Continuous renal replacement therapy in neonates and small infants: development and first-in-human use of a miniaturised machine (CARPEDIEM)

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Summary

Background Peritoneal dialysis is the renal replacement therapy of choice for acute kidney injury in neonates, but in some cases is not feasible or effective. Continuous renal replacement therapy (CRRT) machines are used off-label in infants smaller than 15 kg and are not designed specifically for small infants. We aimed to design and create a CRRT machine specifically for neonates and small infants.

Methods We prospectively planned a 5-year project to conceive, design, and create a miniaturised Cardio-Renal Pediatric Dialysis Emergency Machine (CARPEDIEM), specifically for neonates and small infants. We created the new device and assessed it with in-vitro laboratory tests, completed its development to meet regulatory requirements, and obtained a licence for human use. Once approved, we used the machine to treat a critically ill neonate.

Findings The main characteristics of CARPEDIEM are the low priming volume of the circuit (less than 30 mL), miniaturised roller pumps, and accurate ultrafiltration control via calibrated scales with a precision of 1 g. In-vitro tests confirmed that both hardware and software met the specifications. We treated a 2·9 kg neonate with haemorrhagic shock, multiple organ dysfunction, and severe fluid overload for more than 400 h with the CARPEDIEM, using continuous venovenous haemofiltration, single-pass albumin dialysis, blood exchange, and plasma exchange. The patient’s 65% fluid overload, raised creatinine and bilirubin concentrations, and severe acidosis were all managed safely and effectively. Despite the severity of the illness, organ function was restored and the neonate survived and was discharged from hospital with only mild renal insufficiency that did not require renal replacement therapy.

Interpretation The CARPEDIEM CRRT machine can be used to provide various treatment modalities and support for multiple organ dysfunction in neonates and small infants. The CARPEDIEM could reduce the range of indications for peritoneal dialysis, widen the range of indications for CRRT, make the use of CRRT less traumatic, and expand its use as supportive therapy even when complete renal replacement therapy is not indicated.

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Introduction

The increase in incidence of acute kidney injury and its association with poor outcomes in the general population have led to a call for action to improve early diagnosis, institute new preventive measures, and develop new treatments to improve clinical outcomes. Acute kidney injury in adult patients, and to a lesser extent in children, has received a great deal of attention, with the development of standard classification systems, assessment of novel biomarkers, and recognition of the association between acute kidney injury and the development of chronic kidney disease. However, such progress has not been made for infants and neonates.

Acute kidney injury has been described as a rare disorder in neonates, occurring in 1–2% of the hospital-admitted neonatal population. However, more recent single-centre systematic investigation into neonatal acute kidney injury using modern definitions showed that it occurs in 16% of newborn infants weighing more than 2 kg who are admitted to neonatal intensive care. Previous underappreciation of the prevalence of the disorder has made neonatal acute kidney injury an orphan-like disease, and has held back the development of technology specifically for renal replacement therapy in infants.

Existing technology for renal replacement therapy is designed for use in adults and has been inadequately adapted for use in neonates and infants, providing challenges to safe and effective treatment. Because of the unique nature of acute kidney injury in infants and its severe complications, a dedicated technology capable of managing blood purification and fluid balance in very small children is sorely needed. Therefore, we undertook a project to develop a continuous renal replacement therapy (CRRT) machine designed specifically for patients of less than 10 kg bodyweight (CARPEDIEM; Cardio-Renal Pediatric Dialysis Emergency Machine), particularly neonates and premature infants. Here we describe the development of the project and report the
first use of the CARPEDIEM for the treatment of a newborn baby with clinical indications for CRRT.

Methods
Development
We prospectively planned a 5-year project to conceive, design, and create a new miniaturised CRRT machine for neonates and small infants. First, we assessed the limitations and problems with existing CRRT technology and identified the technical and clinical requirements for a new device. The goal was to create a machine with reduced priming volumes and the capacity to accurately handle very low blood and ultrafiltration flows. In small children, total blood volume ranges 200 to 800 mL, and total body water ranges from 1 to 5 L.

