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EMERGENCY PRESERVATION AND RESUSCITATION: NOVEL APPLICATION OF EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO) AND CLOSED-LOOP PHYSIOLOGIC MONITORING

Peter Hu, Ph.D.
Shiming Yang, Ph.D.
William Teeter, M.D.
Jody Cantu, Ph.D. (AFRL)

Center for Shock, Trauma and Anesthesiology Research
University of Maryland, Baltimore

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AIR FORCE RESEARCH LABORATORY
711TH HUMAN PERFORMANCE WING,
AIRMAN SYSTEMS DIRECTORATE,
WRIGHT-PATTERSON AIR FORCE BASE, OH 45433
AIR FORCE MATERIEL COMMAND
UNITED STATES AIR FORCE

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//signature//	//signature//
ALICIA N. BURKE	**MATTHEW DALTON, DR-III**
Program Manager	Product Area Lead, En Route Care Section
Product Development Branch	Product Development Branch
Airman Biosciences Division	Airman Biosciences Division

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*Peter Hu, Ph.D.
*Shiming Yang, Ph.D.
*William Teeter, M.D.
**Jody Cantu

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*University of Maryland, Baltimore
620 W. Lexington Street, 4th floor
Baltimore, Maryland 21201-1508

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14. ABSTRACT

Extracorporeal membrane oxygenation (ECMO) is a well-characterized intervention that can play a significant role in autonomous transport and the temporary preservation of physiology in the most critical of casualties through Emergency preservation and resuscitation and closed-loop physiologic monitoring. This study designed a protocol to standardize each of the dependent variables that may affect the pressure data during the experiment. The information will help guide the construction of the closed loop feedback system. Moreover, the prediction results showed that the key physiologic instability during ECMO could be predicted up to 120 minutes ahead of the event. This early-events-detection process could be used to alert care providers to critical physiologic instability. Additionally, this could serve as a key decision point in the development of a close loop or human-in-the-loop-semiautomatic ECMO control system.

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1.0 EXECUTIVE SUMMARY

Prolonged field care in the context of anti-access area denial (A2AD) theaters of operation could result in the inability to expeditiously evacuate critical casualties. Concepts like autonomous transport may provide critical evacuation platforms that can mitigate risk to crew and providers, however medical technology to support such platforms is limited. Extracorporeal membrane oxygenation (ECMO) is a well-characterized intervention that can play a significant role in autonomous transport and the temporary preservation of physiology in the most critical of casualties through Emergency preservation and resuscitation (EPR) and closed-loop physiologic monitoring. In this study, we achieved early prediction of key physiologic criteria suggesting developing instability during ECMO. This early-events-detection process could be used to alert care providers to decompensation and need for intervention in ECMO. Additionally, this could serve as a key decision point in the development of close-loop or human-in-the-loop semiautomatic ECMO control system.

The study protocol was reviewed and approved by the Institutional Animal Care and Use Committee at the Oregon Health and Science University in collaboration with the University of Maryland, Baltimore and in compliance with all federal and applicable regulations governing the protection of animals and research.

The views expressed are those of the authors and do not reflect the official guidance or position of the United States Government, the Department of Defense the United States Air Force or the United States Space Force.

2.0 INTRODUCTION

ECMO and extra-corporeal life support (ECLS) concepts have significantly advanced over the past decade. With the advent of adult-ECMO and lung support for combat casualties, ECLS technology continues to evolve to meet the needs of the modern battlefield – with applications ranging from cardiac arrest to traumatic injury. Most recently, ECMO, through adoption of logistically simplified technologies like the Cardiohelp, has been deployed in the field at the site of injury and has been used to facilitate patient movement during aeromedical evacuation by the USAF Critical Care Air Transport Teams (CCATT). Service d'Aide Médicale Urgente (SAMU) de Paris and London Air Ambulance already employ a prehospital-physician model capable of ECMO in the field for both cardiac arrest and cardiac injury. This resource combined with promising laboratory data regarding future endovascular interventions for trauma and hemorrhage-induced cardiac arrest including Selective Aortic Arch Perfusion (SAAP) [1, 2], suggest the development of these capabilities will offer further synergies for ECMO and ECLS in the traumatically injured in the prehospital setting.

While in its infancy, EPR is a potential novel advanced use of ECMO technology. For this study's purposes, we use ECMO to provide rapid cooling and oxygen support for critical physiologic states for EPR. Rapid cooling in the presence of enhanced oxygenation of blood has the potential to slow cellular metabolism, apoptosis, inflammation, and end-organ damage, extending the survival time of combat casualties both on the field and during transport. EPR in the context of autonomous evacuation platforms would require significant independent and redundant closed loop control systems allowing autonomous and unsupervised operation, as would be needed in far forward locations and on CCATT aeromedical evacuation flights. Commercially available systems are currently manually controlled. Closed loop control of EPR would require continuous monitoring of peripheral oxygen saturation, partial pressure of carbon dioxide (PaCO2), fraction of inspired oxygen (FiO2), blood flow and automatic adjustment of ECMO settings to compensate. The Center for the Sustainment of Trauma and Readiness Skills (CSTARS) Baltimore/University of Maryland Baltimore (UMB) and University of Maryland Shock Trauma and Anesthesiology Research (STAR) Center have extensive experience in the analysis of continuous physiological data, using machine learning techniques to generate predictive algorithms [3-7], which would be required for autonomous control. We will further leverage the experience of our colleagues at the U.S. Air Force School of Aerospace Medicine (USAFSAM) at CSTARS Cincinnati in the development of a closed-loop mechanical ventilation (MV) system.

2.1 Problem/Area of Improvement

Prolonged field care in the context of A2AD theaters of operation could result in the inability to expeditiously evacuate critical casualties. Concepts like autonomous transport may provide critical evacuation platforms that can mitigate risk to crew and providers, however medical technology to support such platforms is limited. ECMO is a well-characterized intervention that can play a significant role in autonomous transport and the temporary preservation of physiology in the most critical of casualties through EPR and closed-loop physiologic monitoring.

2.2 Specific Aims and Hypotheses

2.2.1 Specific Aim 1: Evaluating the efficacy of ECMO-induced deep hypothermia

In addition to developing closed-loop control of the ECMO machine, we propose to investigate the use of ECMO-induced deep hypothermia to achieve the emergency preservation of critical physiology in a swine model of controlled hemorrhage and severe physiologic dyshomeostasis. Briefly, contemporary flightworthiness tested ECMO technology (Cardiohelp, MAQUET Holding B.V. & Co. KG) will be adapted to rapidly cool animals post-hemorrhage. Continuous electroencephalography (EEG) will be used to monitor brain activity under anesthesia. Measures of metabolic and physiologic derangement will be assessed in addition to marker of inflammation and cell death to determine both the efficacy and the degree of preservation achieved by ECMO-induced EPR. Continuous physiological data will be collected to generate closed loop control algorithms.

2.2.2 Specific Aim 1 Hypotheses:

- $H1_0$ (Phase I) – Phase I involves refinement of a large animal model
- $H2_0$ (Phase II) – ECLS-induced hypothermia will not improve physiologic dyshomeostasis in the presence of Class V hemorrhage shock.
- $H3_0$ (Phase III) – ECLS-induced hypothermia will not improve physiologic dyshomeostasis as an adjunct to SAAP in a model of non-compressible torso hemorrhage.

2.2.3 Specific Aim 2: Developing physiologic homeostasis prediction algorithm for support the closed loop control system development.

Analysis of continuous physiological data collected from the Oregon Health and Science University in all three phases for the development of physiological homeostasis closed loop control system. Advanced machine learning techniques will be used to process and select waveform features of the continuous physiological data for algorithm development. Waveform features will be compared to outcomes to ascertain whether certain physiological episodes are associated with worse outcomes and would suggest earlier intervention is required.

2.2.4 Specific Aim 2 Hypotheses:

- $H4_0$ (Phase I, II, III) – Advanced machine learning-based prediction algorithm could support the development of a closed loop control system to optimize physiologic homeostasis.

2.3 Military Relevance

Prolonged field care in the context of A2AD theaters of operation is anticipated for the next theatre of engagement could result in the inability to expeditiously evacuate critical casualties. Concepts like autonomous transport may provide critical evacuation platforms that can mitigate risk to crew and providers, however medical technology to support such platforms is limited.

The following gaps are addressed in this study:

1. 2014: Air Education and Training Command (AETC) # 11: Extending the Golden Hour Hemorrhage accounts for greater than (>)50 percent (%) of Operation Iraqi Freedom and Operation Enduring Freedom (OIF/OEF) battlefield fatalities. Severe blood loss causes irreversible injury by decreasing oxygen and substrate delivery to tissues. Evacuation times are prolonged (4-6 hours) due to urban and mountainous terrains, eliminating the possibility of rapid blood or fluid resuscitation. Need ability to improve patient survivability. Training and doctrine change is needed to effect rapid transfer of critically injured patients.
2. 2015 Air Force Medical Service (AFMS) # 8 Air Mobility Command (AMC) Advanced Point of Injury (POI) & En Route Care (ERC) Resuscitation: Lack research on advanced POI and ERC resuscitation
3. 2015 AFMS # 4: AMC Feasibility/Practicability of Emergency Preservation and Resuscitation (EPR) Lack the feasibility and practicability of EPR (suspended animation) for patient transport.
4. 2015 AFMS # 15 ERC Decision Support: Lack physiological monitoring mechanism for situational awareness electronic medical alerts and decision support
5. 2015 AFMS # 26 Automated Intervention for Patient Care Lack of closed loop technologies to provide patient care to assist with patient transport
6. 2015 AFMS # 5 (AMC) Improving Patient Outcomes through Autonomous Controls Lack autonomous control (e.g., oxygenation, ventilation, hydration, resuscitation, sedation, and open/ closed loop control) to improve patient outcome.
7. 2015 AFMS # 7 (AMC) Feasibility / Practicability/ Applicability of Robotic Support / Treatment Lack the feasibility, practicability, and applicability of robotic support and/or treatment for ERC patients.
8. 2015 AFMS # 10 (AETC) Use of Extracorporeal Life Support Systems (ELCS) Devices in Complex Clinical Scenarios Research is needed to address the lack of knowledge of the use of Extracorporeal Life Support Systems in a complex clinical setting.

