Autonomic Effects of Synthetic Cannabinoids: A Literature Review and Overdose Simulation

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Abstract

Synthetic cannabinoids (SCs) act as cannabimimetics but have a higher risk than cannabis of serious physiological complications including seizures, arrhythmias, myocardial infarction, and respiratory depression which may result in death. However, there is no clear toxidrome and symptoms can vary widely based on the SC used and other risk factors. Only symptomatic care is available, with a survey in 2013 suggesting that many clinicians feel underprepared to treat SC overdose. This project therefore utilised high-fidelity human patient simulation software (Müse iStan) to build two simulations involving serious autonomic complications of SC overdose: cardiac toxicity involving atrial fibrillation with haemodynamic instability and respiratory depression with respiratory acidosis and hypoxaemia. Case studies were used to determine target parameters, modelled in the simulations using physiological gains and factors. Medical interventions and their associated parameter changes were also modelled for training, including electrical cardioversion for atrial fibrillation, and intubation (with associated preparation) for respiratory depression. The simulations were mostly compliant with target parameters apart from pH and responses to certain drugs (rocuronium). Overall, the simulations closely resembled real-life incidences of SC toxicity and are expected to be useful for practical and online teaching. However, Müse cannot model psychological symptoms of SC overdose including agitation and psychosis, meaning the simulations would be best utilised alongside with VR technology for effective teaching. Implementation of these in a teaching session for clinicians is expected to improve patient care and survival rates in SC overdose.

Introduction

History and Epidemiology

Synthetic cannabinoids (SCs) are designer drugs of abuse that mimic the effects of cannabis [1]. They were primarily developed for CB1 receptor research [2]. Recreational use of SCs began in the 2000's, with compounds JWH-018 and CP 47,497 [3]. There are now nearly 200 different SC compounds detected in Europe [4], with more synthesised each year to avoid detection by updated drug testing. Typically, compounds are dissolved in ethanol and sprayed on to plant for distribution [5]. They have a much higher potency than Δ9-THC [6] but are perceived to be safer than other recreational drugs and are therefore popular among teenagers and young adults [1]. The 2016 Psychoactive Substances Act in the UK placed a ban on all novel

compounds with psychoactive effects, but reports of SCs remain high in Europe [4] and the UK [7] compared to other novel psychoactive substances.

Pharmacology and Autonomic Symptoms

Most SCs are full agonists at the CB1 receptor, a G-protein coupled receptor (GPCR) with Gi/o coupling [2,8]. CB1 receptors show expression throughout the autonomic nervous system, where their main role appears to be modulation of neurotransmitter release by hyperpolarisation, due to inhibition of adenylyl cyclase and activation of GIRK channels (Figure 1). Importantly, Δ9-THC is a partial agonist at CB1 receptors, and has a lower potency compared to SC's.

Symptoms of SC toxicity encompass sympathomimetic activity and central nervous system (CNS) depression [5]. Tachycardia is common and often observed with hypertension and nausea [9]. However, bradycardia has also been reported in some patients [10] and commonly observed in animal studies [11,12]. In pithed rabbits, the SC's WIN55212-2 and CP55940 dose-dependently inhibited pre-ganglionic fibre induced decreases in heart rate, but also dose-dependently inhibited electrically evoked increases in heart rate [13]. These paradoxical autonomic effects could therefore arise due to differences in CB1 receptor expression on sympathetic and parasympathetic nerves between individuals, contributing to the different clinical presentations. These, changes in heart rate also demonstrate how arrhythmias including supraventricular tachycardia [14] and atrial fibrillation (AF) [15] may arise. Arrhythmias such as these may then predispose patients to more serious cardiovascular complications that have been reported such as myocardial infarction and stroke [16].

Respiratory complications including respiratory depression [17] and acute respiratory distress syndrome (ARDS) [18] have also been reported. They are speculated to be due to downregulation of CB1 receptors in the CNS (via prolonged CB1 phosphorylation), as well as effects on peripheral chemoreceptors causing increases in bronchial airway resistance [17]. The pharmacological basis for SC symptoms is complex, and likely to be affected by other factors such as comorbidities (i.e., epilepsy, diabetes, and underlying cardiovascular disease), and polydrug use. The lack of a toxidrome also makes SC overdose difficult to distinguish from other overdoses such as opioids [19].

