Adjacent central venous catheters can result in immediate aspiration of infused drugs during renal replacement therapy

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Summary

Dual-lumen haemodiafiltration catheters enable continuous renal replacement therapy in the critically ill and are often co-located with central venous catheters used to infuse drugs. The extent to which infusions are immediately aspirated by an adjacent haemodiafiltration catheter remains unknown. A bench model was constructed to evaluate this effect. A central venous catheter and a haemodiafiltration catheter were inserted into a simulated central vein and flow generated using centrifugal pumps within the simulated vein and haemodiafiltration circuit. Ink was used as a visual tracer and creatinine solution as a quantifiable tracer. Tracers were completely aspirated by the haemodiafiltration catheter unless the infusion was at least 1 cm downstream to the arterial port. No tracer was aspirated from catheters infusing at least 2 cm downstream. Orientation of side ports did not affect tracer elimination. Co-location of central venous and haemodiafiltration catheters may lead to complete aspiration of infusions into the haemodiafilter with resultant drug under-dosing.

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Acute renal failure in the critically ill is common and has a high associated hospital mortality of 6% [1]. Continuous renal replacement therapy is often utilised in the management of renal failure and requires the placement of a dual lumen haemodiafiltration (HDF) catheter. In patients where other vascular sites have either occluded or are unsuitable for puncture, an HDF catheter may be sited in the same major vein as the central venous catheter (CVC), with the consequence being that their tips lie in close approximation. This may result in a detrimental effect on drug delivery to the patient via the CVC due to immediate aspiration by the adjacent HDF catheter. Consequences may include the loss of vasoactive drugs or of minimally protein-bound antibiotics, to name but two possibilities. This effect has never been quantified. An extensive literature search using combinations of the terms ‘central’, ‘venous’, ‘catheter’, ‘haemodiafiltration’, ‘haemofiltration’, ‘haemodialysis’, ‘elimination’, ‘removal’, ‘same vein’, ‘medications’, ‘drug’ and ‘dual lumen’ within Google and the Embase, Medline, PubMed and Cochrane databases revealed no relevant studies. We found two case reports where a vasopressor infused via a CVC was suspected to be eliminated by a neighbouring HDF catheter, causing an acute decrease in cardiac output [2, 3].

Our aims were to construct a bench model replicating local flow characteristics within a human central vein during continuous renal replacement therapy and to use this model to quantify the extent of drug infusate aspiration. A further objective was to elucidate methods of minimising this aspiration effect by studying the effect of...
Changes in catheter position, rotational orientation and luminal flow direction.

Methods
No ethical approval was deemed necessary for this in vitro study due to the nature of the bench model.

Apparatus and bench model of the central vein
The dimensions and features of our model in comparison with a human inferior and superior vena cava are shown in Tables 1 and 2, respectively. A 70-cm length of transparent polyvinyl chloride (PVC) tubing was used as a model of a central vein. The tubing was round and 2.5 cm in internal diameter, the most physiological sized tubing available in our laboratory [4, 5]. Throughout this study, this tubing was positioned horizontally. This section of our model will be referred to as ‘the central vein’.

Water was used to simulate circulating blood. A centrifugal pump (Type 1250; Eheim, Deizisau, Germany) was used to pump water through the central vein, at a volume flow rate measured using a variable area acrylic flowmeter with an integral valve to enable control of flow rate (Cole-Parmer, London, UK). Although normal central venous flow has been shown to be pulsatile in humans, with average flow velocity in our model compared with native inferior and superior vena caval flow resulted mostly from our use of a diameter of tubing towards the higher end of the normal range of central vein diameter. The central vein circuit was open, i.e. fluid flowing distally via the mixing chamber (Fig. 1) did not recirculate into the central vein. This method enabled accurate tracer dilution calculations to be made, but resulted in a need for large volumes of fluid to supply the flow and therefore precluded the use of substitutes for blood with similar viscosity. However, according to the calculations below this did not significantly affect the nature of flow.

Reproducing laminar flow
We created a laminar flow environment in the region of the central vein in which the catheters would lie to avoid unphysiological turbulence. This was confirmed both mathematically and using colour Duplex ultrasound imaging.

The Reynold’s number (Re) predicts laminar flow if its value is below approximately 2100, with turbulence predicted above 4000 and transitional flow between these two values. It can be calculated thus:

$$\text{Re} = \frac{\rho V D}{\mu}$$  \hspace{1cm} (1)

where \(V\) is the average velocity in the pipe, \(D\) is the diameter of the pipe, \(\rho\) is the fluid density and \(\mu\) is the dynamic viscosity of the fluid.

$$V = \frac{4 Q}{\pi D^2}$$  \hspace{1cm} (2)

where \(Q\) is the volume flow rate.