2.4 Impact Statement and Return on Investment

This study seeks to provide the translational foundation for the significant enhancement of critical care and extension of the golden hour for the most critically injured combat casualties.

3.0 BACKGROUND

Critically ill patients frequently require and circulatory support among other assistive devices. ECMO has been recommended for patients with acute, potentially reversible, life-threatening respiratory failure that are unresponsive to conventional therapy. ECMO is effective for treating patients with severe, reversible myocardial dysfunction (e.g., myocarditis, cardiomyopathy, or post-operative cardiogenic shock) or as a bridge to another treatment modality. The use of ECMO has now become widespread in critically ill adult patient, which was recently identified as a medical phenomenon, especially in the Conventional ventilation or ECMO for Severe Adult Respiratory failure (CESAR) trial in 2009 for patients in respiratory failure. As of July 2018, the Extracorporeal Life Support Organization (ELSO) has reported survival rates of

59% for adult patients with respiratory failure, 42% for cardiac failure patients, and 29% in extracorporeal cardiopulmonary resuscitation (E-CPR) [8]. Furthermore, several studies have investigated improving outcomes with ECMO, including managing ECMO patients using close-loop autoregulation, and predicting successful outcomes based on various lab values and scoring systems. The following subsections will detail the use and complications (and solutions) of ECMO use in patients requiring this life-saving technology.

3.1 Therapeutic Hypothermia in ECMO

One of the complications observed in patients on ECMO is a neurologic injury that at times can be devastating. In a retrospective review of 23,952 patients on ECMO between 2001 to 2011 in the United States, 2,604 patients (10.9%) were reported suffering from a neurological injury [9]. Numerous studies claim neurological injuries from 10% to 50% [10, 11]. Induced hypothermia protocols are hoping to decrease neurological injuries and improve outcomes.

The landmark study by Bernard et al. [12] established the viability of using therapeutic hypothermia (TH) after cardiac arrest, demonstrating improvements in neurologic outcomes and decreased mortality rates. Most studies have noted a maximal benefit in neurologic outcomes in patients with ventricular fibrillation or ventricular tachycardia who are cooled to 32 degrees Celsius (°C) to 34°C for 12 to 24 hours [13]. This hypothermic temperature should be reached as quickly as possible. Therapeutic induced hypothermia via surface cooling has been shown to lower the rate of neurological complications in patients resuscitated from cardiac arrest by up to 23%.

Initially, publications of small case reports demonstrated the success of using TH post-cardiac arrest with patients on ECMO, which are summarized in reference [14]. Specifically, a case study using TH demonstrated positive results with longer duration of hypothermia to ameliorate neurological injury associated with cardiac arrest syndrome [15]. Guenther and colleagues reported two cases where TH was used on two patients on ECMO for 5-6 days. In both cases, the patients' temperature was maintained at 34-35°C until cerebral edema, intracranial hemorrhage, and any post cardiac arrest syndrome was excluded. The patients were then rewarmed between day five and six with positive outcomes.

New studies have now demonstrated initiating ECMO in the management of cardiac arrest using E-CPR to improve survival and neurological outcomes compared to conventional CPR. Overall survival and survival with good neurological function rate is currently 29% from the ELSO group [8]. Since E-CPR and TH have been shown to be beneficial, studies are combining therapies. Furthermore, Pang and et al published preliminary results of a randomized study that TH and ECMO is safe to use in adult patients [16]. Finally, a recent study called the Mechanical CPR, Hypothermia, ECMO and Early Reperfusion (CHEER) trial was created to test this hypothesis. This study included 26 patients placed on the CHEER protocol including hypothermia (T = 33°C) for the initial 24 hours [17]. ECMO can induce hypothermia quickly due to the high blood flow rates circulating within the ECMO circuit. Therefore, ECMO has the capability to re-warm the patients. The CHEER protocol demonstrated results of 54% of the patients survived and discharged with resulting cerebral performance category of 1 – indicating full neurological recovery [17].

3.2 EEG Monitoring during ECMO

Electroencephalography (EEG) is used to detect seizures and post-anoxic status epilepticus in cardiac arrest patients which are associated with poor outcomes (10-40%), especially in early in TH [18]. Patients meeting ECMO criteria due to poor perfusion or oxygenation are at increased risk for hypoxic-ischemic brain injury and require the use of EEG for further assessment. EEG usage is growing among ECMO patients since they are at risk for developing both diffuse and focal neurological injuries. A bedside neurologic assessment is the gold standard for evaluating neurological deficits; however, this assessment may not be as accurate due to the TH. In these cases, an EEG could assist in an early prognosis of neurological problems after a cardiac arrest because a reactive EEG would indicate positive outcomes versus a non-reactive EEG that would be associated with poor outcome. For example, in one study, the presence of an unexplained burst suppression pattern was associated with an increased risk of death or severe disability [11]. There are some case reports using adult ECMO patients, but the majority reports of EEG are with neonates and pediatric patients with and without ECMO [19]. However, given the sparsely of patient data on the use of EEG monitoring during ECMO, more studies are required, especially in the use of EEG in adult populations on ECMO.

3.3 Indicators of Increased Mortality in Patients on ECMO

Identifying indicators of increased mortality in patients on ECMO is essential to develop tools that monitor and recognize important markers of patient outcomes. One such indicator is lactate concentration. As one study recently revealed, early lactate behavior following the initiation of ECMO support can predict in-hospital mortality in post-cardiotomy patients. An elevated mean lactate concentration and a low lactate clearance in the first 6 and 12 hours after the initiation of ECMO were associated with increased mortality in both univariate and multivariate analyses. Another study concluded, “lactate, is a prognostic factor in acute respiratory distress syndrome (ARDS) patients and lactate clearance at 72 hours after ECMO initiation helps in risk stratification of these patients, being independently associated with death.” Although the lung is not commonly considered as a source of lactate, inability of ECMO patients to clear their lactate could be related to the MV strategy of “lung rest” leading to poor oxygenation [14] as a positive lactate gradient across the lung has been reported in various conditions, including ARDS [20, 21]. Additionally, a recent study by Kim and et al examined bedside parameters to determine if the patients on ECMO contribute to indication of outcome. They assessed vital signs, arterial blood gas (ABG) results, ECMO variables, regional cerebral oxygen saturation (rScO2), Swan-Ganz catheter parameters, transthoracic echocardiography parameters, and outcomes and evaluated for 28 days for mortality. They discovered that the patients that did survive on ECMO had high rScO2 and lower lactate levels compared to the non-survivors, concluding that these parameters can be used in predicting mortality rate on ECMO patients [22]. While future studies should evaluate lactate clearance with oxygenation and MV strategies, it is clear that monitoring lactate concentration may be essential to improve the outcome and survival of patients on ECMO.

3.4 ECMO and Mechanical Ventilation

Venoarterial (VA)-ECMO or venovenous (VV)-ECMO have been described in the literature as the best method to provide “lung rest”. Specifically, ELSO describes lung rest being

achieved by reducing the ventilation pressure and decreasing inspired oxygen. The lung rest settings are very controversial since there is no data or studies to support these suggestions [23]. Importantly, there has been a significant increase in the use of adult ECMO since the outbreak of H1N1 and the CESAR trial in 2009. The CESAR trial concluded that there was a significant decrease in 6 month mortality using ECMO versus standard treatment in patients with severe ARDS [24]. The CESAR study used rest settings that consisted of Pressure Control (PC) of 10 centimeters (cm) water (H2O), positive end-expiratory pressure (PEEP) of 10cm H2O and a respiratory rate of 10 breaths per minute, although they did not state a desired tidal volume per patient. ELSO has now adopted this setting for MV during ECMO with no data to support them. These settings were very similar to the baby lung and ARDSnet, which used a plateau pressure < 30 cm H2O to protect the lung. The PEEP/FIO2 titration would be difficult to use since oxygenation is now being provided by ECMO. Since this strategy could no longer be used, patients could be on lower PEEP than desired on MV [25]. Most centers using ECMO have chosen the recommended ELSO settings in pressure control ventilation, which can result with minimum gas exchange. If ventilating in a volume control mode, some centers will use ultraprotective tidal volumes (Vt) as low as Vt ≤ 4 milliliters (mL)/kilograms (kg), which is referred to ultraprotective ventilation [26].

New research now suggests that lung injury can be prevented if the driving pressure (ΔP) is < 15 cm H2O during MV instead of a plateau airway pressure (Pp) < 30 cm H2O that was described in the ARDSnet study [27]. Driving pressure (defined as ΔP=VT/static compliance of the respiratory system (CRS) or ΔP = plateau airway pressure (Pp) − PEEP) is the factor that has been associated with improved mortality among ARDS patients [27]. New studies also show using a higher PEEP level to decrease driving pressure among ECMO also improves mortality [23]. This suggests that more work must be done to determine the appropriate settings required to achieve effective lung rest in ECMO patients.

There have been several lab studies demonstrating that airway pressure release ventilation (APRV) is beneficial in ARDS [28, 29]. For example, Lim and et al demonstrated that 34 patients who met CESAR criteria for ECMO were placed on APRV and only 1 patient required ECMO [30]. Importantly, APRV maintains a sustained airway pressure over a large proportion of the respiratory cycle, and therefore this ventilation strategy has a high-pressure time profile [28]. The Lim study demonstrated that APRV recruited and improved gas exchange within the lungs with patients that met the criteria for ECMO [30]. One additional case study demonstrated weaning a patient quickly from MV to APRV while on ECMO [31]. Unfortunately, there have not been studies published using APRV during ECMO.

A group recently described a design for closed loop physiologic control for automation of MV and ECMO based on recent MV studies. Their strategy was based on the data of driving pressure, oxygen toxicity, and the open lung approach [32, 33]. In this study, PEEP was set to best static compliance and to maintain a driving pressure of 10 cm H2O with an FIO2 goal of 30%, and a plateau pressure < 25cm H2O for a tidal volume of 3 and 6mL/kg [25]. In this animal study, the pig was sedated and placed on the aforementioned ventilator strategy. The ECMO circuit was set up with a sensor connected to a CDI^{TM} system to monitor venous carbon dioxide (CO2). ECMO was then adjusted to maintain an oxygen saturation (SPO2) + 95% and a PaCO2 in venous blood (PVCO2) = 46 millimeters of mercury (mmHg) [25]. Their results showed feasibility of a robust patient-in-the-loop control system in to control oxygen supply and CO2 removal using ECMO [25].