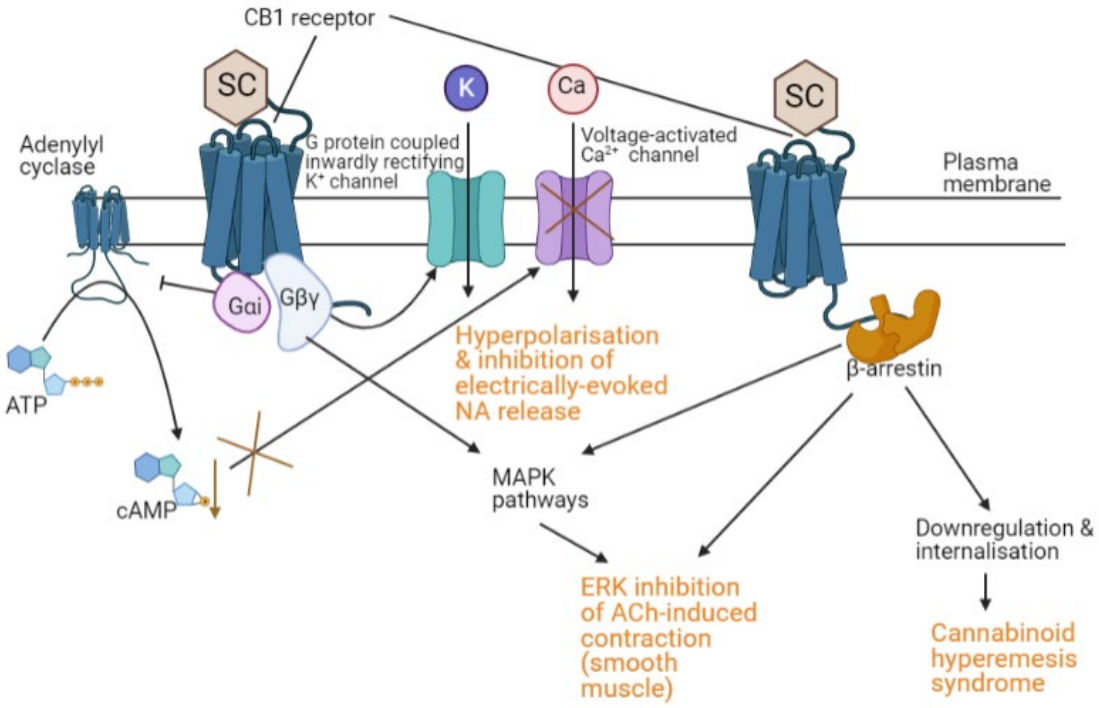


Figure 1: *CB1 receptor signalling and examples of associated effects of SCs (orange). Figure adapted from [20] with information from [12,21,22]. MAPK, mitogen-activated protein kinase. ATP, adenosine triphosphate. cAMP, cyclic adenosine monophosphate. Created with BioRender.com.*

Human Patient Simulation

Human patient simulators (HPS) are widely used to teach physiology, medicine, and nursing students with positive learning outcomes [23,24]. They utilise a medical manikin and high-fidelity physiology software to simulate normal and pathological physiology. CAE Müse is a highly integrated HPS software with the ability to respond to changes in physiology or medical interventions [25]. It is used to create simulated clinical experiences (SCEs), which are advantageous compared to hospital teaching due to the realistic but low risk environment. Müse iStan software was introduced to the cardiovascular curriculum for medical students with improvements in engagement and learning outcomes [26]. It was also used in simulations of opioid overdose used to train a lay audience on intranasal administration of naloxone with moderate success [27]. In the case of SC overdose, there is no simulation, yet a study in 2013 revealed 80% of clinicians feel underprepared to treat a patient with SC toxicity [28]. Therefore, the aims of this project were to analyse case studies of SC overdose to find typical physiological parameter values and utilise this information to construct two distinct simulations of SC overdose for training emergency department clinicians. The focus will be on autonomic symptoms as these are often the cause of death and life-threatening complications [9,29].

Methods

Literature Review for Target Parameters

Phrases including 'synthetic cannabinoid OR synthetic cannabis' were searched alongside 'overdose', 'toxicity' and 'death' (using 'AND') on PubMed and PMC databases. Searches for common compounds such as 'JWH-018' and 'AB-FUBINACA' were also used. Papers included were in English only. When reviewed, the typical dose of SCs that caused different symptoms showed a broad range, but two types of symptoms tended to be most severe and most frequently required emergency treatment: cardiovascular and respiratory. Therefore, a 'Cardiac' and 'Respiratory' simulation were chosen to incorporate these. Reported physiological parameters (e.g., heart rate) from 32 case studies were examined to create a parameter table (Table 1) of target ranges for the simulation, categorised into starting values for Baseline, Cardiac and Respiratory simulations. As there is no typical presentation of overdose, the simulation events were primarily informed by 5 case studies involving severe cardiac and respiratory events [14,15,17,18,30] as well as starting physiological parameters (Table 1), events recorded in other relevant case studies and National Institute for Health and Social Care (NICE) guidelines covering treatments.

Simulation Building

CAE iStan software was used, as this is a male simulator and a large proportion of cases of SC overdose involve young males [9]. The Cardiac Simulation involved tachycardia progressing to atrial fibrillation with haemodynamic instability requiring cardioversion treatment and the Respiratory Simulation involved respiratory depression and hypoxia with intubation. Whilst myocardial infarction and stroke are rare complications of SC toxicity [16], these already have detailed simulations [31]. Arrhythmias are more likely to occur [32] and may cause further cardiovascular complications [16], hence the choice to simulate atrial fibrillation. Also, in the case of SC toxicity, respiratory depression is a severe effect that could be mistaken for opioid overdose but often cannot be reversed with naloxone [17], justifying inclusion of respiratory depression as part of the training scenario. Both simulations involved a series of states with different physiological parameters, reflecting either worsening of condition or a medical intervention. Simulation building involved an iterative approach, as parameter values were changed by changing physiological gains and factors (for example, when 'Heart Rate Factor' increases, heart rate increases). The display used for this can be seen in Figure 2. Once the target parameters are reached (monitored using the 'Patient Status Display'), the factors changed to give rise to these are programmed into the script for the corresponding state.

