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Experimental paper

Evaluating current guidelines for cardiopulmonary resuscitation using an integrated computational model of the cardiopulmonary system



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Abstract

Objective: We aimed to use a high-fidelity computational model that captures key interactions between the cardiovascular and pulmonary systems to investigate whether current CPR protocols could potentially be improved.

Methods: We developed and validated the computational model against available human data. We used a global optimisation algorithm to find CPR protocol parameters that optimise the outputs associated with return of spontaneous circulation in a cohort of 10 virtual subjects.

Results: Compared with current protocols, myocardial tissue oxygen volume was more than 5 times higher, and cerebral tissue oxygen volume was nearly doubled, during optimised CPR. While the optimal maximal sternal displacement (5.5 cm) and compression ratio (51%) found using our model agreed with the current American Heart Association guidelines, the optimal chest compression rate was lower (67 compressions min⁻¹). Similarly, the optimal ventilation strategy was more conservative than current guidelines, with an optimal minute ventilation of 1500 ml min⁻¹ and inspired fraction of oxygen of 80%. The end compression force was the parameter with the largest impact on CO, followed by PEEP, the compression ratio and the CC rate.

Conclusions: Our results indicate that current CPR protocols could potentially be improved. Excessive ventilation could be detrimental to organ oxygenation during CPR, due to the negative haemodynamic effect of increased pulmonary vascular resistance. Particular attention should be given to the chest compression force to achieve satisfactory CO. Future clinical trials aimed at developing improved CPR protocols should explicitly consider interactions between chest compression and ventilation parameters.

Keywords: Cardiac arrest, Cardiopulmonary resuscitation, Chest compressions, Computational simulation, Modelling

Introduction

Cardiac arrest (CA) is a leading cause of death in many countries – despite years of research, survival rates remain consistently low.¹ Cardiopulmonary resuscitation (CPR) is an emergency procedure consisting of chest compressions combined with positive pressure ventilation, intended to restore flow of oxygenated blood to the brain and heart. Some clinical trials in humans have attempted to identify optimal CPR strategies.^{2–5} However, ethical and practical constraints, short time scales, the presence of confounding variables, and heterogeneity of the patient population present major obstacles to performing clinical research in this area. Animal models often fail

to represent the severity of human CA accurately, due to inter-species physiological differences and lack of methodical rigor.^{6–7} Computer simulation is a novel and promising alternative to animal and clinical trials that is free of most ethical and practical constraints, allows complete reproducibility of methods and results, and offers mechanistic insight into the effectiveness of treatment strategies.

When performing chest compression (CC), three main components are typically considered: depth, rate, and compression ratio. While the European Resuscitation Council (ERC) advanced life support guideline⁸ advises a compression depth of 5–6 cm, a rate of 100–120 compressions min⁻¹, and a compression ratio (i.e. the proportion of compression time during the compression / decompression cycle) of 50%, the majority of studies have failed to find an

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association between these parameters and outcomes. A recent systematic review and meta-analysis by Considine *et al.*,⁹ which included more than 15,000 subjects, reported outcomes associated with CC rate. Overall, the majority of the studies did not find any associations between the CC rate and outcomes (survival with good neurological outcome, survival to hospital discharge and return of spontaneous circulation [ROSC]) in out-of-hospital cardiac arrest). Only two studies found otherwise; Idris *et al.*² found an association between CC rate and ROSC with the rate of ROSC peaking at 125 compressions min^{-1} , and Idris *et al.*³ found that CC rates between 100 and 120 compressions min^{-1} were associated with greatest survival to hospital discharge.

The evidence regarding the effect of CC depth on ROSC and survival is more consistent. In the study of Babbs *et al.*,¹⁰ for shocks delivered after 5 min of CA, a CC depth >5 cm compared with CC depth <5 cm was associated with a greater chance of transient ROSC. Similarly, Stiell *et al.*¹¹ found a strong association between survival outcomes and increased compression depth, and that maximal survival was in the depth interval of 4.03–5.53 cm,¹² suggesting that the target depth in the AHA guidelines may be too great. The effect of the CC compression ratio on ROSC and long-term outcome has not been investigated in any clinical studies. However, in a study by Johnson *et al.*¹³ the median compression ratio was 38.8% and a relatively shorter compression phase (lower compression ratio) was associated with a greater chance of survival.

