was observed as early as 24 h, peaked at 3–7 days, and remained at 3 weeks (Scholz et al., 2000). This matches murine studies of LMA growth, where proliferation is visible as early as 24 h poststroke (Okyere et al., 2018; Okyere et al., 2020). The delay from occlusion to the start of cellular proliferation, may help emphasize the potential importance of collateral vasodilation in the early hours following stroke. However, given that the time of onset for large vessel occlusion until clinical admission can be several hours to days (E. J. Lee et al., 2021; Tong et al., 2012), it is likely that efficient LMA remodeling that includes endothelial cell activation, division, and remodeling may contribute to patients with good collateral function and stroke outcome.

In addition to EC proliferation, integration of endothelial progenitor cells (EPCs) could contribute to LMA expansion and remodeling. In ischemic stroke patients, EPCs are elevated compared to healthy controls and lower levels of circulating EPCs are a predictor of worse neurological outcome (Yip et al., 2008). Additionally, in myocardial infarction patients, reduced numbers of circulating EPCs were associated with poor collateral status (Lambiase et al., 2004). However, in LMAs following ischemic stroke, it remains controversial if these cells integrate into the collateral vessel wall, and if they do, how much of a role they play in total growth. In studies of hind limb ischemia, supplementation of EPCs

or nanofibrillar scaffolds seeded with ECs enhanced arteriogenesis (Nakayama et al., 2015; Zhou et al., 2017). Although these studies are limited as they looked at total vascular volume instead of direct measurements of the collateral vessel wall, as integration of the EPCs was not demonstrated. In a murine, hind limb ischemia model, integration of bone marrow-derived EPCs was shown using a chimeric mouse containing GFP labeled bone marrow. However, the GFP labeling was not colocalized to the collateral endothelial or smooth muscle cell layer, instead the GFP-positive cells surrounded the abluminal wall (Ziegelhoeffer et al., 2004). This could indicate a role for EPCs and bone marrow-derived cells in paracrine signaling of growth factors and chemokines that support arteriogenesis (Kinnaird et al., 2004; Rehman et al., 2003).

5 | DUAL ROLE OF IMMUNE MODULATION AND LMA

When activated by shear stress, the endothelium has been shown to mediate the process of recruiting peripheral immune cells to the collateral vessel, where they help create the balanced inflammatory environment required for arteriogenesis. Unfortunately, most of the research regarding immune cell attraction, adhesion, and activation in collaterals have not been performed in animal models of stroke. Due to the unique niche properties of LMAs, further investigation could assist in uncovering the role of immune mediators and lead to the discovery of pro-arteriogenic immune cell types that may benefit stroke patients.

Studies in hind limb ischemia, have shown that monocytes accumulate by 12 h and recruitment peaks between 1 and 3 days after occlusion (Heil et al., 2002). Depletion of these monocytes through op/op knockout mice or treatment with 5-fluorouracil and other agents resulted in severely impaired arteriogenesis (Bergmann et al., 2006; Heil et al., 2002; Millenaar et al., 2013; Pipp et al., 2003). Conversely, studies using clodronate liposome and cyclophosphamide did not show negative results on arteriogenesis, with the authors hypothesizing that resident macrophages may play a more prominent role than circulating cells in the early stages of collateral growth (Jetten et al., 2013; Khmelewski et al., 2004). Work by Schirmer, found 244 genes that were differentially expressed in circulating monocytes from patients with poor vs good coronary collateral circulation and development. They observed that genes related to type 1 interferons were overexpressed in the patients that had poor collateral networks, also highlighting the importance of looking at monocyte-specific pathways in the regulation of LMAs (Schirmer et al., 2008).

One of the most well-regarded chemo attractants in LMA remodeling is monocyte chemoattractant protein 1 (MCP-1), with the ability to attract immune cells, especially monocytes, to the collateral arteriole. In human patients, high levels of MCP-1 were associated with good collateral grade before treatment for ischemic stroke (Mechtouff et al., 2020). A later study, found no significant difference in MCP-1 levels of human stroke patients with different collateral grades (Yu et al., 2021). This discrepancy could be due to the difference in collateral scoring technique, samples size, or blood collection time. In addition, Apelin-17, an endogenous *apelin* receptor agonist which plays a role in vascular health and immune modulation (Y. Yang, Lv, et al., 2015), was positively associated with human ischemic stroke patients that had good collateral circulation (Jiang et al., 2019). Apelin can be secreted by many cell types, including endothelial cells and peripheral immune cells, and the main apelin receptor is most highly expressed on endothelial cells (Helker et al., 2020). These findings indicate that the peripheral immune response may play a vital role in LMAs, although additional research is needed.