To prevent hypotension during renal replacement therapy, we developed miniaturised circuits with a reduced priming volume (27 mL including filter) and new miniature roller pumps with the capacity to run continuously at a flow as low as 5–50 mL/min. Ultrafiltrate and replacement fluid pumps have the same degree of accuracy, running at 0–10 mL/min and being finely regulated by two precision scales accurate to 1 g. We developed the machine with three configurations, with filters of different surface areas to adjust for patient size (0·075, 0·15, and 0·25 m²). After designing two early prototypes, we developed a final working prototype that could be used for various treatment modalities—continuous venovenous haemofiltration in predilution or post-dilution modes, plasma exchange, blood exchange, and continuous venovenous haemodiafiltration or single-pass albumin dialysis (appendix).

Testing
We did complete in-vitro laboratory assessments of the functioning prototype in accordance with design specifications and regulatory requirements. Four independent operators (ZR, CR, FG, AB) took part in several sessions of in-vitro testing with specific objectives. We thoroughly tested flows, pressures, and safety features using dual-lumen catheters of different sizes (4 and 7 French; appendix).

Because in-vivo tests on critically ill babies would have exposed the patients to very high risks, we did extensive in-vitro tests to verify the functionality, accuracy, and reliability of the equipment, under the strict control of qualified technical and medical personnel (CR, ZR, MB, FC, AB, MZ). Tests included simulated treatments lasting for 24 h. After these tests, we did a general clinical assessment of the CARPEDIEM system, establishing the safety and technical capability of the device and its accessories.

First-in-human use
On Aug 29, 2013, we identified a neonatal patient with clinical indications for CRRT, and started treatment with the CARPEDIEM after receiving informed consent from the patient’s family and authorisation from the institutional board of San Bortolo Hospital (Vicenza, Italy). The patient was a female neonate who presented with a subgaleal haemorrhage (caused by vacuum extraction) and consequent haemorrhagic shock. Because of severe and persistent anaemia (haemoglobin less than 70 g/L) the patient was transfused several times (28 units of packed red blood cells and ten units of platelets). She was intubated and mechanically ventilated; after resuscitation and on admission to the neonatal intensive care unit she had severe thrombocytopenia, acidosis, and 63% fluid overload (bodyweight at birth, 2·9 kg; bodyweight at start of CRRT, 5·2 kg) with hyponatraemia and oliguria. Bleeding was controlled at the expense of a huge anasarca. We treated the patient with the diuretic drug furosemide, progressively increasing the dose 2 to 5 mg/kg per day, reaching a maximum of 16 mg per day.

72 h after birth we decided to start CRRT and a 5 cm dual-lumen 22 Ga (4 French) catheter was placed surgically into the femoral vein (no other vascular access was possible because of generalised oedema). The neonate was placed on post-dilution continuous venovenous haemofiltration with the CARPEDIEM. The blood-pump flow rate was set between 9 and 13 mL/min, depending on catheter access and return pressures, and a daily clearance between 2·2 and 2·8 L (a volume exchange close to patient’s total body water) was prescribed. The smallest configuration of the extracorporeal circuit was used (27 mL), allowing maximum haemodynamic tolerance. The CARPEDIEM was monitored continuously to ensure an accurate and reliable delivery of the prescribed treatment, a smooth resolution of alarms, and easy troubleshooting. Particularly, because these were the first prolonged in-vivo sessions, ultrafiltration bags were weighed during bag changes, which showed that net ultrafiltration never exceeded an error of 1 g/h.

Circuit changes were scheduled every 24 h on days when only CRRT was done and on demand when other techniques (blood exchange, plasma exchange, or single-pass albumin dialysis) were prescribed. No circuit had premature clotting or functional decay. No specific blood contact reactions were noted during extracorporeal treatments. Anticoagulation was not used initially because of the patient’s low platelet count. When the platelet count had normalised, small doses (2–3 international units per kg per h) of heparin were used as the sole anticoagulant. Citrate was not used and the machine is not currently equipped with specific citrate anticoagulation circuits. A commercially available haemofiltration bicarbonate solution (Bellco, Mirandola, Italy) was used for fluid reinfusion.

Results
After 30 months in development, the CARPEDIEM was approved for human use. The machine features
miniaturised components and fluid control capability suitable for newborn babies and small infants within a weight range of 2.5–10.0 kg (appendix). It can operate at a unique range of low flows and pressures, with an accuracy of fluid balance of about 1 g. All of these specifications have been thoroughly validated in several sessions of in-vitro laboratory tests done by four independent operators.

