Arterial hypertension and unusual ascending aortic dilatation in a neonate with acute kidney injury: mechanistic computer modelling

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Abstract

Background: Neonatal asphyxia caused acute kidney injury and severe hypertension in a newborn patient. An unusually dilated ascending aorta developed within a few weeks. Dialysis and hypertensive treatment led to partial recovery of the aortic diameters. It was hypothesized that the aortic dilatation may be associated with cardiovascular changes induced by the acute kidney injury. Mathematical modelling was used to better understand the underlying mechanisms of hypertension and aortic dilatation.

Methods: Patient observation included systolic blood pressure recording and echocardiographic exams. To explore underlying mechanisms of aortic dilatation and hypertension, a previous whole-body lumped parameter hemodynamics model was adapted to this study. Computer simulations were designed to permit dissection of individual mechanisms. The hypertension inducing effects of altering systemic vascular resistances, stiffnesses, and heart rate on blood flows and pressures were simulated.

Results: In agreement with our clinical diagnosis, the mathematical model showed that an increase of systemic small vessel resistance is the prime cause of hypertension. Further, aortic stiffening may also cause hypertension, it was found to be secondary to the potency of systemic small vessel resistance. The cardiac output, as quantified using pressure-volume loop area, reduced significantly due to hypertension. Simultaneous left ventricle hypertrophy and small vessel blocking increased ascending aorta blood flow as well as pressure indicating an enlarged ascending aorta. In contrast, increased arterial stiffness appeared to lower the aortic blood flow and pressures.

Conclusions and discussion: Systemic small vessel resistance is an important factor in arterial hypertension, and may also be a key clinical therapeutic target. Left ventricle hypertrophy may also be simultaneously ameliorated when treating systemic small vessels. Treatment of arterial stiffness appears to provide significant benefit but may be secondary to treatment of the systemic small vessels. The quantitative grading of pathophysiological mechanisms provided by the modelling may contribute to treatment recommendations. Further development and individualization of the model will augment its applicability in clinical practice.

1. Introduction

1.1 Clinical Background: The mechanisms of ascending aortic dilatation secondary to arterial hypertension appear to be related to loss of aortic wall elasticity causing the artery's stiffening (Milan *et al.*, 2013). Aortic dilatation has recently been identified as a frequent complication of chronic kidney disease (Kaddourah *et al.*, 2015). Patients with kidney injury often have simultaneous aortic abnormalities as well as peripheral and pulmonary vasculature abnormalities. In this study, we present the development of severe and reversible aortic dilatation in a neonate with acute kidney injury, both of which may be related to arterial hypertension and ascending aorta dilatation. The patient developed arterial hypertension owing to volume overload despite dialysis. A validated lumped parameter computer model of whole-body hemodynamics was used to explore the effects of vascular resistances and arterial stiffnesses on blood pressures and flows.

1.2 Biophysical modelling background: *In silico* biophysical modelling is now an established diagnostic-prognostic methodology which is increasingly assisting clinicians in their practice (Marsden, 2013). Recent studies by Kharche *et al.* (Kharche *et al.*, 2017; Kharche, 2018) demonstrate the application of modelling in the interpretation and integration of clinical-imaging-experimental data to enhance knowledge and understanding. Mathematical models integrate multiple individual processes to simulate emergent behavior in complex biological systems such as the focus of this study, i.e. whole-body hemodynamics. Further, a mathematical model is an ideal tool to dissect the roles of individual processes on the complex system's emergent behavior. Modelling of hemodynamics deploys a multi-scale methodology that involves lumped parameter (0D) to spatially extended (1D and 3D) components that can be personalized to patient measurements (Marsden & Moghadam, 2015; Caruso *et al.*, 2016). Whereas spatially extended (1D, 2D, and 3D) modelling permits computation of relevant quantities such as velocity profiles and accurate wall shear, they remain computationally intensive. In contrast, 0D models based on Windkessel elements are themselves powerful tools that incorporate blood vessel resistances, stiffness, and flow reserve (see Supplementary Materials, Table S1 for electrical-hemodynamic equivalence of components) as well as being computationally tractable (Korakianitis & Shi, 2006b; Heldt *et al.*, 2010; Shi *et al.*, 2011). The presented numerical results are based on the 0D model by Korakianitis and Shi (Korakianitis & Shi, 2006a). It was adapted because it is validated using clinical data, as well as encompasses biological information relevant to this study.

1.3 Clinical-computational aims: In line with our clinical hypothesis, the aims of this study were to:

- i. identify mechanisms in the model (Korakianitis & Shi, 2006a) based on blood vessel resistances, stiffness, and heart rate that promote hypertension and aortic dilatation;
- ii. demonstrate the associated effects of hypertension inducing processes; and
- iii. identify upstream causes of ascending aortic dilatation.

2. Case Report

The patient was born at term by Caesarean section with fetal heart rate decelerations following induction of labor for premature rupture of membranes at 41 + 6 weeks of gestation. APGAR (appearance of skin color, pulse providing heart rate, grimace responses to assess reflexes, activity to assess muscle tone, and respiration assessed using breathing rate and effort) scores were 2, 7, 7 (risk of high mortality) at one, five and ten minutes, respectively (Natarajan *et al.*, 2013). The patient required resuscitation with positive pressure ventilation. The patient developed significant hypotension and poor perfusion needing fluid bolus and vasopressors.

The patient developed acute kidney injury with oligoanuria and hematuria needing peritoneal dialysis by day 5 of life, which was continued for 9 days. This treatment was based on sudden onset anuria, macrohematuria, hypertension, bilaterally large kidneys on ultrasound with high resistive indices exceeding 1 (normal 0.7-0.8, (Bude *et al.*, 1992)) and low blood flow in the apparent patent renal veins, as well as transient thrombocytopenia, the diagnosis of bilateral renal vein thrombosis was assumed, although no thrombus was seen in the vena cava (Resontoc & Yap, 2016). Dialysis was stopped because the patient regained sufficient urinary output.

Contrast angiography was avoided given the patient's critical status. Heparin therapy was also avoided because of concerns of intracranial bleeding. Despite the continuous dialysis treatment (hourly dwells using 2.27% physioneal at 10 mL/kg) with reasonable ultrafiltration up to 1.5 mL/kg/h, she developed arterial hypertension with blood pressures consistently above the 99th percentile. She was therefore given a 5-day course of amlodipine with good initial response, but at one month of age the blood pressure increased again to > 99th percentile (National High Blood Pressure Education Program Working Group on High Blood Pressure in & Adolescents, 2004), requiring ongoing anti-hypertensive therapy, including the addition of enalapril. Figure 1A shows systolic blood pressure in the first month of life. Echocardiogram was performed at day one of life showing normal cardiac structure and normal ascending aortic diameter, as well as two small muscular ventricular septal defects. The repeated echocardiogram at 1 month of age showed significant ascending aortic dilatation (see Figures 1B). Aortic dilatation was reduced considerably by month 5. Weight and heart rate are shown in Figure 1C. Clinically the patient did not have stigmata of Marfan's or Loeys-Dietz syndromes.