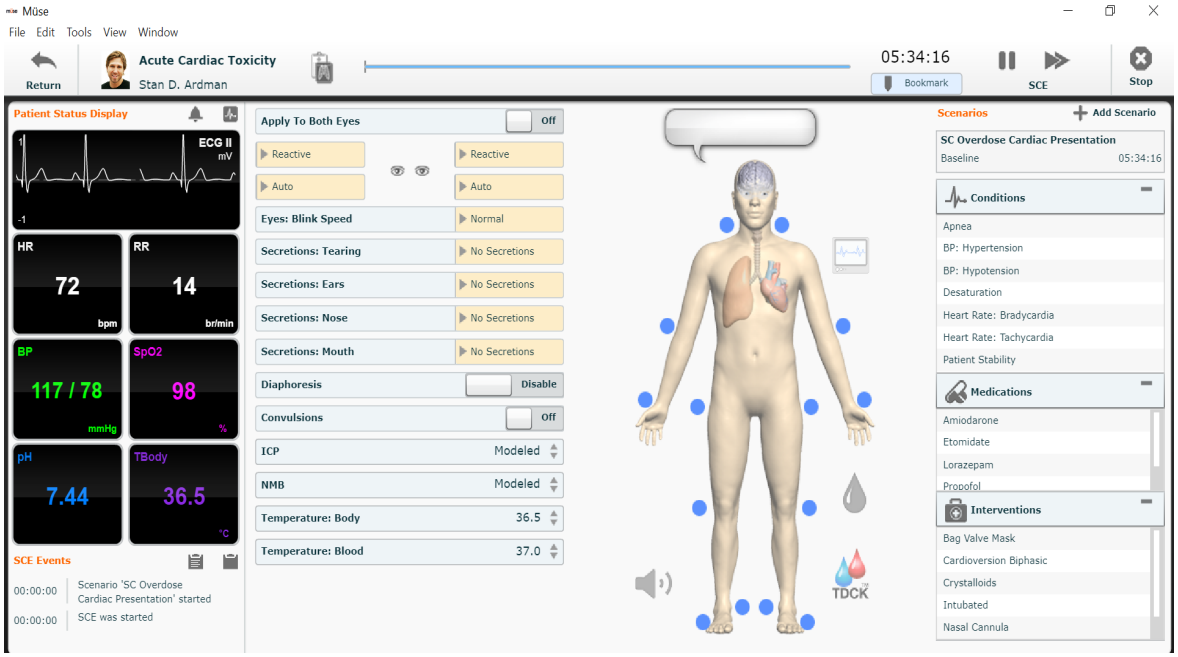


Figure 2: *The Müse interface during simulation. Neurological, cardiac and respiratory gain factors were changed by selecting the brain, heart and lungs respectively.*

Results

Target Parameters and Baseline

The target parameters derived from the literature review can be seen in Table 1. The parameters that were not modelled in Müse were included in a follow-up activity which included diagnosis and treatment of acute kidney injury (of which high creatine kinase is a marker for) following Respiratory Simulation stabilisation. The Baseline states for each simulation had the same script and complied with target parameters, with only two changes made: Respiratory Rate Factor was set to 1.23 and O2 Consumption set to 308 ml/min.

Table 1: *Target parameters used in simulation building and learning materials. *not simulated in Muse. References shown below values.*

Parameter	**Baseline**	**Acute Cardiac Toxicity**	**Acute Respiratory Toxicity**
Heart rate (bpm)	60-100 [33]	140 (115-170) [14,34-36]	110 (102-118) [18,19,37]
Blood pressure (mmHg)	120/80 [33]	Systolic: 140-170, Diastolic: 70-120 [14,34,38,39]	80/60 [18]
Respiratory rate (bpm)	12-20 [33]	22 (14-33) [34,38,40]	6-8 [10,18,19,37]
Body temperature (°C)	37 (36.2-37.7) [33]	33.0-36.5 [15]	33.0-36.4 [18,36]
pH	7.35-7.45 [41]	7.25-7.35 [30,36,42,43]	6.98-7.20 [17,18]
Creatine Kinase (IU/L)*	38–174 [44]	104-229 [38]	364 (202-1163) [10,17,18,45]
SpO2 (%)	95-100 [46]	87-98 [30,38,47]	80 (69-96) [17-19]
PaO2 (mmHg)	75-100 [46]	99 (75-100) [42]	83 (59-107) [17]
PaCO2 (mmHg)	35-45 [46]	45-63 [10,42,43]	57-84 [10,17]
Blood Na+ (mmol/L)*	133-146 [48]	134 (133-146) [39]	135-146 [17]
Blood K+ (mmol/L)*	3.5-5.3 [48]	2.8-3.0 [47,49]	3.51-4.45 [10,17]
Blood glucose (mmol/L)*	2.6-6.0 [48]	6.7-8.0 [38,47]	7 (5.6-18.0) [17,18]

Cardiac Simulation

This simulation involved acute cardiac toxicity, with the initial presentation state showing tachycardia and mild hypothermia. Progression to atrial fibrillation occurs after 5 minutes in the state, and then haemodynamic instability when AF is untreated for 1 minute. Emergency electrical cardioversion with an input of 100J transitions the simulation to a Post-cardioversion state where blood pressure increases. The states can be seen in Figure 2.

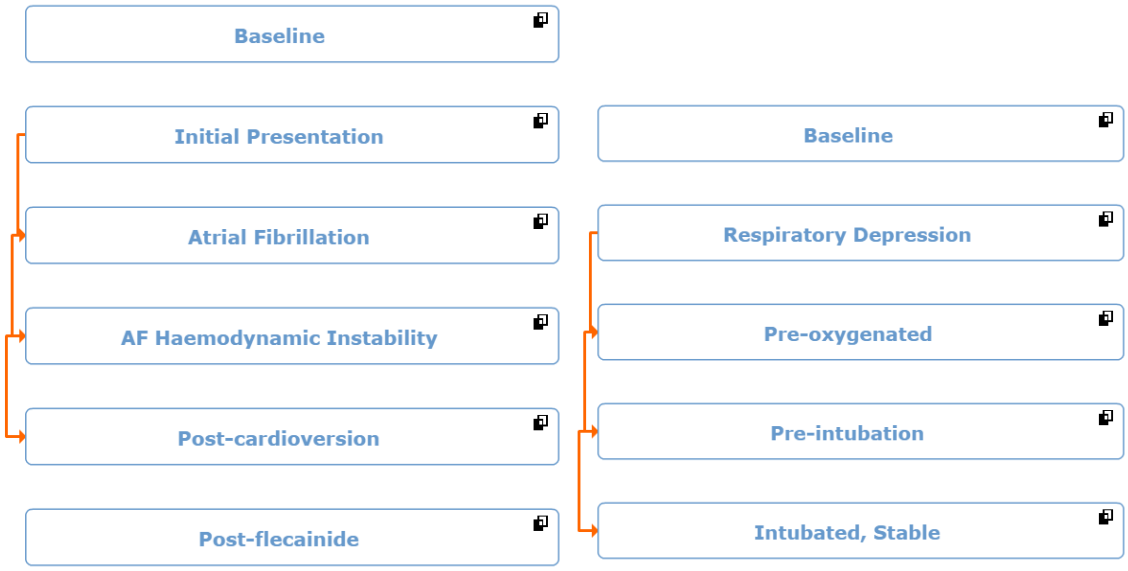


Figure 2: *Screenshot of states in the Cardiac (left) and Respiratory (right) simulations. Orange arrows indicate transitions between states.*

For the 'Initial Presentation' state, the major changes made were an increase in heart rate factor, right and left ventricle contractility factors and body temperature set to 35°C. Respiratory rate factor was increased to achieve mild hyperventilation. 5 minutes in this state without treatment transitioned the simulation to the 'Atrial Fibrillation' state (Figure 4).