The haemodynamic effects of pulmonary ventilation during CPR also remain unclear. Some researchers¹⁴ have argued that whilst modest PEEP could help mitigate alveolar collapse, high intrathoracic pressure during decompression could prevent venous return and thus reduce stroke volume and organ perfusion, while others¹⁵ have speculated that high intrathoracic pressure could enhance CC-generated CO by further ejecting blood out of the left ventricle. There is therefore an urgent need for further research into the combined impact of different airway strategies, ventilation techniques, positive end expiratory pressures (PEEP) and inhaled oxygen (FiO_2) on CPR effectiveness.¹⁶

This study presents a highly integrated computational model of the cardiopulmonary systems that can be used to investigate these variables in detail. Preliminary results from this study were presented in.¹⁷

Methods

Cardiopulmonary computational model

The model used in this study is a high-fidelity, integrated, computational model of the respiratory and cardiovascular systems which has been extensively validated in multiple previous investigations.^{18–22} The respiratory model includes a series deadspace volume and 100 independently configurable alveolar compartments (each with distinct gas and blood flow models). The cardiovascular model comprises 20 compartments with 4 cardiac chambers, 3 compartments representing the pulmonary circulation and the remainder representing the systemic vasculature. Extensive, novel modelling was undertaken to adapt the model for the specific purposes of this study; this is described in detail in the [Supplementary online materials](#).

Cohort of virtual subjects

We used human haemodynamic and gas exchange data from three sources to validate our model; the end-compression and end-

decompression pressures from Kim *et al.*,²³ which describes the mechanisms of forward blood flow generation during CPR in ten patients with non-traumatic CA; the end-compression and end-decompression left ventricular volume from Redberg *et al.*²⁴ which used transoesophageal echocardiography in 18 subjects; and the end tidal CO_2 (ETCO_2) ranges from Sheak *et al.*²⁵ which examined CPR in 583 in- and out-of-hospital CAs.

To match these data, we used a Genetic Algorithm (GA) to find combinations of the 58 cardiovascular parameters in the model that produce the closest matching between the model outputs and the haemodynamic and gas exchange data on CPR^{23–25} (Table 1). Details of the GA and the 58 cardiovascular parameters tuned for the thoracic model validation are presented in the [Supplementary Material](#). The cost function (Cost_{val}) to be minimised is:

$$\begin{aligned} \text{Cost}_{\text{val}} = & w | \text{PeakLV}_m - \text{PeakLV}_d | + w | \text{EDLVP}_m - \text{EDLVP}_d | \\ & + w | \text{PeakSA}_m - \text{PeakSA}_d | \\ & + w | \text{EDSAP}_m - \text{EDSAP}_d | + w | \text{PeakRA}_m - \text{PeakRA}_d | \\ & + w | \text{EDRAP}_m - \text{EDRAP}_d | \\ & + w | \text{CPP}_m - \text{CPP}_d | + w | \text{SV}_m - \text{SV}_d | + w | \text{EF}_m - \text{EF}_d | \\ & + w | \text{EDVLV}_m - \text{EDVLV}_d | \\ & + w | \text{ESVLV}_m - \text{ESVLV}_d | + w | \text{ETCO}_2_m - \text{ETCO}_2_d | \end{aligned} \quad (14)$$

where, PeakLV is the peak left ventricular pressure, EDLVP is the left ventricular end-compression pressure, PeakSA is the peak aortic pressure, EDSAP is the aortic end-compression pressure, PeakRA is the peak right atrial pressure, EDRAP is the right atrial end-compression pressure, CPP is the coronary perfusion pressure, SV is the stroke volume, EF is the ejection fraction, EDVLV is the end diastolic left ventricular volume, ESVLV is the end systolic left ventricular volume and ETCO_2 is the end tidal CO_2 partial pressure. The subscript 'm' defines the model simulation output parameters, the subscript 'd' defines the desired value of these output parameters, and $w = \frac{1}{12}$ is the weight assigned to each objective, which has been assigned equal in order to avoid favouring or disfavouring the matching of one model output over another. The desired value for each of the parameters was defined based on the haemodynamic and gas exchange data in Table 1.

Based on the optimisation results, we chose ten sets of model parameters that produced adequate levels of variability within the physiological bounds for the model outputs, to create a cohort of ten virtual subjects (Table 1).

Optimisation of the CPR parameters

To identify optimal personalised CPR parameters, we employed a GA to simultaneously vary all CPR parameters and find those that minimise the cost function (Cost_{opt}) defined as:

$$\begin{aligned} \text{Cost}_{\text{opt}} = & w \left| \frac{\text{CPP}_m - \text{CPP}_d}{\text{CPP}_d} \right| + w \left| \frac{\text{CO}_m - \text{CO}_d}{\text{CO}_d} \right| \\ & + w \left| \frac{\text{brainO}_2_m - \text{brainO}_2_d}{\text{brainO}_2_d} \right| \\ & + w \left| \frac{\text{heartO}_2_m - \text{heartO}_2_d}{\text{heartO}_2_d} \right| \end{aligned} \quad (15)$$

where CPP is the coronary perfusion pressure, CO is the cardiac output, brainO_2 is the cerebral tissue oxygen volume, heartO_2 is the myocardial tissue oxygen volume, the subscript 'm' defines the simulation output parameters, the subscript 'd' defines the desired

Table 1 – Literature human data^{26,29–30} versus model outputs during CPR.

