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ORIGINAL RESEARCH ARTICLE

The effect of high-flow arteriovenous fistulas on systemic haemodynamics and brain oxygenation

Jan Malik[1*†], Anna Valerianova[1†], Vladimir Tuka[1], Pavel Trachta[1], Vladimira Bednarova[2], Zdenka Hruskova[2], Marcela Slavikova[3], Mitchell H. Rosner[4] and Vladimir Tesar[2]

[1]*Third Department of Internal Medicine, General University Hospital, First Faculty of Medicine, Charles University, U Nemocnice 1, Prague, 128 08, Czech Republic;* [2]*Department of Nephrology, General University Hospital, First Faculty of Medicine, Charles University, Prague, Czech Republic;* [3]*Second Department of Surgery, General University Hospital, First Faculty of Medicine, Charles University, Prague, Czech Republic; and* [4]*Department of Medicine, University of Virginia Health System, Charlottesville, VA, USA*

Abstract

Aims High-flow arteriovenous fistula (AVF) for haemodialysis leads to profound haemodynamic changes and sometimes to heart failure (HF). Cardiac output (CO) is divided between the AVF and body tissues. The term effective CO (COef) represents the difference between CO and AVF flow volume (Qa) and better characterizes the altered haemodynamics that may result in organ hypoxia. We investigated the effects of Qa reduction on systemic haemodynamics and on brain oxygenation.

Methods and results This is a single-centre interventional study. Twenty-six patients on chronic haemodialysis with high Qa (>1500 mL/min) were indicated for surgical Qa reduction for HF symptoms and/or signs of structural heart disease on echocardiography. The included patients underwent three sets of examinations: at 4 months and then 2 days prior and 6 weeks post-surgical procedure. Clinical status, echocardiographical haemodynamic assessment, Qa, and brain oximetry were recorded. All parameters remained stable from selection to inclusion. After the procedure, Qa decreased from 3.0 ± 1.4 to 1.3 ± 0.5 L/min, $P < 0.00001$, CO from 7.8 ± 1.9 to 6.6 ± 1.5 L/min, $P = 0.0002$, but COef increased from 4.6 ± 1.4 to 5.3 ± 1.4 L/min, $P = 0.036$. Brain tissue oxygen saturation increased from 56 ± 11% to 60 ± 9%, $P = 0.001$.

Conclusions Qa reduction led to increased COef. This was explained by a decreased proportion of CO running through the AVF in patients with Qa > 2.0 L/min. These observations were mirrored by higher brain oxygenation and might explain HF symptoms and improved haemodynamics even in asymptomatic high Qa patients.

Keywords High-output heart failure; Arteriovenous fistula; Effective cardiac output; Brain oximetry

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**Correspondence to: Jan Malik, Third Department of Internal Medicine, General University Hospital, First Faculty of Medicine, Charles University, U Nemocnice 1, 128 08 Prague 2, Czech Republic. Tel: (+420)224962363; Fax: (+420)224962765. Email: jan.malik@vfn.cz*
†The first two authors contributed equally to the study.

Introduction

Heart failure (HF) is a common complication of end-stage renal disease (ESRD) patients treated by haemodialysis and a leading cause of their mortality. Practically all heart structures could be affected by the presence of ESRD, and the term 'uraemic cardiomyopathy' is sometimes used,[1] although adequately treated patients do not suffer uraemia. This is due to a complex of metabolic, endocrine, and haemodynamic changes typical for advanced chronic kidney disease. Haemodynamic changes include cyclical water retention and the presence of an arteriovenous fistula (AVF), created as a vascular access for haemodialysis. Surgically created AVFs are the most recommended haemodialysis vascular access because their use is associated with better outcomes than the use of dialysis catheters.[2] Surgical creation of an AVF leads to a decrease of systemic vascular resistance (afterload) and to increase in preload, which, in turn, leads to increased cardiac output (CO) at the cost of higher myocardial demands of blood supply.[3] Although there is no general agreement about the safe values of AVF flow volume (Qa), nor about the definition of high-flow AVF, there is little doubt that AVF flow should be considered too high if signs of HF develop. Some experts speak of high-flow AVF, when Qa exceeds 1.5–2.0 L/min even if there are no symptoms of HF.[4,5] Qa can increase due to remodelling, especially of the feeding

