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Validation of a patient-specific hemodynamic computational model for surgical planning of vascular access in hemodialysis patients

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Vascular access dysfunction is one of the main causes of morbidity and hospitalization in hemodialysis patients. This major clinical problem points out the need for prediction of hemodynamic changes induced by vascular access surgery. Here we reviewed the potential of a patient-specific computational vascular network model that includes vessel wall remodeling to predict blood flow change within 6 weeks after surgery for different arteriovenous fistula configurations. For model validation, we performed a multicenter, prospective clinical study to collect longitudinal data on arm vasculature before and after surgery. Sixty-three patients with newly created arteriovenous fistula were included in the validation data set and divided into four groups based on fistula configuration. Predicted brachial artery blood flow volumes 40 days after surgery had a significantly high correlation with measured values. Deviation of predicted from measured brachial artery blood flow averaged 3% with a root mean squared error of 19.5%, showing that the computational tool reliably predicted patient-specific blood flow increase resulting from vascular access surgery and subsequent vascular adaptation. This innovative approach may help the surgeon to plan the most appropriate fistula configuration to optimize access blood flow for hemodialysis, potentially reducing the incidence of vascular access dysfunctions and the need of patient hospitalization.

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KEYWORDS: access blood flow; hemodialysis access; vascular access

More than 940 patients per million population in Europe are affected by end-stage renal disease and live on chronic renal replacement therapy. Approximately 80% of these patients are treated chronically by hemodialysis (HD) (European Renal Association–European Dialysis and Transplantation Association (ERA-EDTA) Guidelines). The total number of patients on HD in Europe exceeds 500,000, and it increases annually at a constant rate of ~7%.[1] Despite the major advances of HD procedure during the past three decades, the Achilles heel of this treatment is the vascular access (VA) required to connect patient's blood circulation to the artificial kidney.

For safe and long-lasting VA, the native arteriovenous fistula (AVF), surgically created in the arm by anastomosis of an artery to a vein, is recommended by international guidelines (National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF K-DOQI) Guidelines; ERA-EDTA European Best Practice Guidelines on HD).[2] However, short- and long-term AVF dysfunctions, including inadequate increase in blood flow volume (BFV) after surgery (nonmaturation), vein thrombotic occlusion, ischemic circulation in the distal arm and in the hand (steal syndrome), and massive increase in VA BFV with risk of cardiac failure, are among the major causes of morbidity and hospitalization in HD patients.[3,4] Indeed AVF primary patency at 2 years after surgery was recently estimated to be ~50%[5–7] and even lower in the United States.[8,9] Prediction and prevention of VA dysfunction are still open clinical challenges, with more than 90,000 procedures/year performed in Europe for revision or reoperation.[10]

Currently, the choice of location and type of the anastomosis is based, beyond evaluation of systemic factors, on blood vessel diameter only, following the indication that radial arteries <2 mm will probably result in AVF failure (NKF K-DOQI Guidelines), and considering that distal VA more likely results in lower BFV and in a high incidence of early nonfunction,[11] whereas proximal VA more likely results in very high BFV, increasing the risk of steal syndrome and cardiac failure.[12,13] However, BFV enhancement following VA creation is influenced by the combination of geometrical factors (for example, vascular diameters and lengths along the arterial tree), vessel topology (for example, number and size of venous side branches), peripheral resistance, type of anastomosis, and vessel adaptation. An objective and reliable prediction of postoperative increase in BFV over time could be extremely relevant for planning the optimal AVF configuration, and may reduce the incidence of VA dysfunctions.

A number of computational approaches have been proposed for the simulation of hemodynamics and vascular wall dynamics in complex vascular networks, which could potentially be used to predict BFV change after VA creation. Among them, 0D and 1D pulse-wave propagation methods allow to efficiently model BFV, pressure distributions, and wall displacements throughout vascular networks at low computational costs.[14,15] Recently, a pulse-wave propagation model[16] based on boundary layer theory and approximated velocity profile[17,18] has been developed to accurately predict preoperative and postoperative BFV over different AVF types and locations with a fast computational approach. More recently, a sensitivity analysis has been carried out for the identification of parameters most sensitive for patient-specific BFV prediction.[19,20] As these models enable to estimate changes in BFV only immediately after surgery, we extended this modeling approach to include a simulation of vessel wall remodeling and consequent hemodynamic changes that are responsible for the so-called access maturation.[21]

Despite promising results, the potential clinical use of these computational tools needs assessment of their reliability and of the accuracy of model prediction in terms of BFV redistribution in arm vasculature. To this aim, a multicenter longitudinal clinical prospective study was conducted in patients with end-stage renal disease awaiting VA creation for HD treatment in the context of the EU-FP7 research project ARCH.[22] In the present study, we used an *ad hoc*–developed computer program to predict, on the basis of preoperative ultrasound (US) measurements, patient-specific potential changes in BFV that take place immediately after VA surgery and during the subsequent 6-week period (VA maturation). We then compared predicted postoperative results with data measured within the ARCH clinical study to assess the reliability of theoretical prediction and to provide evidence on the potential use of the computational model as a tool for planning VA surgery in HD patients.