With \(Q = 1.45\) L.min\(^{-1}\) in vivo and in our set-up,

$$V = \frac{4 \times 0.00145 \text{ m}^3}{60 \text{ s} \pi (0.025 \text{ m})^2}$$

$$V = 0.049 \text{ m.s}^{-1}$$

Substituting Equation 3 into Equation 1 for our model at 25 °C using water:

| Table 1. Comparison of our bench model with the flow parameters through the human inferior vena cava. |
|---------------------------------|-----------------|-----------------|
| Parameter                       | Values for human | Values for model |
| Volume flow rate; l.min\(^{-1}\) | 1.2 (infrarenal) | 1.45            |
| Flow velocity; cm.s\(^{-1}\)    | 1.6 (0.6–3.4)   | 4.9             |
| Flow quality                    | Pulsatile       | Constant        |
| Diameter; mm                    | 20 (13–30)      | 25              |
| Viscosity of circulating fluid; N.s.m\(^{-2}\) | 4.6 x 10\(^{-3}\) | 1 x 10\(^{-3}\) |
| Temperature; °C                 | 37              | 25              |
| Compliance of wall              | Large           | Small           |

| Table 2. Comparison of our bench model with the flow parameters through the human superior vena cava. |
|---------------------------------|-----------------|-----------------|
| Parameter                       | Values for human | Values for model |
| Volume flow rate; l.min\(^{-1}\) | mean (SD) [9]   | 1.45            |
| Flow velocity; cm.s\(^{-1}\)    | Mean (range)    | 4.9             |
| Flow quality                    | Pulsatile       | Constant        |
| Diameter; mm                    | Mean (range)    | 25              |
| Viscosity of circulating fluid; N.s.m\(^{-2}\) |                     |                 |
| Temperature; °C                 | 37              | 25              |
| Compliance of wall              | Large           | Small           |
Re = \frac{998.2071 \text{[kg.m}^{-3}] \times 0.049 \text{[m.s}^{-1}] \times 0.025 \text{[m]}}{0.001 \text{[N.s.m}^{-2}]}
= 1223 \tag{4}

and at 37 ºC for blood with the same size of central vein,
Re = \frac{1050 \text{[kg.m}^{-3}] \times 0.049 \text{[m.s}^{-1}] \times 0.025 \text{[m]}}{4.6 \times 10^{-3} \text{[N.s.m}^{-2}]}
= 280 \tag{5}

This predicted that the laminar nature of flow would not be jeopardised by using water as circulating fluid. The value for density of human blood was taken from work by Trudnowski et al. [10].

**Catheter insertion and the haemodiafiltration circuit**

A dual lumen HDF catheter (CS-12123-F (12Fr, 16 cm), Arrow-Howes, Erding, Germany) with an unused 16-G central lumen, was inserted into the central vein. Its tip was at a position within laminar flow as confirmed by colour Duplex. This catheter and the CVC ((8.5-Fr, 20-cm) Arrow-Howes) were inserted into the central vein using the Seldinger technique through a silicone patch to prevent leaking. Water was pumped into the central vein through the venous lumen of the HDF catheter at 200 ml.min\(^{-1}\), and out of the arterial lumen at the same volume flow rate. Centrifugal pumps (Type 1048; Eheim) and flowmeters (Cole-Parmer) were used to generate and control flow. An open circuit was again used.

**Tracers**

Black ink (Parker Quink\textsuperscript{TM}, Parker, France) was used as a visible tracer. Creatinine solution was used as a dilutional tracer to enable calculation of the amount of tracer aspirated by the HDF catheter. Creatinine solution of a target concentration 398 000 \text{μmol.l}^{-1} (45 mg.ml\(^{-1}\)) was prepared from anhydrous creatinine (C4255; Sigma Aldrich, UK) and distilled water. This high concentration was chosen to be safely below the 50 mg.ml\(^{-1}\) solubility limit quoted by the manufacturer and to allow for a dilution in excess of 1:14 000 before the concentration became too small for hospital creatinine analysers to detect reliably. All creatinine measurements were performed using the same automated analyser in the Royal Marsden Hospital biochemistry laboratory.

Once the two HDF circuit pumps were turned on, ink tracer was infused continuously using a syringe pump (Model 22; Harvard Apparatus, Kent, UK) via the CVC at 0.1 ml.min\(^{-1}\), a rate within the range used in clinical practice, which allowed a thin stream of ink to form a plume with clearly delineated edges. The longitudinal distance between the infusion point within the central vein and the proximal limit of the arterial side port of the HDF catheter was altered by 0.5-cm intervals, starting at 2 cm upstream and finishing at 2 cm downstream to the arterial side port (Fig. 1). Photographs were taken to record details of ink infusion plume flow at each interval. To avoid confusion, the location of each side port is always defined by its proximal limit in this report, and the side port is always named arterial or venous depending on the actual flow direction through it (thus, the arterial port always aspirates blood towards the haemodiafiltration machine, regardless of whether this is the distal or proximal port). Distances are always defined as the upstream distance of the infusion point from the proximal limit of the arterial port (distance ‘X’ in Fig. 2). In our HDF catheter, the proximal side port was 5 cm proximal to the tip of the catheter and the distal side port 3 cm proximal. Each side port was 8 mm long in total (consisting of two holes) and the ports were positioned on opposite sides of the catheter.

