



ORIGINAL ARTICLE

Wearable artificial kidney and wearable ultrafiltration device vascular access—future directions

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ABSTRACT

Background. Since 2005, three human clinical trials have been performed with the Wearable Artificial Kidney (WAK) and Wearable Ultrafiltration (WUF) device. The lack of an adequate vascular access (VA) has been pointed out as the main limitation to their implementation. Based on the current level of understanding, we will make the first conceptual proposal of an adequate VA suitable for the WAK and the WUF.

Methods. All the literature related to WAK and WUF was reviewed. Based on eight main publications the VA major characteristics were defined: a mean blood flow of 100 mL/min; the capability to allow prolonged and frequent dialysis treatments, without interfering in activities of daily living (ADL); safe and convenient connection/disconnection systems; reduced risk of biofilm formation and coagulation; high biocompatibility. A research was done in order to answer to each necessary technological prerequisites.

Results. The use of a device similar to a CVC with a 5Fr lumen, seems to be the most feasible option. Totally subcutaneous port devices, like the LifeSite(R) or Dialock (R) systems can be a solution to allow WAK or WUF to operate continuously while patients carry out their ADL. Recently, macromolecules that reduce the risk of thrombosis and infection and are integrated into a CVC have been developed and have the capability of overcoming these major limitations.

Conclusion. With an adequate VA, portable HD devices can be acceptable options to address several unmet clinical needs of HD patients.

Keywords: end-stage renal disease, renal replacement therapy, vascular access, wearable artificial kidney, wearable ultrafiltration device

Received: 9.3.2018; Editorial decision: 5.8.2018

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INTRODUCTION

In the last decade, the prevalence of the population on dialysis has almost doubled and is expected to rise even more in the coming years [1, 2]. Although there are a range of renal replacement therapy (RRT) options, the majority of end-stage renal disease (ESRD) patients are treated intermittently with conventional haemodialysis (HD). This RRT reduces the freedom and health-related quality of life (HRQOL) of ESRD patients and is less physiological, implying the use of numerous drugs to optimize all the complications associated with chronic kidney disease.

Recently recognition of RRT limitations has given rise to increasing interest in the development of totally portable HD devices. In fact, the initial idea of the first portable HD device—the wearable artificial kidney (WAK)—goes back to the 1970s. However, implementation of WAK was limited by the technologies available at that time [3–5]. The first trial with a WAK in animals was reported in 2005 [6] and 2 years later it was tested in humans [7]. Gura *et al.* [8] described the first wearable ultrafiltration (WUF) device to manage fluid overload. In 2016, Gura *et al.* [9] published the first 24-h WAK treatment human clinical trial. Importantly, in all these trials there were no significant cardiovascular changes or acid–base or electrolytic serum disturbances and the target ultrafiltration (UF) was achieved. Additionally, the involved ESRD patients reported significant satisfaction with the WAK, owing to greater freedom (Table 1) [9].

In the future, WAK and WUF will require significant technological improvement in the currently used dialysis equipment in order to allow adequate treatment oriented towards the particular clinical and personal needs of each patient (Table 2) [4, 10].

The development of an appropriate vascular access (VA) with a mean blood flow of 100 mL/min has been identified as the first and limiting challenge for implementation of WAK/WUF treatment. Thus, over the last few years, multidisciplinary discussions have emerged about the optimal VA for these portable devices. The possibilities proposed always revolved around catheters for HD, the arteriovenous fistulas and grafts. However, none of these vascular accesses seem to fulfil the needs associated with the WAK: mobility, flexibility and reduced risk of complications. Therefore it seems necessary that something new should emerge.

The aim of this study is to conceptualize the first proposal of an adequate VA for the WAK and WUF.

MATERIALS AND METHODS

WAK/WUF VA

Currently, three main types of VA for HD are available, namely the arteriovenous fistula (AVF), the graft and the central venous catheter (CVC). The AVF remains the preferred VA due to better outcomes, namely less serious infections, lower morbidity and higher survival rates [11]. However, it has been demonstrated that poorer results with CVCs can be due to selection bias (CVCs tend to be used in sicker patients), and the infection risk with venous catheters, especially in elderly patients, has been found to be relatively low [12]. On the other hand, adherence to hand washing and catheter care protocols, such as those suggested by the US Centers for Disease Control, has resulted in a marked reduction of overall dialysis catheter infection rates [13]. Thus, in certain particular clinical circumstances, the chronic CVC can remain a useful form of VA.

