Pro: The arteriovenous fistula is a blessing of God

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Introduction

Life-sustaining haemodialysis (HD) requires durable vascular access (VA) to the circulatory system. The ideal permanent VA must provide longevity of use with minimal complication rate and supply high enough blood flow to deliver the prescribed dialysis dosage [1]. While evidence from randomized controlled trials is lacking, there is a broad consensus that the VA type not only contributes to patient morbidity but also may contribute independently to patient mortality [2–6]. The native arteriovenous fistula (AVF) is considered the best access to initiate patients on HD because of its longer survival and lower complication rates as compared with other forms of VA, such as the synthetic arteriovenous grafts and the central venous catheters (CVCs) [2–6]. Large studies show a graded mortality risk from both cardiovascular (CV) and infectious diseases depending on access type, with the highest risk associated with catheters, followed by grafts and then AVFs [2–6].

The major cause of death in HD patients is a CV event. More than 50% of subjects treated by chronic HD die from CV diseases [7]. The presence of an AVF has an adverse effect on cardiac function, but its exact contribution to CV morbidity is not clear.

Heart failure (HF) is frequently associated with a reduction in glomerular filtration rate (GFR). The prevalence of moderate to severe kidney impairment (defined as a GFR <60 mL/min/1.73m²) is ∼30–60% in patients affected by HF [8, 9]. The following observations are illustrative: (i) in 80 000 hospitalized and non-hospitalized patients affected by HF, moderate to severe kidney impairment (defined as an estimated GFR <53 mL/min, a serum creatinine ≥1.5 mg/dL) has been described in 29% of patients [8]; (ii) in the Acute Decompensated Heart Failure National Registry database, ∼30% of over 100 000 patients affected by HF requiring hospitalization had a diagnosis of chronic kidney disease (defined as a serum creatinine >2.0 mg/dL) [9].

Congestive heart failure (CHF) is present in more than one-third of new dialysis patients [10] with an incidence of 71/1000 person-years. This figure is substantially greater than the incidence of acute coronary syndromes in end-stage renal disease (ESRD) (29/1000 person-years in US Renal Data System Morbidity and Mortality Study Wave 2) [11]. CHF in ESRD patients differs from CHF states in subjects with preserved renal function by several factors. Interdialysis volume overload and VA blood flow (Q̇va) are specific only for ESRD. Therefore, HD contributes per se to the development of CHF.

The opening of an AVF

AVF is a left to right extracardiac shunt. Cardiac output (CO) increases greatly and immediately on opening an AVF in experimental models. This increase in CO is achieved by means of a reduction in peripheral resistance, an increase in sympathetic nervous system activity (increasing contractility) and an increase in stroke volume and heart rate [12, 13].

The presence of an AVF lowers systemic vascular resistance, resulting in an increase in stroke volume and CO in order to maintain blood pressure [14]. Circumferential wall stress, calculated with the same value of mean arterial pressure (96 ± 14 mmHg) on the radial artery feeding the AVF and on the contralateral radial artery taken as a control, is significantly increased on the AVF side. A 6-fold increase in mean Q̇a is observed on the AVF side compared with the contralateral side [15]. In men, we have very few prospective data about the impact on the heart of the opening of an AVF. A prospective short-term echocardiographic study was performed in order to assess the influence that the creation of an AVF exerted on cardiac function: a significant elevation in left ventricular (LV) end-diastolic diameter (+4%), fractional shortening (+8%) and CO (+15%) occurred when comparing data obtained immediately before and 13 days after the creation of an AVF [16]. Furthermore, in a study of 12 pre-dialysis patients, LV mass index increased by 5.1 g/m² at 1 month and 8.7 g/m² at 3 months post-AVF creation [17].

The effects on myocardium, due essentially to the volume overload, translate into a remodelling of the
cardiac muscle which is characterized by the four-chamber enlargement and by the addition of new sarcomeres in series. Thus, an eccentric LV hypertrophy (LVH) is realized, which must be distinguished from the concentric LVH in which the addition of the new sarcomeres is parallel and the pathogenetic mechanism is a pressure overload. In both cases, an increase in LV muscle mass occurs with normal relative wall thickness in eccentric LVH [18]. Several studies showed regression of LVH following AVF closure in renal transplant patients [19, 20]. However, whether this decrease in volume is caused either by restoration of normal fluid balance or removal of the AVF per se is unknown. There is only one prospective study of the long-term changes of AVF closure on cardiac functional and structural findings in HD patients [21]. This 6-month observational study showed several echocardiographic modifications including a significant improvement in LV ejection fraction, a significant decrease in LV mass and LV mass index and a more favourable shift of cardiac geometry towards normality [21].