3. Computational Methods

3.1 Clinical data interpretation, blood pressure measurements: Clinical systolic blood pressure recordings were averaged over 3 days (Figure 1A) and compared to the average healthy systolic blood pressure of a neonate which is approximately 100 mmHg.

3.2 Clinical data interpretation, ascending aortic diameter assessment: Parasternal long-axis view echo

exams were performed to assess ascending aortic diameters. Four echo exams were recorded using a commercially available echocardiographic machine Philips iE33 each at day 1, day 30, day 60, and day 150. The pixel size in the echo images was $DX = 0.075$ mm and $DY = 0.075$ mm. From each exam, individual frames for the duration of 1 cardiac cycle were extracted. In each exam, four diameters (Figure 1B, inset) namely the outflow tract, sinuses of Valsalva, sinotubular junction, and tubular ascending aorta diameters were measured according to clinical recommendations (Evangelista *et al.*, 2010; Flachskampf *et al.*, 2014). The measurements were performed using our semi-automatic segmentation method based on ImageJ-FiJi software (Schindelin *et al.*, 2012). Details of the segmentation method are provided in Supplementary Materials, Section S1.

3.3 Biophysical model implementation: The model (Korakianitis & Shi, 2006a) consists of coupled hemodynamic inter-relationships described by ordinary differential equations, and was obtained from CellML repository (Beard *et al.*, 2009). It was implemented in both MATLAB and C languages. The equations were solved using our in house robust implicit solvers as described previously (Kharche *et al.*, 2014; Kharche *et al.*, 2017). Preliminary simulations were performed using the MATLAB version to prototype and assess overall behavior. The numerically efficient C version was used in the larger parameter sweep simulations. The model codes used in this study are available from the corresponding author.

3.4 Simulation protocols: The model and its components are illustrated in Figure 2. The model consists of a systemic loop, pulmonary loop, and representations of the heart chambers and corresponding valves. The hemodynamic loops consist of various large and small blood vessels whose resistances and compliances are implemented as shown. The heart has four chambers and uni-directional blood flow values. Each chamber pumps blood to the next downstream component of the model. The pumping strength of each chamber is summarized by its elastance, E . In particular, E_{lv} dictates the elastance of the left ventricle and oscillates sinusoidally between a maximum ($E_{lv,max}$) and minimum ($E_{lv,min}$) values.

In all simulations, parameter values were chosen and 1000 seconds of hemodynamics activity simulated to provide dynamics that were independent of initial conditions. The final 20 seconds of data were analyzed to generate results. In simulation experiments, model parameters were assigned the following case specific interpretation. The systemic artery resistance, R_{SAT} , represented aortic resistance; the systemic capillary bed resistance, R_{SCP} , and systemic arterioles resistance, R_{SAR} , represented small artery resistances; the systemic vein resistance, R_{SVN} , represented the vena cava resistance; the systemic aortic sinus resistance, R_{SAS} , represented the coronary vasculature resistance; the systemic artery capacitance or compliance, C_{SAT} , represented the inverse of aortic stiffness; and the systemic artery inductance, L_{SAT} , represented the aortic flow reserve. The main modeling parameters are highlighted in gray in Figure 2. The model behavior was characterized by systolic and diastolic values of pressures and blood flows. Specifically, the following were recorded in all simulation experiments: left ventricle systolic blood pressure, P_{lv} ; systemic artery systolic

blood pressure, P_{SAT} ; systemic vein pressure, P_{SVN} ; pulmonary artery and vein pressures, P_{PAT} and P_{PVN} respectively; coronary sinus pressure, P_{SAS} ; aortic root blood flow, Q_{AO} , systemic artery flow, Q_{SAT} , coronary sinus blood flow, Q_{SAS} ; systemic vein blood flow, Q_{SVN} ; pulmonary artery and vein blood flow, Q_{PAT} and Q_{PVN} respectively. $E_{IV,max}$ was taken to represent an increase in left ventricle wall thickness. In addition, a pressure-volume loop was constructed and its area which represented the ventricular stroke volume work was computed. Baseline model behavior is illustrated in Figure 3. All model parameters and variables used in this study are listed in Supplementary Materials, Tables S2 and S3.

3.5 Modelling definitions of clinical conditions: Within the scope of the model, the following definitions were used. Parameters in the systemic loop were used in all simulation experiments. The volume overload due to the acute kidney injury, as well as autoregulatory responses such as to the renin-angiotensin-aldosterone system were assumed to increase systemic loop resistances. Compliances were reduced to simulate increase of stiffness. The effect of increased heart rate was simulated by altering the pacing period of the heart as described in the model (Korakianitis & Shi, 2006b, a). Finally, it is also known that kidney injury may cause cardiac hypertrophy. Left ventricle hypertrophy was simulated by increasing the maximum elastance as described in the model (Korakianitis & Shi, 2006b, a). Multiple outputs characterized hypertension, venous flow status, pulmonary sufficiency, and ascending aortic size. Increase of systemic artery systolic pressure (maximum of P_{SAT} waveform) was defined as hypertension. Simultaneous increase of flow through the aortic valve, Q_{AO} , and left ventricle systolic pressure, P_{LV} , was assumed to be directly proportional to ascending aortic size. The flows in the systemic vein (or vena cava), Q_{SVN} , pulmonary artery, Q_{PAT} , as well as the pressure in the pulmonary artery, P_{PAT} , were used to assess status of venous flow and pulmonary sufficiency. The left ventricle pressure, P_{IV} , and volume, V_{IV} , were recorded to construct pressure-volume loops. Areas of pressure-volume loops represent cardiac stroke work and were used to compare cardiac status under normal, hypertensive, hypertrophied, and other conditions.

3.6 First order dynamic sensitivity analysis: Mathematical sensitivity analysis was performed to assess the sensitivity of relevant variables (e.g. systemic artery pressure, P_{SAT}) to hypertension and aortic dilation inducing parameters (e.g. arterial resistances, R_{SAR}) under various pathophysiological conditions. The analysis was designed to demonstrate the effectiveness of treatments. The sensitivity of state variables to modeling parameters was computed using dynamic sensitivity analysis (Gul & Bernhard, 2015; Gul *et al.*, 2016). Whereas global sensitivity measures provide information regarding overall model metrics (Kharche *et al.*, 2009), the present model was analyzed using dynamic sensitivity measures (Saltelli, 2002; Ferretti *et al.*, 2016). The definition of the dynamic sensitivity index is derivative based. For a given variable V_i , and a parameter p_j , the normalized sensitivity index of V_i with respect to p_j at a given parameter value $p_j = p_{j,o}$ is defined as:

$$S_{ij} = \frac{\partial V_i}{\partial p_j} \quad \text{Equation 1.}$$

The indices S_{ij} were computed using finite difference based direct differentiation. S_{ij} were computed for each (V_i, p_j) combination of interest. As S_{ij} is local, it was computed under control and pathological conditions to permit assessment of the changes in sensitivity of relevant variables V_i to p_j at different values $(p_{j,o1}, p_{j,o2}, \dots)$, thus permitting to assess the maximum effectiveness of a given treatment in a range of parameter values. The sensitivity indices of equation 1 were computed at two heart rates, corresponding to periods of 1 s (normal heart rate) and 0.5 (high heart rate). The pathological conditions were simulated by increasing R_{SAR} by 25 fold, reducing C_{SAT} (to simulate increased arterial stiffness) to 0.25 of its baseline value, and increasing E_{IV} by 10 fold. The simultaneous implementation of these hypertension inducing alterations was assumed to partially serve as a model of the patient's status. The interpretation of the sensitivity indices, S_{ij} , was performed as follows. S_{ij} curves of a variable V_i with respect to a parameter p_j in the baseline and pathological state were compared. If S_{ij} was found to be positive, V_i was deemed to increase as p_j increased. If S_{ij} was negative, then V_i was deemed to reduce as p_j increased. If S_{ij} increased under pathological conditions in comparison to baseline conditions, then treatment that brought parameter p_j to physiological values would be preferred over other treatments that altered $p_k, k \neq j$.