According to the main published literature related to WAK and WUF (Tables 1 and 2), ideal WAK devices must be wearable and comfortable, allowing prolonged and frequent dialysis

treatments, without interference in the activities of daily living [3–10]. Ideal WAK devices must be wearable and comfortable, allowing prolonged and frequent dialysis treatments without interference in the activities of daily living. Although AVF is the preferred VA for HD, a small needle dislodgment can result in haematoma or more severe complications such as vessel laceration and active bleeding. Given a mean AVF blood flow of ~1000 mL/min, is easy to understand how an AVF laceration, if not controlled, can result in patient death within minutes. Therefore AVF is not a suitable VA for WAK/WUF systems. The same complications may also occur with grafts.

Considering the previous WAK experiences, the expected outcomes and possible complications, the use of a device similar to a chronic CVC currently seems to be the most feasible option. A newer needle-free AV access device has been developed—the HemaPort (Hemapure, Uppsala, Sweden) system, which comprises a titanium connector attached to a polytetrafluoroethylene graft [14]. The only clinical data available is from a study involving six centres and 13 implanted devices. A mean blood flow of 364 mL/min (ranging from 100–450 mL/min) was reported. Fourteen percent required thrombosis interventions to establish functional VA, and six devices had to be removed due to insufficient flow, thrombosis and/or infections. Thus further clinical evaluation is required to demonstrate potential clinical advantages.

RESULTS

VA Port

One major consideration regarding CVCs is the port. This is the point of contact of the CVC with the external environment and also with the HD system. Considering the most frequent CVC model, the external portion is likely to be at an increased risk of physical damage and contamination, consequently leading to infection and hospitalization. Additionally, this portion can also be affected by changes in body position during HD treatments, leading to erratic performance [15]. This knowledge gave rise to the development of the first totally implantable HD access systems, the LifeSite Hemodialysis Access System (Vasca, Tewsbury, MA, USA) and the Dialock Hemodialysis Access System (Biolink, Manfield, MA, USA) [16–20]. They are both completely subcutaneous systems and have implantable structural components (including valves and cannulas) and do not use a subcutaneous cuff.

The LifeSite system valve (Figure 1) comprises titanium, stainless steel and silicon elements, which connect to a 12-Fr silicon cannula and is placed in the central venous system. Its utilization requires implantation of two valves: one for drawing and the other for return of blood. The unique design of this valve allows isolation of the cannula relative to the fluid pathway when not in use. Blood access is made by a specific 14-gauge cannulation set, using the same needle site for each dialysis treatment, resulting in the development of a fibrous tissue tract that eventually becomes insensitive to pain [15].

The Dialock system (Figure 2) consists of a single titanium body with two internal valves and two attached cannulas that are accessed via specially designed 15-gauge cannulation sets. This system has an internal mechanism designed to prevent needle dislodgement during dialysis.

The two subcutaneous systems are recommended to be placed in the upper chest, preferably in the right internal jugular vein, but they can also be positioned in other locations according to each individual patient's requirements. The right internal