3.5 ARDS Scoring System

An ARDS scoring system that could predict mortality within 24 hours of diagnosis was developed by a team of physicians. This system, called the STANDARD network, includes the following: age, partial pressure of oxygen in the arterial blood (PaO2)/FIO2, and plateau pressure score based on individual data from three variables routinely collected (age, PaO2/FIO2, and plateau pressure) at 24 hours after ARDS diagnosis while patients were on MV [34]. Importantly, this score could indicate which patients should be placed on ECMO based on their ARDS value. Specifically, a score > 7 had a mortality of 83.3% but a score < 5 had a mortality rate of 14.5% [34]. The STANDARAD scoring system suggests that high-performing predictive models could be co-opted in the use of automated or semi-automated decision making in ECMO.

4.0 METHODS

4.1 Study Design

Animal studies were conducted in three distinct phases. In phases I & II Yorkshire pigs were anesthetized with Telazol (intramuscular, IM) injection and maintained with Isoflurane after orotracheal intubation. Vascular access was achieved by percutaneous technique and includes arterial catheters for monitoring and blood draws, venous catheters, and a pulmonary artery catheter. Animals were instrumented for physiologic telemetry including physiologic monitoring (systolic blood pressure (SBP), mean arterial pressure (MAP), diastolic blood pressure (DBP), pulmonary artery pressure (PAP), central venous pressure (CVP), continuous cardiac output (CCO), systemic vascular resistance (SVR), end-tidal carbon dioxide (ETCO2), venous oxygen saturation (SVO2), skeletal muscle oxygen saturation (STO2), sulfur dioxide (SO2), oxygen uptake (VO2), and electrocardiogram (EKG)), near-infrared spectroscopy, continuous EEG, and carotid flow. Laparotomy, splenectomy, and closure were performed and then a ten-minute stabilization period was observed. The end of the stabilization period was designated T = 0. At T = 0 minutes, the controlled hemorrhage phase initiated and lasted for 60 minutes. Controlled hemorrhage was performed to remove 60% of total blood volume based on the calculated rate of 65mL/kg. This was performed using a peristaltic pump for accurate volume and rate monitoring. To ensure animal survivability, the hemorrhage was stopped when MAP dropped below 25mmHg and continued once the MAP recovered. At T = 60 minutes animals underwent ECLS in the presence or absence of hypothermia. Animals were observed for up to 360 minutes following ECLS and physiologic parameters recorded in high-fidelity. Arterial blood was sampled at Q60MIN intervals and analyzed (ABG, complete blood count (CBC), rotational thromboelastometry (ROTEM), coagulation (COAG), and serum banking). At the end of the observation period, animals were euthanized, and gross pathology was performed. Tissues (heart, lung, liver, kidney, pancreas, and small bowel) were collected for histopathological analysis.

In phase III, induction of anesthesia was achieved with Telazol (IM), and a surgical plane of anesthesia achieved with 2-4% Isoflurane following orotracheal intubation. Vascular access was achieved using ultrasound-guided percutaneous technique. A Cordis was placed in the left and right external jugular (EJ) veins to accommodate blood removal/fluid perfusion and a Swan-Ganz catheter, respectively. A 3fr micro-puncture catheter was placed in the right or left femoral artery to measure invasive arterial pressure and for arterial blood sampling. Animals were instrumented

for physiologic telemetry as follows: rectal temperature, invasive arterial blood pressures (invasive systolic blood pressure (SVP), invasive diastolic blood pressure (DVP), and MAP), pulmonary arterial pressure, CVP, cardiac output (CO), left ventricular ejection fraction, left ventricular end diastolic volume, skeletal muscle tissue oxygenation (near infra-red spectroscopy – NIRS), and cerebral oxygenation (carotid flow and continuous EEG).

Once telemetry was achieved, a splenectomy and cystostomy (urine output) was performed by mini-laparotomy or by hand-assisted laparoscopy. The left-lateral lobe of the liver (4L) was rotated medially and delivered into the operative field. Utilizing Bovie electro surgery, a transection trajectory was marked on the surface of the 4L. The liver was returned to its normo-anatomical position. Trocars for laparoscopic access were placed in the left and right lower quadrants of the abdomen under direct visualization. Those placements were as follows: 1) midline, cranial to the umbilicus, 2) immediate right lateral to the umbilicus, 3) right lateral to the umbilicus at the mid-clavicular line and 4) left lateral to the umbilicus at the midclavicular line. A three-layer closure was performed including the peritoneum, anterior and posterior fascia and finally the skin, which was closed using staples. The abdomen was insufflated. The 4L was visualized and transected using 5 mm metzenbaum "long-jaws" laparoscopic shears (Stryker Endoscopy). Upon completion of transection, the abdominal space was rapidly evacuated of all instruments, the abdomen desufflated, trocars removed, and the skin closed with surgical staples. The time at which the liver parenchyma was first disrupted marks T = 0. At T = 5 minutes, animals underwent selective aortic arch catheterization for control of hemorrhage. At T = 25 minutes, ECLS was initiated in the presence or absence of hypothermia. The SAAP catheter was removed, and a primary repair of the injury was performed. Hypothermia was maintained for an additional 360 minutes. Animals were observed for cardiovascular, tissue oxygenation and physiologic changes.

Whole blood was administered to maintain pressure until hemoglobin of 10 was achieved. Once hemoglobin (HB) = 10, fresh frozen plasma (FFP) was used to maintain a blood pressure compatible with normal physiology. If HB falls below 10, and systolic pressure was < 100mmHg, whole blood was administered in lieu of FFP. Whole arterial and venous blood was sampled at the following time points: Prior to splenectomy (Baseline 1), immediately following splenectomy (Baseline 2), at time of injury (T = 0 minute), T = 5, 10, 20, 30, 45, 60, 75, 90, 105, 120, 180, 210, 240 and 360 minutes. 11 mL whole arterial blood and 1 mL whole venous blood was required for all draws at all time points. Whole arterial blood was used in the following assays: 1) blood gas and chemistry, 2) CBC, 3) ROTEM, 4) Platelet function assay (Multi-plate) and 4) COAG panel (prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio, fibrinogen, d-dimer, full blood picture, von Willebrand factor (vWF)). Whole venous blood was used for blood gas and chemistry only. Arterial blood gas samples were taken more frequently during the critical care phase of the experiments to guide resuscitation. At the completion of the experimental procedure, animals were euthanized, and necropsy/gross pathology performed. Tissues of interest were collected for histological analysis, as necessary. Samples of organ tissue were collected and banked for further analysis in future studies.

4.2 Animal Experiment Details

4.2.1 First Two EPR Pilot Experiments

The first normothermic control animal of the pilot experiments took place on 12/05/2018. The preparation was completed without any issues. Warmed lactated ringers were infused into the pericardial space and created tamponade physiology without any appearance of leak from the injury site. ECMO flow was maintained without any major issues and a single bolus of lactated ringers was given at the beginning of the tamponade due to chatter on the venous line. During the one hour of tamponade time, no vasopressors were needed. Forty minutes into tamponade time, the animal's heart went into ventricular fibrillation. At the sixty-minute mark, the chest was opened, and the tamponade was relieved. With the internal access, internal defibrillation was attempted and successful after multiple attempts. The critical care algorithm was then followed until the time of euthanasia at T = 260 minutes. The animal was maxed out on norepinephrine and dobutamine but continued to be hemodynamically unstable. The end lactate was shown to be trending down.

The first hypothermic control animal of the pilot experiments took place on 12/06/2018. The preparation was completed without any issues. Warmed lactated ringers were infused into the pericardial space and created tamponade physiology without any appearance of leak from the injury site. ECMO and cooling went well. Internal temperature (from pulmonary artery (PA) catheter) reached 13 ºC at the end of the tamponade time. During the cooling process, the heart rate decreased to <10 beats per minute (bpm), without ever true asystole. At T = 60 minutes, per protocol, the tamponade was relieved through the transventricular catheter, and the re-warming process began. At approximately 33ºC, the normal sinus converted into ventricular fibrillation which required opening the chest and internal defibrillation. There was a small defect found on the anterior aspect of the heart, which was repaired, and the experiment continued to completion without any issues.

4.2.2 Animal Experimental Protocol – Five Experiments

Five model development experiments were conducted in October 2018. Preparation was as follows, a 7Fr Cordis was placed in the left carotid artery to monitor invasive pressures. The right carotid artery was instrumented with a flow probe to monitor cerebral perfusion. A 10Fr Cordis was placed in the left EJ for maintenance fluids and pharmaceutical administration. A pulmonary artery catheter was placed into this introducer to monitor CO and mixed venous oxygenation. Animals were properly anticoagulated using heparin to establish an activated coagulation time (ACT) of double the baseline values. A pigtail catheter was placed into the left ventricle (LV) to monitor LV pressure. Veno-arterial ECMO cannulas were placed. A dual lumen catheter was placed through the right EJ through the right ventricular wall into the pericardial space to monitor pericardial pressure and administer fluid. The animal was then transitioned from inhaled anesthetic to total intravenous anesthesia. A ten-minute stabilization period was observed prior to the initiation of tamponade. Baseline fluoroscopy of LV and coronary perfusion was collected. The tamponade was induced by infusion of warmed lactated Ringer's solution (LR) into the pericardial space using a pressure bag. Once tamponade was achieved (pulseless electrical activity (PEA) arrest), PEA fluoroscopy was taken to show no flow. At that time, ECMO started at 2 liters (L)/minutes (min) (T = 0). ECMO fluoroscopy was used to show flow. The ECMO algorithm

below for bolus, vasopressor, and ventricular fibrillation management during ECMO is provided below (section 4.2.4). Sixty minutes after ECMO (T = 60), tamponade was relieved. If the subject was not actively deteriorating, we would then wean off ECMO 0.5L/min every 5 minutes. Once off ECMO, we collected post-ECMO fluoroscopy for comparison. Our critical care algorithm continued until T=300min. At that time tissues were collected for histology including the terminal ileum, cardiac apex, and lung and stored in formalin. The specific details of each of the five models used for the development experiments are described as follows:

