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Commentary

Fluid shear stress sensing in vascular homeostasis and remodeling: Towards the development of innovative pharmacological approaches to treat vascular dysfunction

Nicolas Baeyens[a,*]

[a] Laboratoire de physiologie et pharmacologie, Faculté de Médecine, Université libre de Bruxelles, ULB, Belgium

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ABSTRACT

Blood circulation, facilitating gas exchange and nutrient transportation, is a quintessential feature of life in vertebrates. Any disruption to blood flow, may it be by blockade or traumatic rupture, irrevocably leads to tissue infarction or death. Therefore, it is not surprising that hemostasis and vascular adaptation measures have been evolutionarily selected to mitigate the adverse consequences of altered circulation. Blood vessels can be broadly categorized as arteries, veins, or capillaries, based on their structure, hemodynamics, and gas exchange. However, all of them share one property: they are lined with an epithelial sheet called the endothelium, which typically lies on a basement membrane. This endothelium is the primary interface between the flowing blood and the rest of the body, and it has highly specialized molecular mechanisms to detect and respond to changes in blood perfusion. The purpose of this commentary will be to highlight some of the recent developments in the research on blood flow sensing, vascular remodeling, and homeostasis and to discuss the development of innovative pharmaceutical approaches targeting mechanosensing mechanisms to prolong patient survival and improve quality of life.

1. Introduction: physiology of blood flow sensation and adaptation

One of the earliest observations of vascular adaptation in response to changes in hemodynamics was made in the nineteenth century by Thoma and these were further investigated by Chapman and Murray in the chick yolk sac; adequate perfusion was found to determine which premature, non-perfused, and unspecified vessels undergo arterial specification and maturation, while under-perfused vessels remain closed and regress [1–3]. These earlier observations are striking: blood vessels are not merely biological pipes, they are dynamic structures shaped by blood flow itself. This dynamic adaptation is not restrained to the developmental stages of the vasculature, with a transient increase in arterial flow being associated with a transient dilation of the mature arteries under increased flow, through vasorelaxant release [4–8]. Furthermore, a sustained increase in flow, as observed in the muscular arteries of physically trained individuals [9,10] or in the uterine artery during pregnancy [11,12], triggers active remodeling of the concerned arteries by increasing their lumen diameter, improving tissue perfusion. Similarly, hypoperfusion of mature blood vessels, following stenosis for example, leads to the inward remodeling of under-perfused vessels. Interestingly, this inward remodeling could not be linked to an increased contraction of the mural cells as vasorelaxants could not relieve it [13]. This indicates a more profound, structural adaptation of the vessel in response to changes in flow. This was later confirmed after observing that mice lacking matrix metalloproteinases could not undergo successful inward remodeling in response to decreased flow due to the lack of remodeling of the collagen matrix [14,15].

These observations, in various animal models as well as in humans, emphasize the fact that living organisms have developed strategies to maintain organ perfusion by adapting the lumen diameter of their blood vessels, either very rapidly by modulation of the contractile status of the muscular media or by a permanent alteration of the vessel structure if the hemodynamics alteration is chronic. Such responses led

Abbreviations: Alk, activin receptor-like kinase; BMP, bone morphogenic protein; ECM, extra-cellular matrix; EndMT, endothelial to mesenchymal transition; eNOS, endothelial nitric oxide synthase; FGF, fibroblast growth factor; FRET, fluorescence resonance energy transfer; FSS, fluid shear stress; HHT, hereditary hemorrhagic telangiectasia; MMP, matrix metallo-proteinase; NADPH, nicotinamide adenine dinucleotide phosphate oxidase; NFkB, nuclear factor kappa B; NO, nitric oxide; PECAM, platelet endothelial cell adhesion molecule; PI3K, phosphoinositide 3-kinase; VEGF, vascular endothelial growth factor

* Address: Laboratoire de physiologie et pharmacologie, CP604, 808 Route de Lennik, 1070 Anderlecht, Belgium.
E-mail address: nicolas.baeyens@ulb.ac.be.