Table 1. Clinical trials performed with the WAK/WUF in humans

References	Number of patients	VA	Average blood flow \pm SD (mL/min over 24 h)	Average dialysate flow \pm SD (mL/min over 24 h)	Average urea/creatinine clearance \pm SD (mL/min over 24 h)	Average ultrafiltration volume \pm SD (mL over 24 h)	Technical problems observed	Clinical aspects
Davenport et al. [27]	8	Usual HD VA	58.6 mL/min	47.1 mL/min	22.7/20.7	-	Accumulation of carbon dioxide bubbles (by decomposition of urea by urease in the sorbents cartridge) in the dialysate circuit Clotting of the CVC and the circuit in two patients related to aPTT decrease Dislodgement of a fistula needle in one patient. Safety mechanisms ensured that the blood pump stopped immediately and treatment continued with no sequelae	No evidence of important cardiovascular changes, haemolysis, serum electrolytes or acid-base balance disturbances
Gura et al. [8]	6	-	116 \pm 11 mL/min	-	-	1084.33 \pm 335 mL	No technical complications or untoward effects in terms of blood pump mal-function, disconnections and/or ultra-filtration/heparin pump errors Clotting of the CVC in one patient Appearance of a pink discoloration in the dialysate in one patient without analytical evidence of haemolysis	Cardiovascular and biochemical parameters remained stable
Gura et al. [9]	7	CVC	42 \pm 24 mL/min	43 \pm 20 mL/min	17 \pm 10, 16 \pm 8	-	-	No important cardiovascular changes, acid-base or electrolytic serum disturbances The target UF was achieved No need of dietary restriction or phosphorus-binding medications Significantly greater satisfaction owing to the greater freedom, convenience and flexibility

aPTT, activated partial thromboplastin time.

Table 2. Technical components and future improvements in the WAK and WUF

Component	Requirement/future improvement
Pumping system: blood pumps, fluid pumps	Miniaturized and wearable shape; no haemolysis; high biocompatibility
Dialysis membrane	Miniaturized and wearable shape; mimics physiological functions of the nephron; allows portability; a geometry that allows for a replaceable disposable pump, an effective surface area and pore distribution for longer treatment time; no haemolysis; high biocompatibility
Dialysate regenerating system	Lightweight; easily replaceable sorbent cartridge; replace smart sorbent material with high adsorption capacity of uremic toxins; accurately monitor the dialysate composition (with pH, temperature, volume, composition and bacterial contamination sensors)
Patient monitoring system	Monitor fluid balance, pressure in the dialysis system, pump power battery, blood leakage, bubble detection and VA disconnection; done by remote control
Battery	Small and light; provides enough energy for a significant period of time
VA	Allows comfortable, prolonged and frequent dialysis treatments without interference in activities of daily living; safe and convenient connection/disconnection system; reduced risk of biofilms formation and coagulation; high biocompatibility

jugular vein is the preferred site because it offers a more direct route to the right atrium, and CVC insertion and maintenance into this vessel are associated with a lower risk of complications compared with other sites [19].

Until now, the majority of the studies performed with LifeSite and Dialock devices have demonstrated that they have very good survival and a low risk of device-related complications.

Schwab *et al.* [16] performed a 6-month prospective multicentre clinical trial to compare the efficacy and safety of the LifeSite system with the Tesio-Cath HD CVC. The main findings of the study were that mean blood flow was significantly higher with LifeSite than with the Tesio-Cath (358.7 versus 331.8 mL/min; $P < 0.001$); the device-associated infection rate was significantly lower for the LifeSite group, where 70% isopropyl alcohol was used as an antimicrobial solution, compared with the Tesio-Cath group (1.3 versus 3.3 events/1000 patients-days; $P < 0.05$) and the LifeSite group with 70% isopropyl alcohol also needed significantly fewer thrombolytic infusions than the Tesio-Cath group ($P = 0.0295$).

In a 12-month multicentric prospective study, Rosenblatt *et al.* [20] enrolled 68 patients requiring HD and compared the performance between the LifeSite and Tesio-Cath systems. In the LifeSite group, a lower number of device-related adverse events were observed ($P < 0.016$), there was a lower need for thrombolytic infusions ($P < 0.002$) and, importantly, fewer device-related infections were reported ($P < 0.013$) when compared with the Tesio-Cath group. After censoring for planned removals, the LifeSite device also had a significantly higher probability of device survival at 1 year.

Preliminary clinical results with the Dialock device were published by Canaud *et al.* [21] in 10 HD patients. The mean survival of the device was 5.7 (1.3–9.6) months. They identified three cases of bacteraemia that occurred in the early phase of the study and were solved with antibiotic therapy, but no device was removed. The mean blood flow was 307 ± 3.3 mL/min, venous pressure was 195 ± 39 mmHg and the Kt/V delivered was 1.36 ± 0.03 . In a later study, Canaud *et al.* [22] reported the results of this device in 23 HD patients. The average duration of the device was 11 (range 4–19) months. The Dialock was removed in two patients due to infection that involved the skin, the tissue and the device and had no response to topical or systemic antibiotic therapy. The mean Kt/V was 1.48 ± 0.23 .