artery and arteriovenous anastomosis, even months or years after AVF creation. The haemodynamic effects of AVF could be easily understood by considering the AVF as a systemic shunt.[6] Therefore, part of the CO generated by the heart is used to feed the AVF and not the body's tissues and organs. The term 'effective CO' is used to better define haemodynamics in ESRD patients and is defined as the difference between the (total) CO and AVF flow volume.[5,6] Although AVF increases CO, less is known about the effect of high-flow AVF on systemic haemodynamics and especially on COef. High-flow AVF could be responsible for high-output HF (HOHF), a somewhat counterintuitive HF phenotype, characterized by HF symptoms, increased filling pressures and a cardiac index (CI) $>$ 3.9 L/min/m^2.[7] Moreover, very high values of CO could lead to the development of pulmonary hypertension, when the pulmonary arteries are not able to further dilate. The determination of the link between HOHF and high-flow AVF is based mostly on the experience with AVF closure.[8] However, this cannot be generally recommended for ESRD patients on haemodialysis.

Both HF and ESRD are associated with a number of functional and structural brain changes.[9] Inadequate brain oxygenation due to decreased CO, and/or the narrowing of cerebral arteries, is probably one of the mechanisms responsible for cognitive decline. Recently, brain oxygenation can be measured non-invasively by near-infrared spectroscopy—by estimation of regional mixed blood saturation (rSO_2) in the frontal lobe. Cerebral oximetry was analysed in haemodialysis ESRD patients (without HF), and the mean rSO_2 values reached 50%, while in controls, it was 68.5%.[10] Lower rSO_2 values were linked to cognitive decline in haemodialysis patients.[11,12] Generally, structural brain changes and cognitive decline are typical for both HF and ESRD populations. Moreover, our recent study documented an increase of brain oxygenation during a short-term manual compression of AVF.[13]

We hypothesized that AVF flow reduction would result in improved brain oxygenation due to the improved haemodynamics and higher effective CO. This study was aimed at describing haemodynamic changes after AVF high-flow reduction and at investigating the effects of AVF flow reduction on brain oxygenation.

Methods

Selection and description of participants

We conducted a prospective single-centre interventional study. The study was approved by the institutional ethics committee. All included patients signed the informed consent and were included between March 2018 and January 2020. The study conforms to the principles outlined in the Declaration of Helsinki.

We selected ESRD patients over 18 years of age with a high-flow AVF (AVF flow volume $>$1500 mL/min) having at least one of the following: HF (New York Heart Association Class II or higher); and/or structural heart changes on echocardiography defined as left ventricular dilatation (left ventricular end-diastolic indexed volume $>$70 mL/m^2), systolic dysfunction [ejection fraction (EF) $<$ 50%] or hypertrophy, pulmonary hypertension (estimated pulmonary artery systolic pressure $>$35 mmHg). The selected patients were re-evaluated before their planned flow-reducing procedure (inclusion visit) and indicated to undergo surgical AVF flow reduction (banding, de novo anastomosis or aneurysmorrhaphy) and reviewed 6 weeks thereafter (follow-up visit). If the patients had signs of water overload at the inclusion visit, dry weight correction was recommended, and the patient did not continue in this study. The patients were referred to our Vascular Access Centre from various haemodialysis units because of HF symptoms or when the AVF looked too 'big'.

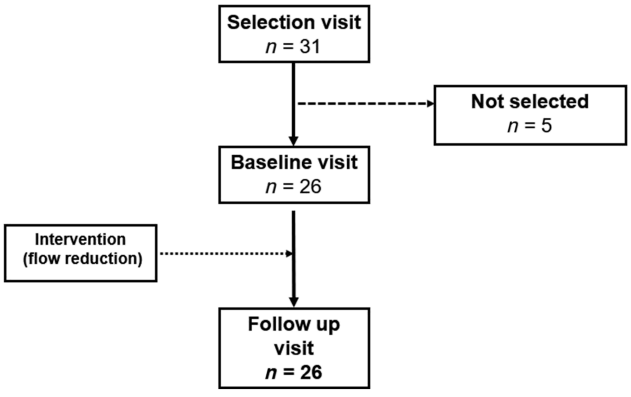
Exclusion criteria were unstable clinical condition (acute infection, myocardial infarction, or stroke within last 3 months prior to inclusion), overt dementia, inadequate acoustic window for echocardiography, or significant valvular disease. See *Figure 1* for the study design.

