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Original Article

ORIGINAL ARTICLE

The impact of haemodialysis arteriovenous fistula on haemodynamic parameters of the cardiovascular system

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Abstract

Background: Satisfactory vascular access flow (Qa) of an arteriovenous fistula (AVF) is necessary for haemodialysis (HD) adequacy. The aim of the present study was to further our understanding of haemodynamic modifications of the cardiovascular system of HD patients associated with an AVF. The main objective was to calculate using real data in what way an AVF influences the load of the left ventricle (LLV).

Methods: All HD patients treated in our dialysis unit and bearing an AVF were enrolled into the present observational cross-sectional study. Fifty-six patients bore a lower arm AVF and 30 an upper arm AVF. Qa and cardiac output (CO) were measured by means of the ultrasound dilution Transonic Hemodialysis Monitor HD02. Mean arterial pressure (MAP) was calculated; total peripheral vascular resistance (TPVR) was calculated as MAP/CO; resistance of AVF (AR) and systemic vascular resistance (SVR) are connected in parallel and were respectively calculated as AR = MAP/Qa and SVR = MAP/(CO – Qa). LLV was calculated on the principle of a simple physical model: LLV (watt) = TPVR·CO^2. The latter was computationally divided into the part spent to run Qa through the AVF (LLV_{AVF}) and that part ensuring the flow (CO – Qa) through the vascular system. The data from the 86 AVFs were analysed by categorizing them into lower and upper arm AVFs.

Results: Mean Qa, CO, MAP, TPVR, LLV and LLV_{AVF} of the 86 AVFs were, respectively, 1.3 (0.6 SD) L/min, 6.3 (1.3) L/min, 92.7 (13.9) mmHg, 14.9 (3.9) mmHg·min/L, 1.3 (0.6) watt and 19.7 (3.1)% of LLV. A statistically significant increase of Qa, CO, LLV and LLV_{AVF} and a statistically significant decrease of TPVR, AR and SVR of upper arm AVFs compared with lower arm AVFs was shown. A third-order polynomial regression model best fitted the relationship between Qa and LLV for the entire cohort ($R^2 = 0.546$; $P < 0.0001$) and for both lower ($R^2 = 0.181$; $P < 0.01$) and upper arm AVFs ($R^2 = 0.663$; $P < 0.0001$). LLV_{AVF} calculated as % of LLV rose with increasing Qa according to a quadratic polynomial regression model, but only in lower arm AVFs. On the contrary, no statistically significant relationship was found between the two parameters in upper arm AVFs, even if mean LLV_{AVF} was statistically significantly higher in upper arm AVFs ($P < 0.0001$).

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Conclusions: Our observational cross-sectional study describes statistically significant haemodynamic modifications of the CV system associated to an AVF. Moreover, a quadratic polynomial regression model best fits the relationship between LLV_{AVF} and Qa, but only in lower arm AVFs.

Key words: arteriovenous fistula, cardiac output, haemodialysis, high-output heart failure, vascular access blood flow

Introduction

Maintenance of a functioning haemodialysis (HD) vascular access (VA) is one of the most important challenges for nephrologists today [1]. Our clinical approach to the VA issue includes two main points: 'patient first, not fistula first, but avoid a catheter if at all possible' [2]; all VAs are performed by experienced nephrologists from our Unit (C.L., F.C., P. Libutti and P. Lisi). All arteriovenous fistulas (AVFs) and arteriovenous grafts (AVGs) are created in our unit after a standardized vascular mapping including both a physical examination and a Colour Doppler ultrasound scanning of the venous as well as of the arterial beds of the upper extremity (all performed by V.V.) [3].

Satisfactory vascular access flow (Qa) is necessary for dialysis adequacy. A technique employing the saline ultrasound dilution method to measure Qa (Transonic Hemodialysis Monitor HD02, Transonic Systems Incorporated, Ithaca, NY, USA) has been developed [4] and there are published data supporting its efficacy for the regular monitoring of Qa of both AVGs and AVFs [5, 6]. The same ultrasound dilution technique can also be used to measure cardiac output (CO) [7]. The Transonic CO technique was validated by van der Mark *et al.* by comparing this technique with echocardiography (using standard transthoracic two-dimensional and Doppler echocardiographic recordings) in 35 stable HD patients [8].