Previous studies demonstrated that the Dialock and the LifeSite systems could be good options for patients being

treated with chronic HD. However, most of these studies date back to the 2000s, with the latest study being published in 2008. This may be attributed primarily to the fact that CVCs are considered the 'last line' of VA for the current most frequent option of short intermittent and in-centre HD. However, with the development of fully portable HD devices and more biocompatible materials with reduced risk of infection and thrombosis, these devices should be reconsidered. In the case of the WAK and WUF, given the possibility of using a reduced lumen CVC, it may be possible to significantly reduce the dimensions of both these devices. On the one hand, the placement becomes easier and can be done in a way similar to a conventional tunnelled CVC, avoiding a surgical intervention. On the other hand, it is now also possible to increase comfort and reduce its aesthetic impact, as is the case with ports of CVCs used in chemotherapy. Another limiting factor associated with the use of these devices is that they require needles, which is not the case with the current CVCs, and may cause pain and discomfort. This also provides a window of opportunity for the development of punch/connection systems that do not use needles and that are certainly the future in HD. Finally, the use of these systems probably has a higher associated cost. Given the high percentage of patients initiating HD using CVCs, if the use of these devices becomes widespread, it could entail very high costs. However, if the use of these devices is made with the WAK and WUF in mind, and they are miniaturized, their cost may possibly be reduced.

Although subcutaneous systems are associated with a reduced risk of infection, aseptic measures have to be carefully taught and reinforced. Thus, similar to tunnelled CVCs, protocols for all aspects of these implantable devices need to be implemented.

VA Lumen

In order to select the correct lumen of the catheter, from a haemodynamic point of view, it is necessary to take into account the Hagen–Poiseuille law:

$$\Delta P = \frac{(128 \eta Q L)}{(\pi d^4)}$$

where ΔP is the pressure drop along the catheter, η is the viscosity, Q is the blood flow, L is the catheter length and d is the inner diameter of the catheter.



FIGURE 1: The LifeSite system. Adapted from Levin and Ronco [15].

Considering that blood viscosity does not vary much (it depends on blood characteristics like haematocrit and protein concentration), the main parameters affecting the pressure drop are the geometric characteristics of the catheter (diameter and length). In particular, the pressure drop is proportional to the fourth power of the diameter. Consequently, it would be desirable to increase the diameter in order to reduce as much as possible the pressure drop and to avoid catheter collapse.

On the other hand, the catheter diameter cannot be excessively large because it may fill the vein too tightly, possibly leading to damage of vein wall, together with an increased risk of stenosis or thrombosis. A good compromise between these two aspects needs to be reached.

In Figure 3, a theoretical Hagen–Poiseuille law–based selection of the minimum diameter of a single-lumen catheter for a wearable device is represented. In particular, the following assumptions were considered:

- desirable blood flow of 100 mL/min;
- constant and standard length of the catheter for adults ($L = 19$ cm) and
- patient venous pressure of 10 mmHg.

The pressure drop between the patient vessel and the access pressure detecting point in the extracorporeal circuit is due almost entirely to the catheter.



FIGURE 2: Dialock system. Adapted from Levin and Ronco [15].

On the access side of the catheter, more critical for the selection than the return one, the minimum pressure difference (ΔP) along the length of the device should not exceed 350 mmHg [23], to avoid haemolysis and catheter collapse. However, this value does not take into account blood flow that is not uniformly laminar, the curvilinear deformation of the catheter after implantation and the tubing roughness. For these reasons, a strict safety factor of 2 was taken into account to determine an acceptable value of pressure drop, $\Delta P'$:

$$\Delta P' = \frac{\Delta P}{2} = 175 \text{ mmHg.}$$

Under these conditions, a minimum size of a 5-Fr single-lumen catheter is required, matching technical requirements and clinical/ergonomics needs.