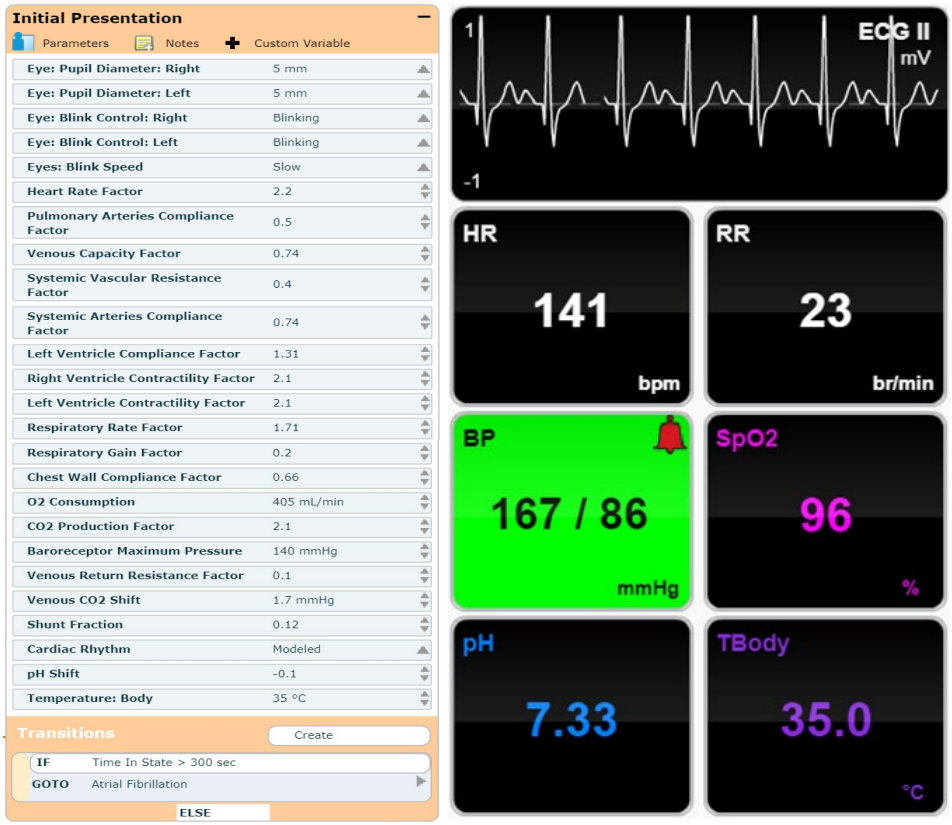


Figure 3: *Script and resulting parameters for the 'Initial Presentation' state in the Cardiac Simulation.*

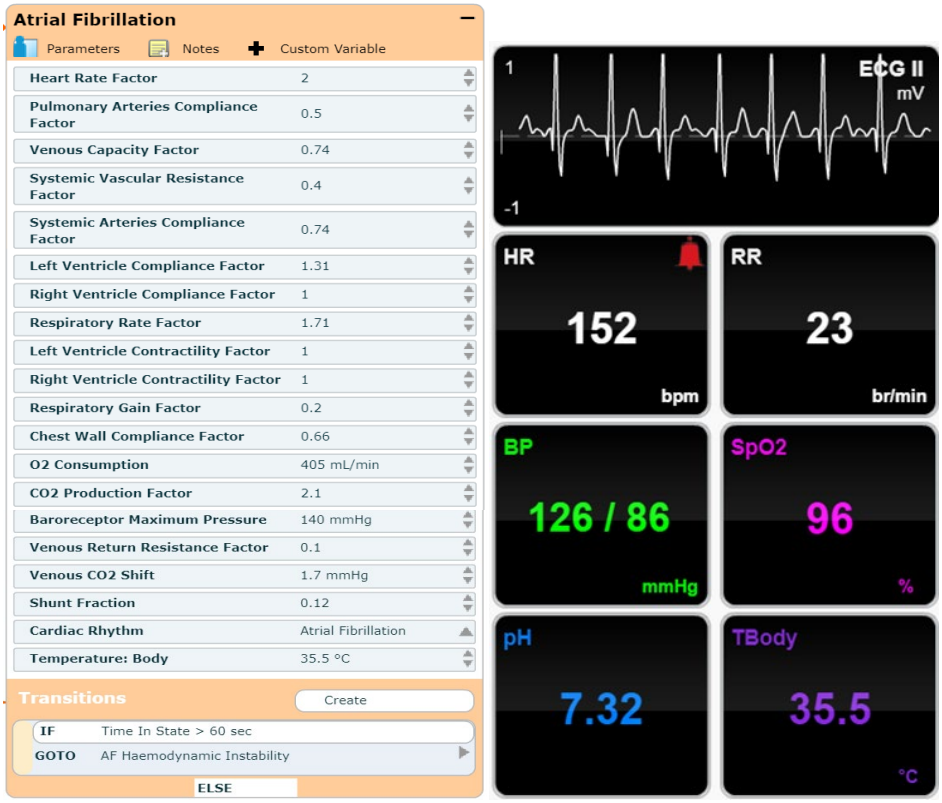


Figure 4: *Script and resulting parameters for the 'Atrial Fibrillation' state in the Cardiac Simulation.*

The ‘Atrial Fibrillation’ state showed little change compared to ‘Initial Presentation’, but the ECG trace showed the characteristic waveform of AF. Clinicians would normally be expected to monitor new-onset AF without treating it to allow the possibility of spontaneous return to sinus rhythm [50]. However, after 1 minute in this state, the simulation transitions to the ‘AF Haemodynamic Instability’ state (Figure 5).