If, on one hand, low Qa are indicative of access dysfunction, on the other hand, high Qa are postulated to increase CO and cause high-output heart failure. The latter is defined as symptoms of cardiac failure (dyspnoea either at rest or with varying degrees of exertion, orthopnoea, paroxysmal dyspnoea and oedema, either pulmonary and/or peripheral) in the presence of an above-normal cardiac index (CI) (>3.0 L/min/m^2) [9]. There is a paucity of literature data regarding high-output heart failure in HD patients other than some case reports and case series [9–16]. The link between Qa and increased mortality due to pulmonary hypertension or high-output heart failure probably exists, but still has not been directly evidenced [17].

Currently, there is no definition of when Qa is too high. The concept of using the ratio Qa/CO (cardio-pulmonary recirculation, CPR) has been put forth by Pandeya and Lindsay in their study of stable long-term HD patients. They found that the average Qa was 1.6 L/min and the average CO was 7.2 L/min, thus describing an average CPR of 0.22 [18]. The Vascular Access Society guidelines define an AVF with a high Qa as that having a Qa of 1.0–1.5 L/min and a CPR >0.20 [19]. The relative dependency of Qa and CO on each other is unknown. At one end of the spectrum, one may hypothesize a linearity in the relationship between Qa and CO, which one might expect if Qa is believed to drive CO. However, recent literature data suggest that the relationship between Qa and CO is not linear, but that a third-order polynomial regression model best fits this relationship [8, 20–22].

The aim of the present observational cross-sectional study was to further our understanding of haemodynamic modifications of the cardiovascular (CV) system of HD patients associated with an AVF. The specific objective of the present study was to calculate using real data in what way an AVF influences the load of the left ventricle (LLV), particularly in patients bearing an AVF with a high Qa, on the principle of a simple physical model [23].

Materials and methods

Study protocol

Approval of the study (being conducted according to the Declaration of Helsinki) was obtained from the Research Ethics Committee of the Miulli General Hospital. After giving written informed consent, all HD patients treated in our dialysis unit and bearing an AVF were enrolled into the present cross-sectional study. Enrolment and studies were performed in the last trimester of the year 2015. Eighty-six patients entered the study. In that time period, another 19 end-stage renal disease patients were being treated by HD in our Centre, 17 by means of a tunnelled central venous catheter and 2 by means of an AVG. Measurements were performed on a mid-week dialysis run. Qa was evaluated by means of the ultrasound dilution Transonic Hemodialysis Monitor HD02 as previously described [4]. For the measurement of Qa the blood lines were reversed in a sterile manner and a temporary recirculation was created. Qa was determined as the average of three separate measurements taken ~5–10 min apart during the first 30 min of dialysis session. In short, a heated (37°C) bolus of 30 mL NaCl 0.9% (indicator) is injected into the venous line with the blood pump rate set at 200 mL/min, and the change in velocity of ultrasound waves produced by the returning dilution curve (S) is detected by a probe attached to the arterial line. By comparing the dilution curve S with a calibration curve (Scal) produced by injecting 30 mL of isotonic saline in the venous bubble trap, CO was calculated [7]

$$\mathrm{CO\,(L/min)} = 3 \cdot \mathrm{blood\ flow} \cdot \mathrm{(S/Scal)} \tag{1}$$

Arterial blood pressure (BP) was measured immediately after the above measurements in the contralateral arm. It is expressed as mean arterial pressure (MAP) [24]

$$\mathrm{MAP\,(mmHg)} = \mathrm{diastolic\ BP} + \frac{1}{3}(\mathrm{systolic\ BP} - \mathrm{diastolic\ BP}) \tag{2}$$

All measurements were performed by the same operator (V.V.).

Total peripheral vascular resistance (TPVR) was calculated as [24]

$$\mathrm{TPVR\,(mmHg \cdot min\,/L)} = \frac{\mathrm{MAP}}{\mathrm{CO}} \tag{3}$$

Resistance of AVF (AR) and systemic vascular resistance (SVR) are connected in parallel (Figure 1) and were respectively calculated as [23]

$$\mathrm{AR\,(mmHg \cdot min\,/L)} = \frac{\mathrm{MAP}}{\mathrm{Qa}} \tag{4}$$

and

$$\mathrm{SVR\,(mmHg \cdot min/L)} = \frac{\mathrm{MAP}}{(\mathrm{CO} - \mathrm{Qa})} \tag{5}$$