Examinations were performed at the same time interval since their last haemodialysis session to exclude the impact of hydration status. There were no changes in dry weight settings or medications between the examinations.

Technical information

Echocardiography and AVF ultrasonography were recorded using a Vivid E9 device (GE Healthcare, USA) and stored for further analysis. The latter was done off-line by one senior examiner using the EchoPAC Software (GE Healthcare, USA).

Figure 1 Study design.



Echocardiographical haemodynamic assessment was performed according to current international guidelines[14] and included the analysis of CO by the left ventricular outflow tract cross-sectional area and velocity time interval, the estimation of systolic pulmonary artery pressure (maximal pressure gradient of tricuspid regurgitation plus estimated central venous pressure), and left ventricular ejection fraction (multi-disk method). The same values of the left ventricular outflow tract diameter were used in all examinations. AVF flow volume (Qa) was measured by ultrasonography in the brachial artery, as reported elsewhere.[13] Effective CO was calculated as the difference between the measured CO and AVF flow volume. Furthermore, the percentage of the CO running through the AVF was also calculated. Obtained data were used for estimation of the access resistance (access flow volume divided by the difference between mean arterial pressure and estimated central venous pressure), systemic vascular resistance (with the use of the effective CO) and total vascular resistance (with the use of total CO). All resistance data were expressed in Wood units. Basic laboratory data (full blood count and biochemical analysis) were analysed at both sessions.

The studied group of patients was divided into two subgroups according to the presence or absence of HF symptoms. Additionally, we recorded HF phenotype [(HF with reduced EF $<$ 40% (HFrEF), HF with mid-range EF 40–50% (HFrEF), HF with preserved EF $>$ 50% (HFpEF)] as recommended by the guidelines.[6] Subjects with preserved EF, but with CI $>$ 3.9 L/min/m^2 were classified as having HOHF according to previous studies.[7,15]

Basic laboratory data included blood haemoglobin, albumin, and total protein.

Cerebral tissue saturation (rSO_2) was measured using the INVOS 5100C Oximetry system (Medtronic, Essex, UK). The INVOS probe was placed over the dominant frontal lobe and the value was recorded after 10 min of rest for at least 2 min; the mean value was used for further analysis. The stability of rSO_2 was tested in our previous unpublished study that included a cohort of 40 clinically stable haemodialysis patients, who were examined twice within 2 weeks. The resulting intraclass coefficient of variation[16] was 0.892.

We screened 31 patients and included 26 of them aged 59 ± 14 years (7 female), dialysis vintage 6.3 ± 4.9 years, all of them of Caucasian ethnicity. The aetiology of ESRD was hypertension (3 pts), glomerulopathy (3 pts), IgA nephropathy (3 pts), diabetes mellitus (3 pts), polycystic kidney disease (3 pts), other inherited syndromes (3 pts), tubulointerstitial nephritis (3 pts), obstructive nephropathy (3pts), and multiple myeloma (2 pts). Five patients were excluded due to lung disease being their leading cause of shortness of breath (n = 1), dementia (n = 1) or inadequate acoustic window for echocardiography (n = 3).

Heart failure phenotypes in 14 symptomatic patients were as follows: HOHF eight patients, HFpEF three patients, HFmrEF one patient and HFrEF two patients. In 12 asymptomatic patients, who were not diagnosed as having HF according to the guidelines,[6] left ventricular EF was $>$50% in 10 subjects (of them, eight with CI $>$ 3.9 L/min/m), and two patients had EF 40–50%.

Statistics

Statistical analysis was performed using the STATISTICA software (StatSoft, USA). The results of continuous variables are presented as mean ± SD; the percentages are reported for categorical variables. The results from the measurements [selection vs. inclusion (pre-procedural) visits and inclusion vs. follow-up] were compared by a paired t test and $P < 0.05$ was considered significant. The relations between regional cerebral tissue oxygenation and echocardiographic parameters were analysed using the Pearson correlation analysis.

Results

The baseline characteristics of our 26 included patients are noted in the 'Materials and Method' section and shown in detail in *Table 1*. During the observation period, there was no significant change in included haemodynamic data.