VA Materials

The improvement of silicone materials that was observed in the 1940s gave rise to more biocompatible, relatively non-thrombogenic, chemically resistant CVCs that had better longevity and fewer complications such as thrombosis and infection [24]. Advances in material technology have resulted in the transition from silicone-based dialysis catheters to the use of polyurethane. Polyurethanes are polymers with thermoplastic [25]. Silicone and polyurethane CVCs are not significantly different in terms of duration and function. However, polyurethane has a greater tensile strength, allowing a larger inner lumen with the same outer diameter, which improves the flow rate. Polyurethane/polycarbonate copolymers (such as carbothane) are the most recent generation of CVC materials. They offer greater strength for longevity and softness for flexibility and patient comfort and still retain all the advantages of polyurethane. Additionally, these copolymers are also resistant to iodine, peroxide and alcohols.

Coatings

Although there has been significant developments in CVC materials, making them more biocompatible and reducing the

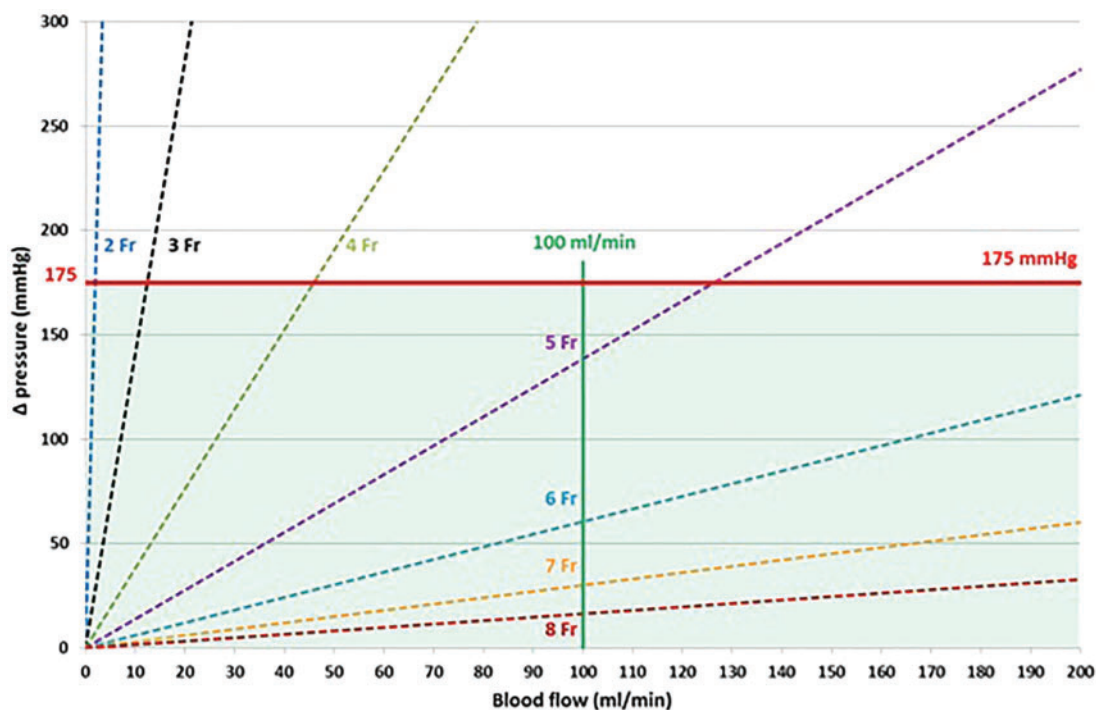


FIGURE 3: Graph comparing the reachable blood flow and pressure drop inside the catheter. Coloured lines represent catheters with different lumen sizes. Only single-lumen catheters were considered. Green area represents the acceptable range between ΔP and catheter size for the desired blood flow. For blood flow of 100 mL/min, a 5 Fr is the minimum acceptable size of the lumen.

rate of infection and thrombosis, these still remain the most common complications associated with this type of VA. Two different kinds of CVC surface coverings were developed: antithrombotic and antimicrobial coatings.

Heparin is the most studied antithrombotic substance and coverage of the CVC lumen allows this molecule to exert its activity in three main ways: locally inactivating the coagulation cascade, electrostatically repulsing the charged platelets and decreasing the adhesion of bacteria to the CVC through their hydrophobic interactions [26]. Until now, studies that showed the efficacy and safety of heparin utilization in decreasing bacteraemias and colonizations were mainly performed in intensive care units [26]. The number of studies in HD patients is limited.