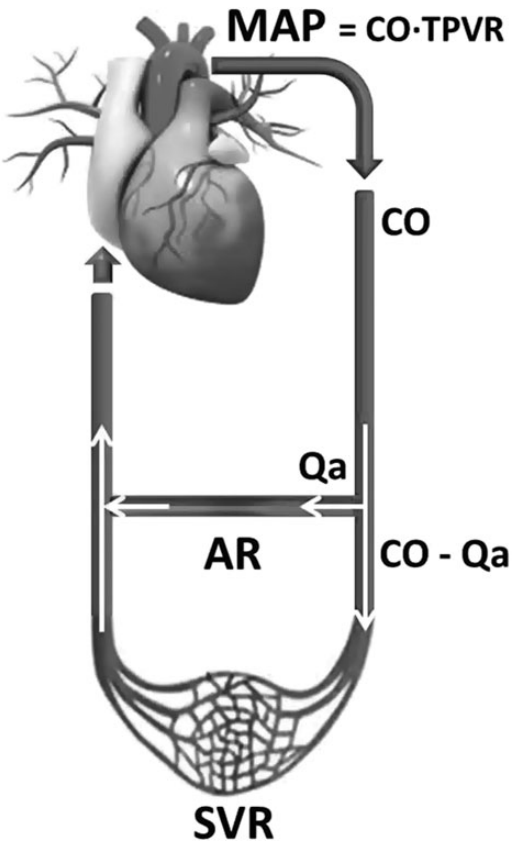

Fig. 1. As blood is pumped out of the left ventricle into the arteries, pressure is generated. MAP is determined by CO, TPVR and central venous pressure (CVP), according to the following relationship, which is based upon the relationship between flow, pressure and resistance [24]: MAP = (CO·TPVR) + CVP. Because CVP is usually at or near 0 mmHg, this relationship is often simplified to MAP = CO·TPVR. AR and SVR are connected in parallel. This figure is reproduced as a colour image in the online Supplementary data.

The workload of the left ventricle (LLV) was calculated as a product of flow (in this case CO) squared and hydraulic resistance (TPVR) [23]

$$\text{LLV (watt)} = \text{TPVR} \cdot \text{CO}^2 \quad (6)$$

Combining equations (3–6), we can easily derive a formula to calculate the part of the overall LLV spent to run the flow (Qa) through the AVF (LLV_{AVF}) and that part ensuring the flow through the entire remaining vascular system without the AVF (LLV_S) from CO, Qa and MAP values [23]

$$\text{LLV}_{\text{AVF}}\,(\text{watt}) = \text{AR} \cdot \text{Qa}^2 \quad (7)$$

$$\text{LLV}_{\text{S}}\,(\text{watt}) = \text{SVR} \cdot (\text{CO}-\text{Qa})^2 \quad (8)$$

Cardio-pulmonary recirculation (CPR) was calculated as [18]

$$\text{CPR} = \frac{\text{Qa}}{\text{CO}} \quad (9)$$

Statistics

The distribution of the data was studied by means of the Shapiro–Wilk test. The relationships between Qa and CO and Qa and LLV were studied by means of the bivariate analysis of the best-fit model. In case of a non-linear best-fit model, analysis of the regression equation should be carried out in order to calculate the Qa values (cut-off points) where the CO and LLV trends significantly changed their slopes (points of maximum, minimum or flex of the function). Student's *t*-test and Mann–Whitney *U* test for unpaired data were performed when appropriate in order to compare the data. The χ^2 test was utilized for the distributions between groups of the categorical variables. All statistical inferences were made using SPSS, version 11.0 software (SPSS Inc., Chicago, IL, USA). Data were expressed as means (SD), and values of $P < 0.05$ were assumed as statistically significant.