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to the hypothesis that there should exist a preferential value of blood flow for a given vessel and that any alteration is sensed and integrated in such a way that changes in lumen caliber restore steady state values of flow [16]. Blood is fluid and therefore exerts a dragging force on the surface of the endothelial layer, commonly referred to as fluid shear stress (FSS). The intensity of this force is directly proportional to blood velocity and viscosity and inversely proportional to the lumen diameter. Several canonical endothelial flow responses, such as the production of nitric oxide (NO), secretion of prostacyclin or induction of the flow mechanoresponsive gene *klf2*, have been shown to be dose-dependent [6,17,18], displaying the existence of fine-tuned mechanical sensors, responding precisely to changes in FSS. This mechanical force, in the context of the cardiovascular system, is very modest, ranging from 0.01 to 5 Pascals (0.1–50 dynes/cm^2) across the vascular tree, while other mechanical stresses such as the circumferential stretch can reach up to 1000 Pascals [19–22]. Nevertheless, FSS is the actual parameter that governs adaptation to changes in flow; increased flow velocity is associated with a temporary increase in FSS, which is sensed by the vessel, subsequently increasing its internal diameter until FSS values are restored to normal. Hence, there is an FSS set point [16,23]. When confronted with an FSS approximating that of the set point, endothelial cells align in the flow direction, activate stabilizing signaling pathways, and repress inflammatory responses. This set point is not constant across the vasculature, because of the wide range of FSS values at steady state; lymph FSS is one order of magnitude lower than the average blood FSS magnitude, therefore lymphatic endothelial cells exhibit a much lower FSS set point than their blood counterpart [21,23–25].

FSS is characterized by its magnitude, but other parameters bear crucial importance in blood vessel physiology. Because of its pulsatile nature, blood flow and therefore FSS, is not particularly steady. The time-varying pattern of blood flow generates FSS with complex frequency content, which contributes to different endothelial cell responses than steady FSS alone [26]. Indeed, recent work investigating the contribution of pulsatile frequency and frequency harmonics unveiled a modulatory role of these parameters on endothelial cells responses [27,28]. More importantly, drastic changes in frequency harmonics contribute to the initiation of atherosclerosis, indicating that endothelial cells can sense and respond to changes in time-varying components of FSS [29].

The vascular network can be roughly described as linear cylindrical portions where the flowing fluid is laminar, with a forward direction and very little turbulence, while vessel bifurcations induce a local disruption of the laminar nature of the flow, with highly dispersed directions, flow reversal during some phases of the cardiac cycle, and rarely, a truly chaotic behavior as observed in the aortic arch [30–32]. En-face observation of the aorta provides some of the most compelling proof that endothelial cells are sensitive to *flow direction* [33–35]: the endothelium in the straight portion of the thoracic aorta, where flow is mostly laminar with a forward direction, is characterized by a uniform pattern of elongated endothelial cells, with their major axes facing the flow direction. On the other hand, the portions of the endothelium located near the bifurcations of smaller vessels (carotids, intercostal arteries) and within the aortic arch inner curvature, are experiencing a turbulent flow profile, dispersing in various directions, translating in a pattern of randomly organized endothelial cells with a polygonal shape and no clear polarity. The consequence in terms of physiology is drastic, and endothelial cells subjected to flow with varying directions, in association with risk factors, initiate atherosclerosis development, with plaque localization correlating extremely well with multidirectional flow [32,36]. These observations lead to the conclusion that there exist atheroprone flow profiles (varying directions and disturbed frequency harmonics) and atheroprotective flow profiles (laminar flow) [37,38].