Variable	Unit	Literature human data	Model outputs
EC LV pressure	mmHg	112 ± 37 ¹	111 ± 13
EC aorta pressure	mmHg	105 ± 41 ¹	110 ± 13
EC RA pressure	mmHg	89 ± 27 ¹	88 ± 9
ED LV pressure	mmHg	8 ± 11 ¹	11 ± 7
ED aorta pressure	mmHg	33 ± 10 ¹	36 ± 4
ED RA pressure	mmHg	8 ± 6 ¹	6 ± 3
CPP	mmHg	25 ± 9 ¹	30 ± 7
Stroke volume	ml	19 ± 6 ²	19 ± 1
EC LV volume	ml	50 ± 7 ²	72 ± 6
ED LV Volume	ml	70 ± 10 ²	70 ± 7
Ejection fraction	%	34 ± 16 ¹	50 ± 8
ETCO ₂	mmHg	30 ± 5 ³	26 ± 1

EC, end compression; ED, end diastolic; LV, left ventricle; RA, right atria; CPP, coronary perfusion pressure; ETCO₂, end tidal CO₂; 1: Kim *et al.*²⁶, 2:Redberg *et al.*³⁰, 3:Sheak *et al.*³¹.

value of these output parameters, and $w = \frac{1}{4}$ is the weight assigned to each objective, which has been assigned equal in order to avoid favouring or disfavoured the matching of one model output over another. The desired value of CPP, CO, brainO₂ and heartO₂ during CPR were defined as those observed during baseline (i.e. spontaneous ventilation) since the primary objective of CPR is to restore spontaneous circulation and return to baseline values (Table 3).

We selected these outcome parameters (CPP, CO, brainO₂ and heartO₂) because of their association with return of spontaneous circulation; in an animal study by Naim *et al.*,²⁶ targeting a systolic blood pressure of 100 mmHg and CPP >20 mmHg improved survival compared to the AHA guidelines. The CO is the amount of blood flow restored during CPR and is therefore crucial to achieve return of spontaneous circulation.

We added constraints to the optimisation problem related to the safety and practicality of the CC. The end compression force (F_{max}) was allowed to vary between 0 and 500 N, the CC rate (CC_{rate}) between 60 and 150 compressions min⁻¹, the compression ratio ($Duty_{cycle}$) between 20% and 80%, tidal volume (V_T) between 100 and 1000 ml, the ventilatory frequency (V_f) between 0 and 20 breaths min⁻¹, the positive end expiratory pressure (PEEP) between 0 and 15 cmH₂O, and the fraction of inspired oxygen (FiO₂) between 21% and 100%.

We then simulated CPR using the median values of the optimised compression depths, rates, duty cycles, and ventilation found for the entire cohort, to determine whether a modified CPR protocol could offer advantages over current guidelines.

CPR simulation protocol

While the ten virtual subjects were identical during spontaneous ventilation, during CA and CPR their cardiovascular input parameters were different to allow a variation in model outputs during CPR. The 58 cardiovascular parameters that define each subject can be found in the online [supplementary material](#) (Table S1).

After 5 minutes of spontaneous ventilation, CA was simulated for 5 minutes by setting the heart rate to 0, effectively forcing the heart to be in constant diastole. Additionally, the apnoea module was activated with the upper airway obstructed. During CPR, the subjects were no longer apnoeic, and the airway was no longer obstructed. The baseline CPR strategy followed as closely as possible the one used in Kim's work²³ which in turn followed the American Heart

Association (AHA) guidelines: CC rate 100 compressions min⁻¹, compression ratio 50%, CC depth 5 cm, tidal volume 650 ml, ventilation rate 12 breaths min⁻¹ and fraction of inspired oxygen 100%. However, the effect of repeated epinephrine administration was not modelled.

Ethical statement

Approval from a research ethics committee was not sought, since the data were obtained from previously published literature (whose studies had already received ethical approval).

Results

Model validation

Table 1 compares the simulated cardiovascular model outputs when CPR was performed following the AHA guidelines *versus* the haemodynamic and gas exchange data during CPR from the literature described above.^{23–25} All the model outputs are within the physiological ranges observed during standard CPR in humans (see also the online [supplementary material](#)).