After AVF flow reduction there was a significant decrease in CO, CI, estimated pulmonary artery systolic pressure, and also in the percentage of CO running through the AVF, while there was an increase in COef, SVR, and access resistance—refer to *Table 1* for details. The change of CO, COef and percentage of CO running through AVF were interrelated—although the total CO decreased, the effective CO increased due to a lower percentage of CO running through the AVF (*Figure 1*). Cerebral rSO_2 increased after the AVF flow reducing surgery (from 56 ± 11% to 60 ± 9%, P = 0.001). However, this rSO_2 increase did not have a significant relationship to any of the haemodynamic data.

Only 54% (n = 14) of the included patients had HF symptoms and thus a real diagnosis of HF; in the other half, surgical AVF flow reduction was indicated due to the pathological findings on echocardiography (defined earlier). In patients indicated for symptomatic HF, New York Heart Association classification improved (from 2.0 ± 1.0 to 1.3 ± 0.6, P = 0.00005). Asymptomatic patients had the following echocardiographic abnormalities at inclusion: diastolic dysfunction 75%, pulmonary hypertension 67%, left ventricular hypertrophy 67%, left ventricular dilatation 42%, and decreased EF 17%. At baseline, asymptomatic patients significantly differed from symptomatic ones by lower pulmonary artery pressure and by higher systemic mean arterial pressure, refer to *Table 2* for details.

Table 1 Haemodynamic and clinical changes after AVF flow reduction

Parameter	Selection	Baseline	Follow-up	*P* value baseline vs. follow-up
Serum albumin (g/L)	ND	38 ± 6	39 ± 5	0.27
Total blood protein (g/L)	ND	67 ± 9	69 ± 8	0.39
Blood haemoglobin (g/L)	ND	118 ± 15	117 ± 15	0.94
Mean arterial pressure (mmHg)	110 ± 11	104 ± 17	99 ± 16	0.23
AVF flow (L/min)	3.1 ± 0.6	3.0 ± 1.4	1.3 ± 0.5	0.000001
Cardiac output (L/min)	8.2 ± 2.6	7.8 ± 1.9	6.6 ± 1.5	0.0002
Cardiac index (L/min/m^2)	4.4 ± 1.0	4.1 ± 0.9	3.5 ± 0.8	0.0004
Effective cardiac output (L/min)	5.1 ± 1.5	4.6 ± 1.4	5.3 ± 1.4	0.04
Percentage of CO through AVF	37 ± 13	39 ± 12	21 ± 9	0.000002
LV ejection fraction (%)	58 ± 11	57 ± 12	61 ± 11	0.07
Pulmonary artery systolic pressure (mmHg)	49 ± 14	47 ± 14	36 ± 11	0.0002
SVR (Wood units)	20.0 ± 4.2	21.9 ± 7.7	18.5 ± 5.4	0.03
TVR (Wood units)	12.8 ± 3.4	12.9 ± 3.7	14.4 ± 3.5	0.08
AVF resistance (Wood units)	44 ± 22	36 ± 14	101 ± 128	0.03

AVF, arteriovenous fistula; LA, left atrium; LV, left ventricle; ND, not done; SVR, systemic vascular resistance (without AVF); TVR, total vascular resistance. Effective cardiac output is the difference of cardiac output and AVF flow volume. No differences between selection and baseline visits were statistically significant.

Table 2 Differences between symptomatic and asymptomatic patients

	Symptomatic HF	Asymptomatic	*P* value of the difference
Serum albumin (g/L)	39.0 ± 5.6	38.2 ± 6.4	0.75
Total blood protein (g/L)	69.1 ± 8.8	64.9 ± 9.4	0.29
Blood haemoglobin (g/L)	116 ± 13	121 ± 12	0.31
Mean arterial pressure (mmHg)	9 7 ± 16	111 ± 16	0.048
Brain oxygenation %	53 ± 6	59 ± 13	0.14
AVF flow (L/min)	3.0 ± 1.3	3.0 ± 1.6	0.91
Cardiac output (L/min)	7.5 ± 2.4	7.9 ± 1.6	0.69
Cardiac index (L/min/m^2)	4.0 ± 1.1	4.1 ± 0.9	0.66
Effective cardiac output (L/min)	4.6 ± 1.7	4.7 ± 1.2	0.83
Percentage of CO through AVF	40 ± 12	40 ± 13	0.91
LV ejection fraction (%)	57 ± 13	57 ± 10	0.99
Pulmonary artery systolic pressure (mmHg)	52 ± 14	40 ± 10	0.03
SVR (Wood units)	23 ± 9	21 ± 4	0.44
TVR (Wood units)	12 ± 4	14 ± 4	0.41
AVF resistance (Wood units)	34 ± 12	39 ± 16	0.40