Beyond the FSS parameters themselves, the nature of the extracellular matrix (ECM) on which endothelial cells lie is another crucial (but often neglected) factor when it comes to interpreting the biological responses to FSS. In a developed and healthy vessel, endothelial cells interact with a basement membrane mostly constituted of collagen IV, laminin, proteoglycans, and a small amount of fibronectin [39]. Contrastingly, the ECM composition can vary widely during development and disease, notably with the inclusion of fibronectin, which is abundant in atheroprone areas [40] or during vascular morphogenesis [41]. *In vitro* studies with endothelial cells plated on different ECM molecules showed that cells plated on basement membrane-associated proteins actively repress flow-associated inflammation while cells plated on fibronectin activate inflammatory signaling pathways and express surface markers recruiting inflammatory cells, as observed during atherosclerotic plaque development [42,43]. Integrins are the main molecular receptors involved in interaction with the ECM and its subsequent intracellular transduction [44]. Of note, different members of the integrin family bind to different ECM molecules, transducing vastly different intracellular signals upon activation [45]. Consequently, when producing integrin chimeras by switching the cytoplasmic tail of integrin alpha 5 (binding fibronectin and promoting inflammatory responses) with the one of integrin alpha 2 (binding basement membrane proteins), Yun et al. observed a repression of flow-mediated inflammation by atheroprone flow as well as a reduction in atherosclerosis development in mice [46], consolidating the role of ECM signaling and integrins in the determination of flow responses.

FSS is a complex stimulus involving different kinds of sensors. Understanding how endothelial cells sense the various parameters of FSS and activate cellular and tissue responses is a major area of present and future research.

2. Cell biology of flow sensing: recent insights into an intricate network of signaling pathways in equilibrium

The array of evidence pointing towards the existence of active flow sensors present in the endothelial cells has generated an ever-growing body of literature in the last 15 years. It is important to start this section by mentioning that many cells types do respond to FSS, yet only endothelial cells encode for the correct molecular components leading to their specific remodeling responses. For example, when subjected to laminar flow, smooth muscle cells, *in vitro*, respond by aligning perpendicularly to flow, while endothelial cells align in the flow direction [47]. Exposure to flow for smooth muscle cells would only be the result of extensive damage to the intima and the basal membrane and therefore perceived as a form of stress. Hence, smooth muscle cells realign in a perpendicular orientation to minimize exposure to this unusual mechanical stress. First, to identify an endothelium-specific flow sensor, Tzima and colleagues reported the existence of an endothelial junctional mechanosensory complex, comprising three proteins highly specific to the endothelial cell phenotype: VE-cadherin, PECAM-1, and VEGF receptors [48]. In the absence of PECAM-1, endothelial cells cannot respond to flow, and blood vessels can no longer remodel in response to hemodynamic changes [49,50]. Further, endothelial cells lacking PECAM-1 expression display a constitutive activity of eNOS, highlighting the contribution of the junctional mechanosensory complex to its fine regulation [51,52].

Strikingly, it has been reported that VEGF receptors directly interact with VE-cadherin molecules through their mutual transmembrane domain [53]. Expression of N-cadherin, a more ubiquitous cadherin also expressed in endothelial cells, cannot compensate for VE-cadherin loss. However, switching N-cadherin transmembrane domain with that of VE-cadherin fully restores flow sensitivity [53]. This body of work also highlights the importance of having a fully mature network of endothelial cells, joined by stable endothelial junctions, to allow for physiological responses to flow to develop. The development of FRET-based molecular sensors to study tension at the molecular level [54–56] allowed for a better mechanistic insight. Upon flow onset, VE-cadherin molecules, which are under high tension, withstand a rapid drop in tension. On the other hand, PECAM-1 molecules, which are in a

"rested" state in the absence of flow, experience a rapid increase in tension [57]. This switch in tension can be explained by a reorganization of vimentin molecules and displacement of myosin molecules, connecting the endothelial junctional complex to the cell cytoskeleton. Therefore, FSS force transfer is not passive but instead relies on a cascade of active molecular mechanisms. Implementation of VE-cadherin tension sensors in zebrafish endothelial cells revealed dynamic changes occurring throughout fish vascular development [58]. Of interest, the authors could not observe a change in tension in response to blood flow cessation, either because of technical limitations associated with the limited range of the FRET-based tension sensor or the perception of decreased blood flow by endothelial cells is associated with a different molecular mechanism.