Optimal CPR parameters

Table 2 shows the optimal personalized CPR parameters for each subject identified by the GA, as well as the median optimised values over the cohort. The CC rate and compression ratio are the two parameters with the largest ranges over the cohort, from 62–104 compressions min⁻¹ and 41–58%, respectively. The PEEP, CC force and its associated maximal sternal displacement are the two parameters that remain relatively constant at 0 cmH₂O and 495 N (5–6 cm of displacement), respectively. Similarly, all the ventilatory parameters varied with a mean tidal volume of 250 ml, ventilatory frequency of 6 breaths min⁻¹ and a fraction of inspired oxygen of 80%. Overall, the median optimal minute ventilation was 1500 ml min⁻¹.

Tables 3 and 4 show the model outputs, CPP, CO, brainO₂ and heartO₂ during spontaneous ventilation, after CA, during CPR following the AHA guidelines (AHA-CPR), during CPR with optimal personalized CPR parameters (PERS-CPR), and during CPR with the new optimised protocol based on the median values of the optimised CPR parameters (OPT-CPR). CPP and CO were partially restored after 5 minutes for all CPR protocols. However, compared to the AHA pro-

Table 2 – Optimal CPR parameters for the cohort of 10 subjects.

Subjects #	CC rate	Max Force	CC depth	Compression ratio	V _T	V _f	PEEP	FiO ₂
AHA	100–120	400–500	5–6	50	650	12	0	100
Median ± SD	67 ± 15	498 ± 3	6.2 ± 0.1	52 ± 5	250 ± 103	6 ± 2	0 ± 0	85 ± 16
Subject 1	66	495	6.1056	41	550	2	0	70
Subject 2	62	500	6.3431	50	200	9	0	70
Subject 3	80	494	6.0817	49	250	8	0	50
Subject 4	104	494	6.0023	58	250	6	0	70
Subject 5	65	498	6.2379	46	300	5	0	100
Subject 6	60	493	6.2813	51	200	8	0	90
Subject 7	67	500	6.3807	58	300	2	0	90
Subject 8	65	499	6.3365	53	300	5	0	100
Subject 9	87	497	6.0989	52	200	6	0	90
Subject 10	93	499	6.0654	52	250	6	0	80

CC rate, chest compression rate (compressions min⁻¹); Max Force, maximal chest compression force (N); CC depth, maximal sternal displacement (cm); Compression ratio (%); V_T, tidal volume (ml); V_f, ventilatory frequency (breaths min⁻¹); PEEP, positive end expiratory pressure (cmH₂O); FiO₂, fraction of inspired oxygen (%).

Table 3 – Model outputs during spontaneous ventilation (SPV) and cardiac arrest (CA).

Parameters	Unit	SPV	CA
CPP	mmHg	80	0
CO	ml min ⁻¹	5000	0
brainO ₂	ml	1.83	0
heartO ₂	ml	0.32	0

CPP, coronary perfusion pressure; CO, cardiac output; brainO₂, cerebral tissue oxygen volume; heartO₂, myocardial tissue oxygen volume.

Table 4 – Model outputs using the standard CPR protocol (AHA-CPR), the optimised CPR protocol (OPT-CPR) and personalised CPR (PERS-CPR).

	AHA-CPR				OPT-CPR				PERS-CPR			
	CPP	CO	brainO ₂	heartO ₂	CPP	CO	brainO ₂	heartO ₂	CPP	CO	brainO ₂	heartO ₂
	mmHg	ml min ⁻¹	ml	ml	mmHg	ml min ⁻¹	ml	ml	mmHg	ml min ⁻¹	ml	ml
Median	30 ± 7	1853	0.80	0.061	39 ± 7	2822	1.73	0.326	38 ± 8	2830	1.68	0.320
± SD		± 100	± 0.7	± 0.05		± 143	± 0.06	± 0.05		± 300	± 0.1	± 0.02
subject1	30	1806	0.75	0.048	38	2946	1.74	0.327	35	2891	1.71	0.331
subject2	34	2014	0.88	0.121	45	3105	1.80	0.324	46	3151	1.78	0.325
subject3	32	1912	0.89	0.166	39	3001	1.82	0.379	38	2920	1.68	0.339
subject4	20	1759	0.79	0.002	25	2778	1.77	0.450	22	2404	1.5	0.323
subject5	27	1761	0.74	0.002	34	2700	1.68	0.291	35	2740	1.73	0.304
subject6	30	1765	0.73	0.002	42	2765	1.69	0.305	43	2763	1.71	0.322
subject7	31	1873	0.78	0.002	41	2780	1.64	0.281	41	2855	1.65	0.283
subject8	30	1920	0.83	0.002	39	3031	1.77	0.305	39	3049	1.81	0.313
subject9	37	1862	0.81	0.129	48	2864	1.71	0.377	46	2799	1.62	0.326
subject10	27	1859	0.83	0.137	30	2720	1.71	0.371	31	2731	1.66	0.33