Using creatinine tracer infused at 0.75 ml.min\(^{-1}\), the CVC infusion point was shifted by 0.5-cm intervals, as shown in Fig. 2a. At each distance interval, fluid was...
collected in duplicate for measurement of creatinine concentration at sampling points A and B (Fig. 1) after 2 min of equilibration time. These sampling points represented the concentration of tracer avoiding aspiration and the concentration of aspirated tracer leaving through the arterial lumen of the HDF catheter, respectively. The rate of 0.75 ml.min\(^{-1}\) was chosen for creatinine infusion so that, without any aspiration, the central vein creatinine concentration would be approximately 200 \(\mu\)mol.l\(^{-1}\) (assuming a 1:1450 dilution), allowing at least a further 1:10 dilution before reaching the limit of sensitivity of our biochemistry machines. To show that the altered rate of infusion had no effect on plume behaviour, ink was infused at rates of 0.1 and 1 ml.min\(^{-1}\) to assess whether a 10-fold increase changed infusion plume behaviour near the HDF arterial port.

The above ink and creatinine infusions were then repeated at 1-cm intervals with the HDF catheter rotated, so that the arterial side port was facing the wall of the central vein (i.e. away from the CVC; Fig. 2b), followed by another repeat run with the HDF catheter lumens reversed (Fig. 2c). A fourth configuration was also tested: ink and creatinine tracer was used to examine for aspiration during infusion through the separate central lumen of the HDF catheter, with both reversed and conventional HDF catheter lumen flow. Tracer concentration in the central vein was measured with the HDF circuit turned off, to verify the amount of infused creatinine. Water entering the central vein was used as a negative control.

When presenting results, concentrations of creatinine were converted to amounts aspirated or remaining per minute by multiplying by 1.45 l for sampling point A and 0.2 l for sampling point B.

Figure 2 Schematic diagram of the catheter configurations tested: (a) Aspirating (arterial) haemodiafiltration (HDF) catheter port facing central venous catheter (CVC); (b) Aspirating HDF catheter port facing away from CVC; (c) HDF catheter lumens reversed. Measurement ‘\( \times \)’ denotes the upstream distance of the infusion point from the arterial lumen of the HDF catheter. The small central lumen of the HDF catheter is not shown and the configuration where tracer was infused via this small central lumen is not included in this figure.
the infusion plume near the adjacent arterial port of the active HDF catheter, regardless of whether the infusion point was upstream or downstream of this port.

**Tracer studies**

When the arterial port was facing the infusion point and flow direction in the HDF catheter lumens was conventional (Fig. 2a), all visible ink infused via the CVC was aspirated by the arterial port of the HDF catheter unless the point of infusion was at least 1 cm downstream of the arterial port. This result was confirmed using creatinine dilution studies (Fig. 3), that showed 100% creatinine tracer aspiration up to a point 1 cm distal to the arterial port. Creatinine tracer (concentration 402 500 μmol.l⁻¹ for this and following dilution studies) was fully aspirated up to this same point.

Reversing the HDF catheter lumens (Fig. 2c) caused ink tracer to be scattered by the venous lumen outflow, so that less appeared to be entering the now distal arterial lumen. This effect occurred at all distances. Careful analysis revealed that a linear ink plume infused proximal to the venous side port was focused into a point near the venous port and was scattered from there in the form of a turbulent jet. Dilution studies showed that aspiration was nearly abolished, with almost all creatinine remaining in the central vein (Fig. 4).

When the HDF catheter was rotated, so that the arterial port faced the central vein wall (Fig. 2b), there was no measurable difference in aspiration. All visible ink was aspirated up to an infusion point 1 cm distal to the arterial port. Creatinine tracer (concentration 402 500 μmol.l⁻¹ for this and following dilution studies) was fully aspirated up to this same point.

Figure 3 Calculated amounts of aspirated creatinine exiting the central vein per minute, depending on location of the infusion point (aspirating haemodiafiltration catheter port facing central venous catheter as in Fig. 2a). Differently shaded bars denote duplicate measurements and demonstrate the high reproducibility of results from repeat tests.