There are few publications regarding the use of antibiotic-impregnated catheters (AICs) in the dialysis population; however, they have demonstrated significant anti-infective benefit. The most commonly studied AIC is the combination of minocycline and rifampin covering the inner and outer surfaces of the catheter. Raad *et al.* [27] performed a multicentric, randomized clinical trial with 281 hospitalized patients who needed triple-lumen CVCs: 147 catheters were pretreated with tridodecylmethylammonium chloride and coated with minocycline and rifampin and 151 non-coated catheters were used as controls. Coated CVCs demonstrated a statistically significant superiority in colonization (26 versus 8%; $P < 0.001$) and catheter-related bloodstream infection (0 versus 5%; $P < 0.01$) and a multivariate logistic regression analysis showed that coating catheters with minocycline and rifampin is an independent protective factor against catheter-related colonization ($P < 0.05$). However, there can be two main problems associated with antibiotic coating: the possibility of antibiotic resistance and antibiotic impregnation longevity [25].

The understanding of the key role of the fibrin sheath in the development of CVC-related thrombosis and bacteraemia parallel to

the evolution in nanotechnology allowed the recent emergence of very promising CVC coatings. In a recently published *in vitro* study, Hugoni *et al.* [28] evaluated fibronectin, monocyte response and thrombus formation on two surface-modified polyetherurethanes. They used two surface modifiers: an anionic/dihydroxyl oligomeric additive that enables cell adhesion and a fluorinated polypropylene oxide oligomer known to reduce platelet adhesion. The results of the study demonstrated that these molecules promote an anti-inflammatory character, with longer clotting times, suggesting their potential for the reduction of thrombus formation.

Endexo technology [developed by Interface Biologic and currently licensed to AngioDynamics for VA devices (<http://www.interfacebiologics.com/endexo.htm>)] consists of surface-modifying macromolecules that are permanently combined with the polyurethane in the inner and outer surface of the catheter. These macromolecules appear to be similar to anionic/dihydroxyl oligomeric additives that reduce the adhesion and activation of blood proteins and components, thereby reducing thrombus formation.

Similarly, the development of anti-infective polymers may contribute to the reduction of infection rates associated with the use of CVCs. In this case, however, the potential for developing resistance of microbial agents should always be taken into account.

DISCUSSION

Possible future path for WAK and WUF VA

ESRD prevalence is expected to more than double in the next decade [2]. Although renal transplantation is considered the best option for ESRD patients, there are still several limitations to its wider use. Portable HD devices can be acceptable options to address several unmet clinical needs of HD patients. However, their implementation depends primarily on the

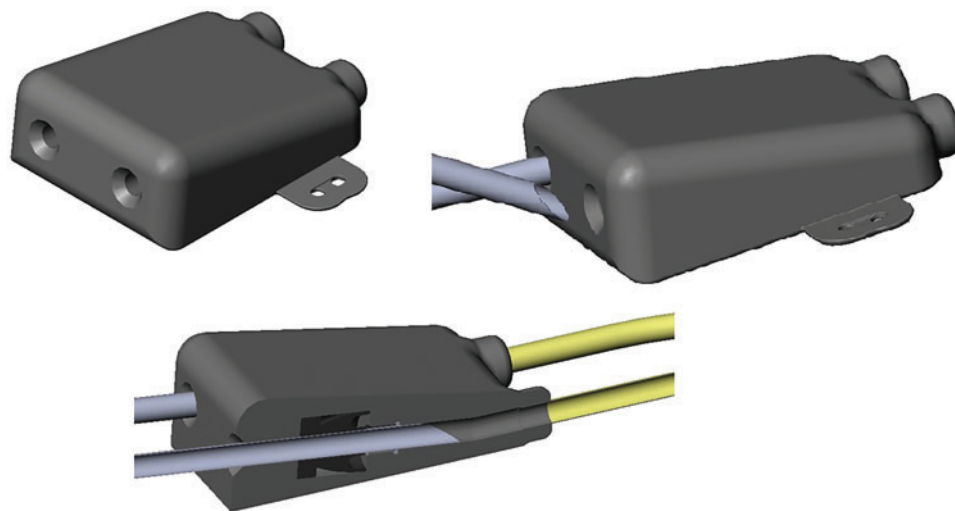


FIGURE 4: The miniaturized port concept, with biocompatible-material needle-free system, connected to two 5-Fr single-lumen catheters.