4. Results, clinical observations

As shown in Figure 1A, the systolic arterial blood pressure increased in the initial stages of treatment. However, the pressure normalized within a month. The blood pressure remained well controlled on a combination therapy of amlodipine (0.24 mg/kg/day, dosing range is 0.1-0.5 mg/kg/day), enalapril (0.15 mg/kg/day, dosing range is 0.1-0.5 mg/kg/day). The patient was continued on a combination of amlodipine and enalapril. The home blood pressure readings using an aneroid device are within the 50th percentile (Flynn *et al.*, 2008).

The neonate's first echocardiogram at day one showed normal tri-leaflet aortic valve, a normal mitral valve with no evidence of mitral valve prolapse, two small muscular ventricular septal defects, normal left ventricular mass 45 g/m², and normal ascending aortic diameter 1.1 cm with a Z score (Warren *et al.*, 2006) of 0.95 (Figure 4, A). Echocardiogram was repeated at one month of life, which showed increased left ventricle mass 105.3 g/m², moderate ascending aortic dilatation 1.6 cm with a Z score of 4.88 (Figure 4, B). At two months of age, the ascending aortic diameter was 1.5 cm, at five months of age the aortic diameter remained at 1.5 cm (Z score 2.81) and 12 months the ascending aortic diameter was normal for weight and height measuring 1.4 cm (Z score 1.37). As the dimensions of the heart constantly change in a growing child, cardiac dimensions are compared using age-independent standard deviation scores or Z

scores. Further analysis of the echo images (Figure 1B) show four standard ascending aortic diameters. Each of the diameters increased at one month. After 1 month and up to 6 months, all diameters consistently reduced closer towards physiological values. Representative echocardiography images are presented in Supplementary Materials Figure S1. At last follow up, the aortic dimensions returned to the normal range (data not shown).

5. Modelling results

5.1 Interpretation of the clinical data, systolic blood pressure recordings and urine measurements: As shown in Figure 1A, the systolic blood pressure changed significantly over the period of the month. Immediately after dialysis onset, the systolic blood pressure reduced markedly. Systolic blood pressure increased by over 27% from 90 mmHg (day 1, normal range 67-84 mmHg) to 115 mmHg (day 15, normal range 72-104 mmHg) showing hypertension. With anti-hypertensive treatment, the systolic blood pressure reduced to around 105 mmHg (normal range 72-104 mmHg) after dialysis was stopped.

5.2 Interpretation of the clinical data, ascending aortic diameters over first six months of patient's life: Analysis of the echocardiography based four ascending aorta diameters (Evangelista *et al.*, 2010; Flachskampf *et al.*, 2014) per cardiac cycle is shown in Figure 1B. The corresponding frame-by-frame variation of the same diameters over a few cardiac cycles is shown in Supplementary Materials, Figure S2. The outflow tract, which is the closest to the left ventricle, showed an increase in it's diameter after which it reduced. In comparison, the diameters measured further away from the ventricle increased over the course of one month, and recovered partially by month five. However, dialysis and anti-hypertensive treatments can be seen to be effective as all diameters reduced significantly after month one of the patient's life. Because of the treatments, the outflow tract diameter reduced by 5% at month 5, while the diameters of sinus of Valsalva, sinotubular junction, and tubular ascending aorta remained at 25.1%, 14.8%, and 17.1% higher as compared to day one diameters. A negative change signifies a reduction of diameter at the end of dialysis-antihypertensive therapies, whereas a positive change signifies sub-optimal reduction of diameter. Therefore, the effect of altering aortic flow (which is directly related to aortic diameter) on model simulated pressures and blood flows in the body was explored.

5.3 Interpretation of the clinical data, other measurements: During dialysis, the patient's urine output was alarmingly negligible. The patient was under weight (Figure 1, Ci) (Meyers *et al.*, 2013). She also had a high heart rate (Figure 1, Ci), in contrast to the development in healthy children where the heart rate decreases during the first month of life (Fleming *et al.*, 2011). These observations led us to investigate the causes of systolic blood pressure and reduced venous blood flow. The roles of hypertension inducing factors on pulmonary circulation were examined using the model, to test its predictive capability. Finally, the model was used to identify the upstream causes of aortic dilatation.

5.4 Baseline model: The model's baseline behavior is shown in Figure 3. The left ventricle and systemic artery (i.e. aorta) generate a systolic blood pressure of 120 mmHg (Figure 3, Ai). The systemic vein has a blood pressure of approximately 15 mmHg (Figure 3, Ai). The pulmonary artery has a systolic blood pressure of 50 mmHg in the model, but a much higher diastolic blood pressure compared to the right ventricle (Figure 3, Aii). The pulmonary vein, in contrast, has a markedly low pressure as well as oscillation amplitude (gray line in Figure 3, Aii). The blood flows in the left ventricle, systemic artery (aorta), and systemic vein (vena cava) are shown in Figure 3, Bi, and of the right ventricle, pulmonary artery, and pulmonary vein in Figure 3, Bii. The model baseline behavior was further characterized by the pressure-volume loop and its area (Figure 3, C).

5.5 Small systemic blood vessel resistance and stiffness cause hypertension: The dependence of systolic arterial blood pressure on model parameters is shown in Figure 4. It was found that the small vessels (capillary and venules) resistances, R_{SAR} and R_{SCP} respectively, were the most significant factors inducing hypertension (Figure 4, Ai). An increase of resistances of larger blood vessels (R_{SAT} or R_{SAS}) also has an appreciable but second to R_{SAR} and R_{SCP} effect. Increasing R_{SAR} and R_{SCP} also reduced the systolic arterial flow, Q_{SAT} (Figure 4, Aii). In contrast, the large vessel stiffness was the most dominant factor affecting systolic arterial blood pressure (Figure 4, Bi) and systolic arterial blood flow (Figure 4, Bii). Finally, an increase of heart rate (i.e. reduction of pacing period) caused both systolic blood pressure and flow to rise (Figure 4, Ci and Cii).

5.6 Effects of hypertension inducing factors on systemic vein flow: Figure 5, A illustrates the effects of altered systemic arteriolar resistance on systemic vein flow, Q_{SVN} . As the small vessel arteriolar resistances increased, venous flow reduced, which is in accordance with the clinical observation of low urine output. Further, as systemic artery stiffness was increased the venous flow reduced (Figure 5, B). As expected, a higher heart rate promoted a higher venous flow (Figure 5, C). The size of the aortic valve opening had an insignificant effect of venous flow (Figure 5, D), or other hemodynamic outputs.