Figure 4 Calculated amounts of aspirated creatinine exiting the central vein per minute, depending on location of infusion point (haemodiafiltration catheter lumen flows reversed as in Fig. 2c). Differently shaded bars denote duplicate measurements and demonstrate the high reproducibility of results from repeat tests.
Infusions through the central lumen of the HDF catheter were not aspirated. Creatinine was undetectable at sampling point B with both conventional and reversed HDF catheter flow; its mean concentration at sampling point A was 188 μmol.l⁻¹ with conventional flow and 194 μmol.l⁻¹ with reversed flow.

**Discussion**

The findings of this in vitro study suggest that medications infused via a CVC placed adjacent to an in-use dual lumen HDF catheter may be completely aspirated into the extra-corporeal circuit if the infusion is made proximal to the arterial side port. This phenomenon, and its startling extent, has to our knowledge never been demonstrated. This effect could lead to significant drug underdosing with potentially severely deleterious consequences for patients in intensive care. The proportion of a drug returning to the circulation following passage through the HDF machine will depend mainly on pharmacokinetic principles, i.e. on the molecular size and the extent of protein binding and intravascular metabolism [11]. Most drugs have a molecular weight less than 500 D and their non-protein-bound fractions can pass through dialysis membranes. Catecholamines, for example, exist mostly in an unbound state; protein bound fractions for noradrenaline and adrenaline in postoperative patients are approximately 31% and 24%, respectively [12].

The reason why the extent of drug aspiration is so large is not entirely obvious. When the infusion point is extremely close to the arterial port of the HDF catheter, a 100% aspiration rate may be expected. However, when the infusion occurs a few centimetres proximal to the arterial port, the prevalent assumption among physicians might be that most of the infusion plume is carried past the HDF catheter by central venous flow, an assumption incompatible with the results of our study. We hypothesise that the presence of the CVC and an in-use HDF catheter in a central vein reconfigures the central venous flow profile significantly, such that flow running off the surface of the CVC is channelled towards the HDF catheter. Our ink studies showed that some of these flow pathways appear to be channelled to certain foci, including both the arterial and venous side ports of the HDF catheter. The infusion plume cannot determine its own flow direction within the central vein, due to the very slow infusion rate compared to the larger volume flow and velocity of flow passing the CVC. Once an infusion plume is captured in a flow pathway destined to flow close enough to the arterial side port, its chances of being aspirated are greatly heightened. This will explain why rotating the arterial port so that it is facing the wall of the central vein makes no significant difference to the extent of aspiration. Reversing HDF catheter lumens may abolish aspiration by scattering the infusion plume in the turbulent jet exiting the venous side port and introducing sufficient turbulence to prevent direct flow from one catheter to another. Reversal of lumens is frequently performed in clinical practice, mostly when there is obstruction to inflow at the arterial side port. The percentage of recirculated blood has been shown to be acceptable in lumen reversal (around 7%), but this percentage is higher in well-functioning catheters (around 14%), so lumen reversal is not recommended unless there is inadequate inflow [13]. Although some catheter designs are specifically designed to reduce recirculation with lumen reversal [14], other models of HDF catheter may not be licensed for use with lumens reversed.

Limitations of our bench model included the lack of pulsatility of central vein flow and the diameter of our central vein, which although within normal limits was larger than average. With a rigid central vein wall and non-peristaltic pumping, it was impossible to recreate the exact venous pressure profile with the effect of right atrial contraction. Although pulsatility of flow and the mild tortuosity in human central veins might generate some rotation of the flow or side-to-side oscillatory movements, this would not be likely to influence the findings of this study, as only longitudinal changes in position of the catheters (and not axial or rotational changes) made a difference to the amount of aspiration. During peak flow velocity during pulsatile flow, in vivo aspiration of an infusion plume could feasibly be reduced by the increased velocity of blood carrying the plume past the HDF catheter arterial port. However, during end-diastole, aspiration of an infusion plume would probably be more likely, as the section of plume near the arterial port will remain there for longer. Although flow velocity would increase with a smaller diameter central vein, the CVC infusion plume would pass closer to the HDF catheter arterial port, thus probably maintaining the chance of aspiration. Although we could not use a substitute circulation fluid with a viscosity similar to blood due to our open circuit, the viscosity difference would only have had an important effect in much smaller vessels.

In conclusion, although our model cannot specify ‘safe distances’ between HDF catheter and CVC ports due to its in vitro nature, the 100% aspiration rate demonstrated in certain positions is alarming and clear-cut enough to suggest that the amount of immediate drug aspiration with adjacent catheters could be dangerously underestimated. Catheter tips of CVCs and HDF catheters should not be co-located (unless other venous sites are unavailable), or if they are, infusions should be given through ports that emerge distal to the arterial port of an adjacent HDF catheter.
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Competing interests
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References