development of innovative VA systems. Based on previous studies, completely subcutaneous port devices, similar to the LifeSite and Dialock systems, seem to be the best solution that allows the WAK or WUK to operate continuously while keeping patients mobile enough to carry out their daily life activities without any impediments. The LifeSite system has more studies proving its safety and superiority comparable to the Tesio-Cath; the Dialock system can also provide some advantage in terms of convenience and its safety mechanism prevents needle dislodgement during dialysis. However, these systems need to be further improved upon in terms of miniaturization, improved biocompatibility and reduced risk of infection and thrombosis. Thus their placement will eventually become easier, patient comfort will be improved and aesthetic impact will be reduced. The development of punch/connection systems that do not use needles and can be controlled by the patient could become emerging opportunities for development. These systems should support patient mobility during HD treatment. According to previous studies, the blood flow rate required for the WAK/WUF at optimal usage is ~ 100 mL/min, which allows the size of the CVC lumen to be significantly reduced. So, according to the Hagen-Poiseuille law, two 5-Fr single-lumen catheters composed of polyurethane/polycarbonate polymers could be used. Different kinds of coatings have been studied, namely heparin and antibiotics such as minocycline and rifampin. However, use in patients with ESRD is still not well understood. Recent advances in nanotechnology have given rise to the development of macromolecules that are added to the inner and outer surfaces of the CVC and thus may reduce the risk of thrombosis. This is the basis for Endexo technology (<http://www.interfacebiologics.com/endexo.htm>). The use of these macromolecules may make it possible to overcome thrombosis, which is one of the major limitations associated with CVC use. In conclusion, a prototype of the WAK/WUF VA should be developed along the lines of a miniaturized version of the Dialock system made with a biocompatible substance and ideally should be free from needle use. This system could be placed in the right internal jugular vein (similar to a tunnelled CVC). The miniaturized system would connect to two 5-Fr single-lumen catheters composed of polyurethane/polycarbonate polymers with antithrombotic/anti-infectious macromolecules (Figure 4).

CONCLUSION

Despite significant technological evolution in RRT, HD continues to be associated with poor morbidity, mortality and HRQOL outcomes in ESRD patients. The development of WAK and WUF devices may be an important turning point in the care of ESRD patients. The development of an appropriate VA with reduced risk of complications is the first step in making the WAK and WUF feasible, safe, efficacious, cost-effective and convenient therapies for needy patients.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Thomas B, Wulf S, Bikbov B et al. Maintenance dialysis throughout the world in years 1990 and 2010. *J Am Soc Nephrol* 2015; 26: 2621–2633
2. Liyanage T, Ninomiya T, Jha V et al. Worldwide access to treatment for end-stage kidney disease: a systematic review. *Lancet* 2015; 385: 1975–1982
3. Stephens RL, Jacobsen SC, Atkin-thor E et al. Portable/wearable artificial kidney (WAK) - initial evaluation. *Proc Eur Dial Transplant Assoc* 1976; 12: 511–518
4. Davenport A. Portable and wearable dialysis devices for the treatment of patients with end-stage kidney failure. Wishful thinking or just over the horizon? *Pediatr Nephrol* 2015; 30: 2053–2060
5. Ronco C, Davenport A, Gura V. The future of the artificial kidney: moving towards wearable and miniaturized devices. *Nefrologia* 2011; 31: 9–16
6. Gura V, Beizai M, Ezon C et al. Continuous renal replacement therapy for end-stage renal disease. The wearable artificial kidney (WAK). *Contrib Nephrol* 2005; 49: 325–333
7. Davenport A, Gura V, Ronco C et al. A wearable haemodialysis device for patients with end-stage renal failure: a pilot study. *Lancet* 2007; 370: 2005–2010
8. Gura V, Ronco C, Nalesso F et al. A wearable hemofilter for continuous ambulatory ultrafiltration. *Kidney Int* 2008; 73: 497–502
9. Gura V, Rivara MB, Bieber S et al. A wearable artificial kidney for patients with end-stage renal disease. *JCI Insight* 2016; 1: e86397