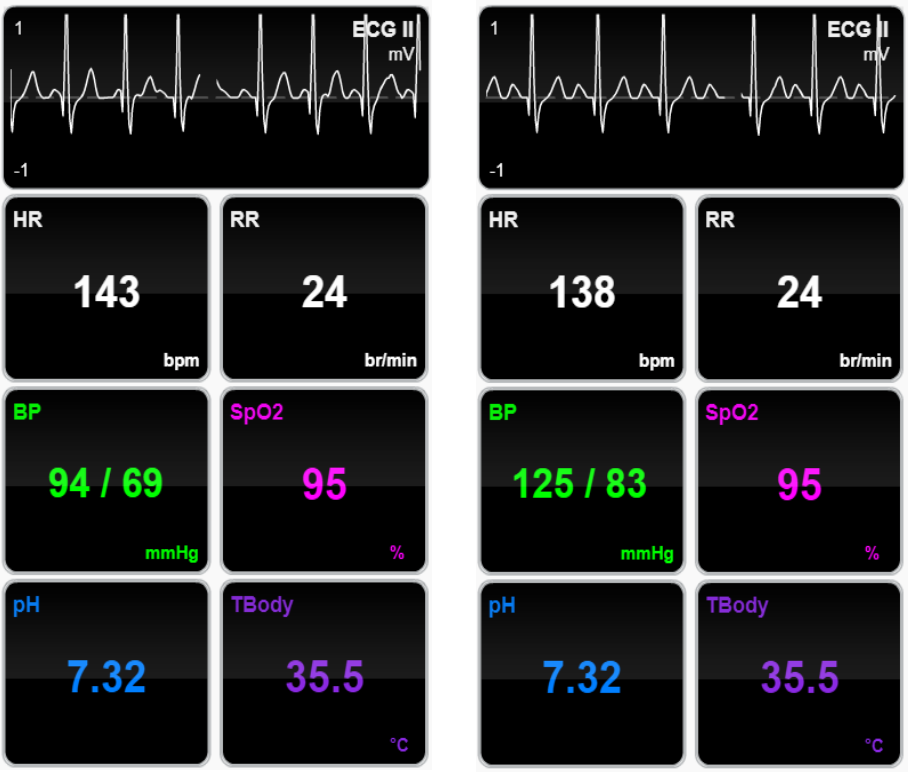


Figure 5: *Resulting parameters in ‘AF Haemodynamic Instability’ (left) and ‘Post-cardioversion’ (right) states in the Cardiac Simulation. Note the return to sinus rhythm and blood pressure increase in the ‘Post-cardioversion’ state.*

The ‘AF Haemodynamic Instability’ state showed a severe decrease in blood pressure (achieved primarily by decreasing right and left ventricle contractility factors), prompting emergency electrical cardioversion to restore sinus rhythm [50,51]. Therefore, an input of 100J (from biphasic cardioversion) transitioned the simulation to the ‘Post-cardioversion’ state, where blood pressure increases [52] and normal sinus rhythm returns (Figure 5), ending the Cardiac Simulation.

Respiratory Simulation

This simulation involved five states including ‘Baseline’, ‘Respiratory Depression’, ‘Pre-oxygenated’, ‘Pre-intubation’ and ‘Intubated Stable’ (Figure 2). The ‘Respiratory Depression’ state showed mild tachycardia and hypotension, as well as hypoventilation at about 6-7 breaths per minute (bpm) and severe hypoxaemia (Figure 6). This would immediately prompt

intubation protocols, which would first include preoxygenation via a bag valve mask with 100% oxygen [17,53]. Therefore, an FiO_2 ≥ 100% transitioned the simulation to the 'Pre-oxygenated' state.