5.7 Effects of hypertension inducing factors on pulmonary circulation: Figure 6 shows that the dominant factors that induce arterial hypertension also cause pulmonary insufficiency. Figure 6, Ai and Aii show that an increase of systemic arteriolar resistance significantly reduced both, the pulmonary pressure (P_{PAT}) and flow (Q_{PAT}). In contrast, P_{PAT} and Q_{PAT} are both increased due to stiffness in the systemic artery.

5.8 Alterations to cardiac stroke work: The pressure-volume loops under four conditions are shown in Figure 7. The four conditions were baseline, R_{SAR} (i.e. increased peripheral resistance), reduced C_{SAT} (i.e. increased aortic stiffness), and an increased heart rate. In all pathological cases, the areas of the pressure-volume loops were significantly smaller than that of that in the baseline case.

5.9 Hemodynamic effects of simultaneous ventricle hypertrophy and increased peripheral resistance: The patient's comorbid condition of simultaneous cardiac hypertrophy and systemic small vessel blocking was

mimicked by simultaneously altering left ventricle elastance and arteriolar resistance (Figure 8). The simulations were performed at two heart rates, corresponding to periods of 1 s taken to be normal, and 0.5 s taken to be high heart rate. The ascending aorta blood flow increased due to increased hypertrophy (Figure 8, Ai and Bi). However, as the peripheral resistance increased, the increase of the blood flow due to hypertrophy reduced (Figure 8, Ai and Bi). However, the aortic pressure increased due to hypertrophy, and that increase was exacerbated by an increased peripheral resistance (Figure 8, Aii and Bii). The pulmonary pressure was affected in a similar manner to the aortic pressure (Figure 8, Aiii and Biii). Whereas stroke work increased due to hypertrophy alone, an increased peripheral resistance blunted the effect of hypertrophy on stroke work (Figure 8, Aiv and Biv). Finally, the effects described above were more marked at a higher heart rate (Figure 8, left column) as compared to those at normal heart rate (Figure 8, right column panels).

5.10 Hemodynamic effects of simultaneous ventricle hypertrophy and arterial stiffening: The patient's comorbid condition of simultaneous cardiac hypertrophy and ascending aortic dilatation was mimicked by simultaneously altering left ventricle elastance and arterial stiffness (Figure 9). Note that arterial stiffness increased as arterial compliance were reduced. Figure 9 has been constructed using compliance parameter rather than stiffness to avoid conversion scaling and maintain a straightforward reading of the model parameters. An increase of ventricular hypertrophy simultaneous to stiffening caused a reduction of ascending aorta blood flow (Figure 9, Ai and Bi). However, increased stiffening promoted hypertension which was exacerbated by the hypertrophy (Figure 9, Aii and Bii). The effects of stiffening on pulmonary artery pressure (Figure 9, Aiii and Biii) appear to be secondary to those effected by increase of systemic small vessel resistance (see Figure 8, Aiii and Biii). In contrast to the effects of thrombosis (Figure 8, Aiv and Biv), arterial stiffening was seen to increase stroke work which was exacerbated by hypertrophy (Figure 9, Aiv and Biv).

5.11 Dynamic sensitivity analysis testing effectiveness of treatments in extreme regions of parameter space: Sensitivity of P_{SAT} and P_{PAT} to parameters R_{SAR} , C_{SAT} , and E_{IV} is shown in Figure 10. The systemic arterial pressure, P_{SAT} , is positively sensitive to the microvasculature resistance, R_{SAR} (Figure 10, Ai). In contrast, P_{PAT} is negatively sensitive to R_{SAR} (Figure 10, Aii). Further, under pathological conditions, the absolute sensitivity of P_{SAR} to R_{SAR} increased (Figure 10, Ai, gray line) but the sensitivity of P_{PAT} to R_{SAR} reduced (Figure 10, Aii, gray line). This indicates that reduction of arterial pressure (i.e. treatment of hypertension) may be effective by treatment of systemic microvasculature resistance inducing mechanisms. However, a singular treatment of R_{SAR} may not alleviate pulmonary insufficiency. As seen in Figure 10, Bi, P_{SAT} is significantly sensitive to arterial stiffness. Simultaneously, the pulmonary arterial pressure, P_{PAT} , has a negative sensitivity to arterial stiffness (Figure 10, Bii). In both cases, the sensitivities are low under baseline conditions and increase significantly under pathological conditions. Thus, there is significant

advantage in treatment of arterial stiffness which will lead to both, alleviation of hypertension as well as improvement of pulmonary function. It appears that systemic and pulmonary arterial pressures are both more sensitive to cardiac elastance under baseline conditions as compared to pathological conditions (Figure 10, Ci and Cii respectively). Thus, treatment of left ventricle hypertrophy may be less important than treatment of R_{SAR} and C_{SAT} . Under a faster heart rate, it was found that the sensitivities were qualitatively similar to those found at heart rate of 1 s. Results at heart rate of 0.5 s for P_{SAT} are shown in Figure 11.

6. Conclusions

6.1 Clinical conclusions: Figure 1 shows the systolic blood pressures of the patient, which increased as dialysis progressed and decreased as anti-hypertensive therapy was given and dialysis stopped owing to some recovery of renal function. The patient had a high heart rate and was volume overloaded (Figure 1, Ci). The patient's heart rate increased, instead of decreasing which is expected for normal paediatric development. In addition, the patient was underweight. Both observations lead us to believe that the acute kidney injury, in the form of renal vein thrombosis, had an undesirable impact on the patient's hemodynamics. Echocardiograph revealed that the patient's aortic root dilated (Figure 2) during dialysis and failed to recover completely after a 6-month period. This observation presents a measurable quantity that is linked to multiple causal factors of hypertension highlighted in this study.

6.2 Mechanistic lumped parameter modelling conclusions: The indicative modelling results presented in this study confirmed as well as revealed multiple pathophysiological mechanisms. Firstly, the primary cause of hypertension could be identified as increased resistances of the smallest blood vessels, namely resistances of the systemic arterioles and venules. In our model arterial stiffening, left ventricular hypertrophy and faster heart rate were associated with arterial hypertension. It may be noted that an increase of systemic resistances reduced both, the systolic pressure and the systolic flow (Figure 4, Ai and Aii). In contrast, increased stiffness increased the systolic pressure but promoted reduced flow (Figure 4, Bi and Bii and Figure 5, A and B). In any case, the model suggests that the same systemic mechanisms that induce hypertension have a significant effect on the pulmonary circulation. Increased systemic small vessel thrombosis, i.e. increased systemic arteriolar resistance, reduced both the pulmonary artery pressure as well as flow. In contrast, stiffening of the systemic artery significantly elevated pulmonary pressure and flow. However, the effects of small vessel thrombosis may be more significant than systemic artery stiffening. Further, the major hypertension inducing mechanisms may also be responsible for severely reducing venous blood flow, which may provide some explanation for the observed severely reduced urine in the patient. Although hypertension increases the amplitude of the arterial pressure's waveform, it may not promote

better cardiac function under pathological conditions due to loss of blood movement. Increased left ventricle hypertrophy, simulated by increasing left ventricle elastance E_{lv} in this study, increased the pressure of blood ejected from the left ventricle. The increased pressure causes blood to flow at a higher pressure into the aorta, simultaneous to high systemic resistance (Figures 8 and 9). As the model shows, ventricular hypertrophy promotes an increased pumping pressure as well as large blood flow out of the ventricle, leading to the conclusion that ventricular hypertrophy is a close upstream cause of aortic dilatation. The sensitivity analysis (Figures 10 and 11) revealed that treatment of arterial stiffness may be effective in improving systemic and pulmonary functions simultaneously. Importantly, it indicates that other clinical measurements such as diastolic values of pressures are also valuable and may assist in diagnosis and treatment design.