1. The first model development animal fibrillated during the injury induction. External defibrillation did not achieve cardioversion; therefore, we decided to use internal cardioversion after the allotted one-hour ECMO time to standardize tamponade/ECMO time.
2. The second model development animal had a successful injury induction. At the time of ECMO initiation, the pump in the oxygenator and the oxygenator itself failed, rendering ECMO impossible. This animal was marked as an exclusion and a replacement circuit was required for the next animal. The animal was properly heparinized before initiating ECMO and the circuit was functional before the experiment. Model animal 2 was an acute mechanical failure.
3. The third model development animal had a successful injury induction. ECMO maintained flows of 2L/min for the full one hour of tamponade time. The tamponade was successfully relieved, and the animal's hemodynamics were stable enough for weaning off ECMO within 30 minutes of tamponade relief. With a successful injury and transition to ECMO, we determined that our next two animals would be used to test the hypothermia aspect of protocol.
4. The fourth model development animal had a successful injury induction and transition to ECMO. Utilizing the Cardiohelp machine, hypothermia of 17.9˚C was achieved over 30 minutes, which was higher than our goal of 10˚C; therefore, we decided that the next animal would be cooled quicker. Relief of tamponade was successful, and the re-warming process worked well. One bolus of epinephrine was required to return spontaneous circulation after the warming process.
5. The fifth model development animal had a successful injury and transition to ECMO. During the cooling period, the animal fibrillated. Internal temperature reached 13˚C. After re-warming, the animal was internally defibrillated which cardioverted the animal to sinus rhythm. ECMO was weaned and the animal was hemodynamically stable throughout the critical care phase.

After the model development animals were completed, the following algorithms (sections 4.2.3 and 4.2.4, below) and blood sample sheet (section 4.2.5, below) were devised for the remainder of the experiments.

4.2.3 ECMO Algorithm

If hypothermia animal: Set Cardioquip to 10C once ECMO starts
If (Art MAP > LV Dia + 5) & (ECMO Flow < 1.9L/min): 500mL bolus of LR
If (Art MAP < LV Dia + 5): 500mL bolus of LR, then start norepinephrine, or up dose
If (Norepinephrine > 0.1 mcg/kg/min): Start vasopressin at 0.1U/min

If (pH < 7.3) & (HCO3- < 20): Administer sodium bicarbonate
If (K+ > 5.5): Administer 10U insulin and 50mL 50% dextrose
If (Glu < 3.0): Administer 50mL 50% dextrose
If ventricular fibrillation during ECMO, do not perform cardioversion until relief of tamponade. Then open chest and perform internal defibrillation: 10J -> 20J -> 30J

4.2.4 Critical Care Algorithm

If hypothermia animal: Increase Cardioquip temperature by 0.5C every minute
If (SBP < 90mmHg or MAP < 50mmHg) or (baseline SBP/MAP – 10mmHg): Start norepi or up dose
If (pH < 7.1) & (HCO3- < 20): Administer sodium bicarbonate
If (K+ > 5.5): Administer 10U insulin and 50mL 50% dextrose
If (Glu < 3.0): Administer 50mL 50% dextrose
If (temp < 37.0): Start warming blanket and cover with blankets
If (temp > 40.0): Apply ice packs
If (pCO2 > 45): Increase RR
If (SpO2 > 92) & (pO2 > 100): Decrease FiO2 by 10 until FiO2 = 40

4.2.5 Cardiac Tamponade – Blood Sample Sheet

Baseline (pre-injury) ABG(65ul), CBC(15ul), SER(4mL), COAG(2.7mL)

- T=000 PEA/ECMO ABG
- T=005 ABG
- T=010 ABG
- T=015 ABG
- T=030 ABG
- T=045 ABG
- T=060 ABG, CBC, SER, COAG
- T=090 ICU ABG
- T=120 ICU ABG, SER, COAG
- T=150 ICU ABG
- T=180 ICU ABG, SER, COAG
- T=210 ICU ABG
- T=240 ICU ABG, SER, COAG
- T=270 ICU ABG
- T=300 ICU ABG, CBC, SER, COAG

4.2.6 Additional Four EPR Pilot Experiments

The second normothermic control animal of the pilot experiment took place on 06/03/2019. The preparation was completed without any issues. Warmed LR was infused into the pericardial space and created tamponade physiology without any appearance of leak from the injury site. ECMO flow started well, then the animal went into ventricular fibrillation 2 minutes post ECMO. As a result, the animal needed multiple boluses of LR and sodium bicarbonate during the one-hour ECMO time. At the sixty-minute mark, the chest was opened, and the tamponade was relieved.

With the internal access, internal defibrillation was attempted and successful after multiple attempts. The critical care algorithm was then followed until the time of euthanasia at T=110min. The animal was non-responsive to norepinephrine and dobutamine and continued to be hemodynamically unstable.

The second hypothermic animal of the pilot experiment took place on 06/04/2019. The preparation was completed without any issues. Warmed LR were infused into the pericardial space and created tamponade physiology without any appearance of leak from the injury site. ECMO and cooling went well. Internal temperature (from PA catheter) reached 15.1ºC at the end of the tamponade time. During the cooling process, the heart rate decreased to <10bpm, without ever true asystole. At T=60, per the protocol, the tamponade was relieved through the transventricular catheter, and the re-warming process began. At approximately 35ºC, ECMO was decreased by 0.5L every 5 minutes, per the critical care algorithm. The animal only required low dose norepinephrine and dobutamine. The experiment continued to completion without any issues.

The third hypothermic animal of the pilot experiment took place on 06/05/2019. The preparation was completed without any issues. Warmed LR was infused into the pericardial space and created tamponade physiology without any appearance of leak from the injury site. ECMO and cooling went well. Internal temperature (from PA catheter) reached <15 ºC at the end of the tamponade time. During the cooling process, the heart rate converted into ventricular fibrillation. At T=60, per protocol, the tamponade was relieved through the transventricular catheter, and the re-warming process began. Once the animal reached approximately 35 ºC, the chest was opened, and internal defibrillation was performed to convert the animal back to sinus rhythm. After cardioversion, ECMO was decreased by 0.5L every 5 minutes, per the critical care algorithm. The critical care algorithm was followed until the time of euthanasia at T=340min.

The third normothermic control animal of the pilot experiment took place on 06/03/2019. The preparation was completed without any issues. Warmed LR was infused into the pericardial space and created tamponade physiology without any appearance of leak from the injury site. ECMO flow was maintained well, and the animal went into asystole while on ECMO. At the sixty-minute mark, the chest was opened, and the tamponade was relieved. With internal access, the pericardial space was completely evacuated. Due to hemodynamic instability, the animal remained on high dose norepinephrine and dobutamine throughout the experiment. The experiment continued to completion without any issues.

4.3 Closed-Loop-Control Experimental Design

A flowchart (Figure 1) was designed to standardize each of the dependent variables that may impact the pressure data during the protocol. This information is used to guide the construction of the closed loop feedback system. There are two main phases of the EPR experiments: EPR initiation with ECMO, and the ECMO weaning/critical care phase. If an experiment is randomized to be part of the hypothermia arm, an active cooling heat exchanger is enabled on the Cardiohelp ECMO device, and the target temperature is set to 10 ˚C.

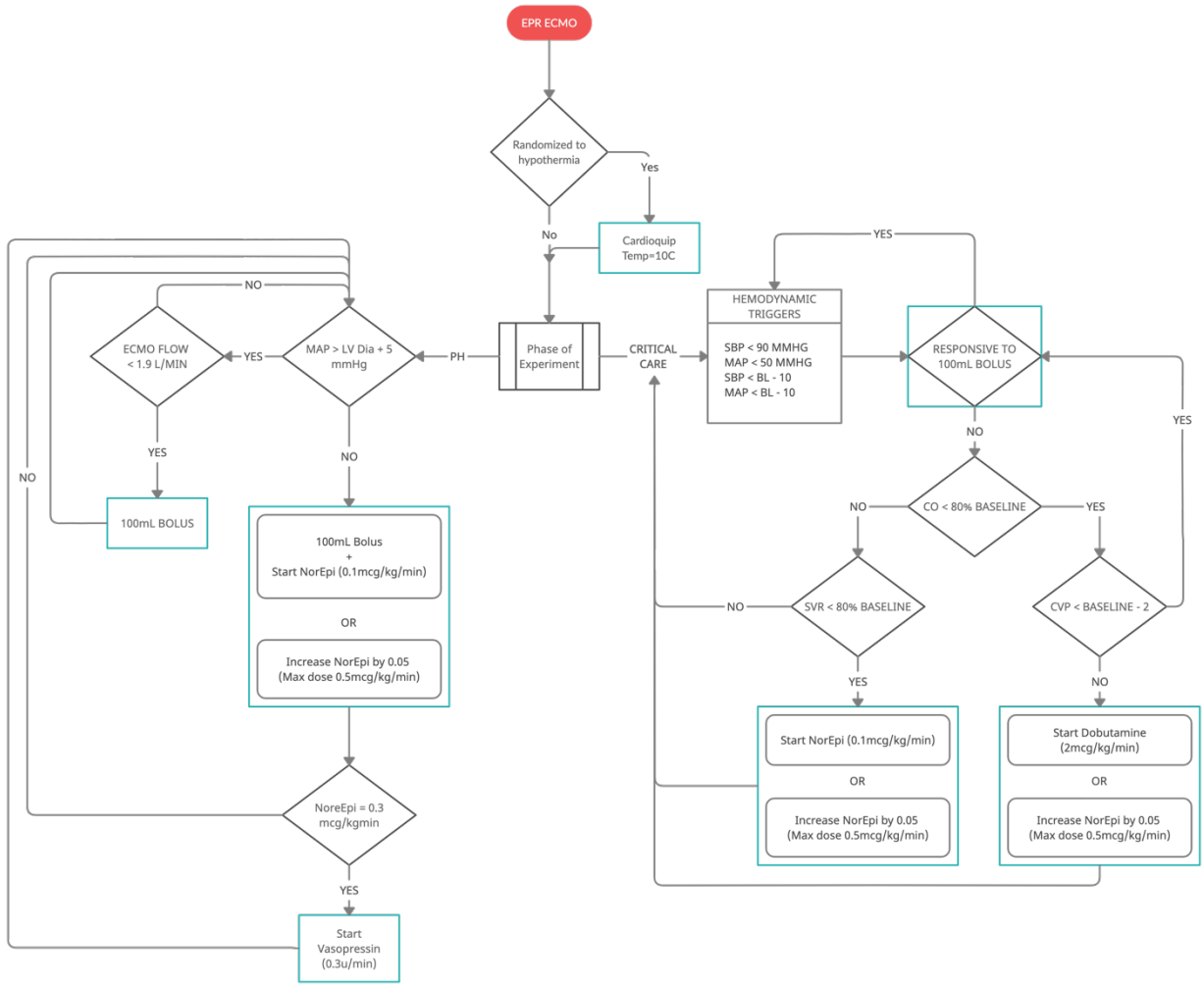

Figure 1. Flow chart depicting the impact of each dependent variable pressure data during the protocol.