CPP, coronary perfusion pressure; CO, cardiac output; brainO₂, cerebral tissue oxygen volume; heartO₂, myocardial tissue oxygen volume; AHA, American Heart Association.

tolcol, all the model outputs were improved with the optimised CPR strategy (Table 4). Whilst the CPP was moderately improved, the myocardial tissue oxygen volume (heartO₂) was more than 5 times higher during optimised CPR. Similarly, the cerebral tissue oxygen volume (brainO₂) was nearly doubled during optimised CPR compared to standard CPR. Considering the reduction in ventilation parameters, this better oxygenation of the vital organs can only be explained by the increased CO.

Discussion

In this study, we developed and validated a new, highly-integrated model of the cardiopulmonary systems. After the onset of CA, the aortic pressure exponentially decreases and reaches a mean systemic filling pressure (MSFP) of 10 mmHg after 4 minutes of CA in keeping with clinical observations (see Fig. S3 in the SM).²⁷ Additionally, the MSFP of around 10 mmHg agrees with the observation in

Repesse *et al.*²⁸ that deceased intensive care unit patients who happened to have central venous catheter and arterial lines had a MSFP of around 12 mmHg.

Our model presented no aortic regurgitation and moderate to severe retrograde blood flow from the left ventricle into the left atrium (3–16 ml) as well as antegrade blood flow from the left ventricle into the aorta during the compression phase of CPR, in keeping with the observations of Kim *et al.*²³ The CO reaches a maximum of 2800 ml min⁻¹ which is 56% of the CO during spontaneous circulation. During CPR, CO can vary dramatically depending on CC quality. In Fodden *et al.*²⁷ the median CO was found to be approximately 2040 ml min⁻¹, which is again in keeping with our results.

During personalized CPR, the CPP is moderately increased from 30 mmHg to 38 mmHg, however, the myocardial tissue oxygen volume (heartO₂) is more than 5 times higher than during standard CPR (Table 2). The cerebral tissue oxygen volume (brainO₂) is nearly doubled during optimised CPR compared to standard CPR. Considering the reduction in minute ventilation and FiO₂ from 7800 ml min⁻¹ to 1500 ml min⁻¹, and 100% to 80%, respectively, during the optimised CPR protocols, the improvements in oxygenation of the vital organs can only be explained by the increase in CO of nearly 1000 ml min⁻¹. Interestingly, these potential benefits were preserved when we applied a single CPR protocol (OPT-CPR) to the cohort, based on the median values of the personalized CPR parameters – indeed in some cases this protocol slightly improved on the personalized results, likely due to the optimisation algorithm failing to find the exact global optimum.

While the median optimised maximal sternal displacement (6.2 cm) and median compression ratio (52%) agree with the AHA guidelines, the median CC rate (67 compressions min⁻¹) identified in our optimised protocol is considerably lower than the range recommended by the AHA guidelines of 100–120 compressions min⁻¹.²⁹ The corresponding optimised ventilation strategy (minute ventilation 1500 ml min⁻¹) suggests that a more restrained ventilation strategy could help mitigate the detrimental hemodynamic effects of mechanical ventilation whilst maintaining sufficient arterial oxygenation.

Whilst the total absence of ventilation during CPR has been shown to be associated with poor outcomes,¹⁵ a similar negative outcome has been observed when hyperventilation is used.³⁰ Indeed, a lower minute ventilation at the beginning of CPR could help mitigate the negative hemodynamic effects of ventilation on CO and could avoid hyperoxaemia, which has been shown to be detrimental to long terms outcomes. However, whilst at the beginning of CPR ensuring blood circulation is key, ventilation becomes crucial as CO₂ clearance becomes necessary during prolonged CPR or after a long period of untreated CA.