During in-vitro testing, circuits were run for 24 h, and no substantial differences in flow accuracy were noted when different sizes of dual-lumen catheters (4 and 7 French) were used. Our tests suggested an excellent accuracy of blood-pump flow rate, with an error of always less than 10%. Reinfusion or dialysis flow errors ranged from –8.0% to 7.5%. Importantly, whereas the accuracy of ultrafiltration always remained within the limit of 1 g/h, no substantial variation in relation to different transmembrane pressure and filtration rates was noted. Microhaemolysis was assessed by measurement of the normalised (by haematocrit) index of haemolysis. We tested three different assembly lines and dialysers in triplicate at maximum blood flow for 10 h. The observed microhaemolysis index (normalised index of haemolysis) was lower than 0.7 g of plasma free haemoglobin released per 100 L of blood pumped, and no differences were seen between the three types of circuit tested.

The name of the machine (CARPEDIEM; Cardio-Renal Pediatric Dialysis Emergency Machine) was chosen on the basis of its potential applications and the range of clinical conditions in which its use might be indicated. Situations in which CARPEDIEM might be used include post-cardiac surgery with fluid overload and renal impairment, and acute kidney injury from various causes in which uraemia, fluid overload, or electrolyte imbalances represent a life-threatening condition requiring urgent management with extracorporeal treatment. CARPEDIEM was developed in accordance with International Organization for Standardization (ISO) standards, both general (ISO 9000) and specific for medical devices (ISO 13485). The equipment system complies with the essential requirements of the European Medical Device Directive 2007/47/EC.

### Longitudinal clinical data and drugs used

<table>
<thead>
<tr>
<th>Clinical measurements</th>
<th>Birth</th>
<th>Day 1 (admission to ICU)</th>
<th>Day 4 (start of CRRT)</th>
<th>Day 10</th>
<th>Day 14</th>
<th>Day 25 (end of CRRT)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine (μmol/L)</td>
<td>56</td>
<td>214</td>
<td>141</td>
<td>64</td>
<td>159</td>
<td></td>
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<tr>
<td>Blood urea nitrogen (mmol/L)</td>
<td>6.4</td>
<td>34.6</td>
<td>59.3</td>
<td>80.3†</td>
<td>44.6</td>
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<tr>
<td>Urine output (mL/kg/h)</td>
<td>0</td>
<td>0.04</td>
<td>1.10</td>
<td>0.78</td>
<td>2.50</td>
<td></td>
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<tr>
<td>Fluid overload</td>
<td>0%</td>
<td>63%</td>
<td>33%</td>
<td>23%</td>
<td>12%</td>
<td></td>
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<tr>
<td>PaO2 (mmHg)</td>
<td>45.8</td>
<td>82.0</td>
<td>51.7</td>
<td>46</td>
<td>43.9</td>
<td></td>
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<tr>
<td>PaCO2 (mmHg)</td>
<td>42.1</td>
<td>51.0</td>
<td>52.3</td>
<td>50</td>
<td>42.2</td>
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<tr>
<td>PEEP (cm H₂O)</td>
<td>4.5</td>
<td>4.0</td>
<td>5.5</td>
<td>5.0</td>
<td>..</td>
<td></td>
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<tr>
<td>FiO2</td>
<td>..</td>
<td>..</td>
<td>..</td>
<td>..</td>
<td>..</td>
<td></td>
</tr>
<tr>
<td>Total bilirubin (μmol/L)</td>
<td>26</td>
<td>82</td>
<td>705</td>
<td>975</td>
<td>496</td>
<td></td>
</tr>
<tr>
<td>Conjugated bilirubin (μmol/L)</td>
<td>5</td>
<td>22</td>
<td>474</td>
<td>835</td>
<td>38</td>
<td></td>
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<tr>
<td>ALT (μkat/L, at 37°C)</td>
<td>0.63</td>
<td>10.86</td>
<td>29.011</td>
<td>2.67</td>
<td>..</td>
<td>2.49</td>
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<tr>
<td>Haemoglobin (g/L)</td>
<td>121</td>
<td>60</td>
<td>114</td>
<td>115</td>
<td>128</td>
<td>114</td>
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<tr>
<td>White blood cell count (&gt;10⁹/L)</td>
<td>31.8</td>
<td>17.0</td>
<td>15.9</td>
<td>22.6</td>
<td>45.6</td>
<td>19.7</td>
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<tr>
<td>Platelet count (&gt;10⁵/L)</td>
<td>236</td>
<td>39</td>
<td>17</td>
<td>6</td>
<td>10</td>
<td>46</td>
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<tr>
<td>Heart rate (beats per min)</td>
<td>150</td>
<td>182</td>
<td>155</td>
<td>140</td>
<td>159</td>
<td>144</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>..</td>
<td>35</td>
<td>52</td>
<td>62</td>
<td>88</td>
<td>103</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>..</td>
<td>13</td>
<td>42</td>
<td>43</td>
<td>49</td>
<td>58</td>
</tr>
</tbody>
</table>