In response to flow, VEGF receptors dimerize and transduce intracellular pathways such as the PI3K-Akt-PKA-eNOS axis [59–61] or integrins activation [53,60,62], with some of the responses being conditioned by the nature of the ECM, as explained above. While being part of the junctional complex, they do not transduce force directly, contrary to VE-cadherin and PECAM-1. In addition, both VEGFR2 and VEGFR3 perform similarly regarding response to flow [53]. However, they play an important role by governing FSS sensitivity to flow: lymphatic endothelial cells exhibit a much higher expression of VEGFR3 than blood endothelial cells, with a gradient of expression ranging from high in lymphatic vessels, to moderate in veins and veinules, and low in arteries [23,63]. Incidentally, lymphatic endothelial cells encode a lower FSS set point than blood endothelial cells [23], in agreement with the much lower values of FSS observed in lymphatic vessels. Overexpressing VEGFR3 in blood endothelial cells significantly shifted the FSS set point of those cells, increasing their sensitivity to FSS [23]. Despite their indirect role in force transmission, VEGF receptor expression levels thus determine one of the most prominent FSS parameters regarding the control of blood vessel homeostasis and remodeling. In this regard, the observation that anti-VEGF signaling therapies induce hypertension [64] might involve a slightly impaired flow-mediated vascular homeostasis.

Flow forces shape the growing vascular network during development [65–68], giving rise to an arterial network distributing blood from the heart in an extensive capillary network responsible for gas and nutrient exchange in tissues, while the venous network brings back the "used" blood through the liver and lungs, for regeneration. Sometimes this goes wrong: the arterial network is directly shunted in the venous network through extensive shunts or arteriovenous malformations, poorly covered by mural cells, and prone to rupture. A fraction of these patients suffers from hereditary hemorrhagic telangiectasia (HHT), a genetic disease characterized by mutations in several proteins involved in the signaling of BMP9 and BMP10, two soluble factors present in the blood, either as monomers or, more intriguingly, as heterodimers generating most of their biological activity [69]. These malformations are characterized by the presence of an arterial flow within the shunted vessel and are therefore characterized as "high flow malformations" contrary to "low flow vascular malformations" such as cerebral cavernous malformations [70] or venous malformations [71]. Therefore, we investigated whether the development of these lesions was due to a defect in "high flow" sensing. BMP9 and BMP10 bind to a receptor complex comprising Alk1 and BMPR2 to induce phosphorylation of Smad1, Smad5, and Smad8, which subsequently associate with Smad4, a co-smad responsible for their translocation to the nucleus where they regulate gene expression [72–75]. Smad1 activation by flow peaks at values of shear stress approximating the set point, linking its activity with the control of vascular homeostasis by flow [23]. BMP9, Alk1, and Smad4 are commonly found as mutated proteins in HHT patients in addition to endoglin, a glycoprotein identified as a co-receptor of Alk1. Contrary to Alk1, we observed that endoglin is not required for BMP9 signaling alone [76]. We also confirmed that Smad1, Smad5, and Smad8 could be phosphorylated and translocated to the nucleus in response to physiological values of flow. This is where endoglin comes into play; in response to flow, it associates directly with Alk1, forming a macromolecular receptor complex, which potentiates BMP9/BMP10 signaling and promotes endothelial cell quiescence as well as recruitment of mural cells [76]. Of interest, not all flow responses were affected by the loss of either Alk1 or endoglin, indicating that shunt formation could be consecutive to an imbalance in the flow response, rather than a fully defective flow sensing mechanism. Indeed, high flow shunts induced by Alk1 or Smad4 loss exhibit an increased flow-dependent activation of the PI3K-Akt pathway, suggesting an imbalance towards flow responses associated with the junctional flow sensor [77,78]. Close to 85% of HHT patients exhibiting arteriovenous malformations bear a mutation for endoglin or Alk1, clearly demonstrating the importance of proper flow sensing through Alk1 and endoglin to maintain vascular homeostasis and to prevent arteriovenous shunt formation. Interestingly, two important and extensive research papers confirmed: 1) the role of endoglin in flow-mediated vessel stabilization [79], where loss of endoglin is associated with flow-dependent expensive remodeling of blood vessels through modification of cell shape and 2) the importance of the identity of the molecular partners in threshold sensitivity. Alk1 signaling is induced by low flow instead of high flow only if the endothelial cell harbors a primary cilium, and in the absence of cilium, it only responds to physiological levels of flow [80]. This last observation proposes an elegant explanation for the maintenance and stabilization of lowly perfused capillaries during vascular development, where cells harboring a primary cilium are more abundant than in the adult vasculature, and higher flow forces seem to reduce the number of cells expressing a cilium. Identifying which mechanosensitive pathways and more importantly, which macromolecular receptor complexes are involved in the sensing of different FSS thresholds would therefore open the gates to the development of specific pharmacological approaches to treat various vascular remodeling disorders. Indeed, as stated before, some malformations develop in "high flow" environments while other are characterized by "low flow" features.