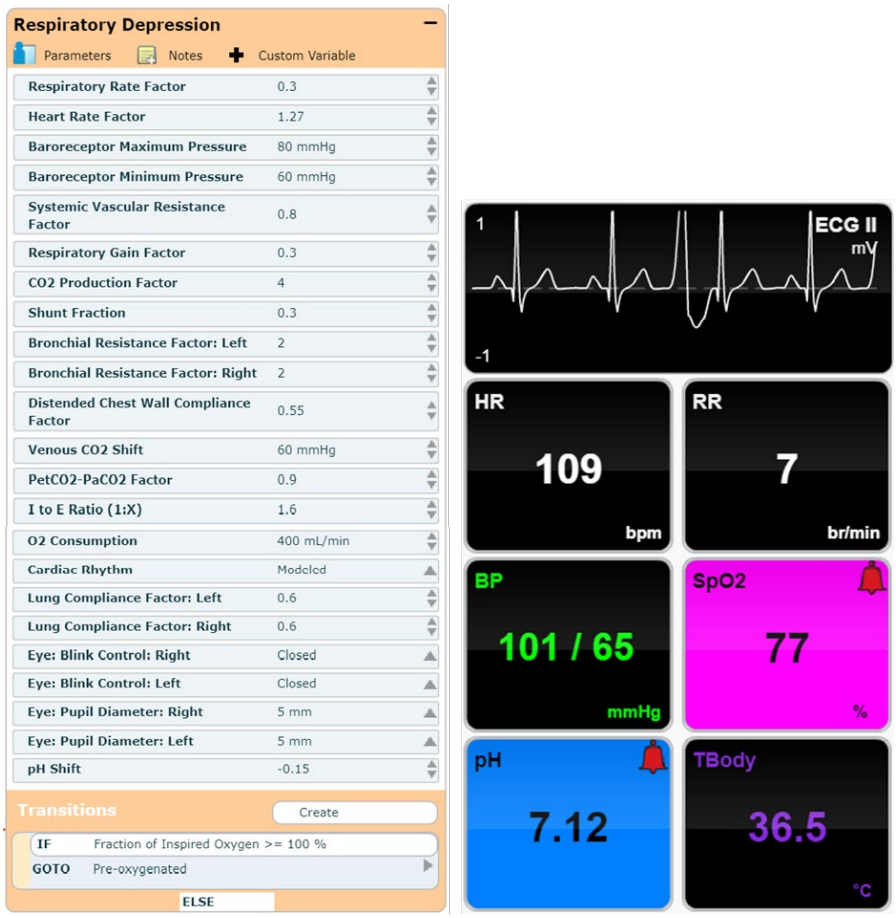


Figure 6: *Script and resulting parameters for the 'Respiratory Depression' state of the Respiratory Simulation.*

In the 'Pre-oxygenated' state, no significant changes were made to factors, but application of the bag valve mask caused a significant increase in oxygen saturation (Figure 7). This is required for the next steps in intubation preparation where anaesthetic (ketamine) and neuromuscular blocker (rocuronium) are administered. Rocuronium > 0mg/kg transitioned the simulation to the 'Pre-intubation' state.

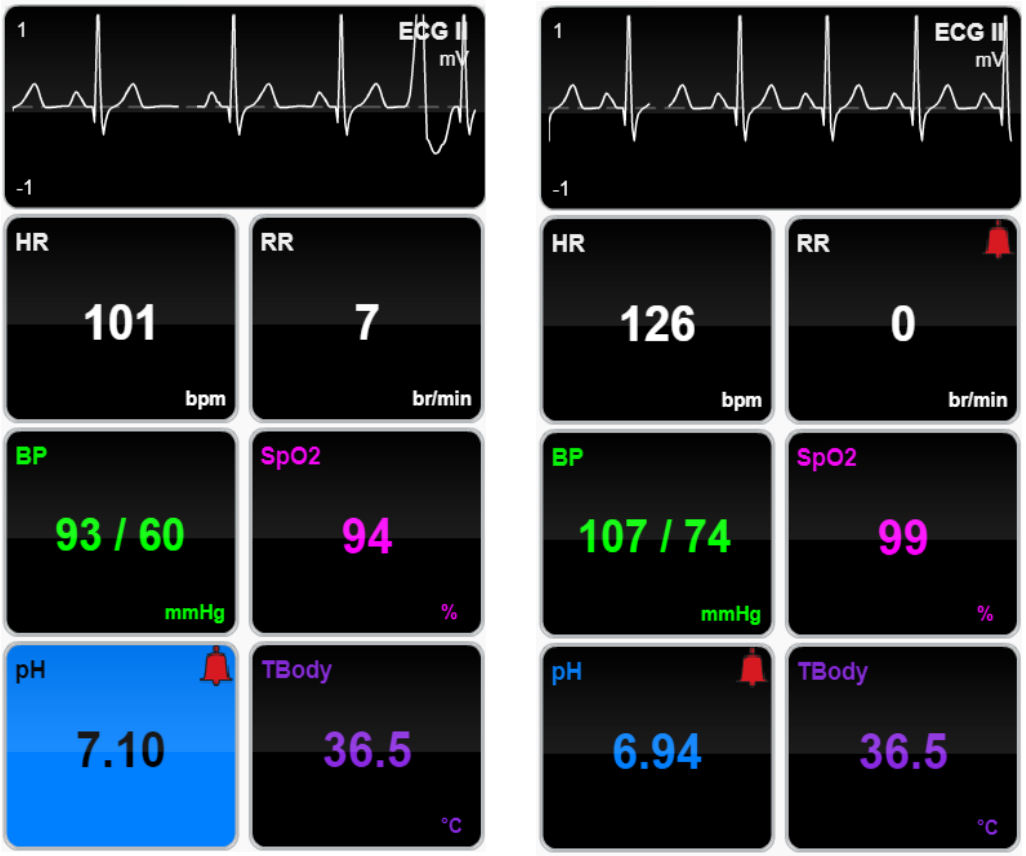


Figure 7: *Parameters in 'Pre-oxygenated' (left) and 'Pre-intubated' (right) states in the Respiratory Simulation.*

In the 'Pre-intubation' state, respiratory rate decreased to 0bpm, simulating neuromuscular blockade to allow intubation. Severe respiratory acidosis was observed (Figure 7), which resulted from respiratory arrest. Finally, intubation would be attempted, so $FiO_2 \geq 21\%$ transitions the simulation to the 'Intubated Stable' state (Figure 8).

