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A Review of the Hemodynamic Factors Believed to Contribute to Vascular Access Dysfunction

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Abstract—A vascular access (VA) is used to facilitate hemodialysis in patients that suffer from end-stage renal disease. However, they suffer from high failure rates due to non-maturation and venous stenosis, with intimal hyperplasia (IH) the underlying cause of both conditions. Abnormal hemodynamic profiles, which arise following VA creation, are believed to lead to the development of IH. However, the exact physiological response that initiates this process is unknown. This review evaluates the different hemodynamic parameters that are hypothesised to correlate with the development of IH. Review studies that examine the correlation between hemodynamic parameters and the onset of IH using computational fluid dynamics. These studies are divided into groups depending on the type of analysis conducted; longitudinal studies, patient specific arteriovenous fistula (AVF) studies, arteriovenous graft studies, idealised AVF studies and studies that analyse the bulk flow. Studies that conduct longitudinal analysis identify an overall reduction in wall shear stress (WSS) as the VA matures. This is further associated with outward remodelling and the successful maturation of the VA. The majority of studies that conduct a transversal analysis find that low/oscillating shear is associated with the development of IH. However, a number of studies find a link between high shear and high spatial and temporal WSS gradients and the onset of IH. This review highlights the lack of unanimity between studies and emphasises the fact that the exact physiological response that leads to the development of IH remains unknown. This accentuates the need for a single, precise hypothesis capable of accurately predicting the onset of IH. If computational modelling is to assist in this process, the number of longitudinal studies conducted must increase. This will provide a better understanding of the effect that hemodynamic parameters have on the remodelling process and potentially identify a single/group of parameter/s that can accurately predict the onset of IH.

Keywords—Vascular access, Intimal hyperplasia, Wall shear stress, Bulk flow, Computational fluid dynamics.

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INTRODUCTION

Patients suffering from end-stage renal disease (ESRD) are often referred to hemodialysis to replace the lost function of their kidneys. In order for patients to receive effective dialysis, a vascular access (VA) capable of supplying high flow rates is required. The most common types of VA are an arteriovenous fistula (AVF) and an arteriovenous graft (AVG). Both access types suffer from high failure rates ranging from 18 to 28% for AVFs and higher again for AVGs.[1] While both access types are considerably different they suffer from the same primary mode of failure, venous stenosis due to intimal hyperplasia (IH).[63,64,68,75]

IH can be characterised as the thickening of the vascular wall due to the migration of smooth muscle cells (SMCs) from the media to the intima which then proliferate into the subintimal layer. Endothelial cells (ECs) play a fundamental role in this process. Once activated, ECs increase expression of growth factors that promote SMC migration from the media to the intima where they then proliferate. The proliferation of SMCs in the intima is associated with the deposition of extracellular matrix, in a process similar to the formation of scar tissue. This process results in the rapid formation of a neointimal layer over the activated ECs.[12,31,49]

It is well documented that IH can occur due to vascular injury caused by surgery, compliance mismatch between the graft and native vessel, dialysis needle insertion, inflammatory response to sutures and hemodynamic stresses.[42,65–67] This review will focus on the impact hemodynamic stresses have on the development of IH and the current hemodynamic parameters utilised to characterise these stresses using computational modelling.

Hemodynamic stresses are detected by the endothelial cells (EC), which act as mechanotrans-

ductors converting stimuli into specific biochemical signals depending on the type of flow they are subjected to. There are 3 predominant types of flow EC experience within a VA; unidirectional flow, flow reversal and multidirectional flow, Fig. 1. It is well documented that unidirectional flow which results in uniform wall shear stress (WSS) triggers endothelial quiescence and alignment in the predominant direction of the flow, resulting in the secretion of anti-inflammatory and anti-coagulant substances. These flow conditions tend to prevent the onset and progression of IH, while nonuniform WSS causes EC activation which in turn causes the expression of pro-inflammatory and pro-coagulant stimulants that predispose to the onset of IH.[23,28,42,54]

AVF maturation failure can be characterised by impaired outward remodelling or by the presence of a clinically significant stenosis in the venous segment of the AVF, both of which prevent the AVF from ever being used for dialysis. Hemodynamic stresses are believed to play a role in this process through the activation of endothelial cells which leads to a reduction in nitric oxide (NO). The low levels of NO can result in IH as NO blocks smooth muscle cell migration and proliferation. This can also result in impaired outward remodelling as NO is a potent vasodilator, Fig. 2.[61]

It has been previously shown that stenoses develop at specific sites within an AVF; the anastomosis floor, the inner wall of the swing segment and the inner wall of the proximal vein where the vein straightens out, Fig. 3.[4,73] This is also true for AVG, where stenoses primarily develop at the venous anastomosis and in the draining vein.[80]

The geometric configuration of an AVF has been shown to strongly influence the hemodynamics. Minor changes in geometry can result in a drastic change in shear stress which is an important mediator of vasodilation and vessel remodelling. Ene-Iordache *et al.*[18] investigated the affect that the anastomosis angle has on producing disturbed flow in a parametrised model of an AVF and found that low/oscillating shear was prominent in the locations predisposed to the development of stenoses, Fig. 3.[4,18,73] They also found that acute anastomosis angles (~30°) are the most efficient at minimising areas exposed to low/oscillating shear, which can lead to the development of IH.[18] A study conducted by Bharat *et al.* tested this hypothesis in a clinical setting and found that compared to traditional AVF configurations, fistulas with smaller anastomosis angles had fewer stenoses.[5]

Computational fluid dynamics (CFD) can approximate analytically complex flow fields, such as those that occur within VA following creation. CFD can also calculate hemodynamic parameters derived from the flow fields such as WSS. Computational modelling is currently utilised to retrospectively analyse VA to determine the cause of failure by attempting to correlate different hemodynamic parameters to the development of IH.