4.3.1 EPR Phase

After initiation of ECMO one of the key parameters monitored is MAP, which ensures coronary arterial perfusion and ECMO flow rate to ensure adequate oxygen exchange. Coronary perfusion occurs during cardiac diastole (relaxation of the myocardium enables blood flow at the arterial and capillary level). Coronary artery perfusion is maintained by ensuring MAP is at least 5 mmHg greater than the left ventricular diastolic pressure. If MAP falls below target, the first line interventions are a 100mL bolus to increase circulating volume and administration of vasopressors (Norepinephrine @ 0.1 microgram (mcg)/kg/min). Alternatively, if the MAP target is met, but ECMO flow falls below the minimum 1.9L/min, additional volume is added to the system. Both coronary perfusion, as measured by MAP, and maintenance of ECMO flow, as measured by the built-in flow meter, can be augmented by titrating Norepinephrine or bolusing normal saline as described in the flow chart.

4.3.2 Critical Care Phase

After the initial EPR phase, the follow-on critical care phase of the experiment focused on maintenance of hemodynamic performance whilst weaning the animal from ECMO. At pre-specified times, the flow rate of ECMO was reduced. This occurred in a stepwise fashion to allow for hemodynamic stabilization during ECMO weaning. If the goal MAP was not met, the primary determinate for subsequent intervention was CO then SVR. SVR and CO were continuously measured by a Swan-Ganz pulmonary artery catheter. If the CO dropped below 80% of the baseline values, the appropriate intervention was selected dependent on the CVP. If the SVR dropped below 80% of the baseline values, SVR was augmented by norepinephrine, which acts by causing peripheral arterial vasoconstriction. CO was augmented by Dobutamine, which acts directly on the heart primarily by increasing contractile force. CVP was adjusted with 100mL boluses of normal saline to increase preload.

4.4 Data Collection

A total of 17 swine were utilized for the study. We collected three kinds of data for each swine, including waveform, trend, and animal records. Nine waveforms, including BP, pericardial pressure, LV pressure, EKG, and carotid flow, were collected at 250 Hertz (Hz) by AcqKnowledge. The waveforms were saved in a .acq file. AcqKnowledge can be used to open the data file and convert the waveform data to a .txt file for further analysis. The average waveform txt file size is 1.5 GB. Trend data were collected every minute for the entire experiment including HR, BP, CO, and SVR. Animal records include event and medication data, which was recorded when an event happened and included the dosage of a certain medication given to the animal. Table 1 lists the detailed variables collected for each swine.

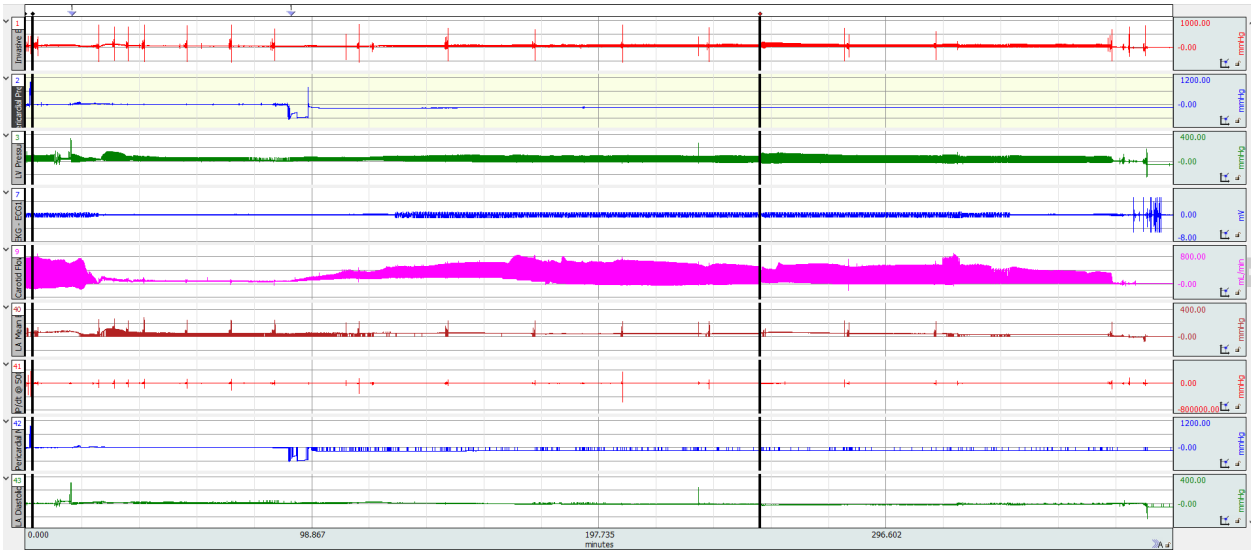

Figure 2. Representative image of all nine full length waveforms collected for one of subject in AcqKnowledge.

Table 1. List of collected study variables

Data type	Variables
Waveform	Invasive BP, Pericardial pressure, LV pressure, EKG, Carotid flow, LA mean BP, dP/dt, Pericardial MAP, LA Diastolic BP
Trend	ARTD, ARTM, ARTS, BT*, C_O_Avg, CCO, Cdyn, CVP, DesCons, dT1, EnfCons, etCO2, etDes, etEnf, etHal, etIso, etSev, GP2D, GP2M, GP2S, GP3D, GP3M, GP3S, GP4D, GP4M, GP4S, HalCons, HR, inDes, inEnf, inHal, inIso, inSev, IsoCons, MVmand, PAD, PAM, PAS, PEEP, PI, PIP, PLS, Pmean, Pplat, R, r2, RESP, RRmand, SevCons, SpO2, STaVF, STaVL, STaVR, STI, STII, STIII, STV, STV*, SV, SvO2, SVR, T1a, T1b, V_CO2, V_O2, VTemand, VTespon, VTispon, x(Pace)
Medication	Amiodarone, D50, Insulin/Dextrose, Dexdomitor, Dobutamine, Epinephrine, Heparin, KCl, Ketamine, LR, Midazolam, Norepinephrine, SodiumBicarb, Bolus (normal insulin)
Event	ECMO start/end/down by 0.5L, injury start/end, defib, VF, ASF

4.5 Peak detection of arterial waveform

Several signal preprocessing procedures were applied on arterial blood pressure (ABP) waveforms to remove noise and outliers. First, we applied a low pass filter with a 10Hz cut-off frequency on the ABP waveform. Frequencies greater than 10Hz were filtered out and removed, leaving the remaining low frequency waveform. Next, we smoothed the remaining noisy data. To detect the peaks and valleys, we located the local maxima and detected a valley between every two peaks (local maxima). The value of the peaks were the SBP readings while the value of valleys was DBP. Then we could calculate the (MAP) using the equation, MAP = 1/3×SBP + 2/3×DBP, and pulse pressure (PP) by measuring the difference between SBP and DBP. We also obtained high resolution HR and respiration rate (RR) from the blood pressure waveform.

Figure 3 shows the peak detection result from one of the 17 swine. Figure 3A shows the peak detection results, and we determined SBP (downward-pointing triangle marker) and DBP (upward-pointing triangle marker) values from the waveform (green line). Figure 3B shows the detected SBP and MAP, which were derived from the equation, MAP = 1/3*SBP + 2/3*DBP. Figure 3C shows the high-resolution heart rate derived from the SBP interval while RR was calculated from the peak detection from the contour of SBP array signal (shown in Figure 3D). Figure 4 provides a closer look of the peak detection results. In short, high-resolution HR, RR, SBP, MAP, DBP and PP were derived and will be used for feature calculations.

The corresponding time stamps of the two data sources (waveform and trend) were aligned using ECMO start time provided from the event sheet. Overall, we used the 6 ABP derived trend and one-minute trend data for feature calculation and outcome calculation.

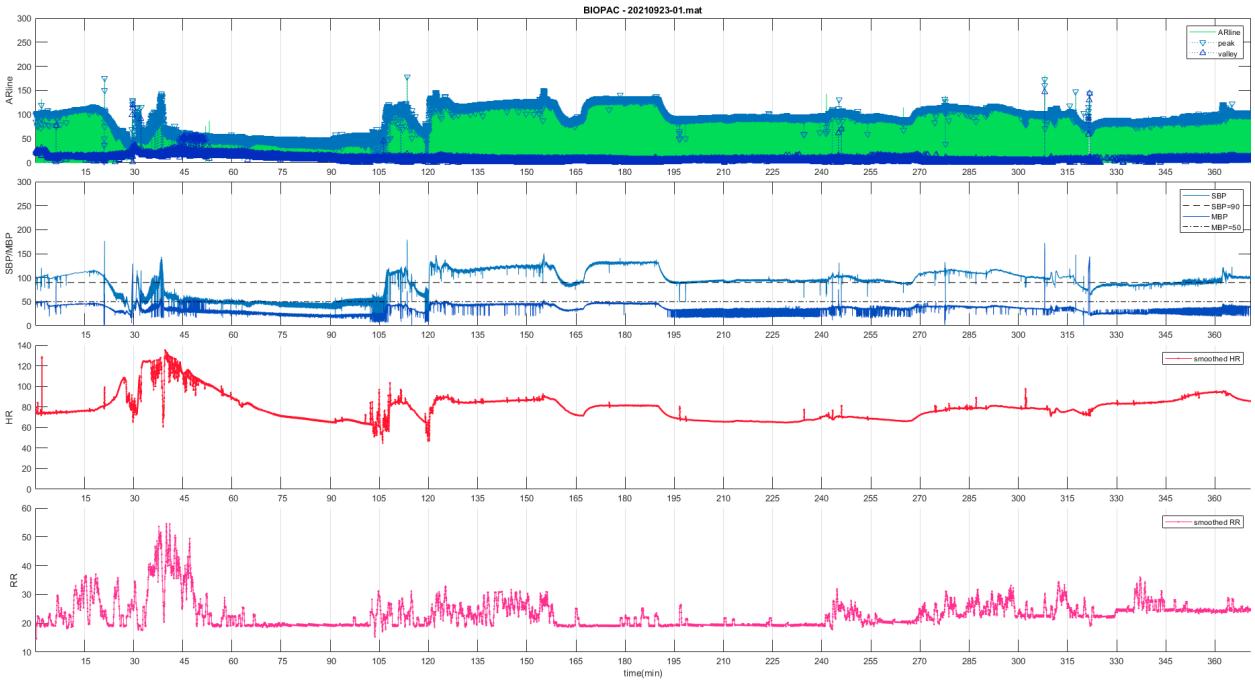

Figure 3. High resolution data (HR, RR, BP) derived from blood pressure waveform.