Results

Demographic, clinical and haemodynamic data for the 86 patients enrolled into the study are reported in Table 1. Data are given for both the entire cohort and for their categorization into lower and upper arm AVFs. Fifty-six patients bore a lower arm AVF and 30 an upper arm AVF (20 brachio-basilic and 10 brachio-cephalic). The Student's *t*-test for unpaired data showed a statistically significant difference among the three groups as far as CO, LLV, LLV_{AVF} and TPVR are concerned (Table 1). The Mann–Whitney *U* test showed a statistically significant difference among the three groups as far as dialysis duration, AVF vintage, Qa, CPR, AR and SVR are concerned (Table 1). Figure 1 illustrates the haemodynamic modifications of the CV system of HD patients associated with an AVF (Figure 1 is reproduced as a colour image in the Supplementary data). A third-order polynomial regression model best fitted the relationship between Qa and CO for the entire cohort of 86 patients ($y = 0.527x^3 - 2.224x^2 + 4.031x + 4.209$; $R^2 = 0.386$; $P < 0.0001$) and for both lower ($y = 0.447x^3 - 1.912x^2 + 3.286x + 3.913$; $R^2 = 0.392$; $P < 0.0001$) and upper arm AVFs ($y = 0.476x^3 - 2.002x^2 + 3.913x + 3.964$; $R^2 = 0.426$; $P < 0.0001$) (results not shown in any table or figure). Similarly, a third-order polynomial regression model best fitted the relationship between Qa and LLV for the entire cohort of 86 patients (Figure 2) and for both lower and upper arm AVFs (Figure 3).

Finally, LLV_{AVF} calculated as % of LLV rose with increasing Qa according to a quadratic polynomial regression model, but only in lower arm AVFs. On the contrary, no statistically significant relationship was found between the two parameters in upper arm AVFs (Figure 4), even if mean LLV_{AVF} was statistically significantly higher in upper arm AVFs (Table 1, $P < 0.0001$).

Discussion

The present study confirms our own previous data and recent literature data showing that the relationship between Qa and CO is not linear, but that a third-order polynomial regression model best fits this relationship with a curve consisting of initial plateau followed by a steep slope [8, 20–22]. The novelty of our study is that it shows for the first time that the relationship between Qa and LLV is complex and that a third-order polynomial regression model best fits this relationship (Figures 2 and 3). One could argue that the latter relationship is strictly related to the previous one. Actually, LLV is equal to $TPVR \cdot CO^2$ and TPVR is equal to MAP/CO; thus, substituting TPVR in the first equation, LLV is equal to MAP·CO. Then, it appears that MAP, which is an independent and actually measured parameter, plays a key role in the calculation of LLV and, consequently, in the relationship between Qa and LLV.

The lack of linearity in the relationships between Qa and CO and Qa and LLV, respectively (which one might expect if Qa is believed to drive CO), confirms the hypothesis of a sort of

Table 1. Demographic, clinical and haemodynamic data for the 86 patients enrolled into the study (data are reported for both the entire cohort and for their categorization into lower and upper arm AVFs)

	All ($n = 86$)	Lower arm ($n = 56$)	Upper arm ($n = 30$)	P
Age (years)	61.0 (11.0)	58.6 (9.4)	63.4 (11.9)	0.453[a]
Gender (males) (%)	53.8	57.2	50.4	0.142[b]
Diabetes mellitus (%)	15.6	15.5	15.7	0.876[b]
Dialysis duration (months)	59.6 (22.9)	65.0 (18.4)	54.2 (21.9)	<0.0001[c]
Haemoglobin (g/dL)	11.6 (1.3)	11.2 (1.7)	12.0 (2.1)	0.654[a]
AVF vintage (months)	74.4 (65.4)	79.8 (62.6)	69.0 (65.7)	<0.0001[c]
MAP (mmHg)	92.7 (13.9)	92.0 (15.1)	93.4 (12.4)	0.320[c]
Heart rate (beats/min)	72.7 (9.5)	71.2 (11.5)	74.2 (8.4)	0.540[c]
CO (L/min)	6.3 (1.3)	5.7 (1.0)	6.8 (1.0)	<0.0001[a]
Qa (L/min)	1.3 (0.6)	0.9 (0.3)	1.6 (0.4)	<0.0001[c]
LLV (watt)	1.3 (0.6)	1.0 (0.3)	1.6 (0.4)	<0.0001[a]
CPR	0.2 (0.3)	0.1 (0.1)	0.3 (0.1)	<0.0001[c]
LLV_{AVF} (% of LLV)	19.7 (3.1)	15.8 (3.2)	23.5 (4.0)	<0.0001[a]
TPVR (mmHg·min/L)	14.9 (3.2)	16.1 (4.2)	13.7 (3.2)	<0.0001[a]
AR (mmHg·min/L)	80.3 (24.6)	102.2 (21.8)	58.3 (15.9)	<0.0001[c]
SVR (mmHg·min/L)	18.6 (4.1)	19.2 (5.3)	17.9 (5.1)	<0.0001[c]

Continuous variables are expressed as mean (SD) while categorical data are expresssed as percentages.
[a]Student's *t*-test for unpaired data.
[b]χ^2 test.
[c]Mann–Whitney *U* test.