RESULTS

ARCH clinical study

A total of 93 consecutive patients (mean age 62 ± 16 (19–85) years, 31% women, 33% diabetic) were enrolled in four European HD centers: Maastricht University Medical Center, The Netherlands ($n=39$); Universzitetni Klinikni Center Ljubljana, Slovenia ($n=10$); Ospedali Riuniti di Bergamo, Italy ($n=39$); and Ghent University Hospital, Belgium ($n=5$). All patients underwent clinical and vascular US examinations preoperatively, and they were systematically followed up after VA surgery through clinical and US examinations for a period of 2 years.[22] During each US examination, brachial, radial, and ulnar artery BFV and size of major arm vessel diameters were assessed.[22] According to the study protocol, any AVF dysfunction occurring during the observation period was recorded and, in case of early end of the study, information on VA function at study end was collected.

In 38 patients, AVF was created in the upper arm, and was either brachiocephalic (BC, $n=28$) or brachiobasilic (BB, $n=10$), whereas in 55 patients AVF was created in the lower arm and it was either radiocephalic (RC, $n=54$) or ulnarcephalic (UC, $n=1$). Anastomoses were side to end (S-E; 20 BC, 10 BB, 22 RC, and 1 UC), end to end (E-E; 28 RC), or side to side (S-S; 8 BC and 4 RC). Clinical data collected during the study documented that early AVF failure (defined as inability to use AVF for HD, or failure within 3 months of initial use) occurred in 20 out of 93 patients (21%). As shown in Figure 1, overall VA patency at 1 year averaged 66% (95% confidence interval (CI) = 57–77%) and 56% (95% CI = 44–70%) 2 years after surgery. Late VA failure was mainly due to stenosis occurring in the venous limb. VA patency was higher in male individuals (71% at

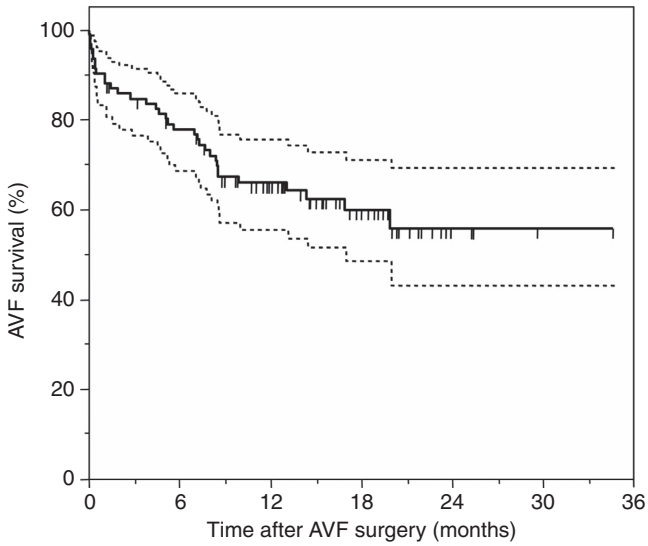

Figure 1 | Kaplan–Meier plot showing vascular access (VA) survival (with 95% confidence intervals) in the 93 patients with end-stage renal disease and newly created arteriovenous fistula (AVF) for hemodialysis treatment enrolled in the ARCH clinical study.

1 year and 60% at 2 years) than in female individuals (55% at 1 year and 49% at 2 years). Only two patients (both with BC S-E anastomosis) developed steal syndrome, probably because of high BFV in the draining AVF vein. Both patients developed concomitant high-output cardiac failure and underwent a successful banding procedure. Three additional patients with BC AVF developed high BFV in the draining vein, at a level that threatened the cardiac function. One of them was subjected to successful vein banding procedure, another developed vein stenosis 15 months after AVF surgery, which required reoperation, and the third patient died 7 months after AVF surgery probably because of heart failure. Other three patients died during follow-up owing to sudden death, liver complications, or intestinal ischemia.

Validation data set

Data from 63 patients of the ARCH clinical study with newly created AVF, from patients at 40 days after surgery, were included in the current validation study, and divided into four groups based on AVF configuration:group 1: lower arm RC E-E AVF ($n=22$); group 2: lower arm RC S-E AVF ($n=17$); group 3: upper arm BC S-E AVF ($n=19$); and group 4: upper arm BB S-E AVF ($n=5$). Out of the 63 patients, 55 were needled and able to perform HD, whereas only 1 patient underwent unsuccessful VA cannulation. In the remaining patients, HD was not started owing to improved renal function. Demographic and clinical parameters, used to generate patient-specific vascular network models, are summarized in Table 1. BFV and the size of major blood vessels in the arm are reported in Table 2 and in Figure 2. BFV measured in brachial artery after VA surgery was lower in distal AVFs as compared with proximal AVFs. Among RC AVFs, E-E anastomosis resulted in higher BFV than S-E (Figure 2a). One interesting finding of our investigation was that brachial artery diameter did not significantly increase after surgery in diabetic patients with upper arm AVF (averaging 4.2 ± 0.8 mm and 4.4 ± 0.6 mm, preoperatively and 40 days postoperatively, respectively; paired t-test $P=0.20$; $n=9$). On the contrary, radial artery did increase after surgery in diabetic patients with distal VA (averaging 2.8 ± 0.6 mm and 4.2 ± 1.2 mm, preoperatively and 40 days postoperatively, respectively; paired t-test $P<0.001$; $n=11$).