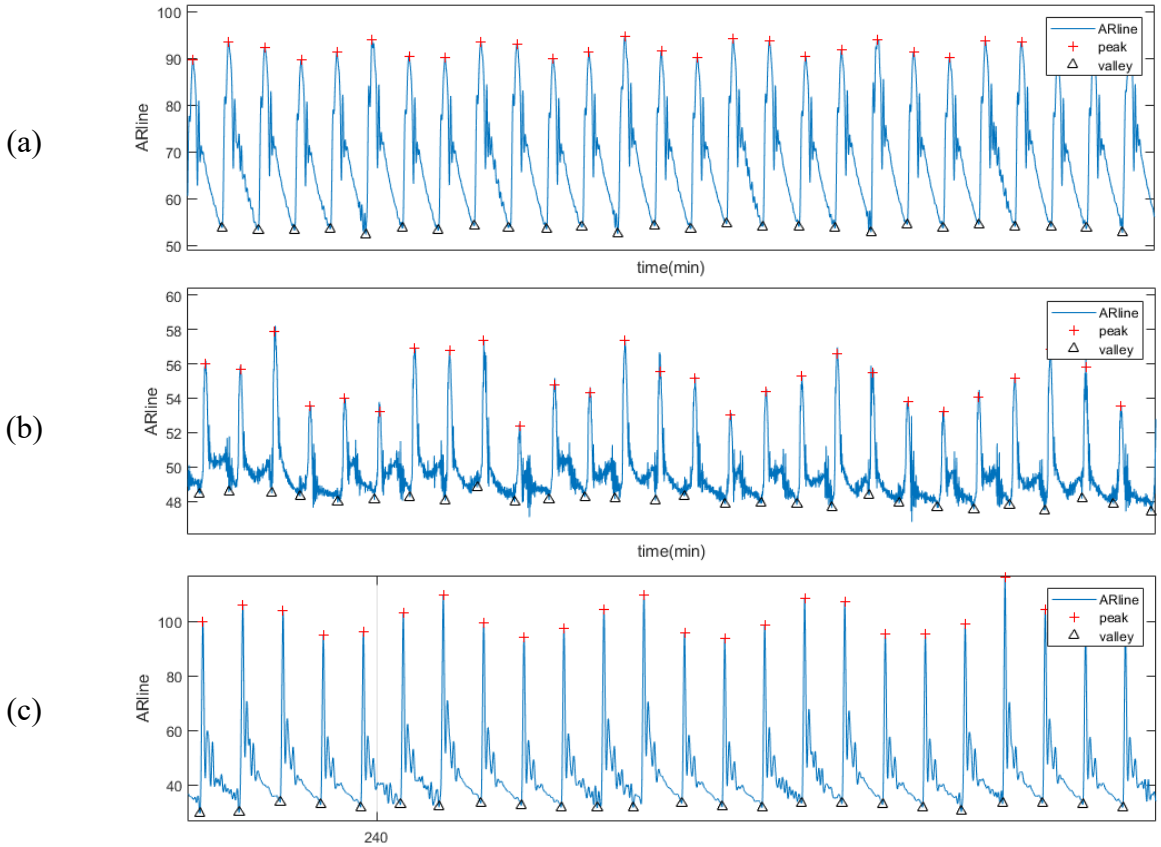

Figure 4. Peak detection results at (a) 15 min, (b) 45min, (c) 240 min after initiating data collection.

4.6 Feature extraction and outcome calculation

We computed features from the high-resolution trend (SBP, MAP, DBP, PP, HR, RR) and one minute trend data by deriving their statistical values including mean, median, minimum, maximum, variances, quartiles, and entropies. Over 1500 features were derived and will be used for outcome prediction. Figure 5 is a visual illustration to describe feature and outcome calculation schema. Features were calculated using a 15-minute window and moved every 5 minutes to predict an outcome ΔT minutes ahead of the current feature window. Outcome was calculated using a 5-minute window. For example, if 80% of data within that 5-minute window met the criteria for hypotension, we would have a positive outcome for hypotension; otherwise, we would claim that it is a negative outcome for hypotension. Table 2 lists the 9 outcomes we were interested in.

As shown in Figure 5, we know that ΔT is the period between feature and outcome. By changing ΔT, we could see how the prediction power changed over time for an outcome. We evaluated the prediction results by looking into ΔT ranges from the Point-Of-Care (POC, ΔT = 0 minute) to 2 hours (ΔT = 120 minutes) with 10 minutes increments.

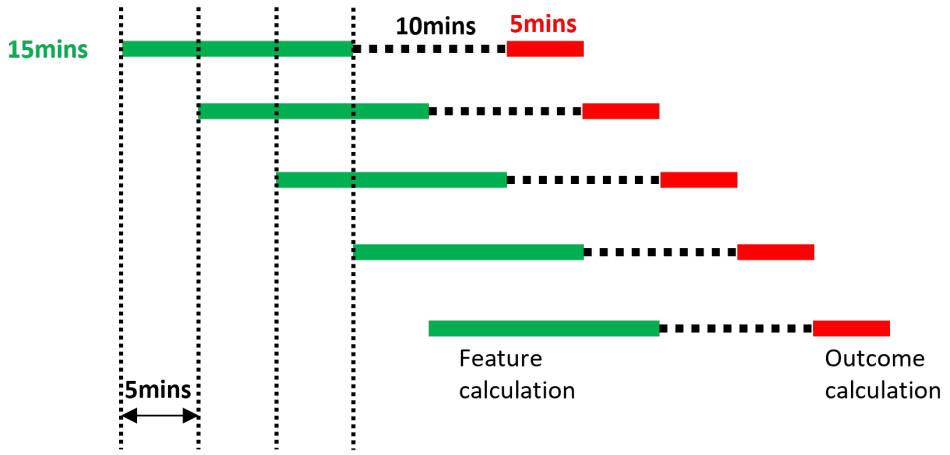

Figure 5. Visual illustration of the feature and outcome calculation pathway.

Table 2. List of outcomes and their definitions

Outcomes	Definition	Physiological response
$Outcome_{SBP \leq 90mmHg}$	SBP ≤ 90 mmHg	Hypotension
$Outcome_{MAP \leq 50mmHg}$	MAP ≤ 50 mmHg	Hypotension
$Outcome_{HR \geq 120bpm}$	HR ≥ 120 bpm	Tachycardia
$Outcome_{HR \leq 60bpm}$	HR ≤ 60 bpm	Bradycardia
$Outcome_{SI \geq 1}$	SI ≥ 1	Mortality/need of blood transfusion
$Outcome_{SI \geq 0.9}$	SI ≥ 0.9	Mortality/need of blood transfusion
$Outcome_{CO \leq 80\%baseline}$	CO ≤ 80% baseline	
$Outcome_{CVP \leq baseline-2}$	CVP ≤ baseline - 2	
$Outcome_{SVR \leq 80\%baseline}$	SVR ≤ 80% baseline	

4.7 Modeling

We used the first 10 cases from the 17 cases as the training dataset. The final 7 cases were used as a testing dataset to evaluate the models built from the training dataset. However, case 7 in the training dataset was dropped due to the lack of one-minute trend data which is essential for outcome calculation. Hence, the training dataset has 9 cases, and the testing dataset included the final 7 cases.

We used Random Forest (RF) to build classification models for prediction using three types of feature dataset. The first type of feature dataset included all statistical features calculated from ABP-derived trend and one-minute trend data, denoted as $Feature_{ABPtr,1mintr}$. The second type of feature dataset included only statistical features calculated from ABP-derived trend data, denoted as $Feature_{ABPtr}$. Finally, the third type of feature dataset included statistical features calculated from one-minute trend data, denoted as $Feature_{1mintr}$. These three types of feature sets were used to predict each outcome listed in Table 2. Area under receiver operating characteristic curve (AUC) was used to evaluate predictive power and Delong's method was used to compare AUCs where $p < 0.05$ was considered statistically significant.

5.0 RESULTS

As mentioned in the previous sections, we divided the 16 cases into a training group and a testing group where the training group had 9 cases and the final collected 7 cases comprised the testing group. Figure 6 shows the training and testing results of $Outcome_{SBP\leq 90mmHg}$ using $Feature_{ABPtr,1mintr}$, $Feature_{ABPtr}$ and $Feature_{1mintr}$. The blue line represents the prediction results from the training group while the red line represents the prediction results from the testing group. As mentioned in the previous section, we investigated the prediction power changes from POC to 2 hours ahead for an outcome.

Several conclusions can be made from Figure 6:

(a) We could predict $Outcome_{SBP\leq 90mmHg}$ 20 minutes ahead of time with 0.781 AUC value using $Feature_{ABPtr,1mintr}$ based model, and 50 minutes ahead with 0.712 AUC;
(b) We could predict 30 minutes ahead by using $Feature_{1mintr}$ based model and 80 minutes ahead of time with 0.724 AUC;
(c) Prediction power of the $Feature_{ABPtr}$ based model was slightly less than the $Feature_{ABPtr,1mintr}$ and the $Feature_{1mintr}$ based model;
(d) We could predict 30 minutes ahead by using the $Feature_{ABPtr}$ based model.