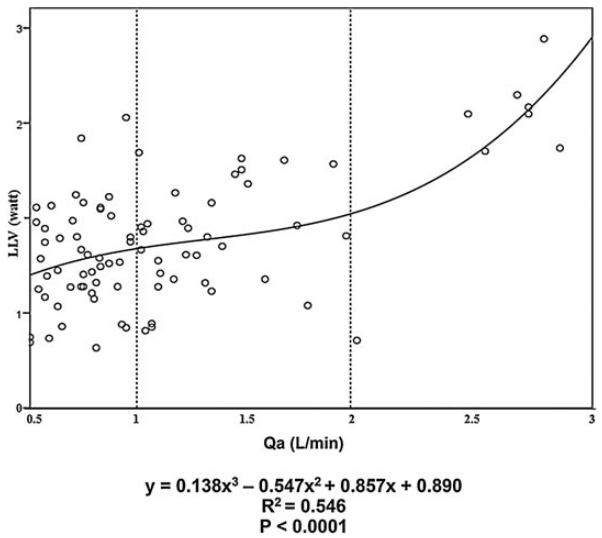

Fig. 2. A third-order polynomial regression model best fitted the relationships between Qa and LLV in the 86 patients.

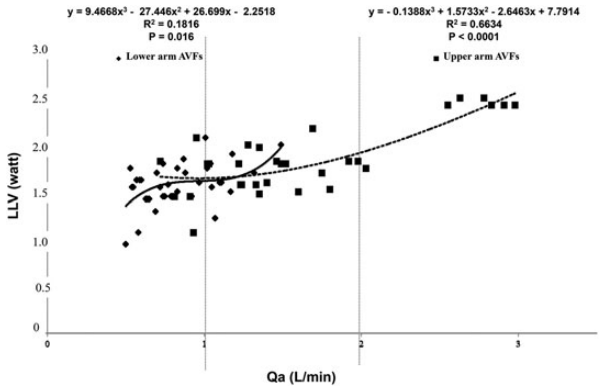

Fig. 3. A third-order polynomial regression model best fitted the relationships between Qa and LLV, respectively, in lower arm AVFs (filled diamond, continuous line = best fitted regression line) and upper arm AVFs (filled square, dotted line = best fitted regression line).

'myocardial functional reserve' and myocardial adaptation to the high-flow state, making the prevalence of symptomatic high-output heart failure much lower than anticipated for the given CO and LLV [20].

Our study quantifies for the second time in the literature the value of the LLV in HD patients and divides it into the part spent to run systemic circulation and the part consumed by the AVF. It substantially confirms the data published by Válek *et al.* [23]: an increase of Qa is associated with a rise of both total LLV and LLV_{AVF} (i.e. the percentage of LLV consumed by the AVF). The novelty of our study is that it shows for the first time the direct relationship between LLV_{AVF} and Qa according to a quadratic polynomial regression model, but only in lower arm AVFs. On the contrary, no stastistically significant association was found between the two parameters in upper arm AVFs, even if mean LLV_{AVF} was statistically significantly higher in upper arm AVFs. In other words, the relationship between Qa and LLV_{AVF} of upper arm AVFs is characterized by an LLV_{AVF} already higher than that of lower arm AVFs, but with no further increase with rising Qa. The LLV values obtained in our study are roughly similar to those reported by Felici *et al.* in a group of seven male healthy sailors [25].