AVF, arteriovenous fistula; CO, cardiac output; LV, left ventricle; SVR, systemic vascular resistance, TVR, total vascular resistance.

Discussion

Our study showed that the surgical reduction of a high-flow AVF increases the effective CO, that is, perfusion of the body organs and tissues. This somewhat counterintuitive finding can be explained by a higher percentage of total CO running through AVF in high-flow fistulas and was confirmed by the increase in brain oxygenation. This observation can also explain at least some 'forward' HF symptoms, such as increased fatigue and dizziness in subjects with HOHF. Similar favourable haemodynamic effects were observed in patients with HF symptoms as well as in asymptomatic ones.

Heart failure

In our group, only 54% of patients fulfilled the diagnosis of HF (i.e. symptoms + structural heart diseases on echocardiography). The remaining 46% of asymptomatic patients had echocardiographic abnormalities known as HF precursors according to the guidelines[14] or pulmonary hypertension. None of them were evidently frail nor did they suffer from any limiting orthopaedic problems. Symptomatic patients differed from asymptomatic ones only by higher pulmonary arterial pressure and by lower systemic arterial pressure. Although HF is very frequent in haemodialysis patients, its diagnosis is tricky, because the symptoms may be caused or mimicked by frailty or pure water overload (due to inadequate setting of the dry weight or lower fluid compliance). ESRD patients could suffer from all HF phenotypes. However, their classification only with regard to EF would be misleading: 11 of 14 symptomatic patients in this study would be classified as HFpEF, but in fact, 8 of them suffered instead from HOHF. The latter phenotype, is not, however, mentioned in the recent guidelines,[14] although it has different haemodynamics and also a better prognosis if the aetiology is reversed.[15] In non-HOHF patients, our study showed HFpEF to be the prevailing HF phenotype, a finding matched in other studies.[17] The explanation lies in the high prevalence of left ventricular hypertrophy on ESRD patients. The Acute Dialysis

Quality Initiative XI workgroup proposed recently a new definition of HF in ESRD patients.[18] These include three elements: (1) echocardiographic evidence of structural or functional heart abnormalities; (2) shortness of breath occurring in the absence of pulmonary disease; and (3) response of congestive symptoms to ultrafiltration. However, this classification did not consider the role of the AVF on HF development nor the level of pulmonary hypertension.

Half of the patients were free of HF symptoms, and the indication of AVF flow reduction was based solely on structural heart changes. This makes our findings clinically important, because asymptomatic high-flow AVFs are not referred for surgical reduction in many centres. Interestingly, symptomatic patients differed from asymptomatic ones only by higher pulmonary artery pressure and lower mean systemic arterial pressure.