7. Model limitations

For efficacy, 0D models should be further informed by 3D simulations and experimental-clinical data to produce physiological flow rates and pressures. The Windkessel parameters can be estimated using non-invasive and routine clinical measurements such as systolic and diastolic pressures, as well as heart rates. 0D models can also be calibrated for patient-specific geometries and measurements (Lambermont *et al.*, 1998; Molino *et al.*, 1998; Kind *et al.*, 2010; Ismail *et al.*, 2013). However, the calculation of velocity fields, wall shear will require 1D and potentially 3D simulations. It can be appreciated that spatially extended simulations of any biological phenomena are computationally intensive, see a past high performance computing study (Kharche *et al.*, 2008).

In our model, the global stress and strain of the heart tissue was not estimated. Other models can shape blood vessels and the walls of heart by adapting signals from mechanically loading the tissues (Arts *et al.*, 2005). Further, the deviations of variables from their target value due to observed clinical changes of geometry may quantitatively affect the presented results (Arts *et al.*, 2012). Suitable future developments are being implemented to account for regurgitation. In future studies, our codes will be augmented to include more sophisticated mechanisms (Arts *et al.*, 2005). Whereas limitations have been identified, the results presented in this work will remain unaffected in the qualitative information they have provided.

Although biophysically detailed, the presented results must be considered cautiously bearing model limitations in mind. Firstly, the model is devoid of an explicit aortic root representation which have limited our capability to simulate its effects directly. More importantly, the model does not encompass autoregulation and baroreflex mechanisms as used by Heldt *et al.* (Heldt *et al.*, 2010). These important feedback and feedforward mechanisms may further explain the return of aortic root size to normal values upon treatment of the hypertension. The model will benefit from incorporating these mechanisms in our future studies. To this end, we are undertaking a clinical-imaging-computational study that will permit

further development and importantly personalization of such models, as done in Duanmu *et al.* (Duanmu *et al.*, 2018). Furthermore, the model is not designed to simulate essential hypertension which will require further model development. At present, we assessed the suitability of the model to reproduce, at least qualitatively, our clinical observations. As the model was found to be able to simulate the effects of thrombosis and hypertension, we intent further developing it to include more physiological features that will assist our future clinical-imaging research. Finally, quantitative *in silico* study of the complex biochemistry and gene regulation is beyond the scope of the modelling but should be addressed to further improve our clinical practices.

8. Clinical discussion

We demonstrated for the first time clinically acute ascending aortic dilatation secondary to arterial hypertension in a neonate, this improved when the blood pressure was controlled. Aortic dilatation in neonates is seen in patients with connective tissue disorders like Marfan's or Loeys-Dietz syndrome, it is also seen in patients with bicuspid aortic valve, however to our knowledge there are no reports of arterial hypertension causing dilatation in neonates (Zarate *et al.*, 2015).

To understand the possible mechanisms that would lead to transient proximal aortic dilatation we need to discuss the physiology the arterial tree. The arterial tree has two functions; first it acts as a conduit relying on width of the arteries and systemic vascular resistance, the second function is to ensure continuous steady flow in systole and diastole by dampening pressure oscillations cause by the intermittent ejection from the left ventricle (Windkessel effect). The arterial blood pressure wave increases as it travels away from the heart, this wave amplification is due to the summation of forward and reflective waves, the reflective waves are higher further away from the proximal aorta (London & Pannier, 2010). The way that the arterial tree adapts to increased blood pressure is by increasing the stiffness and thickness of the arteries, with a gradient from proximal (more compliant and thinner wall) to distal (increased stiffness and thicker walled), which is due to the differences in the medial layer of the aorta, composed by bands of elastin filaments, collagen fibers and smooth muscle cells; there is a higher concentration of elastin filaments and less vascular smooth muscle cells the thoracic aorta and less elastin filaments and more vascular smooth muscle cells in the abdominal aorta (Wolinsky & Glagov, 1969; Humphrey & Na, 2002). The smooth muscle cells have an important role as they contract when subjected to increased blood pressure (Bayliss, 1902), furthermore they become hypertrophied in chronic arterial hypertension to maintain normal wall stress (Berry & Greenwald, 1976). These proprieties ensure that the wall stress remains normal. Using the Laplace law we can calculate the wall stress by the formula $H = (P \cdot r) / 2T$. Where H is the circumferential wall stress, P is the transmural pressure gradient, r in the radius and T is the wall thickness; therefore, for a given transmural pressure and aortic diameter there must be a proportional wall thickness to maintain normal wall stress.

In our case the acute elevation of arterial hypertension without a compensatory thickening of the wall, would increase the wall stress and produce aortic dilatation, this was reverted when the blood pressure was controlled and was not likely related to the kidney injury per se. This is different in children and young adults with arterial hypertension where prevalence of ascending aortic dilatation is 10% this is usually associated with increased ventricular mass, and it appears to be chronic phenomenon (Totaro *et al.*, 2016). In summary, this neonate with acute kidney injury and subsequent CKD had normal aortic dimensions after birth and developed significant aortic dilation within one month due to arterial hypertension. Upon aggressive control of the hypertension, the aortic dilation normalized. This case proves that arterial hypertension needs to be added to the causes of aortopathy in CKD patients.

9. Model discussion

The current model permits exploration of overall blood flow and pressure dynamics in the whole body. Although relatively simple as compared to other contemporary models, it has a large number of variables and parameters that have been validated using clinical data. Therefore, as a first recourse, use of the Shi model is justified. However, in future studies, more detailed representations (OD or otherwise) of organ and whole-body vasculature is required to further permit application of computer models to clinical utility. This is relevant as several clinically identified mechanisms are known to be present (Figure 12). Whereas partly detailed models are already available, integrating them into one consistent representation of the whole human remains a challenge. The model was however capable of simulating baseline pressures and flows (Figure 3). Further, it assisted to highlight the most effective parts of the anti-hypertensive therapy with and without thrombosis.

10. Take home messages

10.1 Clinical

1. To the best of our knowledge, this is the first case report in newborn with arterial hypertension secondary to acute kidney injury who developed significant aortic dilation in one month which was reversible on stringent blood pressure therapy.
2. Ascending aorta dilatation may develop very quickly in a patient with arterial hypertension. The dilatation can be explored as a potential diagnostic marker of arterial hypertension, especially since it can be examined non-invasively using echocardiograms as done in the clinical part of this study.