Validation of computational modeling

Preoperative vessel dimension and arterial BFV measured during US investigations were used as input parameters to predict postoperative diameters and BFVs at different time points after surgery. Predicted results were compared with measurements obtained by US examination at 1 day and 40 days after surgery. The results are reported in Table 2 and in Figures 3 and 4. In general, BFV prediction was more accurate at 40 days than immediately after surgery, regardless of AVF configuration (see Table 2). A good agreement was observed between measured and predicted brachial artery BFV in individual patients 40 days after surgery, for both proximal and distal AVF and for both AVF configurations, and this for the entire range of brachial artery BFV, from <300 ml/min to >2 l/min. The Bland–Altman plot reported in Figure 5 indicates good agreement between predicted and measured brachial artery BFV in the whole simulation data set independently from brachial artery BFV. Furthermore, regression analysis between predicted and measured values of brachial artery BFV showed a high and statistically significant correlation for each of the four AVF configurations (R^2 ranging from 0.77 to 0.96). As shown in Figure 6, a strong correlation was found between measured and predicted results in the whole patient population ($R^2=0.90$, $P<0.001$). In the whole validation data set, a percent error of predicted versus measured brachial artery BFV of $3\pm19\%$ (95% CI -2 to 8%) indicates a high precision of the prediction, with a

Table 1 | Sociodemographic and clinical characteristics of 63 patients with newly created AVF at 40 days after surgery, divided into four groups based on AVF configuration

	RC E-E	RC S-E	BC S-E	BB S-E
N	22	17	19	5
Age (years)	55 ± 21	64 ± 15	66 ± 15	69 ± 10
Gender (females)	3 (14%)	4 (24%)	8 (42%)	2 (40%)
AVF arm (right)	5 (23%)	4 (24%)	3 (16%)	2 (40%)
Height (cm)	171 ± 10	175 ± 9	171 ± 7	173 ± 3
Weight (kg)	74 ± 14	83 ± 12	73 ± 14	77 ± 15
Systolic pressure (mm Hg)	143 ± 20	151 ± 38	145 ± 26	154 ± 14
Diastolic pressure (mm Hg)[a]	83 ± 15	84 ± 17	77 ± 12 (17)	78 ± 8 (3)
Cardiac output (ml/min)[a]	ND	5562 ± 1172 [7]	4621 ± 1411 [15]	6035 ± 2296 [3]
Cardiac frequency (b.p.m.)[a]	74 ± 15	74 ± 10 [12]	68 ± 8 [11]	74 ± 5 [3]
Hematocrit (%)[a]	33 ± 5	34 ± 5	32 ± 6 [18]	35 ± 4
Protein plasma concentration (g/dl)[a]	6.6 ± 0.7 [20]	6.6 ± 0.9 [12]	6.0 ± 1.1 [11]	5.5 ± 1.0 [3]
Hypertension	14 (64%)	10 (59%)	11 (58%)	4 (80%)
Diabetes	5 (23%)	6 (35%)	6 (32%)	3 (60%)

Abbreviations: AVF, arteriovenous fistula; BB, brachiobasilic; BC, brachiocephalic; E-E, end to end; ND, not determined; RC, radiocephalic; S-E, side to end.
Values are mean ± s.d. for continuous variables or frequency (percentage) for gender, AVF arm, hypertension, and diabetes. Hypertension was defined as diastolic pressure + ((systolic pressure − diastolic pressure)/3) ⩾100 mm Hg.
Individual data were used to generate patient-specific vascular network models for hemodynamic simulations.
[a]In case of missing data, the number of available measured data is reported in square brackets.

Table 2 | Measured vessel dimensions and arterial blood flow volumes in 63 patients with newly created AVF, followed up for 40 days after surgery, in comparison with predicted data

		1 Day post-op		40 Days post-op	
	Pre-op	Measured	Predicted	Measured	Predicted
RC E-E					
BA flow (ml/min)	65 ± 42	448 ± 213	341 ± 128	611 ± 163	584 ± 147
RA flow (ml/min)	21 ± 20	355 ± 164	274 ± 110	496 ± 164	503 ± 123
Mid RA diameter (mm)	2.7 ± 0.6	4.0 ± 0.8	3.0 ± 0.6	4.7 ± 1.0	4.1 ± 0.4
Mid lower CV diameter (mm)	2.6 ± 0.8	ND	2.2 ± 0.5	5.1 ± 1.4	4.8 ± 0.5
RC S-E					
BA flow (ml/min)	68 ± 35	268 ± 142	366 ± 139	533 ± 172	525 ± 139
RA flow (ml/min)	17 ± 10	197 ± 164	274 ± 114	404 ± 150	454 ± 126
Mid RA diameter (mm)	2.6 ± 0.4	3.2 ± 0.6	2.9 ± 0.4	4.4 ± 1.4	4.3 ± 0.5
Mid lower CV diameter (mm)	3.3 ± 0.9	ND	2.5 ± 0.6	5.2 ± 1.8	4.9 ± 0.8
BC S-E					
BA flow (ml/min)	49 ± 20	451 ± 170	561 ± 216	918 ± 332	942 ± 321
Mid BA diameter (mm)	4.2 ± 0.7	4.5 ± 0.5	4.3 ± 0.7	4.9 ± 0.7	5.1 ± 0.8
Mid upper CV diameter (mm)	3.3 ± 1.1	ND	2.8 ± 0.7	6.4 ± 1.4	5.2 ± 1.5
BB S-E					
BA flow (ml/min)	40 ± 24	NA	810 ± 338	1338 ± 583	1310 ± 474
Mid BA diameter (mm)	3.9 ± 0.8	4.3 ± 0.7	3.9 ± 0.7	4.8 ± 1.0	5.7 ± 1.2
Mid upper BV diameter (mm)	4.6 ± 2.0	ND	3.3 ± 0.7	6.0 ± 0.7	7.0 ± 1.2

Abbreviations: AVF, arteriovenous fistula; BA, brachial artery; BB, brachiobasilic; BC, brachiocephalic; BV, basilic vein; CV, cephalic vein; E-E, end to end; ND, not determined; post-op, postoperative; pre-op, preoperative; RA, radial artery; RC, radiocephalic; S-E, side to end.
Values are mean ± s.d. Vein diameters were computed as weighted average of long and short diameters.
Preoperative diameters and blood flow volumes were used as data input for the patient-specific model in hemodynamic simulations.