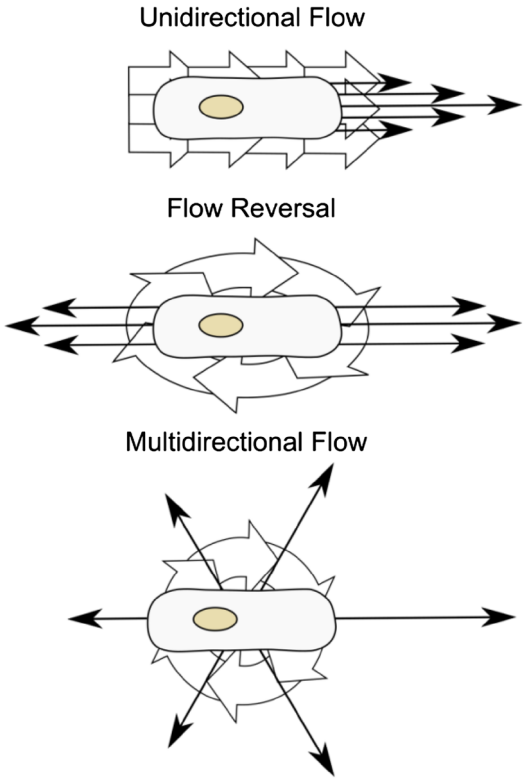

FIGURE 1. The different flow conditions EC are exposed to in a typical VA. The black arrows represent the instantaneous WSS vectors at an arbitrary point in time during the cardiac cycle, while the opaque arrows represent the progression of the instantaneous WSS vector over a cardiac cycle.

There is a significant amount of evidence to suggest that hemodynamic factors, specifically WSS, are involved in the onset and progression of different disease pathologies within the vasculature, a phenomenon Morbiducci *et al.* described as the 'hemodynamic hypothesis'.[52] To date, WSS based parameters have been the predominant indicators of the development of IH by identifying areas that experience disturbed shear.[41] Disturbed shear is characterised as the exposure of the vasculature to adverse, non-physiological shear stress conditions. However, there are different hypotheses regarding this definition, some researchers define disturbed shear as exposure to low/oscillating shear,[6,15,20,35,59,76,79,80] while others identify it as exposure to high shear.[8,10,11,38,45,81] Both classifications of disturbed shear are hypothesised to lead to the development of IH. The majority of relevant research supports the former hypothesis. However, there is not

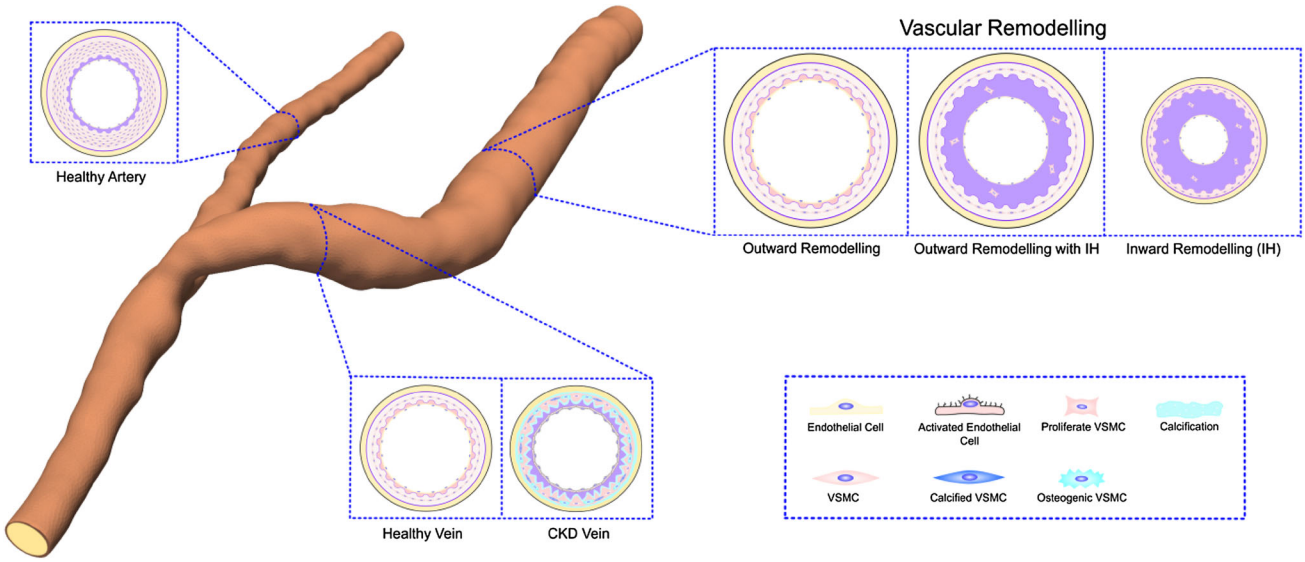

FIGURE 2. A typical configuration of an AVF, highlighting the cross section of a healthy artery, a healthy and chronic kidney disease (CKD) vein as well as the vascular remodelling process, displaying the different remodelling responses following fistula creation. IH, intimal hyperplasia; CKD, chronic kidney disease; VSMC, vascular smooth muscle cells.

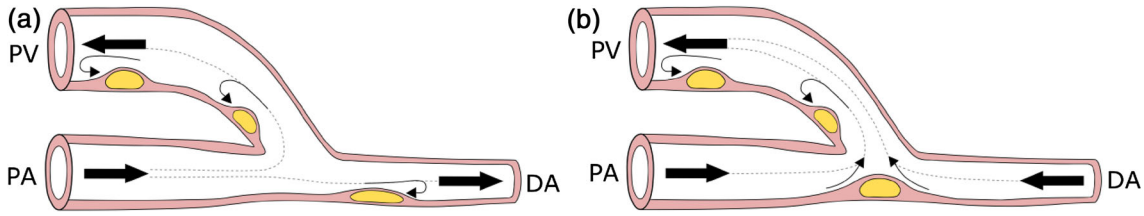

FIGURE 3. The sites within an AVF that are susceptible to the development of IH due to the presence of low/oscillating shear caused by areas of disturbed flow. (a) An AVF with antegrade flow in the DA. (b) An AVF with retrograde flow in the DA. The thick black arrows represent the predominant direction of flow within the AVF, while the thin black arrows represent the locations where recirculating vortexes and flow stagnation occur due to disturbed flow and the dashed lines represent the flow streamlines. AVF, arteriovenous fistula; PA, proximal artery; DA, distal artery; PV, proximal vein.

a general consensus on the matter and there is a considerable amount of research to support the latter.