10. Armignacco P, Garzotto F, Neri M et al. Wak engineering evolution. *Blood Purif* 2015; 39: 110–114
11. Daugirdas JT, Blake PG, Ing TS et al. Arteriovenous fistulas and grafts: the basics. *Handbook of Dialysis, 5th edn*, Philadelphia: Wolters Kluwer Health; 2015, chap. 6
12. Murea M, James KM, Russell GB et al. Risk of catheter-related bloodstream infection in elderly patients on hemodialysis. *Clin J Am Soc Nephrol* 2014; 9: 764–770
13. Patel PR, Yi SH, Booth S et al. Bloodstream infection rates in outpatient hemodialysis facilities participating in a collaborative prevention effort: a quality improvement report. *Am J Kidney Dis* 2013; 62: 322–330
14. Ahlmen J, Goch J, Wrege U et al. Preliminary results from the use of new vascular access (Hemaport) for hemodialysis. *Hemodialysis Int* 2003; 7: 73–104
15. Levin NW, Ronco C. *Hemodialysis Vascular Access and Peritoneal Dialysis Access*. Vicenza: Karger; 2004
16. Schwab SJ, Weiss MA, Rushton F et al. Multicenter clinical trial results with the LifeSite hemodialysis access system. *Kidney Int* 2002; 62: 1026–1033
17. Beathard GA, Posen GA. Initial clinical results with the LifeSite Hemodialysis Access System. *Kidney Int* 2000; 58: 2221–2227
18. Zollo A, Cavatorta F, Galli S. Experience using a new vascular port access device for hemodialysis: preliminary clinical results. *J Vasc Access* 2001; 2: 51–55
19. Daugirdas JT, Blake PG, Ing TS. *Handbook of Dialysis, 5th edn*, Vol. 2015. Chap. 7. New York, USA: Wolters Kluwer Health, 2015, 122–123
20. Rosenblatt M, Caridi JG, Hakki FZ et al. Efficacy and safety results with the LifeSite hemodialysis access system versus the Tesio-Cath hemodialysis catheter at 12 months. *J Vasc Interv Radiol* 2006; 17: 497–504
21. Canaud B, My H, Morena M et al. Dialock: a new vascular access device for extracorporeal renal replacement therapy. Preliminary clinical results. *Nephrol Dial Transplant* 1999; 14: 692–698
22. Canaud B, Nathan Levin N, Ing T et al. Dialock: pilot trial of a new vascular port access device for hemodialysis. *Semin Dial* 1999; 12: 382–388
23. Twardowski ZJ, Haynie JD. Measurements of hemodialysis catheter blood flow in vivo. *Int J Artif Organs* 2002; 25: 276–280
24. Colas A, Curtis J. Silicone biomaterials: history and chemistry. In Ratner BD, Hoffman AS, Schoen FJ et al. (eds). *Biomaterials Science: An Introduction to Materials in Medicine, 2nd edn*. Boston: Elsevier Academic Press, 2004, 80–86
25. Tal MG, Ni N. Selecting optimal hemodialysis catheters: material, design, advanced features, and preferences. *Tech Vasc Interv Radiol* 2008; 11: 186–191
26. Ibeas-Lopez J. New technology: heparin and antimicrobial-coated catheters. *J Vasc Access* 2015; 16(Suppl 9): S48–S53
27. Raad I, Darouiche R, Dupuis J et al. Central venous catheters coated with minocycline and rifampin for the prevention of catheter-related colonization and bloodstream infections: a randomized, double-blind trial. *Ann Intern Med* 1997; 127: 267–274
28. Hugoni L, Montaña-Machado V, Yang M et al. Fibronectin adsorption on surface-modified polyetherurethanes and their differentiated effect on specific blood elements related to inflammatory and clotting processes. *Biointerphases* 2016; 11: 029809