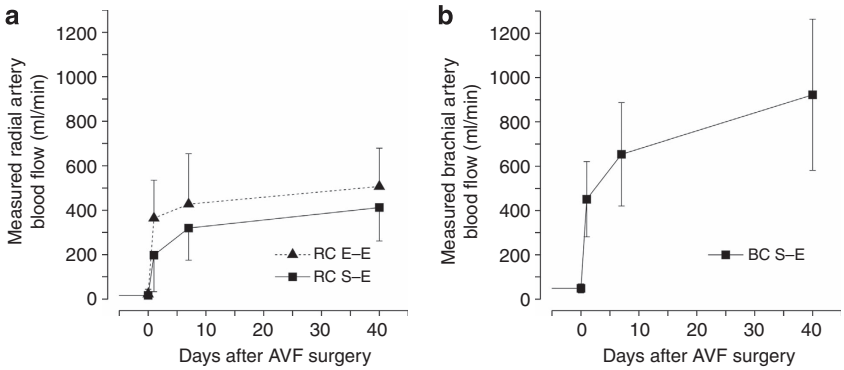

Figure 2 | Blood flow volume (BFV) adaptation following vascular access (VA) surgery in a subgroup of 52 patients (all patients with complete available blood flow volume data) enrolled in the ARCH clinical study. Patients were divided into three groups based on arteriovenous fistula (AVF) configuration ((**a**) radiocephalic (RC) end to end (E-E) and side to end (S-E), and (**b**) brachiocephalic (BC) S-E). BFV was assessed by multiplying the time-averaged outer envelope of the ultrasound (US) Doppler velocity spectrum with the local cross-sectional area by assuming a parabolic blood velocity profile. US examinations were performed both preoperatively (day 0) and 1, 7, and 40 days after surgery. Data are expressed as mean ± s.d.

root mean squared error of 19.5% as an index of prediction accuracy. Considering only patients with RC AVF, percent error of predicted versus measured radial artery BFV averaged 11 ± 25% (95% CI −3 to 19%), with a root mean squared error of 25.4%. In addition to the previously described validation data set, we also simulated AVF function in 12 patients with AVF failure or nonfunction at 40 days after surgery. Mean predicted brachial artery BFV averaged 635 ± 298 (range 415–1293) ml/min in patients with early AVF thrombosis ($n = 8$) and 292 ± 77 (range 183–355) ml/min in four patients with AVF nonmaturation. It is interesting to note that in all of these four patients, predicted brachial artery BFV was below the threshold of 400 ml/min to perform HD.

DISCUSSION

Despite the established indication to use native AVF for HD patients, the incidence of VA complications, such as nonmaturation and early failure, is high.[4,6] In the attempt to predict the best location and type of anastomosis, physical

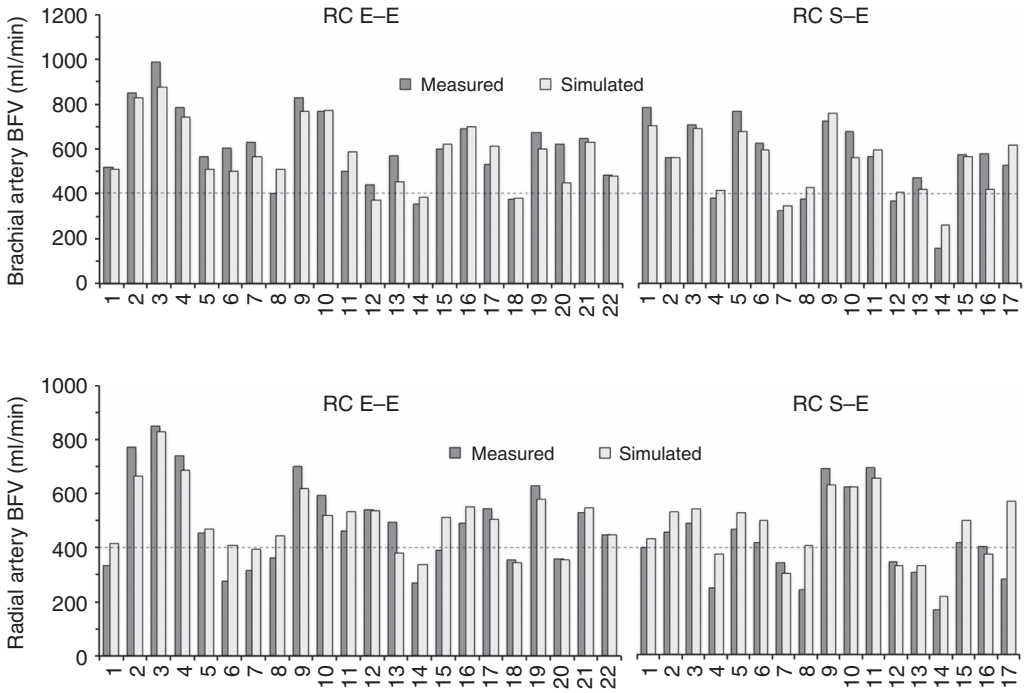

Figure 3 | Comparison between measured and predicted brachial artery and radial artery blood flow volume (BFV) at 40 days after arteriovenous fistula (AVF) surgery in 39 patients with end-stage renal disease and newly created radiocephalic (RC) arteriovenous fistula for hemodialysis treatment. Patients were divided into two groups based on type of anastomosis: end to end (E-E) and side to end (S-E). Dashed line denotes threshold routinely assumed in clinical practice to assess AVF nonmaturation (400 ml/min).