In addition to classical Smad genes, it has been observed that Alk1/ activation either by BMP9/10 or flow induces Notch-related genes in a synergistic manner with Notch1 activation [74,76,81], contributing to vascular maturation and quiescence. In parallel, several studies have demonstrated that Notch1 was cleaved in response to physiological levels of FSS and contributed directly to vessel maturation through reinforcement of endothelial junctions and repression of endothelial cell proliferation and differentiation towards the arterial phenotype [82–85]. It is not yet fully understood how Notch1 activation is linked to Alk1/endoglin activation, but their relationship in inducing vessel stabilization is very clear. Nonetheless, Notch1 mutations have not been associated with HHT patients.

While the Alk1/endoglin/Notch1 axis is associated with vascular homeostasis maintenance, activation of Alk5 (TGFBR1) generates a pathological phenotype switching of endothelial cells to mesenchymal cells, referred to as endothelial to mesenchymal transition (EndMT) [86]. This switch is observed within plaques during atherosclerosis progression in patients [87] and is directly correlated with atheroprone flow profile [87–90]. While our study and others have clearly proven the implication of a flow-dependent activation of Alk5 in this phenotype switch, the exact molecular mechanism remains to be uncovered. It is very unlikely that Alk5 alone can be directly activated by flow, but we could hypothesize the recruitment of other co-receptors in response to disturbed flow, such as endoglin for Alk1 in response to physiological FSS. In addition, FGF signaling is identified as an important negative regulator of Alk5 activation and EndMT [87,91,92]. Whether FGF signaling could be an important contributor to the athero-resistant response to physiological shear stress is another important area of future research. Thus, it is now established that the aberrant remodeling response of the plaque is linked to an aberrant endothelial cell phenotype [93] and local perturbation of flow. That is, atherosclerosis could be seen as an unresolvable flow-induced vascular remodeling [94].

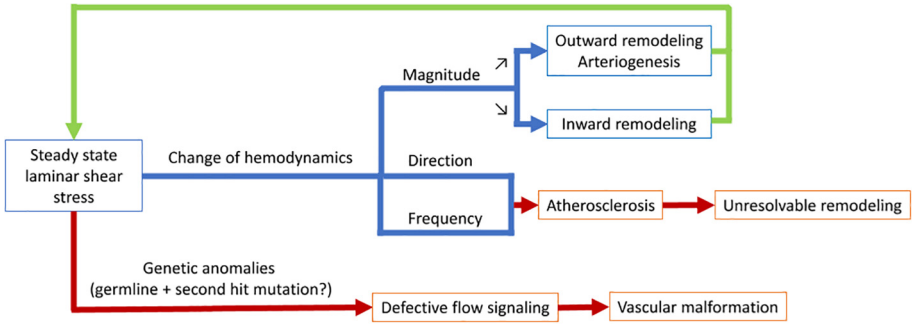

Fig. 1. Contribution of flow signaling in physiological and pathological vascular remodeling. Sustained changes in hemodynamics parameters translate into physiological modification of the blood vessel structure. Modification of FSS magnitude often resolves towards a modification of the vessel lumen until the FSS set point is reached. On the other hand, directional disturbances and/or alteration of frequency harmonics of the pulsatile flow trigger localized formation of an atherosclerotic lesion, a pathological flow-dependent remodeling which never resolves. Finally, the presence of germline mutations, such as observed in HHT, results in partially defective FSS signaling. This contributes to the formation of abnormal structures such as arteriovenous shunts.

However, we currently do not fully understand how those EndMT cells respond to various hemodynamics parameters or if their phenotype can be reversed.

