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 interspecies 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
association between these parameters and outcomes. A recent systematic review and meta-analysis by Considine et al., 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. found an association between CC rate and ROSC with the rate of ROSC peaking at 125 compressions min⁻¹, and Idris et al.²³ 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., 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. 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, 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., 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 researchers 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 others 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 (FIO₂) on CPR effectiveness.

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. 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., 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., which used transthoracic echocardiography in 18 subjects; and the end tidal CO₂ (ETCO₂) ranges from Sheak et al. 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 CPR²²–²⁵ (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 (Costₜₐₓ) to be minimised is:

\[
\text{Cost}_\text{t}_{\text{a}} = w_1 |\text{PeakLV}_\text{m} - \text{PeakLV}_\text{d}| + w_2 |\text{EDLVP}_\text{m} - \text{EDLVP}_\text{d}| + w_3 |\text{PeakSA}_\text{m} - \text{PeakSA}_\text{d}| + w_4 |\text{EDRAP}_\text{m} - \text{EDRAP}_\text{d}| + w_5 |\text{CPP}_\text{m} - \text{CPP}_\text{d}| + w_6 |\text{SV}_\text{m} - \text{SV}_\text{d}| + w_7 |\text{EF}_\text{m} - \text{EF}_\text{d}| + w_8 |\text{EDVLV}_\text{m} - \text{EDVLV}_\text{d}| + w_9 |\text{ESVLV}_\text{m} - \text{ESVLV}_\text{d}| + w_10 |\text{ETCO}_2\text{m} - \text{ETCO}_2\text{d}|
\]

where, PeakLV is the peak left ventricular pressure, EDLVP is the left ventricular end-diastolic pressure, PeakSA is the peak aortic pressure, EDRAP is the aortic end-diastolic pressure, PeakRA is the peak right atrial pressure, ESPAP is the right atrial end-systolic 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 ETOCO is the end tidal CO₂ 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 (Costₜₐₓ) defined as:

\[
\text{Cost}_\text{t}_{\text{a}} = w_1 |\text{CPP}_\text{m} - \text{CPP}_\text{d}| + w_2 |\text{CO}_\text{m} - \text{CO}_\text{d}| + w_3 |\text{brainO}_2\text{m} - \text{brainO}_2\text{d}| + w_4 |\text{heartO}_2\text{m} - \text{heartO}_2\text{d}|
\]

where CPP is the coronary perfusion pressure, CO is the cardiac output, brainO₂ is the cerebral tissue oxygen volume, heartO₂ is the myocardial tissue oxygen volume, the subscript ‘m’ defines the simulation output parameters, the subscript ‘d’ defines the desired
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 disfavouring 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.\(^2^3\) 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 (\(F_{\text{max}}\)) was allowed to vary between 0 and 500 N, the CC rate (\(CC_{\text{rate}}\)) between 60 and 150 compressions min\(^{-1}\), the compression ratio (\(Duty_{\text{cycles}}\)) 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 (FiO\(_2\)) 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 work\(^2^3\) 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.\(^2^3\)–\(^2^5\) 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 (OPT-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-

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**Table 1 – Literature human data\(^2^6\),\(^2^9\)–\(^3^0\) versus model outputs during CPR.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unit</th>
<th>Literature human data</th>
<th>Model outputs</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC LV pressure</td>
<td>mmHg</td>
<td>112 ± 37(^1)</td>
<td>111 ± 13</td>
</tr>
<tr>
<td>EC aorta pressure</td>
<td>mmHg</td>
<td>105 ± 41(^1)</td>
<td>110 ± 13</td>
</tr>
<tr>
<td>EC RA pressure</td>
<td>mmHg</td>
<td>89 ± 27(^1)</td>
<td>88 ± 9</td>
</tr>
<tr>
<td>ED LV pressure</td>
<td>mmHg</td>
<td>8 ± 11(^1)</td>
<td>11 ± 7</td>
</tr>
<tr>
<td>ED aorta pressure</td>
<td>mmHg</td>
<td>33 ± 10(^1)</td>
<td>36 ± 4</td>
</tr>
<tr>
<td>ED RA pressure</td>
<td>mmHg</td>
<td>8 ± 6(^1)</td>
<td>6 ± 3</td>
</tr>
<tr>
<td>CPP</td>
<td>mmHg</td>
<td>25 ± 9(^1)</td>
<td>30 ± 7</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>ml</td>
<td>19 ± 6(^2)</td>
<td>19 ± 1</td>
</tr>
<tr>
<td>EC LV volume</td>
<td>ml</td>
<td>50 ± 7(^2)</td>
<td>72 ± 6</td>
</tr>
<tr>
<td>ED LV Volume</td>
<td>ml</td>
<td>70 ± 10(^2)</td>
<td>70 ± 7</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>%</td>
<td>34 ± 16(^1)</td>
<td>50 ± 8</td>
</tr>
<tr>
<td>ETCO(_2)</td>
<td>mmHg</td>
<td>30 ± 5(^3)</td>
<td>26 ± 1</td>
</tr>
</tbody>
</table>

EC, end compression; ED, end diastolic; LV, left ventricle; RA, right atria; CPP, coronary perfusion pressure; ETCO\(_2\), end tidal CO\(_2\); 1: Kim et al.\(^2^3\), 2: Redberg et al.\(^2^6\), 3: Sheak et al.\(^3^1\).
tocol, 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). Additionally, the MSFP of around 10 mmHg agrees with the observation in
Repsesse et al.\textsuperscript{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.\textsuperscript{29} 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.\textsuperscript{30} 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 (\(\text{heartO}_2\)) is more than 5 times higher than during standard CPR (Table 2). The cerebral tissue oxygen volume (\(\text{brainO}_2\)) is nearly doubled during optimised CPR compared to standard CPR. Considering the reduction in minute ventilation and \(\text{FiO}_2\) 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\(^{-1}\) (Table 2). 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,\textsuperscript{31,32} a similar negative outcome has been observed when hyperventilation is used.\textsuperscript{33} 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 \(\text{CO}_2\) 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,\textsuperscript{31-32} combined chest and abdominal compression and decompression,\textsuperscript{30-31} impedance valve,\textsuperscript{30-37} and passive leg raise.\textsuperscript{38-39} Jung et al.\textsuperscript{40} applied optimal control to identify the CC and decompression frequency and compression ratio that maximized the coronary perfusion pressure (CPP)\textsuperscript{40} and the blood flow as measured by the pressure difference between the thoracic aorta and the right atrium.\textsuperscript{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 study\textsuperscript{42} 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 Jungs et al.\textsuperscript{43} was lower (40%). These discrepancies may arise from the fact that while Jungs’ 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.\textsuperscript{44} 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 Babbs\textsuperscript{45} 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.\textsuperscript{46} 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.\textsuperscript{47} investigated the benefits of continuous CC over the usual 5:1 or 15:2 ratios of compression to ventilation\textsuperscript{44} 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,\textsuperscript{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 (V̇L 250 ml, V̇E, 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**

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2023.109758.

**Author details**

*Anaesthesia & Critical Care, Injury, Inflammation and Recovery Science Academic Unit, School of Medicine, University of Nottingham, Nottingham NG7 2UH, UK*  
*School of Engineering, University of Warwick, Coventry CV4 7AL, UK*  
*Academic Department of Military Anaesthesia and Critical Care, Royal Centre for Defence Medicine, ICT Centre, Birmingham B15 2SQ, UK*  
*Nottingham University Hospitals NHS Trust, Nottingham NG7 2UH, UK*

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