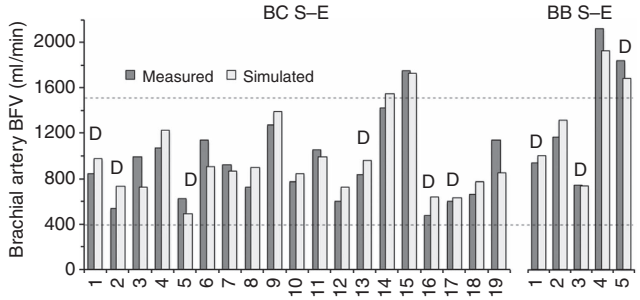

Figure 4 | Comparison between measured and predicted brachial artery blood flow volume (BFV) at 40 days after arteriovenous fistula (AVF) surgery in patients with end-stage renal disease and newly created upper arm side to end (S-E) AVF for hemodialysis treatment. Patients were divided into groups based on AVF configuration: brachiocephalic (BC, $n = 19$) and brachiobasilic (BB, $n = 5$). Letters D denote diabetic patients, for whom no adaptation algorithm was applied during simulation. Dashed lines denote thresholds routinely used in clinical practice to assess AVF nonmaturation (400 ml/min) and high BFV threatening cardiac function (1500 ml/min).

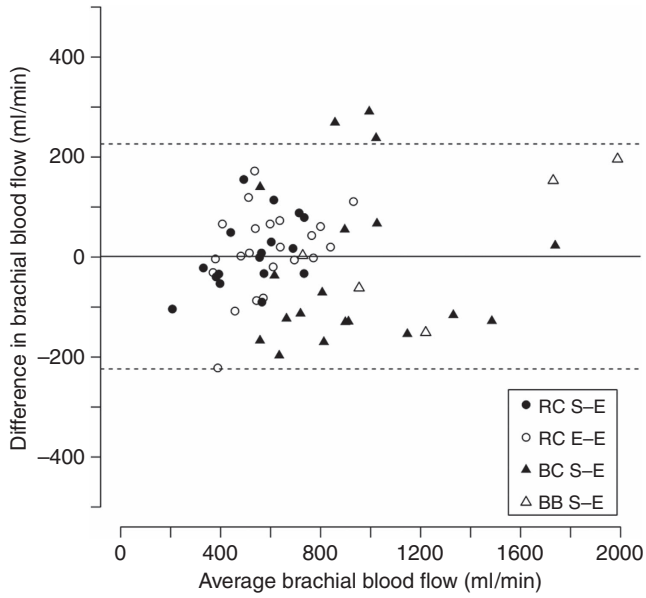

Figure 5 | Bland–Altman plot showing agreement between measured and predicted brachial artery blood flow volume (BFV) at 40 days after arteriovenous fistula (AVF) surgery in 63 individual patients. Different symbols denote different AVF configurations (empty circle: radiocephalic (RC) end to end (E-E); full circle: RC side to end (S-E); full triangle: brachiocephalic (BC) S-E; empty triangle: brachiobasilic (BB) S-E).

examination and US evaluation of brachial and radial artery and venous circulation are currently used.[23] However, owing to the complex interplay of several factors, presurgery evaluation cannot reliably support the decision of the surgeon who is predominantly driven by experience and personal skill. The use of computational models to assist the surgeon in selecting the optimal AVF location and configuration could help perform more efficient planning of the AVF surgery.

The results of our clinical and numerical investigations provide evidence that the patient-specific hemodynamic computational models that we used[16,21] are accurate

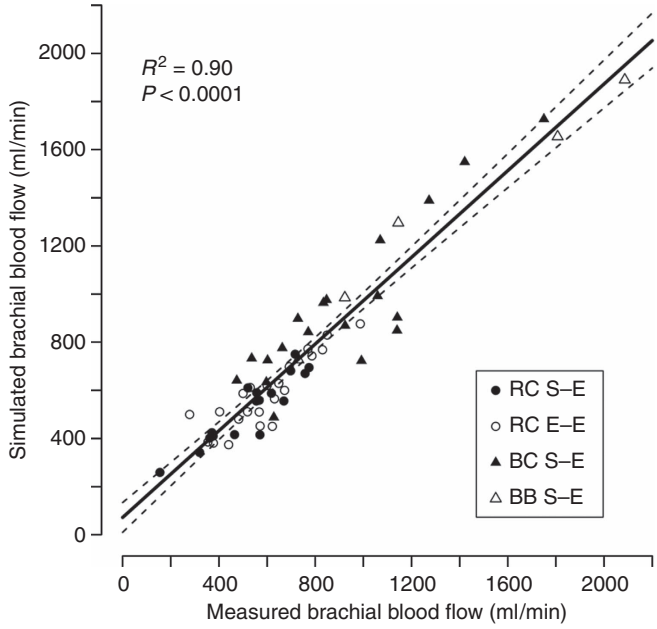

Figure 6 | Correlation between measured and predicted brachial artery blood flow volume at 40 days after AVF surgery in the group of 63 individual patients. (Empty circle: radiocephalic (RC) end to end (E-E); full circle: RC side to end (S-E); full triangle: brachiocephalic (BC) S-E; empty triangle: brachiobasilic (BB) S-E.) Regression line (solid) and 95% confidence intervals (dashed) were estimated using linear regression analysis.