Research on the development of IH has primarily focused on the progression of the disease in the arterial system. However, the development of IH in VAs largely occurs in the venous segment of the access. It is well documented that the remodelling process of arteries and veins is considerably different, especially in the veins of chronic kidney disease (CKD) patients.[62] A characteristic of CKD is the presence of calcifications within the vessel wall resulting in vessel stiffness. In arteries this impairs their ability to expand, limiting remodelling. While there has been limited research on the effect calcifications have in veins, it is likely to reduce venous compliance, also limiting the veins ability to expand during remodelling.[43] This could be detrimental to fistula maturation by inhibiting outward remodelling and ultimately leading to fistula failure.

Retrospectively using WSS parameters to identify areas of disturbed shear within VA is of little clinical benefit to the patient as it will have no impact on the survival of their VA. If new therapeutic strategies that utilise WSS parameters are to have an impact on VA survival, then these parameters need to be quantified *in vivo* so that increased surveillance can take place to ensure that areas of disturbed shear do not transition into something more sinister such as a stenosis, which could result in access failure. A major hindrance to the implementation of WSS parameters *in vivo* is the requirement of expensive clinical imaging techniques such as phase-contrast magnetic resonance imaging (PC-MRI). While PC MRI is widely used in the acquisition of medical images for research purposes, its implementation into the routine surveillance of VA is impractical due to the additional cost per patient and lengthy analysis times.

More recently bulk flow parameters, specifically helicity based parameters, have been shown to correlate with areas of disturbed shear in the carotid bifurcation.[26] If the same correlation exists in VA such parameters could be utilised to identify areas of disturbed shear within the VA *in vivo*, as helicity based parameters are much easier to quantify *in vivo* through the use of ultrasound imaging techniques.[57]

The aim of this review is to conduct an extensive literature review to determine the different hypotheses that surround the development of IH within VAs in an effort to identify the most widely adopted hypothesis.

WSS PARAMETERS

The following section details studies that conduct a computational analysis of VA and attempt to correlate WSS based parameters with the development of IH. This section is divided into 4 subsections related to the type of VA and the analysis performed.

Longitudinal Studies

This section focuses on the computational analysis of realistic AVF that incorporate longitudinal data which is classified as data from two or more time points of the same VA. Such studies allow researchers to monitor the hemodynamics over time and attempt to correlate certain hemodynamic parameters to the development of vascular pathology. The VA analysed in this section are from both human and non-human subjects. Table 1 highlights the studies included in this section in addition to the WSS parameters utilised in their analysis as well as the findings of each study.

Human Models

The most significant longitudinal study conducted to date was carried out by Sigovan *et al.*[71] who analysed the temporal and morphological changes of 3 patient specific AVFs at 5 days, 1 month and 3 months post-surgery. Sigovan *et al.*[71] attempted to correlate certain hemodynamic parameters to vascular remodelling and discovered that disturbed flow (recirculation zones) present in the outflow vein of the AVF was associated with the non-uniform remodelling of the vessel. Out of the 3 AVFs analysed in this study only 1 of them was deemed mature and used for dialysis. However, the other 2 fistulas failed after 3 months and as a result no correlation could be established between the hemodynamics and the ultimate cause of fistula failure.

He *et al.*[32] conducted a similar analysis as Sigovan *et al.*[71] and analysed the temporal and morphological changes of a single AVF at 4, 5 and 7 months post-surgery. The aim of this study was to develop a procedure for the large scale assessment of hemodynamic parameters and lumen cross sectional area changes that occur following fistula creation and therefore this study does not formulate a hypothesis in relation to the development of IH. It was noticed that the AVF analysed in this study underwent an overall reduction in WSS between the 4 and 7 month scans which correlated with an increase in vein diameter. This is in agreement with the results of Rajabi-Jagahrgh *et al.*[58,59] who also found that an overall reduction in WSS over time was associated with outward remodelling and fistula maturation thus adding further merit to this hypothesis.

Boghosian *et al.*[6] analysed a single brachiocephalic fistula for 1 year following its creation. They scanned the fistula at 3 months and 1 year and found that the location where a stenosis developed was subject to low shear. Boghosian *et al.*[6] therefore hypothesises that low shear is associated with the development of IH and ultimately fistula failure. They also propose a secondary hypothesis whereby high shear may cause endothelial damage which could also lead to neointimal hyperplasia (NIH).

Animal Models

Jia *et al.*[35] analysed the effect that WSS has on the development of NIH in 20 canine models. The histological results from this study revealed that NIH correlated with the areas exposed to low/disturbed shear at both 7 and 28 days as quantified from computational models that mimic the *in vivo* conditions of the canine models.

A similar study conducted by Rajabi-Jagahrgh *et al.*[60] attempted to determine the longitudinal effects of different hemodynamic parameters on intimal medial thickening (IMT) in a single porcine model. A radiopaque marker was sutured to the outside of the AVF during its creation, acting as a reference for *in vivo* and *ex vivo* analysis of the AVF. Computational models were created from scans taken at 2 and 28 days from which changes in WSS over time were monitored. The histological results revealed that areas of the AVF that suffered from the most IMT were also exposed to recirculation zones at both 2 and 28 days. While not specifically outlined in this study recirculation zones predominantly correlate with areas of low/oscillating shear.