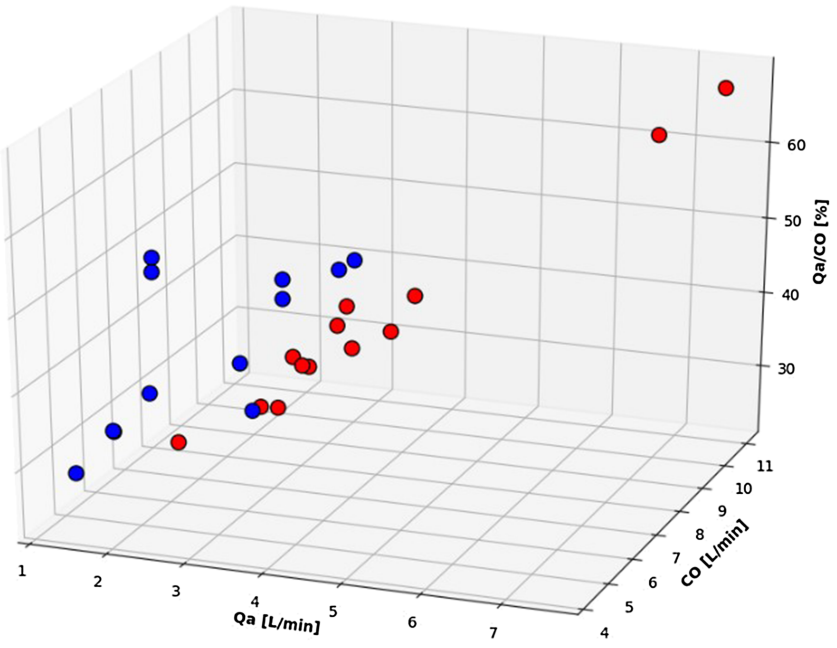
Haemodynamic changes

The relation between AVF flow volume and CO is not linear. Basile *et al*. showed that it is better characterized by the third-order polynomial regression model and the function is steeper if AVF flow is higher than 2000 mL/min.[5] Similar observations were made in our study—prior to surgery, AVF flow volume represented as much as 38% of CO; after the surgery this was 'only' 20%, refer also to *Figure 2*. Thus, one net effect of high-flow AVF is a reduced effective CO; the other is a high cardio-pulmonary recirculation due to an increase in the total CO. After AVF flow reduction, there was a significant increase of the systemic vascular resistance. Low systemic vascular resistance was linked to significantly increased mortality in the largest study of HOHF patients of various aetiologies.[15]

Pulmonary circulation and right ventricle

Pulmonary 'over-circulation' due to CO increase has been observed also in animal models, where the creation of an aortocaval fistula led to the development of pulmonary hypertension accompanied by a significant decrease in pulmonary vascular resistance, but an increase in end-diastolic right ventricular pressure and work index.[19] Our study shows that hyperkinetic pulmonary hypertension is also seen in humans as a consequence of high-flow AVF. Reddy *et al*.[20] documented right ventricular dilatation after AVF creation (which even predicted mortality), but no increase in pulmonary artery pressure. However, Reddy *et al*. examined the patients after a median of 2.5 years, and Qa was not presented. Pulmonary hypertension affects about 50% of ESRD patients and is associated with a higher mortality.[21] Moreover, pulmonary hypertension is usually symptomless in this frequently frail population. Based on the results of this study,

Figure 2 Relation between cardiac output, arteriovenous fistula flow, and the percentage of cardiac output running through the fistula. The interrelationship between fistula flow (Qa), cardiac output (CO), and the percentage of cardiac output running through the fistula instead of feeding tissues is depicted. Note that Qa increase above >2.0 L/min is associated with steeper rise of CO due to increasing Qa/CO ratio. Hence, organ perfusion decreases in patients with Qa > 2.0 L/min. Calculation of only CO instead of effective CO leads to incorrect feeling of organ hyperperfusion in the routine care. Red dots represent patients that fulfilled the criteria of high-output heart failure.



we believe that preventing high-flow AVF could decrease the frequency of pulmonary hypertension in ESRD patients.

Brain hypoxia

Regional or global brain ischemia is a frequent complication of ESRD.[12] The brain is evidently not able to ensure adequate oxygenation by autoregulation. Various mechanisms have been hypothesized, including stenoses of the brain arteries, anaemia, metabolic changes, and HF.[22] Haemodialysis patients suffering from HF had lower and unstable rSO_2 values during haemodialysis, but the values before and after this procedure did not differ.[23] Therefore, it seems probable that rSO_2 values remain low during the time periods between haemodialysis, which could contribute to the worsening of cognitive functions as the brain critically depends upon an adequate oxygen supply. The increase of rSO_2 after the AVF flow reduction in this study and also during a short manual compression[13] could probably be attributed to improved haemodynamics, and in particular to the increased effective CO. In other words, the low values of brain rSO_2 in our patients with high-flow AVF could be explained by a 'systemic steal' as suggested by Amerling *et al*.[6] However, the relation of rSO_2 change to the change of any haemodynamic values was not shown to be significant. Similarly, the detrimental effect of AVF flow on a transplanted kidney has been documented in haemodialysis patients.[24,25] Renal arteries (both native or transplanted) have a physiologically low-resistant flow pattern like brain arteries and AVF. Thus, a flow competition of several low-resistant parts of the arterial tree could represent another involved mechanism. In this study, the increase in brain oxygenation was not numerically profound. However, it should be pointed out that both studies that compared cognitive function and rSO_2 found a significant linear relation between these two variables.[11,12]