The induction of atherogenesis by disturbed flow suggests the existence of *flow direction* sensors. We, among others, uncovered a potential role for syndecans, members of the proteoglycan family, in this respect. Indeed, deletion of syndecans is associated with a lack of endothelial cell alignment in the direction of flow [33,95,96] and the development of atherosclerotic lesions in areas where blood flow is normally atheroprotective [33]. This deletion did not suppress flow sensing but rather only affected the repression of inflammatory responses associated with flow, in addition to endothelial cell polarity [33]. Similarly, inflammatory responses mediated by the junctional complex are sustained when prealigned endothelial cells are subjected to perpendicular laminar flow [97,98]; hence, there exists a very clear link between flow direction and control of vascular homeostasis. It is interesting to note that syndecan 4 biological activity is closely related to FGF signaling, either by functioning as a co-receptor to the FGF receptor or by direct activation by FGF itself [99]. Therefore, syndecan signaling might play a prominent role in the anti-inflammatory response repressing EndMT. Of interest, Alk1/endoglin signaling has been associated with the control of endothelial cell polarized migration during vascular development [79,80,100–102] but not directly involved in flow-dependent polarity *in vitro* [76,79]. This suggests the existence of distinct flow-associated polarity mechanisms during development and in mature vessels, which might be controlled by other factors such as growth factors, shear stress-sensing modulation, or the external environment [100]. To support this, a study published by Poduri and colleagues introduced some interesting elements [103]. They observed that deletion of Smad4 was associated with an enlargement of coronary arteries during development and a defective alignment of coronary endothelial cells subjected to 35 dynes/cm^2 of laminar FSS. Instead, the cells migrate perpendicularly to flow direction. I propose that this feature might indicate that they might be oversensitized to flow and might have shifted their set point; perpendicular alignment of endothelial cells subjected to flow *in vitro* is a characteristic feature of cells subjected to flow beyond their set point [23]. This might explain why alignment is perturbed and why the coronary vessels undergo enlargement in order to adapt to their modified set point for FSS by reducing the magnitude of FSS. Further studies, including analysis of the set point for cells depleted for Smad4, will be needed to follow up on this hypothesis.

The list above is not extensive, as many other receptors and channels have recently been found to be associated with flow sensing, such as Piezo1, which is a mechanosensitive channel [104–106], Wnt signaling [107], or GPCRs and G proteins [108–110]. This profusion of mechanoresponsive receptors, involved in either vasorelaxants release, polarization, vessel regression, or maturation during development and induction of inflammation and EndMT, mostly highlights the need for reaching a comprehensive model where we consider the role of each receptor in the broader picture and regarding the subtle equilibrium generated by the different actors involved. For example, the junctional mechanosensory complex seems to be broadly involved in many responses while other mechanoresponsive receptors such as Alk1/endoglin/notch or Alk5 exhibit a more specific activation and effect on endothelial cell response to flow. Most experimental studies investigating flow responses are conducted via loss of function experiments and typically focus on one or two parameters to characterize flow responses (typically, alignment in flow direction and gene expression) and often with only a given FSS magnitude. It is very unlikely that the loss of one receptor totally abolishes all responses to flow, given its multiple components. Therefore, careful analysis of each of them will be required before we can further define the complex physiopathology of FSS sensing.