Rajabi-Jagahrgh *et al.*[58,59] also analysed the temporal changes in 6 AVF created in 3 porcine models. Results revealed that an overall reduction in WSS from the time of fistula creation was associated with outward remodelling and ultimately successful matura-

TABLE 1. Studies that include longitudinal data on the maturation process of AVF, the WSS parameters utilised to characterise disturbed flow and the findings of each study.

	WSS parameter	Hypothesis/findings
Longitudinal studies		
Jia *et al.*[35]	WSS	NIH was more prominent in areas that experienced *low/disturbed* shear compared to areas that experienced high shear
Rajabi-Jagahrgh *et al.*[60]	WSS, TAWSS, OSI	A *reduction in WSS over time* (regardless of initial value) could result in fistula dilation. Furthermore, areas of *recirculating flow* corresponded with the largest amounts of IMT
Boghosian *et al.*[6]	WSS	Found that *low shear* occurred at a location of future stenosis. Also mentions that *high shear* may be associated with endothelial damage, which could lead to NIH
Rajabi-Jagahrgh *et al.*[59]	WSS, TAWSS	A *reduction in WSS over time* (regardless of initial value) could result in *outward remodelling* and conversely that an *increase in WSS over time* could lead to *inward remodelling*
Rajabi-Jagahrgh *et al.*[58]	WSS, TAWSS	A *reduction in WSS over time* (regardless of initial value) could result in *outward remodelling* and conversely that an *increase in WSS over time* could lead to *inward remodelling*
Sigovan *et al.*[71]	WSS	*Low shear* occurred at zones of *recirculating flow*, which correlated with stenosis development
He *et al.*[32]	TAWSS, OSI, WSSG	A *reduction in WSS over time* was linked to the *successful maturation of an AVF*

tion. Conversely, an overall increase in WSS was found to be detrimental to AVF maturation.

The significance of these results is emphasised by the fact that 4 out of the 7 studies reviewed in this section compared histological results from porcine models sacrificed at 7 and 28 days with WSS profiles obtained through CFD simulations and all came to the same conclusion.

The main conclusions drawn from the longitudinal studies are as follows:

1. Low shear that occurs as a result of recirculating flow is prone to the development of IH.
2. A reduction in overall WSS as the fistula matures is associated with outward remodelling and the successful maturation of the fistula.
3. An increase in overall WSS as the fistula matures is associated with inward remodelling and fistula non-maturation.

Realistic AVF Studies

The results of the realistic AVF studies are more diverse than the longitudinal studies; with only 5 out of the 10 studies supporting the hypothesis that exposure to low/oscillating shear can lead to development of IH, Table 2.

Hammes *et al.*[30] conducted the most recent study in this area and analysed the WSS profile of 22 brachiocephalic AVF between 8 and 32 weeks post-surgery. Results revealed a significant correlation between low shear and the development of NIH. They do state however, that further studies would be required to conclude if low shear is actually associated with the onset of NIH.

Decorato *et al.*[16] support this hypothesis and conducted a fluid structure interaction (FSI) simulation on a patient specific AVF and found that low/oscillating shear correlated with areas that are prone to lesion development as outlined in literature. Previous work conducted by Ene-Iordache *et al.*[20,80] found that low/oscillating shear occurred at locations that correspond closely to sites of future stenosis in idealised models of AVFs. In their most recent study they found that both multidirectional flow (TransWSS) and reciprocating disturbed flow (OSI) also occurred at locations predisposed to IH development.[21]

Kharboutly *et al.*[38] suggest a potential link between exposure to high TWSSG and regions of calcification. Similarly, Carroll *et al.*[11] also found that high WSS, high WSSG and flow reversal persist throughout a mature AVF. They propose that high shear, elevated WSSG and flow reversal result in venous neointimal hyperplasia (VNH) development. Carroll *et al.*[10] tested this hypothesis by applying the elevated WSS waveforms obtained from the computational models to human umbilical vein endothelial cells (HUVEC) using a cone and plate bioreactor. The elevated temporal WSS waveforms induced an early induction of MMP-2 and delayed transcriptional upregulation of MCP-1, suggesting a link between elevated WSS and temporal WSSG and subsequent VNH development. MMP-2 and MCP-1 are inflammatory regulators that play a role in the initiation/contribution to the development of VNH.

Franzoni *et al.*[24] conducted a similar study in which they exposed human umbilical vein ECs (HUVECs) to

TABLE 2. Computational studies conducted on realistic geometries of AVF, the WSS parameters utilised to characterise disturbed flow and the findings of each study or the hypothesis they based the analysis of their results on.

Study	*WSS parameter*	*Hypothesis/findings*
AVF studies		
Hammes *et al.*[30]	WSS, TAWSS	Supports the hypothesis that *low shear* can lead to the development of NIH
Bozzetto *et al.*[7]	TAWSS, OSI, TransWSS, TWSSG	Concludes that the occurrence of *transitional flow* can lead to the development of AVF stenosis
Ene-Lordache *et al.*[21]	TAWSS, OSI, TransWSS	Found that areas exposed to *low/oscillating shear* as well as *multidirectional flow* correlate closely with sites of future stenosis in literature
Decorato *et al.*[16]	TAWSS, OSI, WSSG	States that *high WSS* can lead to an *increase in oxidative stress*, resulting in inflammation and NIH. Also states that *low/oscillating shear* is associated with IH, as well as *elevated WSSG* being associated with EC proliferation and NIH
McGah *et al.*[46]	TAWSS	Concludes that AVF can be subjected to extremely high shear rates without developing any signs of disease progression
McGah *et al.*[47]	WSS, TAWSS, OSI	Concludes that *flow rates* $<$500 mL/min are most at risk of developing disease pathologies. Also supports the hypothesis that *low/oscillating shear* can lead to the development of disease pathologies
Decorato *et al.*[15]	TAWSS, OSI, WSSG, TWSSG	Found that *low/oscillating shear* correlated with areas that are prone to the development of lesions
Carroll *et al.*[10]	WSS, WSSG, TWSSG	*High shear, elevated WSSG* and *reversed flow* can lead to VNH development and VA dysfunction
Carroll *et al.*[11]	WSS, WSSG, TWSSG	*Elevated WSS, WSSG* and *TWSSG* may lead to the development of VNH
Kharboutly *et al.*[38]	WSS, OSI, TWSSG	Found that *high TWSSG* correlated with sites of calcification. Also states that they found *no correlation between areas of calcifications and OSI*