Pulmonary hypertension (PHT) is an elevation of pulmonary arterial pressure that can be the result of heart, lung or systemic disorders. PHT is defined as a sustained elevation of pulmonary arterial pressure to >25 mmHg at rest or to >30 mmHg with exercise. Recently, a 40–50% incidence of PHT has been detected by Doppler echocardiography in patients starting HD treatment via an arteriovenous access [22]. It is suggested that HD patients have inadequate pulmonary vasodilatation in response to the increased flows caused by the AVF, possibly due to suboptimal production of nitric oxide [23]. Furthermore, the partial restoration of normal pulmonary arterial pressure and CO in HD patients undergoing either temporal arteriovenous shunt closure or successful transplantation indicates that excessive pulmonary blood flow is involved in the pathogenesis of the disease [23]. However, the existing evidence does not clearly support the recently proposed policy of not creating an AVF in patients with an increased risk for development of PHT: in fact, pulmonary arterial pressure did not correlate with either the Qs or longevity of AVFs in a prospective study in 20 HD patients [24].

**High-flow rate AVFs**

Currently, there is no definition of when Qs is too high. The concept of using the ratio Qs/CO (cardiopulmonary recirculation—CPR) has been put forth by Pandeya and Lindsay in their study of stable long-term HD patients. They found that the average Qs was 1.6 L/min and the average CO was 7.2 L/min, thus describing an average CPR of 22% [25]. The Vascular Access Society guidelines define an AVF with a high Qs as that having a Qs of 1.0–1.5 L/min and a CPR >20% [26]. Basile et al. [27] and van den Mark et al. [28] showed that a third-order polynomial regression model best fitted the relationship between Qs and CO. In addition, Basile et al. showed in a prospective study on 96 HD patients that CO did not vary significantly for Qs values ranging from 0.95 to 2.2 L/min. In other words, the increase in Qs was not accompanied by a parallel increase of CO [27]. The causes of this phenomenon are not known, but one can hypothesize a sort of myocardial functional reserve and, then, of myocardial adaptation, capable of sustaining increases of Qs in the long-term without the precipitation of HF. There are no published prospective studies looking at the changes in LV end-diastolic volume or LV mass in patients over extended time periods prior to dialysis or on dialysis. Unfortunately, the only way to determine if AVF creation produces LVH in HD patients is with a prospective randomized study comparing a CVC with an AVF and examining the serial changes in LV dimensions and thickness. Due to the increased morbidity and mortality associated with catheters, this is unlikely to be designed [29].

AVF use is associated with lower CV mortality when compared to CVCs [2, 3, 6]: a recent analysis of the US Renal Data System Clinical Performance Measures data comprising 4854 incident patients showed that AVF use was strongly associated with lower all-cause and CV mortality. After adjustment for covariates, AVF use 90 days after the start of dialysis remained significantly associated with lower CV mortality (hazard ratio 0.69, P = 0.0004) compared with catheter use. This advantage was persistent even after 4 years and was independent of the effect of other known risk factors [2]. These findings suggest that AV type influences cause-specific mortality beyond that of infection and support existing guidelines recommending the use of an AVF early in the course of ESRD therapy. Many possible explanations exist for the association between the use of an AVF and decreased risk of CV-related death. These may include greater delivered dose of dialysis and better Qs among patients with AVF, reduced risk of infection and lower levels of inflammatory mediators. It may be that CVCs, being associated with more infection and inflammation, could contribute to worsening the CV disease or, alternatively, that those provided with catheters may not be able to mature an AVF due to poor vascular and cardiac status [2]. Furthermore, the US Renal Data System Morbidity and Mortality Study Wave 2 performed on 5507 prevalent HD patients had already shown that deaths caused by cardiac causes were higher in CVCs than AVFs for both diabetic and non-diabetic patients [3].