Limitations

The main limitations that affected this study include limitations of non-invasive haemodynamic measurements and of non-invasive cerebral oximetry. However, repetitive right-heart catheterization could not be ethically approved of nowadays. Although the number of participants is relatively low in this study, it is one of the largest in this specific situation. The procedural variability of CO measurement was minimized by using the same left ventricular outflow tract diameter on all occasions. One study reported that non-invasive brain oximetry could underestimate brain oximetry when compared with haemoglobin saturation by oxygen in samples from jugular catheters.[26] However, the presence of an AVF could have influenced the results of that study when the catheter tips were in the right atrium.

Brain saturation is only a single measure that does not fully explain functional or structural brain disturbances associated with high-flow AVF. Another, more complex study is warranted.

This is a short-time study, so we cannot exclude recurrence of high Qa after longer times.[27] Regular AVF flow volume measurement even after the procedure is therefore recommended.

Declaration of Interest

Jan Malik declares that he has no conflict of interest.

Anna Valerianova declares that she has no conflict of interest.

Vladimir Tuka declares that he has no conflict of interest.

Pavel Trachta declares that he has no conflict of interest.

Vladimira Bednarova declares that she has no conflict of interest.

Zdenka Hruskova declares that she has no conflict of interest.

Marcela Slavikova declares that she has no conflict of interest.

Mitchell H. Rosner declares that he has no conflict of interest.

Vladimir Tesar declares that he has no conflict of interest.

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References

1. Alhaj E, Alhaj N, Tahman I, Niazi TO, Berkowitz R, Klapholz M. Uremic cardiomyopathy: an underdiagnosed disease. *Congest Heart Fail* 2013; **19**: E40–E45.
2. Yeh LM, Chiu SY, Lai PC. The impact of vascular access types on hemodialysis patient long-term survival. *Sci Rep* 2019; **9**: 10708.
3. Savage MT, Ferro CJ, Sassano A, Tomson CRV. The impact of arteriovenous fistula formation on central hemodynamic pressures in chronic renal failure patients: a prospective study. *Am J Kidney Dis* 2002; **40**: 753–759.
4. Malik J. Heart disease in chronic kidney disease—review of the mechanisms and the role of dialysis access. *J Vasc Access* 2018; **19**: 3–11.