Previous studies have used mathematical models of the cardiovascular system to investigate alternative CPR strategies ranging from interposed abdominal compression,^{31–32} combined chest and abdominal compression and decompression,^{33–35} impedance valve,^{36–37} and passive leg raise.^{38–39} Jung *et al.* applied optimal control to identify the CC and decompression frequency and compression ratio that maximized the coronary perfusion pressure (CPP)⁴⁰ and the blood flow as measured by the pressure difference between the thoracic aorta and the right atrium.⁴¹ In both papers, the authors identified the optimal waveform to include both compression and decompression of the chest to the maximum allowable extent and a compression ratio of 40%. However, one study⁴⁰ found the optimal CC rate to be 90 compressions min⁻¹ and the other 60 compressions min⁻¹. Whilst our optimal maximal sternal displacement

was similarly higher (6.2 cm) than the AHA recommendations and our optimal CC rate lower (67 compressions min⁻¹), our optimal compression ratio was only slightly higher (52%) than the AHA recommendations whereas Jung *et al.* was lower (40%). These discrepancies may arise from the fact that while Jung's studies considered decompression and the waveform shape variation, our study included the optimisation of ventilatory parameters during CPR. Additionally, their model did not include a pulmonary system or mechanisms of gas exchange.

Similarly, Babbs *et al.*⁴² investigated the optimal CC frequency for different sized individuals, from neonates to adults and found that whilst high frequency for neonates (>120 compressions min⁻¹) was advantageous, in adults there may be benefit from lower compression frequencies near 60 compressions min⁻¹. In another study Babbs²⁵ identified the optimal CPR to be reciprocal compression and decompression of the chest and the abdomen to the maximum allowable extent with a CC rate of 80 compressions min⁻¹ and a compression ratio of 50%. Both these studies support our results.

John *et al.*⁴³ investigated the optimal CC pressure and rate to maximize CO and found them to be respectively 100 mmHg, which is approximately a maximal sternal displacement of 5.7 cm, and 110 compressions min⁻¹, both similar to those recommended in the AHA guidelines. However, similarly to the findings of Jung *et al.*, the study of John *et al.* did not include a model of the pulmonary system or gas exchange. Finally, Turner *et al.* investigated the benefits of continuous CC over the usual 5:1 or 15:2 ratios of compression to ventilation⁴⁴ and found that lower ventilation ratios (15:2 and 50:5) produced significantly greater oxygen delivery to the body. These results are in keeping with ours, suggesting that lower ventilatory frequency can effectively oxygenate tissues during CPR.

Compared to previous studies, our model has the unique advantage of using a high-fidelity, computational model of the respiratory and cardiovascular systems that includes extensive cardiopulmonary interactions. Our model is the first to be comprehensively validated against multiple sources of human data during CPR,^{23–25} and our study is the first to use a cohort of ten virtual subjects to study CPR. Finally, the optimal CPR was identified with a genetic algorithm, enabling for the first time optimisation of multiple CPR parameters simultaneously.

Our model has limitations. The lack of complex biological processes (i.e. high levels of inflammatory cytokines) limits its usefulness for the study of post-CA treatment and management which affects the whole body (multi-organ failure). Our model does not account for the electrophysiology of the heart or the cardiovascular control mechanism (i.e. chemoreflex, effect of vasopressors or inotropes) which can be important when studying CPR. Finally, our model does not account for the role of the precipitating aetiology, which can require a particular CPR strategy.

Conclusions

In this study, we identified optimal CPR strategies in a cohort of virtual subjects using a novel, high-fidelity, computational model of the cardiopulmonary systems. Myocardial tissue oxygen volume was more than 5 times greater, and cerebral tissue oxygen volume was nearly doubled during our optimised CPR protocol. Compared to current AHA guidelines, the identified optimal CPR strategy had the same compression ratio (52%), a slightly greater

CC depth (6.2 cm), a lower CC rate (67 compressions min^{-1}), and a less aggressive ventilation strategy (V_T 250 ml, V_i 6 breaths min^{-1}). Our results highlight the potential negative hemodynamic effects of excessive ventilation, which could increase pulmonary vascular resistance, impeding CO. Future clinical trials evaluating modifications in multiple CPR parameters simultaneously could help elucidate optimal CPR strategies with significant benefits to patients.

Conflicts of interest

The authors declare that they have no competing interests.

Availability of data and materials

All data and code used in the study are available upon request from the corresponding author.

Authors' contributions

Conception and design of the study: CDV, DGB, JGH, ML.

Running simulations: CDV.

Analysis and interpretation of data: CDV, DGB, TES, JGH, ML.

Drafting the article and revising it critically for important intellectual content: CDV, DGB, TES, JGH, ML.

Final approval for all aspects of the work: CDV, DGB, TES, JGH, ML.

Final approval of the version to be submitted and agreement to be accountable for all aspects of the work: CDV, DGB, TES, JGH, ML.