Even more paradoxically, there may be cardioprotective aspects related to AVF creation: a recent retrospective study of 820 incident chronic HD patients treated in three Canadian cities did not suggest an increased risk of death at higher levels of Qs [30]. Another study showed that patients with Qs >1000 mL/min had a lower prevalence of LVH and that relatively higher Qs appears to be associated with a lower level of observed HD-induced cardiac stunning [31]. Furthermore, a very recent feasibility study showed that AVF creation results in increased functional exercise capacity in severe chronic obstructive pulmonary disease [32]: a 5-mm iliofemoral AVF was created in 12 patients with end-stage chronic obstructive pulmonary disease: mean CO increased by ~1 L/min by 12 weeks; no significant change in pulmonary arterial pressure was observed, meaning that pulmonary vascular resistance declined. A significant mean increase of 59 m in 6-min walk test 6 and 12 weeks after AVF creation while on room air was observed; the benefit of supplemental O2
was matched by AVF creation, suggesting the therapeutic benefit of an AVF is improved through tissue O₂ delivery, increased mixed venous O₂ content for O₂ diffusion into exercising muscle [32]. Finally, another cardioprotective aspect related to AVF creation is the sustained reduction in arterial stiffness [33, 34]. Namely, Utescu et al. [33] found that the creation of an AVF was associated with a passive improvement of aortic stiffness especially in patients with stiffer arteries. Korsheed et al. [34] found that AVF formation resulted in a sustained reduction in arterial stiffness and blood pressure as well as an increase in LV ejection fraction. Aortic stiffness has been shown to be an independent predictor of all-cause and CV mortality in HD patients [35].

It has long been known that a VA with an inappropriately high-flow rate may be the cause of high-output HF [36–41]. After the creation of an AVF, blood is shunted from the high-pressure arterial side to the low-pressure venous side. This diversion of blood back to the right-sided circulation reduces overall systemic arterial blood flow. The counterregulatory response is an increase in CO mediated by the sympathetic nervous system and circulating catecholamines. Initially, the heart increases CO via an increase in heart rate and stroke volume. With time, excess cardiac stimulation leads to LVH, reduction in LV ejection fraction, and eventual HF [40]. There is a paucity of literature regarding high-output HF in HD patients other than a few case reports [36–41]. The incidence of this complication remains unknown: one study found a 3.7% (17/460) incidence of high-flow rate VAs requiring surgical correction [42]. Why, then, do we not see more patients with high-output HF? Theoretical risk associated with AVF creation is related to both its size and location: in a small AVF, the increase in CO is equal to the AVF Qₐ and in a large AVF, the increase in CO may exceed AVF Qₐ because the compensatory peripheral vasoconstriction may be inadequate to maintain systemic blood pressure. Some authors have stressed that when the CPR exceeds 30%, the onset of high-output HF is possible independently of the absolute value of Qₐ [40].

What cause(s) is able to transform a volume overload LVH in HF is not known. Specific characteristics of either the patients or the AVFs, or both, may predispose to the development of HF [43]. Some authors suggest that cardiac decompensation due to AVFs is likely to occur only in patients with underlying cardiac disease [18]. Patients bearing a high-flow rate AVF and having a greater increase in LV end-diastolic volume are more likely to develop HF [43]. In fact, preliminary data show that patients with Qₐ>2 L/min have a greater tendency to the increase in LV end-diastolic volume when compared with those with Qₐ<1 L/min [44].

Currently, the evidence linking AVFs to the development of HF is indirect, but consistent with what is known about high-output HF in other kinds of conditions, such as traumatic AVFs. The risk factors for the development of high-Qₐ AVFs are male gender, upper arm AVFs and previous access surgery [27, 45]. The recent study by Basile et al. [27] showed that upper arm AVFs are associated with an increased risk of high-output HF. 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 get 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 seems to favour a causative role of the upper arm AVFs in the pathogenesis of high-output HF. Even though it is likely that only a small percentage of patients has overt CHF (one study pointed out that only 2.6% of patients with upper arm AVFs underwent banding or ligation owing to steal or high-output syndromes) [46], the message deriving from this study [27] is clear: the upper extremity AVFs should be placed as distal as possible, as also underlined by the very recent European Best Practice Guidelines [47].

Is AVF a lesser evil or a blessing of God?