Moreover, the advantage of using the $Feature_{ABPtr}$ based model is the features were generated from one signal: the ABP waveform. This indicates that we could use only one signal to have similar prediction power as other models, which used multiple vital signs. Figure 7 shows the prediction results for the $Outcome_{MAP\leq 50mmHg}$. Similar conclusions can be made for $Outcome_{SBP\leq 90mmHg}$. However, for predicting $Outcome_{MAP\leq 50mmHg}$, we observed that by using the $Feature_{ABPtr}$ based model, the prediction power cannot exceed 0.7 AUC while we could predict 50 minutes ahead using the $Feature_{ABPtr,1mintr}$ and the $Feature_{1mintr}$ based models. We could also predict 10 minutes ahead with over 0.9 AUC prediction power.

Figure 8 and Figure 9 show the prediction results for predicting Tachycardia and Bradycardia. Several conclusions can be made:

(a) We could predict 40 minutes ahead by using the $Feature_{ABPtr,1mintr}$ and the $Feature_{1mintr}$ based model with over 0.9 AUC;
(b) We could use the $Feature_{ABPtr}$ based model to predict 50 minutes ahead with 0.9 AUC;
(c) Prediction power from POC to 2 hours are greater than 0.75 AUC among the 3 models.

This could also mean that we can predict Tachycardia using ABP derived features without considering the 70 one-minute trend features. However, we cannot reach a similar conclusion for predicting Bradycardia, as shown in Figure 9. We could predict 20 minutes before the bradycardia event with 0.7 AUC. After the 20 minute mark, the prediction power dropped to 0.5-0.6 AUC.

Figure 10 and Figure 11 are the prediction results for $Outcome_{SI\geq 1}$ and $Outcome_{SI\geq 0.9}$. Several conclusions can be made for predicting $Outcome_{SI\geq 1}$:

(a) We could predict 10 minutes ahead of time using the $Feature_{ABPtr,1mintr}$ and the $Feature_{1mintr}$ based models with 0.9 AUC while the $Feature_{ABPtr}$ based model gives 0.8 AUC;
(b) We could predict 70 minutes ahead with over 0.7 AUC by using any model.

On the other hand, to predict $Outcome_{SI\geq 0.9}$, we could use the $Feature_{ABPtr,1mintr}$ and the $Feature_{1mintr}$ based model to predict 40 minutes ahead of the event with over 0.8 AUC and 0.75 AUC with the $Feature_{ABPtr}$ based model.

Figure 12, Figure 13, and Figure 14 show the prediction power for predicting $\text{Outcome}_{\text{CO}\leq 80\%\text{baseline}}$, $\text{Outcome}_{\text{CVP}\leq \text{baseline-2}}$ and $\text{Outcomes}_{\text{SVR}\leq 80\%\text{baseline}}$. Several conclusions could be made for predicting $\text{Outcome}_{\text{CO}\leq 80\%\text{baseline}}$:

(a) We could use the $\text{Feature}_{\text{ABPtr,1mintr}}$ and $\text{Feature}_{\text{1mintr}}$ based models to predict 20 minutes ahead of time with 0.9 AUC and 60 minutes ahead of time with 0.85 AUC;

(b) We may not be able to use the $\text{Feature}_{\text{ABPtr}}$ based model to predict $\text{Outcome}_{\text{CO}\leq 80\%\text{baseline}}$ since the prediction power is low.

Similar conclusions could be made for predicting the $\text{Outcomes}_{\text{SVR}\leq 80\%\text{baseline}}$. However, for predicting $\text{Outcome}_{\text{CVP}\leq \text{baseline-2}}$, we could predict 30 minutes ahead using $\text{Feature}_{\text{ABPtr,1mintr}}$ and $\text{Feature}_{\text{1mintr}}$ based model with approximately 0.8 AUC or we could use $\text{Feature}_{\text{ABPtr}}$ based model to predict 10 minutes later outcome with 0.8 AUC prediction power, or 50 minutes later with 0.7 AUC prediction power.

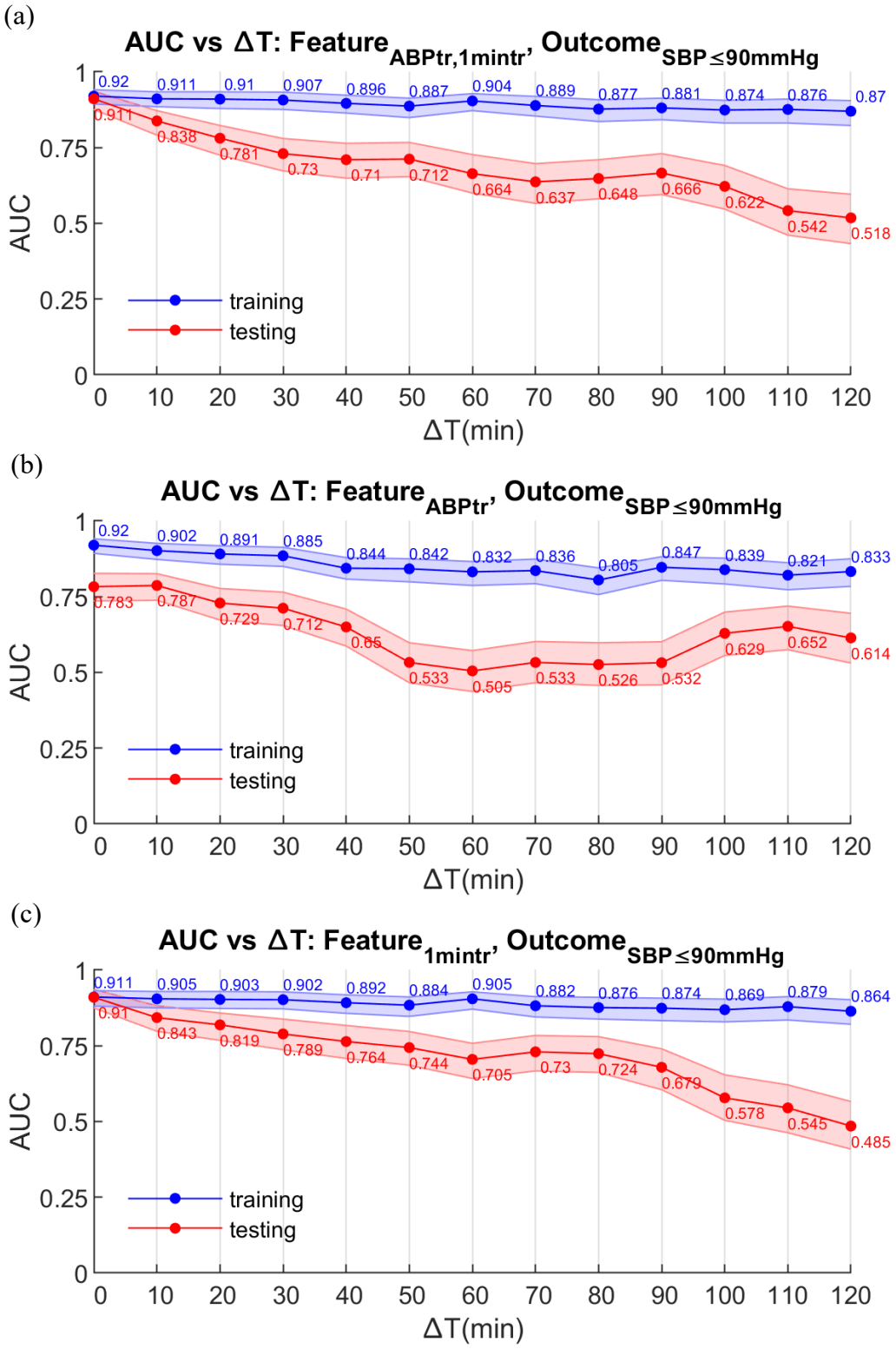

Figure 6. Prediction results of SBP ≤ 90 mmHg.
SBP ≤ 90 mmHg was predicted using (a) ABP_VS and one minute trend based random forest model, (b) ABP_VS based random forest model, and (c) one minute trend based random forest model.