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Appendix A. Supplementary material

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REFERENCES

- Gräsner JT, Wnent J, Herlitz J, et al. Survival after out-of-hospital cardiac arrest in Europe - Results of the EuReCa TWO study. *Resuscitation* 2020;148:218–26.
- Idris AH, Guffey D, Aufderheide TP, et al. Relationship between chest compression rates and outcomes from cardiac arrest. *Circulation* 2012;125:3004–12.
- Idris AH, Guffey D, Pepe PE, et al. Chest compression rates and survival following out-of-hospital cardiac arrest. *Crit Care Med* 2015;43:840–8.
- Vadeboncoeur T, Stolz U, Panchal A, et al. Chest compression depth and survival in out-of-hospital cardiac arrest. *Resuscitation* 2014;85:182–8.
- Kovacs A, Vadeboncoeur TF, Stolz U, et al. Chest compression release velocity: Association with survival and favorable neurologic outcome after out-of-hospital cardiac arrest. *Resuscitation* 2015;92:107–14.
- Fabian-Jessing BK, Vallentin MF, Secher N, et al. Animal models of cardiac arrest: A systematic review of bias and reporting. *Resuscitation* 2018;125:16–21.
- Vognsen M, Fabian-Jessing BK, Secher N, et al. Contemporary animal models of cardiac arrest: A systematic review. *Resuscitation* 2017;113:115–23.
- Monsieurs KG, Nolan JP, Bossaert LL, et al. European Resuscitation Council Guidelines for Resuscitation 2015: Section 1. Executive summary. *Resuscitation* 2015;95:1–80.
- Considine J, Gazmuri RJ, Perkins GD, et al. Chest compression components (rate, depth, chest wall recoil and leaning): A scoping review. *Resuscitation* 2019.
- Babbs CF, Kemeny AE, Quan W, Freeman G. A new paradigm for human resuscitation research using intelligent devices. *Resuscitation* 2008;77:306–15.
- Stiell IG, Brown SP, Christenson J, et al. What is the role of chest compression depth during out-of-hospital cardiac arrest resuscitation? *Crit Care Med* 2012;40:1192–8.
- Stiell IG, Brown SP, Nichol G, et al. What is the optimal chest compression depth during out-of-hospital cardiac arrest resuscitation of adult patients? *Circulation* 2014;130:1962–70.
- Johnson BV, Coult J, Fahrenbruch C, et al. Cardiopulmonary resuscitation duty cycle in out-of-hospital cardiac arrest. *Resuscitation* 2015;87:86–90.
- Cordioli RL, Grieco DL, Charbonney E, Richard JC, Savary D. New physiological insights in ventilation during cardiopulmonary resuscitation. *Curr Opin Crit Care* 2019;25:37–44.
- Yannopoulos D, Matsuura T, McKnite S, et al. No assisted ventilation cardiopulmonary resuscitation and 24-hour neurological outcomes in a porcine model of cardiac arrest. *Crit Care Med* 2010;38:254–60.
- Soar J, Maconochie I, Wyckoff MH, et al. 2019 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations: Summary From the Basic Life Support; Advanced Life Support; Pediatric Life Support; Neonatal Life Support; Education, Implementation, and Teams; and First Aid Task Forces. *Circulation* 2019;140:e826–30.
- Daudre-Vignier C, Laviola M, Das A, Bates DG, Hardman JG. Identification of an optimal CPR chest compression protocol. *Annu Int Conf IEEE Eng Med Biol Soc* 2021;2021:5459–62.
- Hardman JG, Bedford NM, Ahmed AB, Mahajan RP, Aitkenhead AR. A physiology simulator: validation of its respiratory components and its ability to predict the patient's response to changes in mechanical ventilation. *Br J Anaesth* 1998;81:327–32.