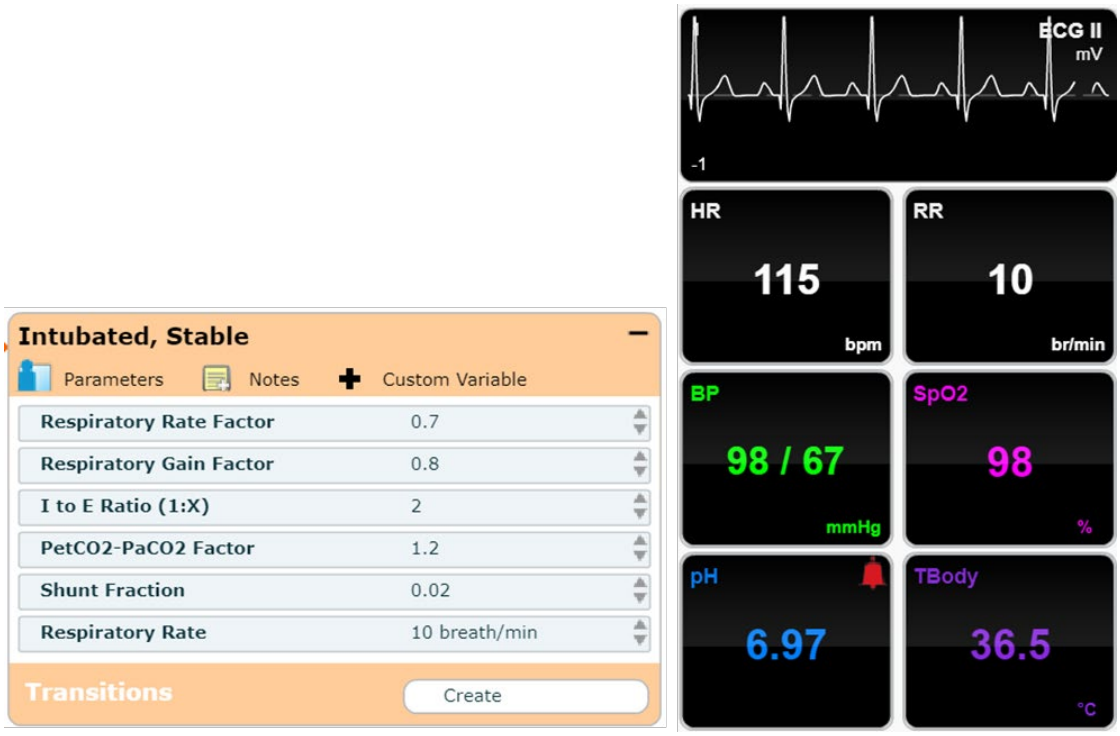
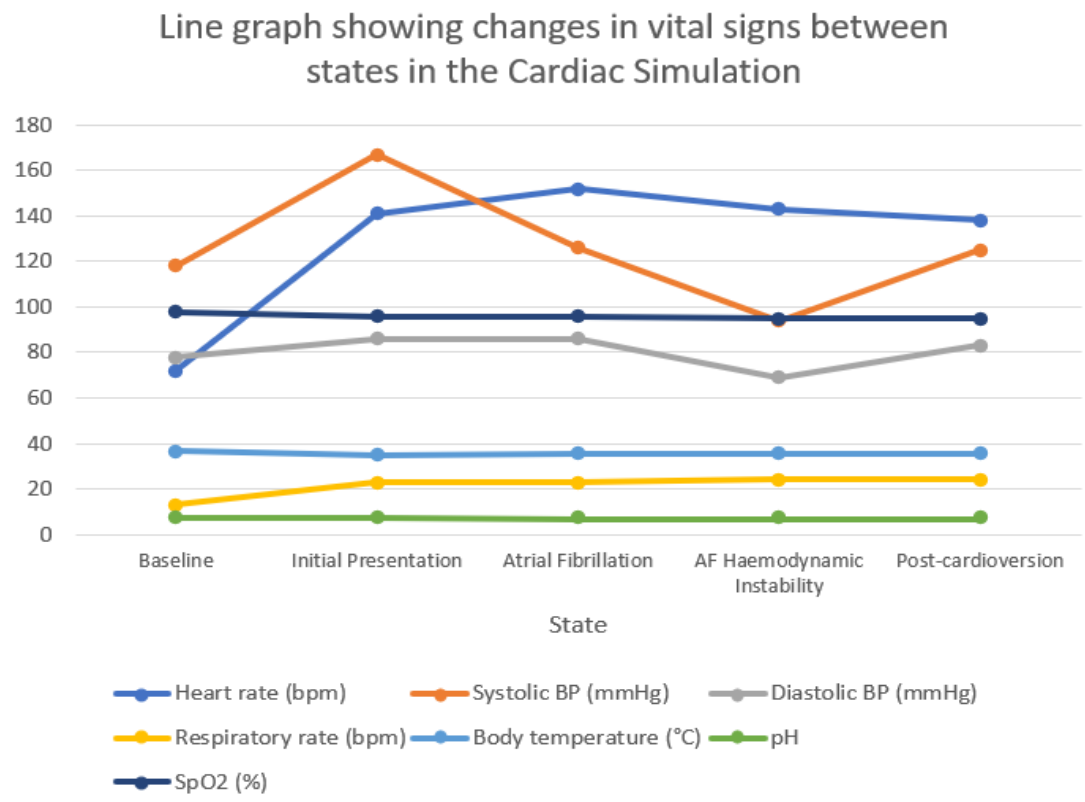


Figure 8: *Script (left) and resulting parameters (right) for the 'Intubated Stable' state of the Respiratory Simulation. Following intubation pH began to rise and respiratory rate was set to 10 to model mechanical ventilation.*

The 'Intubated Stable' state showed similar cardiovascular parameters but increasing pH due to the increase in respiratory rate. This was overridden to 10 bpm (to reflect mechanical ventilation, as this is not available in Müse). Oxygen saturation also normalises in this state, and the Respiratory Simulation ended following stabilisation.