10.2 Model

- i. Micro-vasculature should be treated for most effective treatment of hypertension.
- ii. In the treatment of hypertension, arterial stiffness is important, but secondary to micro-vascular

resistance.

iii. Cardiac hypertrophy is the immediate upstream factor promoting a dilated ascending aorta.

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Author contributions: LD, GF, and CWM designed and performed the clinical diagnostic exams, and delivered the therapy. SRK and CWM designed the modeling study. SRK implemented the computer model codes, designed the simulation experiments, and performed the high throughput computing. ADK assisted in model testing and annotating. SRK and ADK constructed the modeling figure drafts. LD and GF wrote the clinical draft sections. SRK and ADK wrote the modeling draft sections. All authors revised and approved the manuscript.

Open-source model codes: The codes and results data used in this study are available from the corresponding author under suitable agreement (email: Sanjay.Kharche@lhsc.on.ca).

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References

- Arts T, Delhaas T, Bovendeerd P, Verbeek X & Prinzen FW. (2005). Adaptation to mechanical load determines shape and properties of heart and circulation: the CircAdapt model. *Am J Physiol Heart Circ Physiol* **288**, H1943-1954.
- Arts T, Lumens J, Kroon W & Delhaas T. (2012). Control of whole heart geometry by intramyocardial mechano-feedback: a model study. *PLoS Comput Biol* **8**, e1002369.
- Bayliss WM. (1902). On the local reactions of the arterial wall to changes of internal pressure. *J Physiol* **28**, 220-231.

- Beard DA, Britten R, Cooling MT, Garny A, Halstead MD, Hunter PJ, Lawson J, Lloyd CM, Marsh J, Miller A, Nickerson DP, Nielsen PM, Nomura T, Subramaniam S, Wimalaratne SM & Yu T. (2009). CellML metadata standards, associated tools and repositories. *Philosophical transactions Series A, Mathematical, physical, and engineering sciences* **367**, 1845-1867.
- Berry CL & Greenwald SE. (1976). Effects of hypertension on the static mechanical properties and chemical composition of the rat aorta. *Cardiovasc Res* **10**, 437-451.
- Bude RO, DiPietro MA, Platt JF, Rubin JM, Miesowicz S & Lundquist C. (1992). Age dependency of the renal resistive index in healthy children. *Radiology* **184**, 469-473.
- Caruso MV, Gramigna V, Renzulli A & Fragomeni G. (2016). Computational analysis of aortic hemodynamics during total and partial extracorporeal membrane oxygenation and intra-aortic balloon pump support. *Acta of bioengineering and biomechanics* **18**, 3-9.
- Duanmu Z, Yin M, Fan X, Yang X & Luo X. (2018). A patient-specific lumped-parameter model of coronary circulation. *Scientific reports* **8**, 874.
- Evangelista A, Flachskampf FA, Erbel R, Antonini-Canterin F, Vlachopoulos C, Rocchi G, Sicari R, Nihoyannopoulos P, Zamorano J, Pepi M, Breithardt OA & Plonska-Gosciniak E. (2010). Echocardiography in aortic diseases: EAE recommendations for clinical practice. *Eur J Echocardiogr* **11**, 645-658.
- Ferretti F, Saltelli A & Tarantola S. (2016). Trends in sensitivity analysis practice in the last decade. *The Science of the total environment* **568**, 666-670.
- Flachskampf FA, Wouters PF, Edvardsen T, Evangelista A, Habib G, Hoffman P, Hoffmann R, Lancellotti P & Pepi M. (2014). Recommendations for transoesophageal echocardiography: EACVI update 2014. *European heart journal cardiovascular Imaging* **15**, 353-365.
- Fleming S, Thompson M, Stevens R, Heneghan C, Pluddemann A, Maconochie I, Tarassenko L & Mant D. (2011). Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. *Lancet* **377**, 1011-1018.
- Flynn JT, Mitsnefes M, Pierce C, Cole SR, Parekh RS, Furth SL & Warady BA. (2008). Blood pressure in children with chronic kidney disease: a report from the Chronic Kidney Disease in Children study. *Hypertension* **52**, 631-637.
- Gul R & Bernhard S. (2015). Parametric uncertainty and global sensitivity analysis in a model of the carotid bifurcation: Identification and ranking of most sensitive model parameters. *Math Biosci* **269**, 104-116.
- Gul R, Schütte C & Bernhard S. (2016). Mathematical modeling and sensitivity analysis of arterial anastomosis in the arm. *Applied Mathematical Modelling* **40**, 7724-7738.
- Heldt T, Mukkamala R, Moody GB & Mark RG. (2010). CVSim: An Open-Source Cardiovascular Simulator for Teaching and Research. *The open pacing, electrophysiology & therapy journal* **3**, 45-54.
- Humphrey JD & Na S. (2002). Elastodynamics and arterial wall stress. *Ann Biomed Eng* **30**, 509-523.
- Ismail M, Wall WA & Gee MW. (2013). Adjoint-based inverse analysis of windkessel parameters for patient-specific vascular models. *J Comput Phys* **244**, 113-130.
- Kaddourah A, Uthup S, Madueme P, O'Rourke M, Hooper DK, Taylor MD, Colan SD, Jefferies JL, Rao MB & Goebel J. (2015). Prevalence and predictors of aortic dilation as a novel cardiovascular complication in children with end-stage renal disease. *Clinical nephrology* **83**, 262-271.
- Kharche S, Ludtke N, Panzeri S & Zhang H. (2009). A Global Sensitivity Index for Biophysically Detailed Cardiac Cell Models: A Computational Approach. *LNCS* **5528**, 10.
- Kharche S, Seemann G, Margetts L, Leng J, Holden AV & Zhang H. (2008). Simulation of clinical electrophysiology in 3D human atria: a high-performance computing and high-performance visualization application. *Conc Comp Exp* **20**, 10.