The finding that upper arm AVFs are associated with an increased LLV compared with lower arm AVFs is not unexpected in that previous studies had shown that upper arm AVFs are associated with higher Qa and CO [8, 20, 26]. Even though it must be acknowledged that lower arm AVFs are usually positioned in a type of patient with a different phenotype from those who receive an upper arm AVF (among them, usually there are less diabetics, younger people with fewer vascular diseases and cardiac dysfunctions), the fact remains that such an association might favour the hypothesis of a causative role of high-flow AVFs in

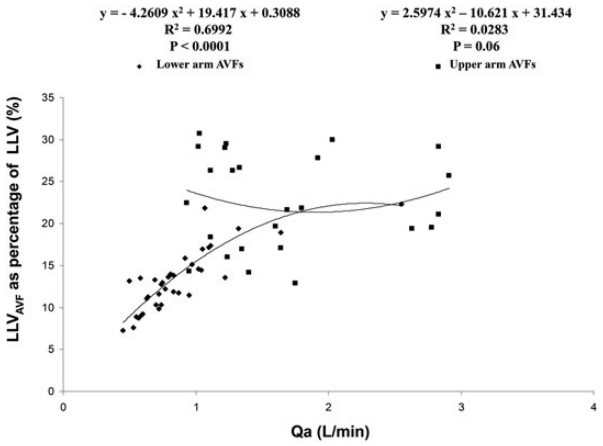

Fig. 4. A quadratic polynomial regression model best fitted the relationships between Qa and LLV_{AVF}, calculated as a percentage of the total load of the left ventricle in lower arm AVFs (filled diamond, continuous line = best fitted regression line). No stastistically significant relationship was found between the two parameters in upper arm AVFs (filled square, dotted line = best fitted regression line).

the pathogenesis of high-output heart failure [20]. Actually, Basile *et al.* clearly showed the high predictive power for high-output heart failure occurrence of Qa cut-off values ≥2.0 L/min [20]. Thus, the message deriving from our study is clear: the upper extremity AVFs should be placed as distal as possible, as also underlined by the recent KDOQI and EBPG guidelines [27, 28].

AR was statistically significantly lower in upper arm AVFs than in lower arm AVFs, thus confirming data obtained by van der Mark *et al.* [8]. This finding is actually not unexpected, if we take into account that the Poiseuille law states that the blood flow in any vessel, and therefore also Qa, is determined by the following relationship [29]

$$\mathrm{Qa} = \frac{\pi \Delta P r^4}{8\eta l} \tag{10}$$

where ΔP is the pressure difference between the extremities of the vessel, r the radius of the vessel, η the viscosity of the fluid and l the length of the vessel. Now, we know that AR is expressed by the ratio shown in equation (4), we can re-write this relationship in the following way

$$\mathrm{AR} = \frac{\mathrm{MAP} \cdot 8\eta l}{\pi \Delta P r^4} \tag{11}$$

It is clearly evident that, among all factors involved, r (at power 4) of a vessel plays the most important role in determining AR. Now, the brachial artery utilized for an upper arm AVF must necessarily have a higher r than the radial artery utilized for a lower arm AVF. Consequently, the AR of an upper arm AVF must be evidently lower than that of a forearm AVF.

Finally, Amerling *et al.* stated in a review article that AVF . . . undoubtedly contributes to excess CV mortality in HD patients and shortens life spans' [30]; furthermore, 'even relatively young and healthy patients will eventually develop CV complications, mostly congestive heart failure, due to the prolonged presence of an AVF' [30]. Basile and Lomonte [31] challenged these conclusions, by stating that:

- large studies show a graded mortality risk from both CV and infectious diseases depending on access type, with the highest risk associated with catheters, followed by AVGs and then AVFs [32–36];
- the presence of an AVF has an adverse effect on cardiac function, but its exact contribution to CV morbidity is not clear [17];
- it has long been known that a VA with an inappropriately high Qa may be the cause of high-output heart failure [9–16]. Even more paradoxically, there may be cardio-pulmonary benefits conferred by an AVF [37–41];
- thus, while emphasizing the real benefits of creating a native AVF, Basile and Lomonte strongly stressed the danger of attaining excessive Qa [31];
- the key word in the case of VA choice is 'eligibility' [42]. A 'patient first, not fistula first, but avoid a catheter if at all possible' approach might be the best [2].

In conclusion, our observational cross-sectional study describes statistically significant haemodynamic modifications of the CV system associated to an AVF. Our associative findings are very likely to entail a causative role; however, appropriately controlled longitudinal studies need to be performed in order to definitively assess the issue. Furthermore, our study shows for the first time that the relationship between Qa and LLV is complex and that a third-order polynomial regression model best fits this relationship. Moreover, a quadratic polynomial regression model best fits the relationship between LLV_{AVF} and Qa, but only in lower arm AVFs.

Supplementary data

Supplementary data are available online at http://ckj.oxfordjournals.org.

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Conflict of interest statement

None declared.

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