both unidirectional and reciprocating flows using a cone and plate device. They found that there was a significant increase in the expression of KLF2 in cells exposed to unidirectional flow. Simultaneously this flow condition induced a decrease in the expression of PLD1, ITGA4 and RASA1. In contrast to this, cells exposed to reciprocating flow did not increase KLF2 expression but did increase in the expression of PLD1, ITGA4 and RASA1. The expression of KLF2 has been previously shown to induce the expression of nitric oxide (NO), which has anti-inflammatory and anti-coagulant properties.[14,17,22] These results suggest that unidirectional flow is necessary to maintain KLF2 related protective function of ECs and that this protective effect is lost in the presence of reciprocating flow where KLF2 expression is not increased.

In contrast to this McGah *et al.*[46,47] found high shear in mature fistulas ranging from 2 to 20 years. This suggests that high shear stress alone may not result in the development of IH or that there may be a threshold value for high shear above which initiation of IH occurs.[37,39,47] While different studies suggest different threshold values for the onset of IH, Tricht *et al.*[81] propose that WSS above 3 Pa could initiate the disease process. Hellums and Hardwick[33] state that WSS values over 7.5 Pa activate leukocytes adhesion, which can lead to the development of IH while values over 10 Pa can cause the growth of platelet aggregation and thrombosis. In addition, WSS over 35 Pa can cause physical damage to the EC resulting in platelet adhesion.[25]

Other relevant theories include a study conducted by Bozzetto *et al.*[7] who analysed the hemodynamics in 4 patient-specific AVF and observed the presence of transitional laminar to turbulent like flow developing in the juxta-anastomotic vein and dissipating towards the venous outlet. This resulted in high frequency fluctuations of the velocity vector, which in turn induced similar fluctuations of the WSS vector in these specific areas. This led them to hypothesis that these fluctuations may impair the physiological response of ECs and could be responsible for the development of IH in AVF.

The findings of these studies carry less significance compared to the findings of the longitudinal studies as there is no way of determining the longitudinal effect that the hemodynamics have on the VA. Therefore, it is difficult to link different hemodynamic parameters to disease progression.

AVG Studies

The most impactful study detailed in this section was carried out by Manos *et al.*[45] who conducted a computational simulation of a realistic AVG model acquired from a porcine model 1 month following graft placement. The results from the computational model were compared to histological sections. Comparison revealed that high WSS and high WSSG cor-

relate with areas of IH and increased vessel wall stiffness.

Two further studies utilised patient specific geometries of AVG in their analysis. However, neither of these studies focused on determining the cause of IH but rather applied hypotheses proposed by other researchers on the development of IH to the analysis of their results. Sung *et al.*[76] followed the hypothesis that low/oscillating shear leads to the development of IH, while Choi *et al.*[13] states that both low shear (less than 0.3 Pa) and high shear (greater than 3 Pa) is associated with the development of IH.

The remainder of the studies included in this section were all conducted on idealised AVG models and utilise hypotheses formulated by other researchers to analyse their results, Table 3. Among these studies there was a wide range of hypotheses adopted.[40,44,69,77,81]

There is little coherence between the studies and the hypotheses they supported in this section, with 3 out of these 8 studies stating that both high and low shear are associated with IH development. Only one of these studies solely supports the hypothesis that low/oscillating shear leads to the development of IH. These findings are considerably different to the findings of both the longitudinal and realistic AVF studies where the majority of researchers agreed with the low/oscillating shear hypothesis.

Idealised Studies

Each of the studies detailed in this section analyse idealised models of AVF, Table 4. Such studies are generally not able to make substantial claims based on their results but rather utilise hypotheses developed by other researchers to analyse their results. This is highlighted here as 5 out of the 6 studies support the hypothesis that low/oscillating shear is associated with the development of IH.[19,20,34,72,79] The most impactful of these studies were conducted by Ene-Iordache *et al.*[20,80] who compared their results to literature and established that areas exposed to low/oscillating shear correlate with sites of luminal reduction. Browne *et al.*[8] utilised CFD to acquire different WSS profiles that are likely to lead to the development of IH. These profiles were then applied to endothelial cells (EC) in a cone and plate bioreactor to monitor EC proliferation which was used as an indicator of IH development. This revealed that the maximum absolute TWSSG had the most significant correlation to EC proliferation.

BULK FLOW PARAMETERS

The inclusion criteria for the studies detailed in this section is less stringent than previous sections as limited research has been conducted on the use of helicity based parameters to characterise the bulk flow. As a result, this section includes studies that conducted computational analyses of VAs as well as the carotid bifurcation, Table 5. The helicity based parameters utilised by each study varied between a quantitative and a qualitative analysis of the bulk flow, with the majority of studies adopting a purely qualitative analysis using the parameter the localised normalised helicity (LNH), which is a useful quantity for the visualisation of complex flow patterns within cardiovascular flows.[70] Some studies do offer a more detailed

TABLE 3. Computational studies conducted on AVG, the WSS parameters utilised to characterise disturbed flow and the findings of each study or the hypothesis they based the analysis of their results on.