Importantly, collateral circulation may play a key role in the broad immunological response to stroke. In stroke patients, it was found that even though the extent of collateral circulation did not impact the concentration of leukocytes circulating in the blood after LVO (Tarkanyi et al., 2020), the extent of collateral circulation was an indicator of how well immune cells were able to infiltrate into the ischemic tissue of the brain (Strinitz et al., 2021). The extent of LMAs coincident with immune status, also predicts hemorrhagic complications, with patients admitted with leukopenia showing poor collateral status coupled are more at risk for intracerebral hemorrhage (Semerano et al., 2019).

6 | THERAPEUTIC TARGETING OF LMA REMODELING

Extensive research has vastly improved our fundamental understanding of the development and function of collateral remodeling in stroke. However, to date, the ability for preclinical therapies to be translated into ischemic stroke treatments or therapeutic enhancement of collateral growth has been limited. In the experimental setting, there have been

numerous compounds targeting endothelial and smooth muscle growth or monocyte recruitment. Once in clinical trials, these compounds led to disappointing results, mostly centered on safety concerns (Table 1).

6.1 | Vascular endothelial growth factor

The role of VEGF-A has been widely studied in endothelial activation and growth. As earlier discussed, while it is highly regarded as a strong promoter of angiogenesis, its exact role in arteriogenesis remains under debate. In contrast to its promising potential for both modes of vascular growth in preclinical studies and success of small patient studies, a larger controlled clinical trial failed to show improvements. The VEGF in Ischemia for Vascular Angiogenesis (VIVA) investigated stimulation of angiogenesis, but failed to show improvements in walking time between patients given the treatment and the placebo (Henry et al., 2003). Clinical investigations into VEGF as a biomarker for ischemic stroke and transient ischemic attacks also revealed increased VEGF serum concentrations were associated with increased incidence and severity of these ischemic events (Bhasin et al., 2019; Pikula et al., 2013).

6.2 | Colony-stimulating factors

Granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) are released by the endothelium following increased shear stress and are noted for their ability to mobilize progenitor cells from the bone marrow (Just et al., 1993; Klein et al., 1982; Kosaki et al., 1998). They can also support the survival, proliferation, and differentiation of hematopoietic cells, such as monocytes. In preclinical models, treatment with GM-CSF or G-CSF showed improvements in collateral artery growth (I. R. Buschmann et al., 2003; Duelsner et al., 2012; Sugiyama et al., 2011; Todo et al., 2008) and was even more promising for its anti-atherogenic properties unlike other potential therapeutic compounds, such as MCP-1. An initial study on the pro-arteriogenic effects of GM-CSF on patients with coronary artery disease showed promising results, but a later study saw safety concerns with two of seven treated patients having acute coronary syndrome vs none in the placebo control group (Seiler et al., 2001; S. Zbinden et al., 2005). The effects of GM-CSF were also tested in peripheral artery disease but no improvements were seen in the primary endpoint (van Royen et al., 2005). Alternatively, G-CSF was tested in acute ischemic stroke patients and while it showed safety and feasibility in small clinical trials (Floel et al., 2011; Moriya et al., 2013; Schäbitz et al., 2010), it failed to show significant improvements to patient outcomes in larger controlled trials (Mizuma et al., 2016; Ringelstein et al., 2013).

6.3 | Statins

Statins are classically known for their ability to lower lipid concentrations in the blood, but they can also exhibit cholesterol-independent effects by directly improving endothelial function through increased NO production. In arteriogenesis, statins may serve as a therapeutic to improve collateral vessel function by improving EPC mobilization and monocyte function (Landmesser et al., 2004). Preclinical data shows a decrease in the efficacy of monocytes in arteriogenesis during hypercholesterolemia and that it could be reversed with statin administration (Czepluch et al., 2007). Clinical trials have shown positive results in stroke patients indicating statins as a potential pharmacological approach to treat stroke (Table 1). However, the effects of statins on augmenting arteriogenesis are less clear. Multiple clinical trials have shown a positive correlation between statin treatment and collateral score (Dincer et al., 2006; Pourati et al., 2003). However, a larger study in patients with coronary artery disease found no effects of collaterals on arteriogenesis when looking at functional collateral flow index measurements (S. Zbinden, Brunner, et al., 2004). Further highlighting the need to understand the collateral remodeling niche response in a site-specific fashion across multiple preclinical models.