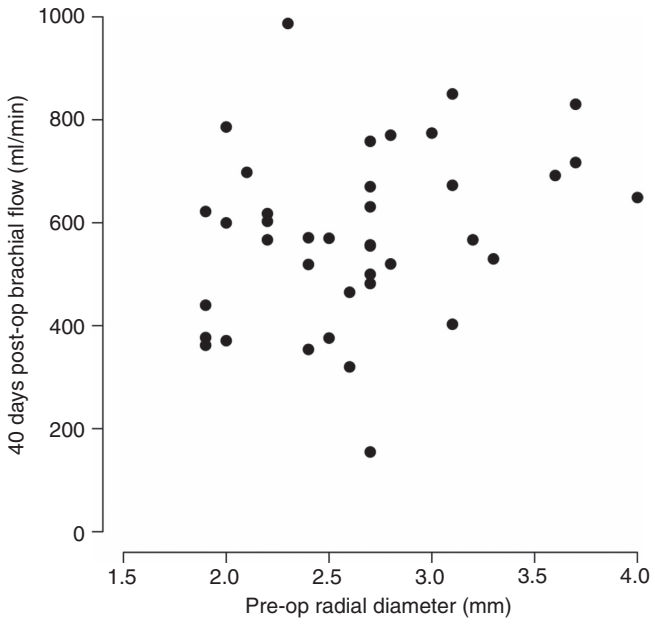

Figure 7 | Correlation between preoperative (Pre-op) radial artery diameter and measured brachial artery blood flow volume at 40 days after surgery (post-op) in 39 patients with distal AVF.

(deviation of predicted vs measured brachial artery BFV averaged 3 ± 19%) and provide reliable prediction of the BFV distribution in the arm vasculature during VA maturation, suggesting that this computational approach is of potential use in surgery planning. Predicted results were reasonably accurate for different configurations and locations of the AVF. The predicted values have been obtained, at the patient-specific level, on the basis of demographic data, systemic parameters, clinical condition, and presurgery US measurements of AVF arm blood vessel diameters and BFVs. This data set can easily be provided during the evaluation usually performed in these patients before surgery.

This study demonstrates that the problem of predicting VA BFV after maturation on the basis of a small set of preoperative evaluations can be successfully faced by a computer-based modeling approach that takes into account basic hemodynamic and biomechanical phenomena, properly fitted to the individual patient's characteristics. The level of accuracy achieved by our model suggests that other aspects, such as genetic or systemic risk factors, may have a secondary role in predicting postoperative BFV and that inaccuracies due to US measurements or the lack of complete patient-specific information about the entire vascular tree do not significantly affect the accuracy of the prediction.

Widely accepted indications suggest that distal VA surgery would result in too low BFV whenever the radial diameter is <2 mm. Our present data allowed us to investigate whether preoperative radial artery diameter and 40 days postoperative BFV are actually correlated. As shown in Figure 7, there is a poor correlation between radial artery diameter and VA BFV, estimated by measured BFV in the brachial artery, after VA maturation. These data clearly show that for distal VA, obtained either by E-E or S-E anastomosis, VA BFV cannot be simply predicted by the size of the radial artery. On the contrary, only the consideration of the entire vascular network in the arm allowed obtaining reliable predictions of actual BFV in distal and probably also in proximal VA. We actually identified a different behavior of vessel remodeling in diabetic patients subjected to proximal AVF. In these patients, we could successfully predict BVF after AVF surgery, neglecting completely the shear-induced vascular changes, indicating that medium-sized arteries in these patients (known to be affected by vessel wall calcification) do not remodel, probably because of endothelial and smooth muscle cell dysfunction. It is interesting to note that this behavior was not observed in diabetic patients with distal AVF, suggesting that vascular changes (that is, vessel wall calcification) in these patients may predominantly affect larger arteries.

The present simulations were performed using a computational modeling tool (http://avfsim.herokuapp.com) that is completely automated, fast (in the order of minutes), involves operator-independent calculations, and enables the user to quantitatively estimate patient-specific postoperative BFV change over different AVF configurations. To date, this application enables simulation of S-E and E-E anastomoses, while a tool for S-S anastomoses is currently under development, as *ad hoc* measures have to obtain BVF in the vessels connected to this anastomosis. Further modeling efforts (that is, pressure drop estimates in S-S anastomosis) are needed to

extend the application to this type of arteriovenous surgical connection. The application accounts for the occurrence of diabetes, which is simulated by omitting arterial vessel adaptation in case of upper arm AVF.

It has been recently reported that a computational vascular network model allowed to predict BFV in AVF immediately after surgery in a group of 25 patients with distal and proximal VA.[24] Our current validation study goes beyond this step. We actually assessed the validity of the computational model to include the simulation of vascular adaptation over time during VA maturation. We were able to accurately predict hemodynamic changes up to 40 days after surgery in a larger patient cohort. We compared the results of the numerical analysis with measured flow rates during a 40-day period after surgery, when measurements have been planned. Our results demonstrate that the model can predict different dynamics of vascular changes, either slow or fast. Actually, if immediately after surgery the blood flow importantly increases owing to vessel dimensions and AVF configuration, then wall shear stress is importantly increased and a fast vessel remodeling is predicted to take place. This condition would determine even larger increases in blood flow in the following time period. On the contrary, if after surgery blood flow increase is limited, then small changes in wall shear stress are computed and consequently little vascular remodeling is assumed. In this case, vascular adaptation and related changes in blood flow would require longer time to develop and to complete the transition phase.