Study	*WSS parameter*	*Hypothesis/findings*
AVG studies		
Sung *et al.*[76]	TAWSS, OSI	Supports the hypothesis that areas exposed to *low/oscillating shear* are prone to the development of disease pathologies
Choi *et al.*[13]	WSS, OSI	States that *high shear* is a major inducer of IH. Also states that *low shear* is associated with IH
Sarmast *et al.*[69]	WSS, OSI, RRT, WSSG	Supports the hypotheses that areas exposed to *high shear, low/oscillating shear and high spatial WSSG* are prone to the development of disease pathologies
Van Canneyt *et al.*[77]	TAWSS, OSI, RRT	Supports the hypothesis that areas exposed to *low/oscillating shear* are prone to the development of disease pathologies
Kim *et al.*[40]	WSS, OSI	Supports the hypotheses that *recirculating flow, low shear, high shear and high OSI* lead to stenosis
Manos *et al.*[45]	WSS, WSSG	Found that *high shear* and *high WSSG* correlate with areas of IH development and vessel wall stiffening
Lee *et al.*[44]	TAWSS	Suggests that *distal flow* in the distal vein segment of an AVG may promote IH
Van Tricht *et al.*[81]	TAWSS, WSSG	Found a correlation between areas of *high shear* and the locations of IH formation as reported in literature

TABLE 4. Studies that were conducted on idealised geometries of AVF, the WSS parameters utilised to characterise disturbed flow and the findings of each study or the hypothesis they based the analysis of their results on.

Study	*WSS parameter*	*Hypothesis/findings*
Idealised studies		
Lori *et al.*[34]	WSS, TAWSS	Impartial to both hypotheses that *unsteady flow* causes IH and *low WSS/or low lumen-to-wall oxygen flux* cause IH
Silva *et al.*[72]	WSS, OSI	Supports the hypothesis that areas exposed to *low/oscillating shear* are prone to the development of IH
Browne *et al.*[8]	WSS, TAWSS, OSI, WSSG, TWSSG	Found that *the maximum absolute TWSSG* correlate with sites of EC proliferation in an *in vitro* study
Ene-Iordache *et al.*[20]	WSS, TAWSS, OSI, RRT	Found that areas exposed to *low/oscillating shear* correlate with sites of luminal reduction in literature
Ene-Iordache *et al.*[19]	WSS, TAWSS, OSI, RRT	Found that areas exposed to *low/oscillating shear* correlate with sites of luminal reduction in literature
Van Canneyt *et al.*[79]	WSS	Proposed that areas exposed to *low shear* may be prone to the development of IH

analysis by quantifying the helical content of the bulk flow, which will be discussed in detail in the following section.

Morbiducci *et al.*[51] highlights that most of the research conducted on the development of vascular pathology focuses primarily on WSS based parameters. They add that the bulk flow also plays a significant role in the progression vascular pathology. They state that the development of vascular pathology involves not only fluid related forces exerted on the wall (WSS) but also transport phenomenon within the blood. They suggest that the reason for this singular approach is partly due to the lack of parameters capable of characterising the bulk flow. In this study Morbiducci *et al.*[51] develop new metrics capable of characterising the helical content of the bulk flow and highlight the possibility of these new metrics being utilised to relate certain aspects of the bulk flow to vascular physiopathology.

Gallo *et al.*[26] elaborated on the work conducted by Morbiducci *et al.*[51] by characterising the relationship between WSS based parameters, specifically disturbed shear (low/oscillating shear) and the bulk flow using helicity based descriptors in the carotid bifurcation. For this study Gallo *et al.*[26] defined new metrics which included the helicity based bulk flow descriptors h1, h2, h3, h4, h5 and h6. These descriptors quantify the helical content of the flow and also the balance between counter rotating helical structures. The LNH was also used to visualise the flow features present in the bulk flow. The study revealed a significant correlation between exposure to disturbed shear and their helicity based descriptors suggesting the possibility of utilising these parameters in large scale *in vivo* studies to identify areas of the vasculature susceptible to the development of vascular pathologies. However, it remains unclear if these parameters possess the same diagnostic capabilities when applied to VAs. Two other studies conducted by this group utilise these parameters to quantify the helicity content of the bulk flow. However, they were not employed to determine areas of the vasculature that are susceptible to disease progression but rather to quantitatively compare the results between different computational models.[27,53]

Bozzetto *et al.*[7] and Browne *et al.*[9] are the only two groups to include a detailed analysis of the bulk flow in their investigation of the hemodynamics within AVFs. Both groups evaluate the velocity within their respective models and observed high frequency fluctuations, which are synonymous with transitional laminar to turbulent like flow in the venous segments of their models.[79] Both groups state that the presence of these fluctuations may impact EC function, which could result in the cascade of events that leads to the development of IH. They also include a qualitative assessment of the bulk flow through the application of the parameter LNH.

Van Canneyt *et al.*[78] investigated the effect that varying degrees of helicity have on the suppression of disturbed shear (low/oscillating shear). They found that the presence of centralised single vertical structures stabilise the flow field by avoiding the breakdown in multiple vortex patterns and fostering the mitigation of transitional effects downstream of the anastomosis. Similarly, to the other studies detailed in this section Van Canneyt *et al.*[78] also provided a qualitative assessment of the bulk flow using the parameter LNH.

DISCUSSION

VAs suffer from high failure rates ranging from approximately 18–28% for AVF and even higher for AVG.[1] The main cause of these high failure rates is stenosis due to IH.[63,64,68,75] Computational modelling is utilised to retrospectively determine the cause of VA

TABLE 5. Studies that included bulk flow parameters in their analysis, detailing the findings of each study or the hypothesis they based the analysis of their results on.