6.4 | Physical exercise

An alternative to pharmacological rescue is physical exercise, which may provide a natural method for improving collateral function. Physical exercise has been shown to promote arteriogenesis through increased FSS across the endothelium and accumulation of macrophages to the collaterals with increased expression of iNOS and eNOS (Dopheide

TABLE 1 Biomarker detection and therapeutic targeting of LMC remodeling

	Author	Disease	n-value	Treatment duration	Major findings
VEGF	Henry et al., 2003	Exertional angina	178	Day 0, 3, 6, and 9	Recombinant human VEGF (rhVEGF) was safe. No significant improvements in myocardial perfusion or quality of life in the first at day 60 in rhVEGF treated compared to controls. High dose rhVEGF improved angina class compared to controls, no difference in low rhVEGF treated group.
	Bhasin et al., 2019	Acute ischemic stroke	250	N/A	VEGF is upregulated in the blood of patients with severe stroke compared to healthy controls. At 3 months poststroke when coupled with clinical scores, VEGF as a biomarker is a predictor of stroke severity and patient functional outcome.
	Pikula et al., 2013	Incident stroke/ transient ischemic attack	3440	N/A	Higher serum concentrations of VEGF associated with increased risk of ischemic event.
Colony Stimulating Factor	Seiler et al., 2001	Coronary artery disease	21	14 days	Coronary collateral flow was measured using invasive collateral flow index (CFI). Treatment with GM-CSF in severe CAD patients resulted in significantly improved CFI compared to the placebo group.
	Zbinden et al., 2005	Coronary artery disease	14	14 days	CAD patients treated with GM-CSF had significantly improved CFI. In the GM-CSF treated group, two of seven patients experience acute coronary syndrome, bringing into question the safety of treatment.
	van Royen et al., 2005	Peripheral artery disease	40	14 days	Collateral flow measured indirectly using laser Doppler flowmetry. No difference in walking time (primary endpoint) was seen between treatment and control patients. GM-CSF treatment did not result in improvements of microcirculatory flow reserve.
	Floel et al., 2011	Chronic ischemic stroke with concomitant vascular disease	41	10 days	No significant improvement in hand motor function seen in G-CSF treated patients. G-CSF resulted in more frequent mild or moderate adverse outcomes compared to controls, demonstrating reasonable safety and tolerability.
	Moriya et al., 2013	Acute and subacute ischemic stroke	18	5 days	No severe adverse outcomes noted, indicating safety and tolerability of low dose G-CSF.
	Schäbitz et al., 2010	Acute ischemic stroke	44	3 days	G-CSF demonstrated safety and tolerability at low and high doses. No improvement in clinical outcome was seen with G-CSF treatment.

(Continues)

TABLE 1 (Continued)

	Author	Disease	n-value	Treatment duration	Major findings
	Mizuma et al., 2016	Acute ischemic stroke	49		G-CSF was well tolerated but did not improve functional recovery or decrease infarct volume 3 months following stroke.
	Ringelstein et al., 2013	Acute ischemic stroke	328	3 days	No improvement was seen in patient outcome or imaging biomarkers in patients treated with G-CSF poststroke.
Statins	Dincer et al., 2006	Diabetes mellitus	149	Variable	Coronary collaterals were graded using Cohen–Rentrop method. Treatment with statins was associated with better coronary collateral score.
	Pourati et al., 2003	Major coronary artery occlusion or stenosis	94	Variable	Coronary collaterals were graded using Cohen–Rentrop method. Patients receiving statins had significantly higher collateral score and left ventricular ejection fraction compared to patients not taking statins.
	Zbinden, Brunner, et al., 2004	Coronary artery disease	500	Variable (avg 9.5 months)	No difference in CFI with statin use and the number of patients with insufficient collaterals was significantly greater in the group taking statins.
Physical exercise	Möbius-Winkler et al., 2016	Coronary artery disease	60	4 Weeks	CFI was significantly increased in patients receiving either high or moderate-intensity exercise compared to controls. Exercise improved peak VO_2 and ischemic threshold compared to patients in control group.
	Togni et al., 2010	Coronary artery disease	30	1 Treatment	CFI of coronary collaterals doubles in patients during supine bicycle exercise compared with resting state.
	Zbinden et al., 2007	Coronary artery disease	40	3 Months	CFI increased in arteries undergoing percutaneous coronary intervention and in normal vessels of the exercise group patients compared to controls. The increase in collateral flow correlated with exercise capacity gained (VO_{2Max} and Watt).
	Zbinden, Zbinden, et al., 2004	Healthy Control	Case study	25+ years	The left descending coronary artery was occluded for 1 min. CFI increased 60% in response to endurance training compared to baseline.
	Petrovic et al., 2020	Coronary Artery Disease	32	2 Weeks + Heparin	Collateral score using CTA, myocardial ischemia, and angina class improved significantly in group receiving exercise and heparin compared to the exercise only group.