**ICU**=intensive care unit. PaO₂=arterial blood oxygen tension. PaCO₂=arterial blood carbon dioxide tension. PEEP=positive end-expiratory pressure. FiO₂=fraction of inspired oxygen. ALT=alanine aminotransferase. *Continuous renal replacement therapy (CRRT) was provided for 6 h daily from days 21 to 25. †Measurement from day 15.

§Furosemide was also used (doses reported in figure 1).

**Table:** Longitudinal clinical data and drugs used
The table presents relevant clinical data for the first patient treated with CARPEDIEM from various timepoints before and during treatment. Although the raised creatinine and fluid overload began to be slowly but effectively corrected with initiation of treatment, the baby developed severe hyperbilirubinemia (up to 975 μmol/L total bilirubin) because of liver dysfunction and massive subgaleal haemorrhage reabsorption. Because the concentration of bilirubin was refractory to phototherapy and there was an urgent need to rapidly decrease bilirubin concentration to avoid secondary cerebral damage, the haemofiltration treatment was subsequently alternated with other modalities: blood exchange (three sessions with 475 mL blood volume exchanged at an isovolumetric exchange rate of 5 mL/min); single-pass albumin dialysis (two sessions of 17 h with 4% albumin dialysate); and finally plasma exchange (four sessions with 270 mL plasma volume exchange). CRRT was discontinued during these other procedures because of poor vascular access. Continuous venovenous haemofiltration with the additional bilirubin-targeted treatments led to a progressive normalisation of fluid overload, creatinine concentration, and bilirubin concentration (figures 1, 2).

The patient was supported with parenteral nutrition, calcium and phosphate supplementation, and intravenous infusion of antibiotics and antifungal drugs (because of positive bacterial and fungal cultures). After 7 days of CRRT, urine output had partly recovered to 1-2 mL/kg/h and had reached 3.2 mL/kg/h at 26 days. 25 days after birth and after more than 400 h of extracorporeal treatment, haemofiltration was discontinued. The patient was then extubated and she started to advance to complete oral alimentation. At this point she was in stable haemodynamic and respiratory condition, bodyweight was restored to 3·2 kg, and serum creatinine had stabilised at 248 μmol/L. After she had reached an adequate status of hydration, progressive physiological weight gain was allowed while a neutral daily fluid balance was maintained.

After 30 days the patient was breathing normally without supplemental oxygen, making adequate amounts of urine, and had normal liver function; at 39 days she was discharged from the intensive care unit. At hospital discharge 20 days later, she still had clinically significant chronic kidney dysfunction with a serum creatinine concentration of 194 μmol/L.

Without a dedicated CRRT platform, renal replacement therapy would have been impossible because of technical and clinical contraindication to peritoneal dialysis and an inability to achieve reliable vascular access for the use of existing machines. We hypothesise an inevitable fatal outcome would have occurred a few days after birth without the use of the CARPEDIEM.

Discussion
CARPEDIEM, a CRRT platform designed specifically for neonates and small infants, was successfully used to manage a critically ill neonate of 2·9 kg bodyweight with multiple organ failure and severe fluid overload (panel). In the past, CRRT machines designed for adults were adapted for paediatric use by simply modifying the
operational parameters via software and by using extracorporeal circuits with lower priming volumes. However, these modifications were adequate only for paediatric patients of more than 15 kg bodyweight. This technological gap has held back the provision of optimum CRRT in neonates, making treatment complex.