5. Basile C, Lomonte C. The complex relationship among arteriovenous access, heart, and circulation. *Semin Dial* 2018; **31**: 15–20.
6. Amerling R, Ronco C, Kuhlmann M, Winchester JF. Arteriovenous fistula toxicity. *Blood Purif* 2011; **31**: 113–120.
7. Mehta PA, Dubrey SW. High output heart failure. *QJM* 2009; **102**: 235–241.
8. Rao NN, Stokes MB, Rajwani A, Ullah S, Williams K, King D, Macaulay E, Russell CH, Olakkengil S, Carroll RP, Faull RJ, Teo KSL, McDonald SP, Worthley MI, Coates PT. Effects of arteriovenous fistula ligation on cardiac structure and function in kidney transplant recipients. *Circulation* 2019; **139**: 2809–2818.
9. Michna M, Kovarova L, Valerianova A, Malikova H, Weichet J, Malik J. Review of the structural and functional brain changes associated with chronic kidney disease. *Physiol Res* 2020; **69**: 1013–1028.
10. Malik J, Kudlicka J, Lachmanva J, Valerianova A, Rocinova K, Bartkova M, Tesar V. Tissue ischemia worsens during hemodialysis in end-stage renal disease patients. *J Vasc Access* 2017; **18**: 47–51.
11. Kovarova L, Valerianova A, Jmentova T, Lachmanova J, Hladinova Z, Malik J. Low cerebral oxygenation is associated with cognitive impairment in chronic hemodialysis patients. *Nephron* 2018; **139**: 113–119.
12. Miyazawa H, Ookawara IK, Ueda Y, Yanai K, Ishii H, Mutsuyoshi Y, Kitano T, Shindo M, Aomatsu A, Hirai K, Hoshino T, Morishita Y. Association of cerebral oxygenation with estimated glomerular filtration rate and cognitive function in chronic kidney disease patients without dialysis therapy. *PLoS One* 2018; **13**: e0199366.
13. Kovarova L, Valerianova A, Michna M, Malik J. Short-term manual compression of hemodialysis fistula leads to a rise in cerebral oxygenation. *J Vasc Access* Published Online First: 3 June 2020.
14. Ponikowski P, Voors SA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur J Heart Fail* 2016; **18**: 891–975.
15. Reddy YN, Melenovsky V, Redfield MM, Nishimura RA, Borlaug BA. High-output heart failure: a 15-year experience. *J Am Coll Cardiol* 2016; **68**: 473–482.
16. Sanchez MM, Binkowitz BS. Guidelines for measurement validation in clinical trial design. *J Biopharm Stat* 1999; **9**: 417–438.
17. Antlanger M, Aschauer S, Kopecky C, Hecking M, Kovarik JJ, Werzowa J, Mascherbauer J, Genser B, Saemann MD, Bonderman D. Heart failure with preserved and reduced ejection fraction in hemodialysis patients: prevalence, disease prediction and prognosis. *Kidney Blood Press Res* 2017; **42**: 165–176.
18. Chawla LS, Herzog CA, Costanzo MR, Tumlin J, Kellum JA, McCullough PA, Ronco C. Proposal for a functional classification system of heart failure in patients with end-stage renal disease: proceedings of the Acute Dialysis Quality Initiative (ADQI) XI Workgroup. *J Am Coll Cardiol* 2014; **63**: 1246–1252.
19. Modesti PA, Vanni S, Bertolozzi I, Cecioni I, Lumachi C, Perna AM, Boddi M, Gensini GF. Different growth factor activation in the right and left ventricles in experimental volume overload. *Hypertension* 2003; **43**: 101–108.
20. Reddy YNV, Obokata M, Dean PG, Melenovsky V, Nath KA, Borlaug BA. Long-term cardiovascular changes following creation of arteriovenous fistula in patients with end stage renal disease. *Eur Heart J* 2017; **38**: 1913–1923.
21. Bolignano D, Rastelli S, Agarwall R, Fliser D, Massy Z, Ortiz A, Wiecek A, Martinez-Castelao A, Covic A, Goldsmith D, Suleymanlar G, Lindholm B, Parati G, Sicari R, Mallamaci F, London G, Zoccali C. Pulmonary hypertension in CKD. *Am J Kidney Dis* 2013; **61**: 612–622.
22. McIntyre CW, Crowley L. Dying to feel better: the central role of dialysis-induced tissue hypoxia. *Clin J Am Soc Nephrol* 2016; **11**: 549–551.
23. Valerianova A, Lachamova J, Kovarova L, Kmentova T, Bartkova M, Malik J. Factors responsible for cerebral hypoxia in hemodialysis population. *Physiol Res* 2019; **68**: 651–658.
24. Ito K, Ookawara S, Ueda Y, Goto S, Miyazawa H, Yamada H, Kitano T, Shindo M, Kaku Y, Hirai K, Yoshida M, Hoshino T, Nabata A, Mori H, Yashida I, Kakei M, Tabein K. Factors affecting cerebral oxygenation in hemodialysis patients: cerebral oxygenation associates with pH, hemodialysis duration, serum albumin concentration, and diabetes mellitus. *PLoS One* 2015; **10**: e0117474.
25. Harrison LE, Selby NM, McIntyre CW. Central venous oxygen saturation: a potential new marker for circulatory stress in haemodialysis patients? *Nephron Clin Pract* 2014; **128**: 57–60.
26. Matsukawa S, Kai S, Mizota T. Near-infrared spectroscopy underestimates cerebral oxygenation in hemodialysis patients. *J Anesth* 2019; **33**: 478–481.
27. Vaes RHD, van Loon M, Vaes SMM, Cuypers P, Tordoir JH, Scheltinga MR. One-year efficacy of the RUDI technique for flow reduction in high-flow autologous brachial artery-based hemodialysis vascular access. *J Vasc Access* 2015; **16**: S96–S101.