Our current results show that both immediate postoperative and final BFV can be accurately predicted. In this way, the possibility to effectively start successful HD treatment can be predicted before performing a given type and location of VA surgery. This is an important piece of information needed by the surgeon and the nephrologist who follow-up the patient under HD treatment. The model was developed and calibrated to predict blood flow change following primary fistula creation. Thus, the effects of repeated access surgery cannot be reliably taken into account for the heterogenous condition of the vasculature that would be implied by more than one anastomosis. Our computational approach takes into account only few biological inputs, which are plasma protein, hematocrit, blood pressure, and diabetes. It is generally accepted that AVF-induced vessel wall changes are related to biological determinants.[25] Our results would indicate that the response of the vascular network is predominantly related to the vascular geometry and the biological effect of shear stress changes on the endothelial cells. In addition, our results indicate that endothelial response to shear stress is rather uniform in this patient population. Finally, the mechanical stimulation of endothelial cells is the trigger of vascular remodeling (that is, outward remodeling), and thus our computational model would allow to identify whether low outward remodeling may be expected in an AVF owing to hemodynamic conditions and vessel morphology.

Although the results of this study are consistent, they are in some way limited by the relatively small sample size and potential inaccuracies due to US measurements. The main drawback of our computational approach is that it does not allow to predict AVF thrombosis on the basis of preoperative data only. Actually, thrombosis is known to take place after the development of intimal hyperplasia that is related to local hemodynamic conditions.[25] However, these local effects of blood flow cannot be derived from predicted average blood flow rate provided by our model. The results we obtained in AVFs that did not mature suggest that predicted AVF flow rate would have been too low to start HD. This would be an interesting result to identify nonfunctioning AVFs; however, owing to the small number of cases, it needs more extensive evaluation.

Another limitation of our investigation is that the comparison of measured and predicted BFV could not be applied at the AVF site. Actually, US signal cannot be used in this location, because flow velocities are not uniformly oriented along the main flow direction, and secondary flows in other directions greatly affect flow rate estimation by this technique. To overcome this limitation, arterial BFV was used as a surrogate of BFV through the AVF, as done in routine clinical practice. Finally, another limitation of our approach is that it cannot be applied for repeated access surgery, as different vessel configurations would have to be taken into account.

This validation study has a number of possible clinical implications. The availability of patient-specific prediction of BFV increase after VA surgery over time, based on different AVF configurations, would allow more efficient planning of AVF surgery and may increase the chance of achieving adequate increases in BFV at the end of VA maturation. For instance, predicting whether a distal anastomosis will result in adequate BFV or not would provide a suggestion to the surgeon for the use of more proximal location for the AVF, potentially reducing the rate of VA nonmaturation and avoiding the need for reoperation. On the other hand, prediction of very high BFV in a proximal VA could indicate the need for a distal VA in order to avoid the risk of cardiac failure and steal syndrome, the major complications of VA surgery that are difficult to predict at the moment and may cause important clinical problems. Furthermore, extending the tool to predict BFV over longer time could help improve the planning of VA surgery for HD treatment.

In summary, our study provides preliminary evidence that the computational model we developed can reliably predict, on the basis of the preoperative work-up of patients awaiting AVF creation, the resulting effect of a given VA surgery procedure in terms of vascular remodeling and changes in VA BFV. In view of the potential translation of such tools into the clinical environment, it would be worth performing a larger, randomized study aimed at proving the clinical efficacy of this approach in improving VA planning and reducing VA complications.

MATERIALS AND METHODS

Patient population

Patients included in this study were enrolled between August 2009 and April 2011 in a multicenter longitudinal clinical prospective observational study (ARCH clinical study) conducted during the

ARCH project (http://www.vph-arch.eu/), aimed at collecting longitudinal data on arm vasculature and VA function in patients with end-stage renal disease awaiting VA creation for HD. Rationale and protocol of the ARCH trial were described previously.[22] Local ethics committees approved the study protocol, and all patients signed written informed consent. Out of the 93 patients enrolled in the ARCH study, 14 did not have complete measured data at 40 days after surgery, owing to early AVF failure ($n=12$) or death within 40 days ($n=2$), and they were excluded from the validation data set (Figure 8). One patient with UC AVF and 12 patients with S-S anastomosis were further excluded from computational analysis, as to date the computational tool does not enable simulation of this type of arteriovenous surgical connection. Finally, one patient was excluded for inconsistent preoperative BFV measurements (brachial artery BFV lower than the sum of radial and ulnar artery BFV) and two patients were excluded for incomplete data. Twelve patients with available preoperative data but no available measured data 40 days after surgery owing to AVF early failure (early thrombosis or nonmaturation) were additionally considered for simulation.