3. Perspective: development of pharmacological strategies to target flow sensing

While more and more evidence points towards a central contribution of flow sensing, in many cardiovascular diseases (Fig. 1) and other systemic disorders such as cancer through stabilization of the tumor vasculature, there is, to date, no drugs aimed at treating aberrances in this very particular endothelial feature. However, we already know that increasing shear stress in collateral vessels following myocardial infarction is beneficial for the patient and increases his/her long-term prognosis [111,112]. Upon reaching a threshold above the set point for FSS, small vessels and capillaries located upstream of the lesion site remodel by progressively expanding their diameter and recruiting more mural cells to the capillaries; this process is known as arteriogenesis [113,114] In case of patients who have low coronary perfusion consecutive to defective cardiac function, an artificial increase in FSS by means such as external counterpulsation with pneumatic cuffs has been suggested [115,116]. While this method might seem a bit questionable, it manages to increase flow and shear stress within the collateral vessels and to statistically improve patient chances for a longer and improved life. Here is the main point of this commentary: should we not aim to develop specific pharmacological agents targeting flow sensing to promote such remodeling? So far, current pharmacological therapies aim mostly to promote vessel dilation with administration of drugs with vasoactive properties such as nitrate compounds with NO donor activities or to reduce inflammation by administration of anti-inflammatory drugs [117]. However, while vasoactive treatments help in the short term by providing a much needed transient increase in blood perfusion and pain relief, they are not associated with an improved outcome for the patient in the long run [117]. One overlooked explanation for this lack of long-term benefit is that vasorelaxant agents act on the smooth muscle cells and temporarily increase blood vessel diameter, therefore drastically reducing shear stress applied on endothelial cells and the likelihood of reaching the FSS threshold, impacting the remodeling process. Mainly, these agents focus only on one aspect of FSS mechanotransduction, the one leading to vasorelaxant release but not the ones leading to the active reconstruction of vessel

structure. By doing so, they abolish the possibility for the upstream vessels to undergo proper arteriogenesis and to durably improve tissue perfusion. Outward remodeling of the small vessels will require transient, local, inflammation to occur; high FSS activates NFkB and NADPH signaling, as well as secretion of MMPs, required for vessel remodeling [15,23,118,119]. Therefore, anti-inflammatory therapies should be used with care, to not alter this process, especially in the earlier stages of arteriogenesis. One potentially successful approach would be then to transiently improve FSS sensing or to promote FSS-induced inflammatory remodeling before switching it off, to reestablish vessel stabilization, another important aspect of successful arteriogenesis. It is worth noting that most clinical trials aiming to improve arteriogenesis have also failed to deliver convincing results, mainly because of delivery method issues but also probably because their objective was mainly to promote angiogenesis [120]. Of interest, FGF administration might be beneficial to either stabilize plaque progression before myocardial ischemia or to stabilize remodeling vessels but probably not to trigger active flow-dependent remodeling because of its activity in promoting vascular quiescence in mature vessels.

Another key aspect of future pharmacological research will be to address the issue of abnormal flow-dependent remodeling such as the development of arteriovenous malformations in HHT. Most of the time, a surgical approach is necessary to treat the hemorrhage, and this approach is limited by accessibility to the lesion site. Recent studies have proposed pharmacological approaches by inhibiting PI3K [77], using thalidomide [121,122], or repressing VEGF activity [123,124], which might prove successful in managing bleeding events for HHT patients, with the two last approaches having the contrasting ability to reduce nose epistaxis events with light to moderate side effects. Therefore, despite those encouraging advances in the pharmacology of HHT, it might be beneficial to consider approaches aiming at reducing flow-dependent responses to treat malformations that are difficult to reach with topical treatments or surgery. Also, further studies on the mechanism of other forms of vascular malformations and their relationship to flow will be needed before developing specific therapeutic approaches for each of them.

Finally, we have covered the fact that most flow responses seem to require the formation of specific macromolecular receptor complexes (VEGF/VE-cadherin, notch/VE-cadherin, or Alk1-endoglin), which might be used as specific targets rather than a receptor alone, to prevent systemic adverse effects. Further structural and computational studies will have to be conducted to understand exactly how these complexes behave in response to various flow profiles. Instead of developing molecules targeting the ligand-binding site, it could therefore be useful to target other sites, which will not prevent ligand-induced signaling but rather flow-mediated signaling.

4. Conclusion

Fluid forces are a major contributor to vascular homeostasis in health and disease. Recent studies have demonstrated that cells react actively to these forces with specific mechanotransduction pathways and that molecular sensors react precisely to changes in various parameters of FSS. Much more work is needed to paint a full picture of this highly complex stimulus, but we can already state that several of those pathways act in balance, and that a perturbance of either flow dynamics or genetics can lead to an imbalance resulting in structural modification of the vessel. In this review, I mostly propose to use our newly acquired knowledge of this imbalance as a means to either promote successful vessel remodeling or to stop abnormal vessel remodeling in its tracks by developing innovative pharmacological approaches.

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