- Kharche SR, So, A., Salerno, F., Lee, T., Ellis, C., Goldman, D., and McIntyre, C. W. (2018). Computational assessment of blood flow heterogeneity in peritoneal dialysis patients' cardiac ventricles. *Frontiers in Physiology* (accepted).
- Kharche SR, Stary T, Colman MA, Biktasheva IV, Workman AJ, Rankin AC, Holden AV & Zhang H. (2014). Effects of human atrial ionic remodelling by beta-blocker therapy on mechanisms of atrial fibrillation: a computer simulation. *Europace* **16**, 1524-1533.
- Kharche SR, Vigmond E, Efimov IR & Dobrzynski H. (2017). Computational assessment of the functional role of sinoatrial node exit pathways in the human heart. *PLoS ONE* **12**, e0183727.
- Kind T, Faes TJ, Lankhaar JW, Vonk-Noordegraaf A & Verhaegen M. (2010). Estimation of three- and four-element windkessel parameters using subspace model identification. *IEEE Trans Biomed Eng* **57**, 1531-1538.
- Korakianitis T & Shi Y. (2006a). A concentrated parameter model for the human cardiovascular system including heart valve dynamics and atrioventricular interaction. *Medical engineering & physics* **28**, 613-628.
- Korakianitis T & Shi Y. (2006b). Numerical simulation of cardiovascular dynamics with healthy and diseased heart valves. *Journal of biomechanics* **39**, 1964-1982.
- Lambermont B, D'Orio V, Gerard P, Kolh P, Detry O & Marcelle R. (1998). Time domain method to identify simultaneously parameters of the windkessel model applied to the pulmonary circulation. *Archives of physiology and biochemistry* **106**, 245-252.
- London GM & Pannier B. (2010). Arterial functions: how to interpret the complex physiology. *Nephrol Dial Transplant* **25**, 3815-3823.
- Marsden A & Moghadam ME. (2015). Multiscale Modeling of Cardiovascular Flows for Clinical Decision Support. *Applied Mechanics Reviews* **67**.
- Marsden AL. (2013). Simulation based planning of surgical interventions in pediatric cardiology. *Phys Fluids* (1994) **25**, 101303.
- Meyers A, Joyce K, Coleman SM, Cook JT, Cutts D, Ettinger de Cuba S, Heeren TC, Rose-Jacobs R, Black MM, Casey PH, Chilton M, Sandel M & Frank DA. (2013). Health of children classified as underweight by CDC reference but normal by WHO standard. *Pediatrics* **131**, e1780-1787.
- Milan A, Tosello F, Naso D, Avenatti E, Leone D, Magnino C & Veglio F. (2013). Ascending aortic dilatation, arterial stiffness and cardiac organ damage in essential hypertension. *J Hypertens* **31**, 109-116.
- Molino P, Cerutti C, Julien C, Cuisinaud G, Gustin MP & Paultre C. (1998). Beat-to-beat estimation of windkessel model parameters in conscious rats. *Am J Physiol* **274**, H171-177.
- Natarajan G, Shankaran S, Laptook AR, Pappas A, Bann CM, McDonald SA, Das A, Higgins RD, Hintz SR & Vohr BR. (2013). Apgar scores at 10 min and outcomes at 6-7 years following hypoxic-ischaemic encephalopathy. *Archives of disease in childhood Fetal and neonatal edition* **98**, F473-479.
- National High Blood Pressure Education Program Working Group on High Blood Pressure in C & Adolescents. (2004). The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics* **114**, 555-576.
- Resontoc LP & Yap HK. (2016). Renal vascular thrombosis in the newborn. *Pediatr Nephrol* **31**, 907-915.
- Saltelli A. (2002). Sensitivity analysis for importance assessment. *Risk analysis : an official publication of the Society for Risk Analysis* **22**, 579-590.
- Schindelin J, Arganda-Carreras I, Frise E, Kaynig V, Longair M, Pietzsch T, Preibisch S, Rueden C, Saalfeld S, Schmid B, Tinevez JY, White DJ, Hartenstein V, Eliceiri K, Tomancak P & Cardona A. (2012). Fiji: an open-source platform for biological-image analysis. *Nature methods* **9**, 676-682.
- Shi Y, Lawford P & Hose R. (2011). Review of zero-D and 1-D models of blood flow in the cardiovascular system. *Biomedical engineering online* **10**, 33.

- Totaro S, Rabbia F, Milan A, Urbina EM & Veglio F. (2016). Aortic root dilatation in the children and young adults: prevalence, determinants, and association with target organ damage. *Journal of the American Society of Hypertension : JASH* **10**, 782-789.
- Warren AE, Boyd ML, O'Connell C & Dodds L. (2006). Dilatation of the ascending aorta in paediatric patients with bicuspid aortic valve: frequency, rate of progression and risk factors. *Heart* **92**, 1496-1500.
- Wolinsky H & Glagov S. (1969). Comparison of abdominal and thoracic aortic medial structure in mammals. Deviation of man from the usual pattern. *Circ Res* **25**, 677-686.
- Zarate YA, Sellars E, Lepard T, Carlo WF, Tang X & Collins RT, 2nd. (2015). Aortic dilation in pediatric patients. *European journal of pediatrics* **174**, 1585-1592.

Figure legends

Figure 1. Clinical observation of patient. A. Observed and running mean of systolic blood pressure (mmHg) over the first 23 days of patient's life. Gray line joined points show the clinical recording. The green dashed line shows systolic BP for healthy infants (Fleming *et al.*, 2011). The running mean is shown as a solid red line. Black vertical dashed lines show day of dialysis onset (left, day 4) and end (right, day 13). B. Parasternal echocardiographic long-axis echo assessment of four ascending aortic diameter dimensions. Top left inset shows the four diameters that were measured, i.e. outflow tract (1), sinuses of Valsalva (2), sinotubular junction (3), and tubular ascending aorta (4). The bar chart shows the four ascending aortic diameters over a six-month period. See Supplementary Materials, Figure S2 for frame-by-frame data. C. Weight (panel Ci) and heart rate (panel Cii) of the neonate patient over 6 months.

Figure 2. Schematic diagram of the model used in this study (Korakianitis & Shi, 2006a). Parameters are shown in gray boxes. The variables in yellow boxes were recorded to construct modeling results.

Figure 3. Main pressures and blood flows in the baseline model. Ai. Pressures in left ventricle (black line), systemic artery (aorta, black dotted line), and systemic vein (vena cava, gray line). Aii. Pressures in right ventricle (black line), pulmonary artery (black dotted line), and pulmonary vein (gray line). Bi. Blood flow in left ventricle (black line), systemic artery (aorta, black dotted line), and systemic vein (vena cava, gray line). Bii. Blood flow in right ventricle (black line), pulmonary artery (black dotted line), and pulmonary vein (gray line). C. Left ventricle pressure-volume loop and baseline stroke work (area inside pressure-volume loop).

Figure 4. Major factors inducing hypertension. Left column shows data for systemic artery (i.e. aorta) systolic pressure, P_{SAT} . Right column shows data for systemic artery systolic flow, Q_{SAT} . A_i and A_{ii} . Systemic arteriolar resistance (black line), systemic capillary resistance (gray line) varied between 1 and 25-fold. B_i and B_{ii} . Systemic artery (black line), vein (gray line) between 0 and 1-fold. C_i and C_{ii} . Heart period varied between 0 and 2.5 seconds.

Figure 5. Effects of arterial hypertension inducing factors on mean systemic venous flow. A. Systemic arteriolar resistance (black line), systemic capillary resistance (gray line) B. Vessel stiffness (inverse of compliance) of the systemic artery (black line), systemic vein (gray line), and pulmonary vein (dashed line) C. Heart rate in seconds. D. Ascending aortic diameter.

Figure 6. Effects of hypertension inducing factors on pulmonary arterial pressure (left column) and flow (right column). A_i and A_{ii} . Systemic arteriolar resistance (black line), systemic capillary resistance (gray line). Vessel stiffness of the systemic artery (black line), systemic vein (gray line), and pulmonary vein (dashed line).

Figure 7. Increased systemic small blood vessel resistance, aortic stiffness, and increased heart rate all reduce stroke work.