Additionally, the indications for renal replacement therapy in small infants have changed over the past 10 years, and the present trend is towards a wider range of applications, including prevention of fluid accumulation and organ support in multiple organ dysfunction syndrome. The development of continuous venovenous haemofiltration and continuous venous haemodiafiltration technologies has made extracorporeal treatments more reliable, but fluid management and treatment delivery has remained an issue with adapted adult machines. With CARPEDIEM, CRRT in neonates is feasible, accurate, and safe.

Different modalities can be used for the management of acute kidney injury in neonates. Classic intermittent haemodialysis might not be well tolerated in infants because of rapid fluid removal and osmotic shifts causing severe haemodynamic instability. Peritoneal dialysis is currently the renal replacement therapy treatment of choice in neonates, unless specific contraindications are present (eg, peritonitis, abdominal masses, or bleeding). However, in peritoneal dialysis, ultrafiltration and solute clearance occur rather slowly and efficiency can be suboptimal. CRRT could be preferable to peritoneal dialysis in some circumstances, especially in critically ill infants who present with fluid overload, sepsis, or recent abdominal surgery. After cardiac surgery, neonates undergo ultrafiltration and peritoneal dialysis during or soon after cardiopulmonary bypass weaning to remove fluid excess and inflammatory mediators. Although used regularly in several centres, the use of continuous and modified ultrafiltration or peritoneal dialysis is still debated. Survivors of CRRT tend to have less fluid overload than non-survivors at the time of CRRT initiation, especially in the setting of multiple organ dysfunction syndrome, independent of other factors. For infants, the effects of unpredictable ultrafiltration seen with peritoneal dialysis and fluid shift intolerance seen with intermittent haemodialysis are magnified, emphasising the need for highly accurate CRRT technology.

We believe that the CARPEDIEM has the potential to change the treatment of neonates with acute kidney injury. Although peritoneal dialysis will remain an important treatment for uncomplicated neonatal acute kidney injury, the ability to accurately and safely prescribe clearance and fluid balance with the routine use of a French dual-lumen catheter will provide a method of renal supportive therapy in neonates with common technical contraindications to peritoneal dialysis. Importantly, no previously available CRRT machine could operate with such a small catheter.

We realise that such small dual catheters are not readily available worldwide, with sizes 7 or 8 French often the smallest options available. However, such larger sizes might not be usable in all infants. In the case reported here, the necessity of using a 4 French catheter precluded the use of other available CRRT machines. For patients in whom larger catheters can be used, we believe that the CARPEDIEM’s performance would be even better.
CARPEDIEM is the first CRRT platform designed and developed for small paediatric patients and could change clinical practice with respect to the management of neonates with acute kidney injury. Additionally, the ability to combine extracorporeal treatments, such as plasma exchange, blood exchange, and single-pass albumin dialysis, with CRRT extends the range of supportive treatments for critically ill infants. We hope that the successful development of CARPEDIEM will encourage the development of other medical technologies (e.g., catheters, fluids, and monitors) specifically designed for infants and small children.

Contributors
CR conceived the machine, and contributed to its design, development, and medical application. He also contributed to the management of the patient, and the preparation and writing of the report. FG contributed to the design specification of the machine, the in-vitro and in-vivo data collection, the management of the patient, and the writing of the report. AB contributed to prescription and delivery of treatment and to the writing of the report. MZ contributed to the management of the patient and to data collection for all treatment parameters. MB contributed to the management of non-renal problems and the general management of the patient. SV contributed to the management of the patient as the attending physician and collected data for case description. FC did the surgical placement of the catheter and contributed to the writing of the report. ZR contributed to the development of the machine, the in-vitro testing, data collection, and the content of the report. SLG was the consultant for paediatric continuous renal replacement therapy, contributed to the design specifications for the machine, and provided input into the prescription parameters for the patient. He also made a substantial contribution to the content of the report.

Declaration of interests
We declare that we have no competing interests.

Acknowledgments
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References