19. Das A, Haque M, Chikhani M, et al. Development of an Integrated Model of Cardiovascular and Pulmonary Physiology for the Evaluation of Mechanical Ventilation Strategies. *Annu Int Conf IEEE Eng Med Biol Soc* 2015;5319–22.
20. Laviola M, Das A, Chikhani M, Bates DG, Hardman JG. Computer simulation clarifies mechanisms of carbon dioxide clearance during apnoea. *Br J Anaesth* 2019;122:395–401.
21. Stolady D, Laviola M, Pillai A, Hardman JG. Effect of variable pre-oxygenation endpoints on safe apnoea time using high flow nasal oxygen for women in labour: a modelling investigation. *Br J Anaesth* 2021;126:889–95.
22. Saffaran S, Das A, Hardman JG, Yehya N, Bates DG. High-fidelity computational simulation to refine strategies for lung-protective ventilation in paediatric acute respiratory distress syndrome. *Intens Care Med* 2019;45:1055–7.
23. Kim H, Hwang SO, Lee CC, et al. Direction of blood flow from the left ventricle during cardiopulmonary resuscitation in humans: its implications for mechanism of blood flow. *Am Heart J* 2008;156(1222):e1–7.
24. Redberg RF, Tucker KJ, Cohen TJ, Dutton JP, Callahan ML, Schiller NB. Physiology of blood flow during cardiopulmonary resuscitation. A transesophageal echocardiographic study. *Circulation* 1993;88:534–42.
25. Sheak KR, Wiebe DJ, Leary M, et al. Quantitative relationship between end-tidal carbon dioxide and CPR quality during both in-hospital and out-of-hospital cardiac arrest. *Resuscitation* 2015;89:149–54.
26. Naim MY, Sutton RM, Friess SH, et al. Blood Pressure- and Coronary Perfusion Pressure-Targeted Cardiopulmonary Resuscitation Improves 24-Hour Survival From Ventricular Fibrillation Cardiac Arrest. *Crit Care Med* 2016;44:e1111–7.
27. Fodden DI, Crosby AC, Channer KS. Doppler measurement of cardiac output during cardiopulmonary resuscitation. *J Accid Emerg Med* 1996;13:379–82.
28. Repessé X, Charron C, Fink J, et al. Value and determinants of the mean systemic filling pressure in critically ill patients. *Am J Physiol Heart Circ Physiol* 2015;309:H1003–7.
29. Soar J, Nolan JP, Böttiger BW, et al. European Resuscitation Council Guidelines for Resuscitation 2015: Section 3. Adult advanced life support. *Resuscitation* 2015;95:100–47.
30. Aufderheide TP, Sigurdsson G, Pirralo RG, et al. Hyperventilation-induced hypotension during cardiopulmonary resuscitation. *Circulation* 2004;109:1960–5.
31. Babbs CF. Relative effectiveness of interposed abdominal compression CPR: sensitivity analysis and recommended compression rates. *Resuscitation* 2005;66:347–55.
32. Zhang Y, Karemaker JM. Abdominal counter pressure in CPR: what about the lungs? An in silico study. *Resuscitation* 2012;83:1271–6.
33. Babbs CF. CPR techniques that combine chest and abdominal compression and decompression: hemodynamic insights from a spreadsheet model. *Circulation* 1999;100:2146–52.
34. Babbs CF. Efficacy of interposed abdominal compression-cardiopulmonary resuscitation (CPR), active compression and decompression-CPR and Lifestick CPR: basic physiology in a spreadsheet model. *Crit Care Med* 2000;28:N199–202.
35. Babbs CF. Design of near-optimal waveforms for chest and abdominal compression and decompression in CPR using computer-simulated evolution. *Resuscitation* 2006;68:277–93.
36. Babbs CF. Effects of an impedance threshold valve upon hemodynamics in Standard CPR: studies in a refined computational model. *Resuscitation* 2005;66:335–45.
37. Babbs CF, Yannopoulos D. A dose-response curve for the negative bias pressure of an intrathoracic pressure regulator during CPR. *Resuscitation* 2006;71:365–8.
38. Shin DA, Park J, Lee JC, Shin SD, Kim HC. Computational simulation of passive leg-raising effects on hemodynamics during cardiopulmonary resuscitation. *Comput Methods Programs Biomed* 2017;140:195–200.
39. Zhang Y, Jiménez-Herrera M, Axelsson C, Cheng Y. Not Bad: Passive Leg Raising in Cardiopulmonary Resuscitation-A New Modeling Study. *Front Physiol* 2016;7:665.
40. Jung E, Babbs CF, Lenhart S, Protopopescu VA. Optimal strategy for cardiopulmonary resuscitation with continuous chest compression. *Acad Emerg Med: Official J Soc Acad Emerg Med* 2006;13:715–21.
41. Jung E, Lenhart S, Protopopescu V, Babbs C. Optimal control applied to a thoraco-abdominal CPR model. *Math Med Biol* 2008;25:157–70.
42. Babbs CF, Meyer A, Nadkarni V. Neonatal CPR: room at the top—a mathematical study of optimal chest compression frequency versus body size. *Resuscitation* 2009;80:1280–4.
43. John AR, Manivannan M, Ramakrishnan TV. Computer-Based CPR Simulation Towards Validation of AHA/ERC Guidelines. *Cardiovasc Eng Technol* 2017;8:229–35.
44. Turner I, Turner S, Armstrong V. Does the compression to ventilation ratio affect the quality of CPR: a simulation study. *Resuscitation* 2002;52:55–62.