	Bulk flow parameter	*Hypothesis/findings*
Bulk flow parameter studies		
Bozzetto *et al.*[7]	LNH	*Transitional flow*, defined as the presence of *high frequency fluctuations* in the bulk flow can lead to the development of IH. Follows the hypothesis that the presence of *centralised single vortical structures*, stabilise the flow field. *LNH* was utilised to qualitatively visualise the helical content of the flow field
Gallo *et al.*[27]	LNH, h1, h2	Supports the hypothesis that *high helical flow* coupled with *dual counter rotating helical structures* may suppress the flow disturbances that can lead to the development of IH
Browne *et al.*[9]	LNH	*Transitional flow*, defined as the presence of *high frequency fluctuations* in the bulk flow can lead to the development of IH. *LNH* was utilised to qualitatively visualise the helical content of the flow field
Morbiducci *et al.*[53]	LNH, h1, h2, h3, h4	*LNH* was utilised to qualitatively visualise the helical content of the flow field. The helicity based descriptors *h1, h2, h3* and *h4* were employed to supply a quantitative comparison between computational models
Van Canneyt *et al.*[78]	LNH, Absolute Kinetic Helicity	Found that the presence of *centralised single vortical structures* stabilises the flow field. *LNH* was utilised to qualitatively visualise the helical content of the flow field
Gallo *et al.*[26]	LNH, h1, h2, h3, h4, h5, h6	Propose that *high helical flow* coupled with *dual counter rotating helical structures* may suppress flow disturbances that can lead to the development of IH. *LNH* was utilised to qualitatively visualise the helical content of the flow field
Morbiducci *et al.*[51]	LNH, Helical Flow Index, streamwise vorticity, spanwise vorticity, vorticity ratio index	Feasibility study that develops new metrics capable of characterising the bulk flow in an effort to relate features of the bulk flow to vascular pathology

TABLE 6. The studies included in this review, highlighting the WSS based parameters they investigated and their correlation, if any to the development of IH.

	Instantaneous WSS	TAWSS	OSI	RRT	TransWSS	WSSG	TWSSG
Jia *et al.* 35	↓	-	-	-	-	-	-
Rajabi-Jagahrgh *et al.* 60	O	↓*	O	-	-	-	-
Boghosian *et al.* 6	↓	-	-	-	-	-	-
Rajabi-Jagahrgh *et al.* 59	O	↓*	-	-	-	-	O
Rajabi-Jagahrgh *et al.* 58	O	↓*	O	-	-	-	O
Sigovan *et al.* 71	↓	-	-	-	-	-	-
He *et al.* 32	-	↓*	O	-	-	O	-
Hammes *et al.* 30	O	↓	-	-	-	O	-
Bozzetto *et al.* 7	-	O	O	-	O	-	O
Ene-Lordache *et al.* 21	-	↓	↑	-	↑	-	-
Decorato *et al.* 16	-	↓↑	↑	-	-	↑	-
McGah *et al.* 46	-	O	-	-	-	-	-
McGah *et al.* 47	↓	↓	↑	-	-	-	-
Decorato *et al.* 15	-	↓	↑	-	-	O	O
Carroll *et al.* 10	↑	-	-	-	-	↑	O
Carroll *et al.* 11	↑	-	-	-	-	↑	↑
Kharboutly *et al.* 38	O	-	O	-	-	-	↑
Sung *et al.* 76	-	↓	↑	-	-	-	-
Choi *et al.* 13	↓↑	-	↑	-	-	-	-
Sarmast *et al.* 69	↓↑	-	O	O	-	↑	-
Van Canneyt *et al.* 77	-	↓	↑	↑	-	-	-
Kim *et al.* 40	↓↑	-	↑	-	-	-	-
Manos *et al.* 45	↑	-	-	-	-	↑	-
Lee *et al.* 44	-	O	-	-	-		-
Van Tricht *et al.* 81	-	↑	-	-	-	O	-
Lori *et al.* 34	↓	↓	-	-	-	-	-
Silva *et al.* 72	↓	-	↑	-	-	-	-
Browne *et al.* 8	↓	↓	↑	-	-	↑	↑↑
Ene-lordache *et al.* 20	↓	↓	↑	↑	-	-	-
Ene-lordache *et al.* 19	↓	↓	↑	↑	-	-	-
Van Canneyt *et al.* 79	↓	-	-	-	-	-	-

O: This parameter was included in the analysis but no correlation to the development of IH was established.

↓: Low values of this parameter correlate to the development of IH.

↑: High values of this parameter correlate to the development of IH.

↓*: A reduction in WSS over time is associated with outward remodelling

↑↑: This parameter has the most significant correlation to the development of IH

↓↑: Both low/high values of this parameter correlate to the development of IH.

Yellow: Formulated their own hypothesis on the development of IH based on the findings of their study.

Red: Based the analysis of their results on a hypothesis from literature.

O: This parameter was included in the analysis but no correlation to the development of IH was established.
↓: Low values of this parameter correlate to the development of IH.
↑: High values of this parameter correlate to the development of IH.
↓*: A reduction in WSS over time is associated with outward remodelling.
↑↑: This parameter has the most significant correlation to the development of IH.
↓↑: Both low/high values of this parameter correlate to the development of IH.
Yellow Formulated their own hypothesis on the development of IH based on the findings of their study.
Red Based the analysis of their results on a hypothesis from literature.

failure by attempting to correlate hemodynamic parameters with the development of IH. The effectiveness of this method is limited as the exact physiological response that leads to IH within VAs remains unknown. This is highlighted by the numerous hypotheses surrounding the development of IH in VAs, exposing the lack of unanimity between studies, Table 6. This review focuses on the hemodynamic parameters utilised by each study to predict the onset of IH. The main hypotheses proposed by the studies included in this review are:

1. An overall reduction in WSS is observed as the AVF remodels. This is associated with outward remodelling and fistula maturation.[32,58,60,71]
2. Exposure to low/oscillating shear can lead to the development of IH.[19,27,29,30*,34,36,37*,39,40,48,49*,50*,51,52*,56,57,59,61]
3. Exposure to high shear can lead to the development of IH.[30*,37*,41,42,43**,49*,50*,52*,53,55,58**]

*Studies that support more than one hypothesis.