Very recently, Amerling et al. wrote a review whose main message was ‘The AVF is a non-physiological anomaly and should be considered a lesser evil…undoubtedly contributes to excess CV mortality in HD patients and shortens lifespans’ [48]. We challenged these conclusions [49], the most important of which was ‘even relatively young and healthy patients will eventually develop CV complications, mostly CHF, due to the prolonged presence of an AVF’ [48]. This statement is not supported by any study: actually, it has been shown that (i) even subtle kidney dysfunction should be considered a medical condition predisposing to increased CV risk [50]; (ii) renal insufficiency is independently associated with increased CV disease-related mortality rates [51]; (iii) patients commencing HD are already highly pre-selected because chances of death are much higher than reaching dialysis in all stages of chronic kidney disease [52]; (iv) thickening of the arterial wall and aortic stiffening are prominent long before the start of HD [53]; (v) on initiation of HD therapy, only 16% of patients had normal echocardiograms [54]; (vi) the standardized CV mortality rate in patients starting dialysis was 38.1 per 1000 person-years higher compared with the general population [55].

Is AVF a lesser evil [48] or a blessing of God [49]? The right answer is obviously the second one. Actually, the review by Amerling et al. [48] denies the life-saving benefit of Brescia–Cimino’s basic idea of AVF for millions of human beings. However, while emphasizing the real benefits of creating a native AVF, we would like to stress also the danger of attaining excessive blood flow rates.

Conclusions

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 grafts and then AVFs [2–6]. The presence of an AVF has an adverse effect on cardiac function, but its exact contribution to CV morbidity is not clear. It has long been known that a VA with an inappropriately high-flow rate may be the cause of high-output HF [36–41]. Even more paradoxically, there may be cardiopulmonary benefits conferred by AVF [31–34]. Thus, while emphasizing the real benefits of creating a native AVF, we would like to
stress also the danger of attaining excessive blood flow rates. The key word in the case of VA choice is ‘eligibility’ [56]. A ‘patient first, not fistula first, but avoid a catheter if at all possible’ approach might be the best [1]. In order to do this, we think that nephrologists must be able to gain the role of coordinator of the VA team [57].

Conflict of interest statement. None declared.

References
29. MacRae JM. Vascular access and cardiac disease: is there a relationship? Curr Opin Nephrol Hypertens 2006; 15: 577–582
45. Wijnen E, Keuter XH, Plancken NR et al. The relation between vascular access flow and different types of vascular access with...
The arteriovenous fistula (AVF) was adopted in the clinical practice of dialysis in the 1960s without prospective randomized trials, simply on the basis of utility. It was widely hailed as a major improvement from the Scribner shunt, and is rightfully credited with allowing chronic hemodialysis (HD) to flourish as a modality [1]. But this history does not negate the fact that the AVF is a harmful, non-physiological anomaly, with considerable downsides. These are either not mentioned or downplayed in programs to increase fistula use [2]. Anointing any particular remedy in medicine is hazardous, in that it deters research into better alternatives.

I am not advocating that the AVF be banned, nor am I a catheter proponent. I wish to encourage a thoughtful, common sense, individualized approach to HD access; an approach that matches the access to the needs of each patient, and that takes into account the negative effects of the AVF. I am suggesting that emotion be removed from this process and replaced by cool, clinical judgment.

We must recognize the complete absence of any prospective, randomized outcome trial of HD access, and the extreme unwillingness of any ever being performed. Let us also accept that observational or retrospective outcome data are inconclusive. This is not a unique situation; the majority of clinical decisions fall outside of territory covered by randomized controlled trials. We must rely on our understanding of physiology, longitudinal observations of patients (i.e. natural history), logic, reason and common sense. The latter three should dictate caution. Patent ductus arteriosis (PDA) and traumatic AVFs lead to cardiac decompensation and are always closed surgically when detected. Why should dialysis patients be immune to these effects? Indeed, due to a high prevalence of underlying cardiac disease, HD patients are more susceptible to the negative consequences of an AVF.

The physiology and hemodynamics of the AVF have been well described [3]. The cardiac output (CO), and thus work of the heart, increases in proportion to the size of the shunt. This usually requires an increase in the blood volume, as total peripheral resistance decreases, and this is reflected in high levels of atrial natriuretic peptide and brain natriuretic peptide. Sympathetic tone increases on a more or less permanent basis, which raises the heart rate, contractility and blood pressure over time. Cardiac remodeling results in chamber dilatation and hypertrophy [4]. Pulmonary flow increases, and in dialysis patients, this frequently leads to pulmonary hypertension [5]. The AVF decreases the subendocardial viability index by increasing the work of the heart while decreasing coronary perfusion. This sets the stage for subendocardial ischemia, myocardial stunning...