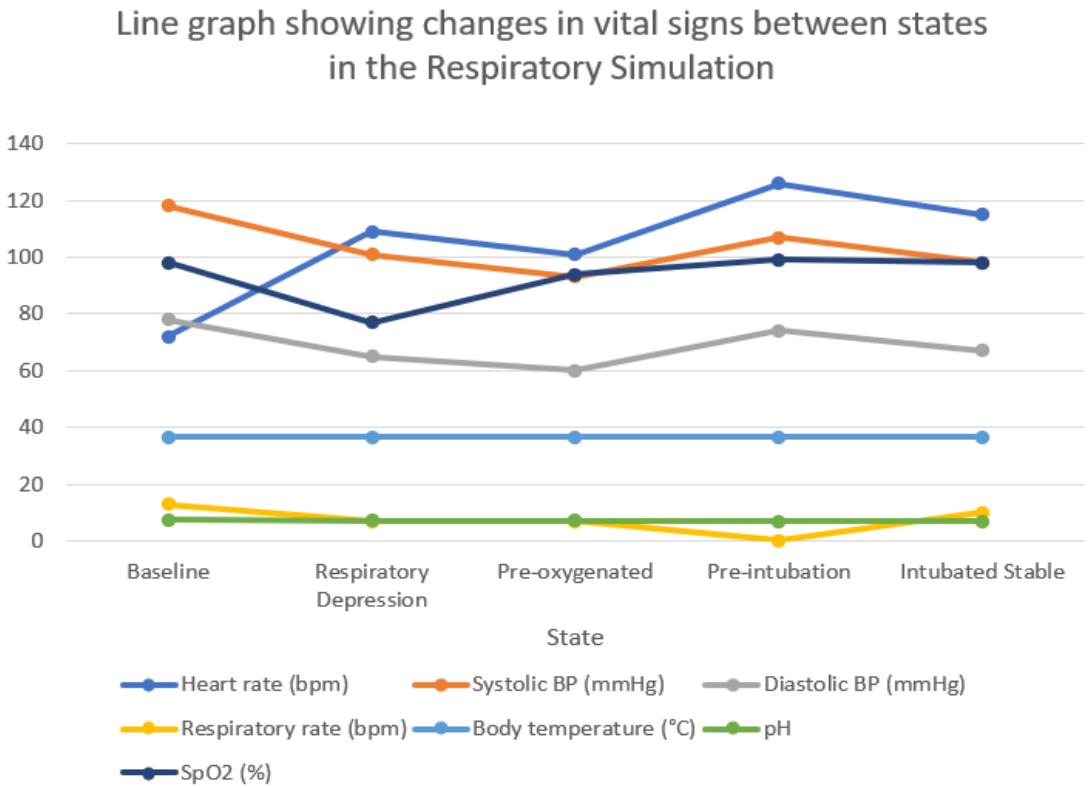


Figure 9: *Line graphs showing parameter changes in each simulation. Parameters were within target ranges derived from SC case reports for all stages. In the final stages, parameters returned to baseline (Table 1) ranges (excluding the low pH in the Respiratory Simulation).*

Discussion

Compliance with Target Parameters and Müse Discrepancies

In both simulations, parameters broadly accorded with the target ranges when gain factors were changed. However, pH required overriding (using the pH shift function to lower pH, shown in Figure 3) in both simulations to reach the target range for the first state. Additionally, the profound acidosis in the Respiratory Simulation (Figures 7 and 8) would likely not be as severe in real overdose cases [17].

However, in the Respiratory Simulation, the NICE recommended dose of 0.6 mg/kg rocuronium [54] caused long-lasting respiratory arrest that could not be corrected using the override function. Whilst this is required for intubation, respiratory would recover relatively quickly at this dose and this is therefore a discrepancy in the drug administration function in Müse. Therefore, a lower dose of 0.3mg/kg rocuronium was administered and respiratory rate was overridden to 10 in the final state (Figure 8). However, administration of ketamine changed physiological parameters correctly, increasing blood pressure in accordance with the literature [55].

In the Respiratory Simulation, an arrhythmia showing a large S wave was present (Figures 6-8). The arrhythmia is likely to be due to the extreme physiology and not the interventions used, as it occurred in all states. No reports of this were found in the literature [32], meaning it is likely an idiosyncrasy of the HPS model. Severe acidosis (Figure 8) may have contributed to the induction of this arrhythmia. As it was infrequent and not reported with SC use, its treatment was not included in the simulation.

Impact and Future Perspectives

Despite Müse discrepancies, the simulations ran correctly when factors were adjusted or overridden. In the cardiac simulations, the Initial Presentation state reflected target ranges (Table 1) and following states where blood pressure decreased following AF reflected real life cases of SC use where AF is present [30]. Similarly, the severe respiratory depression modelled in the Respiratory Simulation is reflective of recently reported SC overdoses [17]. Overall, the events and parameter changes in the simulations (Figure 9) closely resembled real-life examples of SC overdose [14,15,17,18,30] and therefore had high fidelity overall. These similarities demonstrate that HPS is a valuable tool for overdose training for SC's. However, because there is no SC toxidrome, these simulations do not represent all cases of SC overdose. Due to time constraints, priority was given to modelling more severe complications in Müse. This meant that some important symptoms were not included, such as seizures and nausea due to difficulty or inability to model them in Müse. The 'can't intubate, can't oxygenate' scenario was

also not modelled due to time constraints but is likely to occur with difficult airways, like this SCE. In addition, the project focused only on autonomic symptoms meaning that psychological symptoms such as agitation and psychosis, which also contribute to deaths due to SC exposure [29], were not modelled. This should therefore be the next step in producing a training session of SC overdose, and could be addressed by using VR medical simulation [56].

The literature review noted a lack of understanding of the effects of individual compounds and their plasma concentration at which overdose occurs. There is also no widely used antidote like naloxone for opioid overdose. Instead, treatment involves symptomatic care. Research into the CB1 antagonist/inverse agonist rimonabant as a possible antidote has been moderately successful [57], but needs further trials to ensure safety as it has shown possible proconvulsive properties [58], which would be particularly detrimental in cases of SC overdose presenting with seizures. Identification of a safe and effective antidote would likely decrease the need for symptomatic care training.

Conclusion

Two simulations of SC overdose were constructed and accurately represented real-life case studies of overdose. This identifies that Müse HPS can be used as a high-fidelity tool to introduce the autonomic symptoms and required interventions of SC overdose to clinicians online. However, the simulation would be best used in a practical teaching session for clinicians alongside VR technology or videos of intoxicated SC users. Use of these training scenarios is expected to improve patient care and survival rates in cases of severe SC overdose.

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