**Studies that reported a link between high TWSSG and the onset of IH.

The majority of studies support the hypothesis that low/oscillating shear can lead to the development of IH. However, a significant number of studies support the opposite and state that high shear can lead to the development of IH. In addition, a number of studies do not adhere to a single hypothesis and state that both low/oscillating shear and high shear can be detrimental to the survival of the VA.

There are numerous alternate hypotheses proposed by the studies in this review, most notably that the occurrence of high frequency fluctuations synonymous with transitional laminar to turbulent like flow may impact endothelial cell function and contribute to the physiological response that leads to the development of IH. This hypothesis was first proposed by Browne *et al.*[9] in an idealised model of an AVF and later by Bozzetto *et al.*[7] in a patient specific study of AVFs. However, this hypothesis requires further investigation in future studies to determine the full extent of its effect on endothelial cell function and the development of IH.

The most substantial hypothesis is proposed by the studies that conduct longitudinal analyses. These studies find that an overall reduction in WSS (regardless of initial value) as the AVF remodels is associated with outward remodelling and fistula maturation. This emphasises the increased importance of longitudinal studies over single time point studies as it's not possible to determine the longitudinal effect of hemodynamic parameters on the remodelling process from a single time point study.

This review highlights the lack of longitudinal studies to date. A possible reason for this could be due to the complicated process involved in acquiring longitudinal data. This process requires that patients have their VA scanned in an MRI machine. A computational model must then be created of the VA from this scan. CFD simulations can then be conducted to analyse the hemodynamics within the VA. This process is then repeated at several time points to capture the hemodynamic and morphological changes that occur in the VA as it remodels. The typical longitudinal study contains data from three different time points of the same VA, and requires the patient to have their VA scanned on three separate occasions. This process can be overly time restricting for patients who are already undergoing hemodialysis several times a week.

Until recently it was believed that areas exposed to low/oscillating shear are susceptible to the development of IH. However, a review conducted by Peiffer *et al.*[55] investigating the hypothesis that low/oscillating shear correlates with the development of atherosclerosis, found that studies that perform a rigorous point-by-point comparison between WSS and IMT do not find significant correlations, whereas studies that report significant correlations conduct less rigorous analyses.[3,29,36,74,82] Studies that fail to find a correlation are all conducted on human vessels, while a significant number of the studies that find significant correlations are conducted on hypercholesterolaemic animal models.

It should be noted that the studies included in the review by Peiffer *et al.*[55] were conducted on the biological response of arteries and the development of atherosclerosis. This review focuses on the progression of IH in VAs, which predominantly occurs in the venous segment of the access. As discussed previously, the remodelling response of arteries is considerably different to that of veins, particularly the veins of CKD patients. That is why the conclusions drawn by the longitudinal studies discussed in this review are more relevant than the conclusions drawn in the review conducted by Peiffer *et al.*[55]

IH is a complex process that can be trigged by multiple aspects of WSS. It is therefore difficult to ascertain a single WSS metric that is capable of quantitatively identifying areas of the vasculature susceptible to IH development. Peiffer *et al.*[56] propose a relatively new metric called transverse wall shear stress which is a measure of the multidirectionality of disturbed flow. It is characterised as the average magnitude of WSS components acting transversely to the mean WSS vector. This metric could potentially provide a more accurate prediction of the locations of IH. Preliminary studies conducted on animal models have revealed that lesion prevalence correlates strongly

with transWSS while other shear metrics correlate less significantly.[50] While this study was not conducted on a VA model, the results are promising for the use of transWSS as a new metric for the detection of lesion formation/development of IH. Additionally, a more recent study conducted by Anderson *et al.*[2] who analysed the effectiveness of the TransWSS metric in a model of a human aorta, found that in regions of transitional to turbulent flow, similar to the flow found in a VA, TransWSS correlated with areas of low/oscillating shear. The study concludes by saying that the TransWSS metric demonstrated a more multi-featured picture of WSS distribution when exposed to different types of flow regimes. However, this metric must be included in longitudinal studies before any significant conclusions can be drawn about its ability to identify areas of IH in VA.

Conventionally, WSS parameters have been utilised to predict the onset of IH within VA. However, bulk flow parameters have been introduced to provide a more detailed analysis of the flow as it is hypothesised to play a significant role in the physiological response that leads to the development of IH. A limited amount of research has been conducted on the use of bulk flow parameters in predicting VA dysfunction. However, its potential, as highlighted by Gallo *et al.*[26] as a surrogate marker of exposure to disturbed shear in the carotid bifurcation warrants further research in a VA setting. This will determine if bulk flow parameters possess the same diagnostic capabilities in VAs.

CONCLUSION

The diversity of hypotheses detailed in this review reveals that the exact physiological response that leads to the development of IH remains unknown. This emphasises the need for a single, precise hypothesis capable of predicting the onset of IH. The discord among studies weakens the impact of computational modelling and more longitudinal studies must be conducted to assist in predicting the onset of IH. While there has been numerous studies conducted on the hemodynamics within patient specific models of VAs, the number of longitudinal studies that attempt to monitor the remodelling process over time is limited. Single time point studies are useful at accessing the hemodynamics occurring at a particular point in time but there is no way of determining the longitudinal effect they have on VA remodelling process. The future of computational modelling in this field must therefore focus on longitudinal studies with large cohorts of patients. Longitudinal studies will allow for the remodelling process of the newly created VA to be monitored over time, which will provide a greater understanding of the hemodynamic changes that take place during this complex remodelling process. This will also provide the opportunity to investigate different hemodynamic parameters and their ability to predict the onset of IH.

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CONFLICT OF INTEREST

All authors declare that there is no conflict of interest.

ETHICAL APPROVAL

This article does not contain any studies with human participants or animals performed by any of the authors.

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