Measured BFV

In US vascular examinations, BFV is usually automatically estimated as the product of maximum blood velocity (measured in the central area of the vessel) and vessel cross-sectional area. The time-averaged flow volume is obtained by recording the maximum blood velocity during one or more cardiac cycles and calculating the time-averaged blood velocity. Even if widely adopted, this approach is not consistent with physical principles (no slip condition at the vessel wall and parabolic profile of blood velocity across the vessel cross-sectional area), and leads to estimates of BFV higher than the real value. To obtain more accurate estimations of BFV from measurement of maximum velocity by standard duplex US measurements, we assumed a parabolic blood velocity profile, and as a consequence we calculated average velocity as half of maximum, as previously described.[26] Despite being rarely used in clinical studies, this assumption was recently shown to be reliable in estimating real BFV using US investigation.[27] Briefly, luminal diameter was first assessed and then maximum blood flow velocity was recorded for several cardiac cycles using pulsed-wave Doppler, sampling the central volume of the blood vessel (centerline velocity). The time average of maximum velocity spectrum was then calculated and used to estimate BFV as previously described.

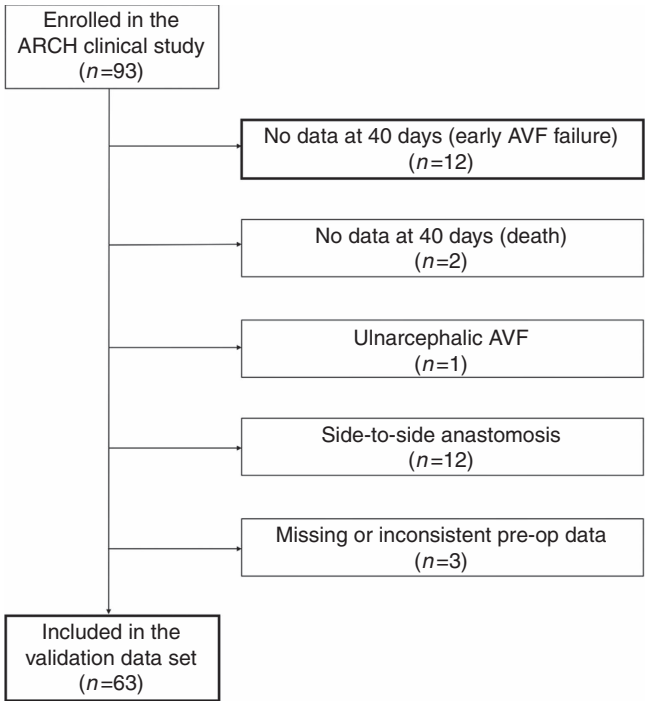

Figure 8 | Flow diagram showing the number of patients included in the validation data set from those enrolled in the ARCH clinical study.

Hemodynamic simulations

Hemodynamic simulations were performed using computer programs embedded in a web application (http://avfsim.herokuapp.com) for calculation of changes in blood vessel dimensions and BFV along the arm vasculature induced by VA creation, immediately after surgery and during VA maturation ($\sim$6 weeks) for different AVF configurations at the patient-specific level. The application is based on a modular numerical solver for 0D/1D problems (pyNS, http://archtk.github.com), which implements a 1D pulse-wave propagation model.[16] Description of the theoretical model is reported in Supplementary Material online (Vascular network computational model). Briefly, the solver represents the vascular network as a graph in which each edge is associated with a mathematical model linking pressure, BFV, and wall-shear stress in the corresponding vascular segment, and includes a lumped model of the anastomosis, which enables the prediction of postoperative BFV. We used 3D computational fluid dynamics to estimate pressure drops occurring over the anastomosis as a function of blood flow and geometrical parameters. In addition, in order to reliably predict changes in BFV several weeks after surgery, the solver embeds a vascular adaptation algorithm[21] calibrated (by setting of model constants, as recently described)[21] using a data set obtained by a previous investigation[26] based on the assumption that changes in blood vessel diameter take place upon changes in BFV to maintain a physiological value of the peak wall shear stress acting on vascular endothelial cells.[21]

Brachial and radial artery BFV and diameter of vessels involved in the anastomosis were predicted according to AVF configuration using patient-specific theoretical vascular network models based on preoperative data (demographic and clinical parameters, blood pressure measurements, cardiac output and frequency, blood analysis, and preoperative brachial, radial, and ulnar artery BFV and major arm vessel diameters, as assessed during preoperative US examination). These theoretical models are based on a previously defined[28] network model of artery and vein segments connected on anatomical basis. Each segment is assumed to have local diameter, length, and compliance. A previously described[14] mathematical model was then used to calculate actual blood flow distribution (pulsatile flow) solving the hydraulic problem in analogy to the computation of electrical networks. The model allows the estimation of propagation of the pulse-wave blood velocity along the vasculature. Patient-specific vascular network models used in the theoretical analysis were obtained on the basis of a generic vascular network model derived from the data available in literature[15] and adapting geometrical parameters (that is, length and diameter of vascular segments) according to body weight, height, age, and sex of individual patients, as previously described in detail.[28] When available, patient-specific information was used to replace the generic one in the model, eventually adjusting all other values, according to rules previously defined.[28] For diabetic patients with

upper arm AVF, simulation was performed without applying any adaptation algorithm in order to reflect the measured lack of adaptation in upper arm vessels owing to diabetes.

Statistical analysis

The agreement between predicted and measured data was investigated using Bland–Altman plots. In addition, R^2 coefficient denoting the correlation between predicted and measured brachial artery BFV was assessed by linear regression analysis. All statistical analyses were performed using the R statistical software.[29] Data are presented as means ± s.d. and 95% confidence intervals, as specified. Values of $P<0.05$ were considered statistically significant.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Vascular Network Computational Model

Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

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APPENDIX

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