et al., 2017; Schirmer et al., 2015). It has also been shown to reduce collateral rarefaction during aging in an animal model (McMullan et al., 2016). FSS rises during physical exercise because of the increase in heart rate and blood pressure needed to maintain cellular function (Duncker & Bache, 2008). The heightened NO can then act on the endothelial and smooth muscle cells to improve collateral vasodilation and growth. Multiple clinical trials using collateral flow

index have shown a significant relationship with exercise and collateral blood flow, indicating the use of exercise in a clinical setting to improve arteriogenesis (Table 1; Möbius-Winkler et al., 2016; Togni et al., 2010; R. Zbinden et al., 2007; R. Zbinden, Zbinden, et al., 2004). The effects of physical exercise on collaterals can also be improved when coupled with pharmacological treatments. A recent clinical trial investigating myocardial ischemia found that patients that received heparin in addition to exercise had improved collateral flow compared to patients in the exercise alone group (Petrovic et al., 2020).

7 | CONCLUSION

LMAs are a vital determinant of ischemic stroke outcome, but their niche properties and mechanism of remodeling remain under intense investigation. Substantial research has been done in other collateral beds, especially the hind limb; however, more work is underway to correlate these findings with LMA niche regulation. This knowledge gap could limit the development of precision therapeutics targeted at LMAs, as their unique characteristics have not yet been fully elucidated. This may also contribute to the poor translational capacity of pro-arteriogenic compounds from preclinical to clinical models. To combat this, more research emphasis is being placed on determining the molecular pathways that propel human arteriogenesis in the LMAs of the brain, as the biological mechanisms driving this critical adaptive response have to remain under-investigated and may differ from animal models. Additionally, the mechanism for arteriogenesis elucidated in preclinical models has been predominantly unsubstantiated in humans. The lack of investigation into human arteriogenesis is largely due to the difficulties in identifying and accessing pial collateral vessels.

An additional factor that could contribute to the disappointing translatability is the lack of a clear definition of what constitutes remodeling. Most studies utilize collateral diameter to indicate remodeling. Currently, the classical definition of arteriogenesis focuses on the cellular remodeling of the LMAs, not on the vessels' ability to dilate or the potential for endothelial cell enlargement; therefore, a clearer definition for what constitutes the full extent of LMA remodeling needs to be further established. Work investigating the cellular changes in the LMAs during the acute phase of ischemic stroke may shed light on how these vessels initially react to changes in blood flow and help establish the temporospatial characteristics of the remodeling process.

Finally, while these specialized vessels harbor numerous differences from distal arterioles, little work has been done on how these differences impact vessel function, notably in the response to mechanical stimuli. What expression patterns exist for VEGFR3 on LMAs, compared to other vessel types, and how does this contribute to their mechanosensing complex? How does the density of primary cilia influence LMAs and does this limit their capacity to fully respond to appropriate changes in shear stress? Are these differences influenced by immune status, age and are they linked to patient collateral scoring? Understanding the basic mechanisms for mechanosensing, specifically in the LMAs given their unique niche properties, opens the door to potential therapeutic enhancement of their growth. Since LMA remodeling will likely have to be targeted poststroke in a combinatory fashion, mechanosensing is a promising target. Numerous studies have shown that increasing FSS results in collaterals with the highest conductance (Eitenmüller et al., 2006; Pipp et al., 2004). Additional emphasis should be placed on understanding how we can sensitize LMAs to small changes in FSS, potentially allowing for the large increase in conductance capacity, without needing to therapeutically shunt additional blood into the LMAs. This priming of the LMAs may also be beneficial as a prophylactic for patients at unusually high risk for having an ischemic stroke. Therefore, additional research into LMA remodeling will aid future investigation aimed at improving novel therapeutic development for ischemic stroke.

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CONFLICT OF INTEREST

The authors have declared no conflicts of interest for this article.

AUTHOR CONTRIBUTIONS

Alexandra M. Kaloss: Conceptualization (equal). **Michelle H. Theus:** Conceptualization (equal).

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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