Figure 8. Simultaneous effects of left ventricular hypertrophy (E_{lv}) and peripheral resistance (R_{SAR}). Left column shows data for heart period of 0.5 seconds, and right columns shows data for heart period of 1 second. A_i and B_i show data for ascending aorta flow (Q_{AO}). A_{ii} and B_{ii} show data for systolic arterial pressure (P_{SAT}). A_{iii} and B_{iii} show data for pulmonary artery pressure (P_{PAT}). Bottom row shows data for pressure-volume loop area, or stroke work.

Figure 9. Simultaneous effects of left ventricular hypertrophy (E_{lv}) and systemic artery compliance (C_{SAT}). Left column shows data for heart period of 0.5 seconds, and right columns shows data for heart period of 1 second. A_i and B_i show data for ascending aorta flow (Q_{AO}). A_{ii} and B_{ii} show data for systolic arterial pressure (P_{SAT}). A_{iii} and B_{iii} show data for pulmonary artery pressure (P_{PAT}). Bottom row shows data for pressure-volume loop area, or stroke work.

Figure 10. Dynamic sensitivity of systemic (i.e. aortic) arterial pressure (P_{SAT} , left column) and pulmonary arterial pressure (P_{PAT} , right column) with respect to hypertension inducing parameters at a heart rate of 1 second. The parameters considered were systemic small vessel resistance (R_{SAR} , top row), aortic stiffness

(inverse of aortic compliance C_{SAT} , middle row), and left ventricular elastance (E_{IV} , bottom row).

Figure 11. Dynamic aortic pressure (P_{SAT} , left column) with respect to hypertension inducing parameters at a higher heart rate of 0.5 second period. The parameters considered were systemic small vessel resistance (R_{SAR} , top row), aortic stiffness (inverse of aortic compliance C_{SAT} , middle row), and left ventricular elastance (E_{IV} , bottom row).

Figure 12. Schematic of the conceptual mechanisms for action of disease (A) and treatments (B). Some components were measured clinically, some demonstrated by the model, some yet to be studied.

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Figures and figure legends.

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Figure 12. Schematic of the conceptual mechanisms for action of disease (A) and treatments (B). Some components were measured clinically, some demonstrated by the model, some yet to be studied.

SUPPLEMENTARY MATERIALS

Arterial hypertension and unusual ascending aortic dilatation in a neonate with acute kidney injury: mechanistic computer modelling

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Keywords: dialysis, hypertension, aortic dilation, computer model, 0D Windkessel model, sensitivity analysis.

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Section S1. Supplementary Methods

Section S1.1 ImageJ (Schindelin et al., 2012) method of aortic diameter assessment from echocardiograph images.

The method can be summarized as the following steps.

1. The DICOM images contain 3 frames each. Using MATLAB functions, individual frames were extracted. In case an animation was exported from the 2D echocardiography machine, functions in the opensource program ImageMagick were used to extract all frames. In all four cases, the echo exams consisted of three heart beat data. The individual frames had the echo image, superposed with an ECG trace to assist in gating.
2. Using the ECG trace, the second heart beat between the second and third R peaks were analyzed for diameters.
3. The sequentially numbered frames were imported into ImageJ using the GUI menu.
4. The brightness and contrast were adjusted to provide a better onscreen image suitable for analysis by the expert. The minimum and maximum brightness were adjusted such that the range contained all peaks of the grayscale distribution.
5. Using information from the literature, and as shown in the inset of Figure 1B, lines were drawn and the distance in terms of pixels was obtained.
7. The resolution of pixels in the images was obtained from the 2D echocardiography machine.
6. The pixel wise distance was converted into mm units using the pixel size of $dx = 0.075$ mm, and $dy = 0.075$ mm.

Section S1.2 Modelling parameters and variables.

Table S1. The analogous metrics between the electrical domain and fluid dynamics along with their typical symbols, and units in each system.

Electrical	Fluid dynamics
Voltage, V [V]	Pressure, P [mmHg]
Current, I [A]	Flow rate, Q [ml s ⁻¹]
Resistance, R [Ω]	Resistance, R [mmHg s ml ⁻¹]
Inductance, L [H]	Inertia, I [mmHg s ² ml ⁻¹]
Charge, Q [C]	Volume, V [ml]
Capacitance, C [F]	Compliance, C [ml mmHg ⁻¹]

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63 Table S2. System states and computed algebraic variables.

States, Symbol.	Units	Description
P_{sas}	mmHg	pressure systemic aortic sinus
P_{pas}	mmHg	pressure pulmonary artery sinus
V_{lv}	ml	left ventricle volume
V_{ra}	ml	right atrial volume
P_{sat}	mmHg	Pressure systemic artery
Q_{sas}	ml/s	blood flow systemic aortic sinus
Q_{sat}	ml/s	blood flow systemic artery
P_{svn}	mmHg	pressure systemic vein
P_{pat}	mmHg	pressure pulmonary artery
Q_{pas}	ml/s	blood flow pulmonary artery sinus
Q_{pat}	ml/s	blood flow pulmonary artery
P_{pvn}	mmHg	pressure pulmonary vein
E_{la}	F^{-1}	left atrium elastance
E_{lv}	F^{-1}	left ventricle elastance
P_{lv}	mmHg	left ventricle pressure
P_{la}	mmHg	left atrium pressure
V_{rv}	ml	right ventricle volume
V_{la}	ml	left atrium volume
Q_{svn}	ml/s	blood flow systemic vein
Q_{ao}	ml/s	Aortic root flow.

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65 Table S3. Parameters in the pulmonary circulation.

Parameters, Symbols.	Units	Description
R_{pas}	mmHg s ml^{-1}	resistance in pulmonary artery sinus
C_{pas}	ml mmHg $^{-1}$	compliance in pulmonary artery sinus
L_{pas}	mmHg s 2 ml^{-1}	inertia in pulmonary artery sinus
P_{pas}	mmHg	Baseline pressure in pulmonary artery sinus.
Q_{pas}	ml/s	Baseline blood flow in pulmonary artery sinus.
R_{pat}	mmHg s ml^{-1}	resistance in pulmonary artery
C_{pat}	ml mmHg $^{-1}$	compliance in pulmonary artery
L_{pat}	mmHg s 2 ml^{-1}	inertia in pulmonary artery

P_{pat}	mmHg	Baseline pressure in pulmonary artery.
Q_{pat}	ml	Baseline blood flow in pulmonary artery.
R_{par}	mmHg s ml ⁻¹	resistance in pulmonary arterioles
R_{pcp}	mmHg s ml ⁻¹	resistance in pulmonary capillaries
R_{pvn}	mmHg s ml ⁻¹	resistance in pulmonary vein
C_{pvn}	ml mmHg ⁻¹	compliance in pulmonary vein.
P_{pvn}	mmHg	Baseline pressure in pulmonary vein. (initializer of Ith 14)

Section S2. Supplementary Results

Figure S1. Representative images of the echocardiography of the ascending aorta. On day 1, the ascending aortic diameter was found to be 1.1 cm (panel A, Z score +0.95). The diameter dilated to over 1.6 cm by day 30 (panel B, Z score +4.88).

Figure S2. Aortic diameters over the course of one heart beat. The means of above data is shown in main manuscript, Figure 1B.