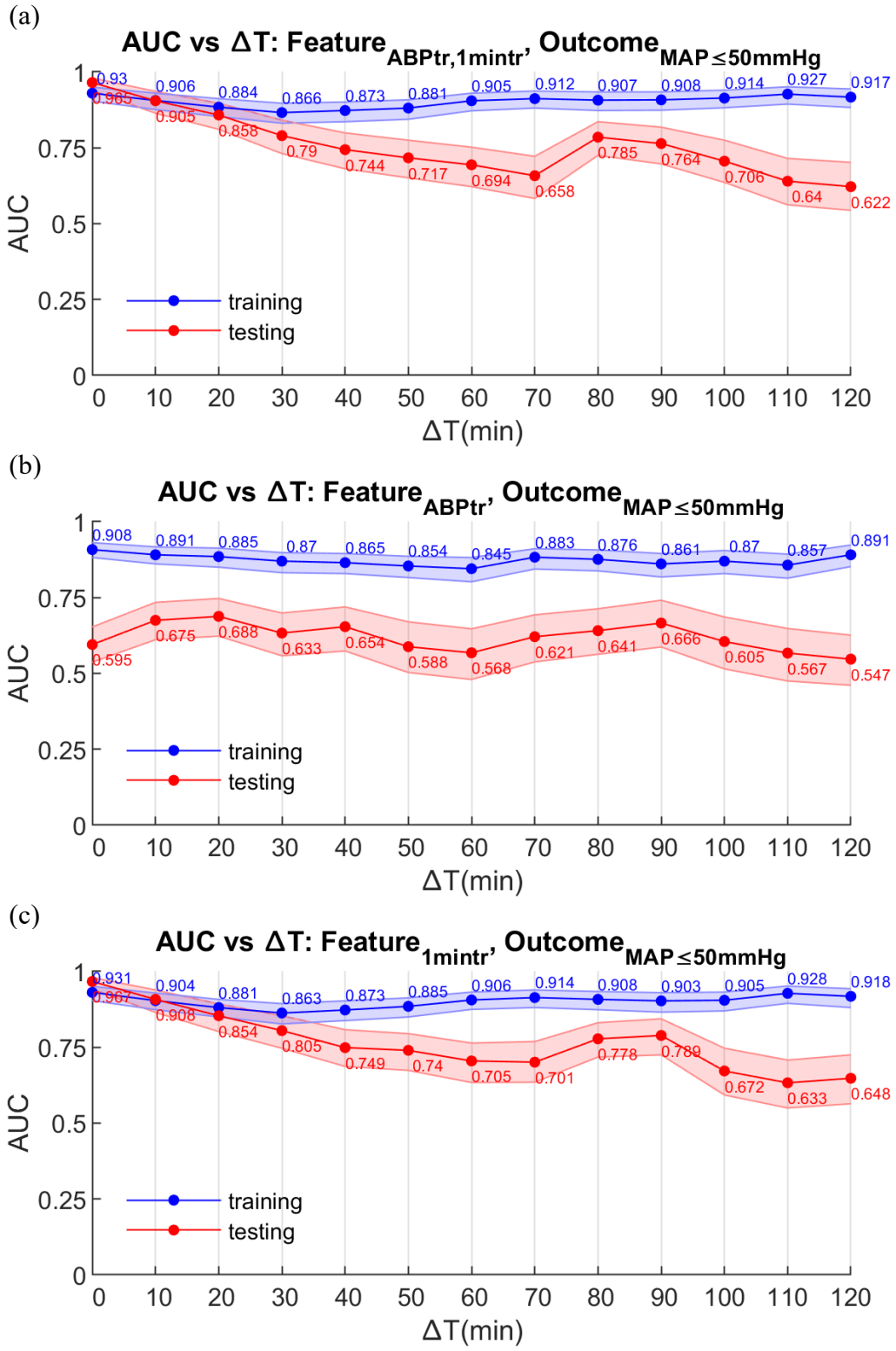

Figure 7. Prediction results of MAP ≤ 50 mmHg.
MAP ≤ 50 mmHg was predicted using (a) ABP_VS and one minute trend based random forest model, (b) ABP_VS based random forest model, and (c) one minute trend based random forest model.

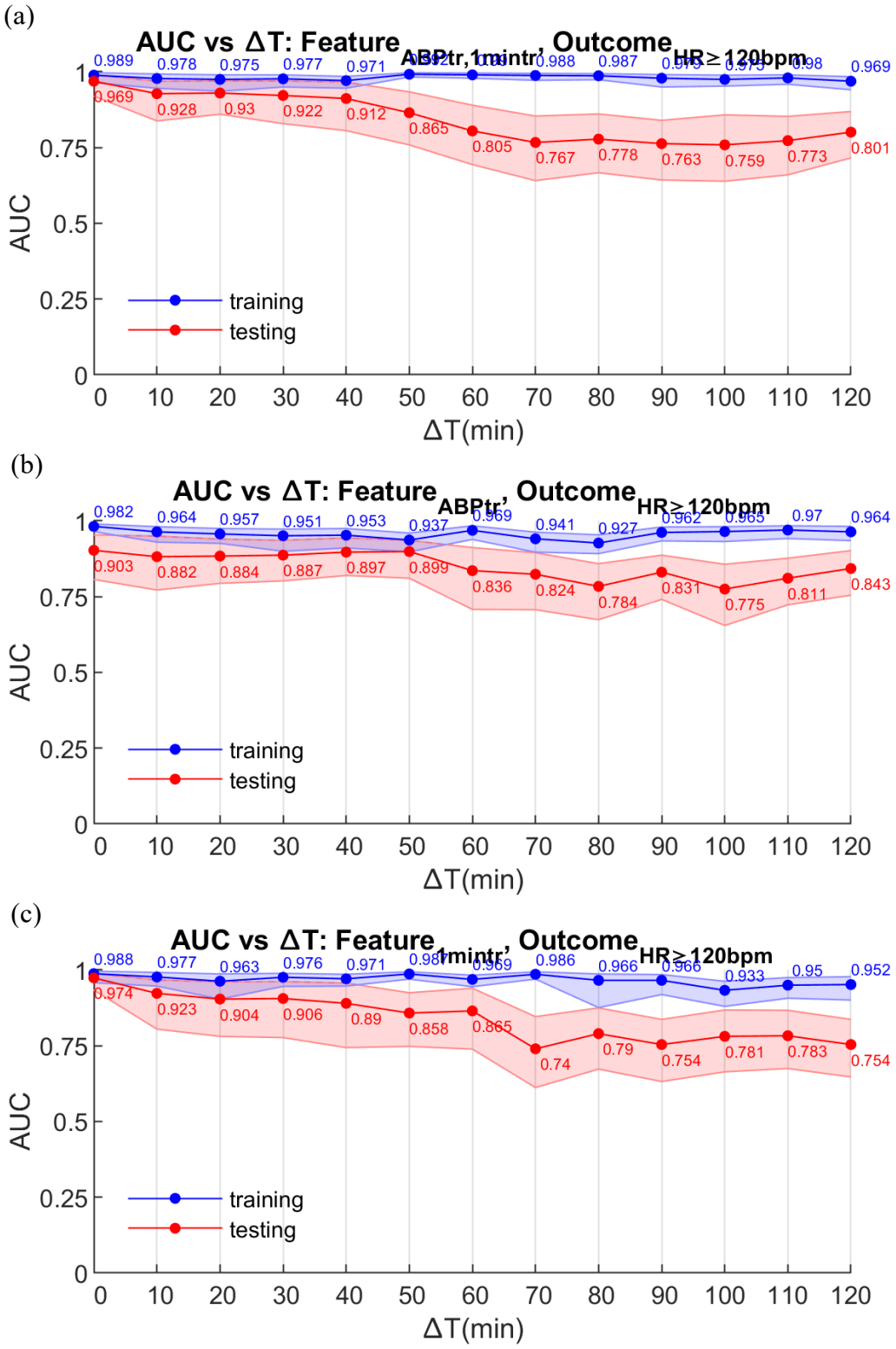

Figure 8. Prediction results of HR ≥ 120 bpm
HR ≥ 120 bpm was predicted using (a) ABP_VS and one minute trend based random forest model, (b) ABP_VS based random forest model, and (c) one minute trend based random forest model.

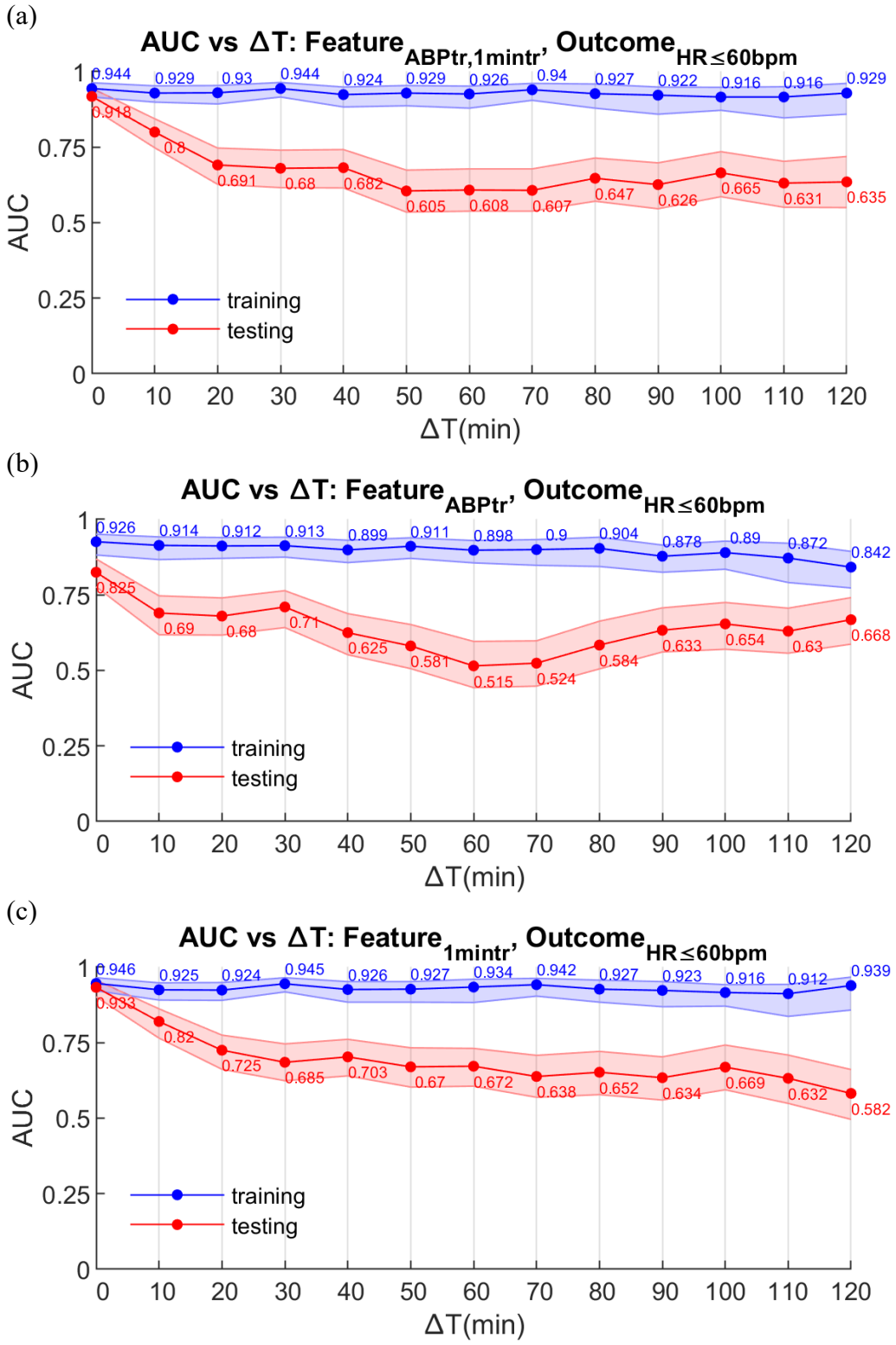

Figure 9. Prediction results of HR ≤ 60 bpm
HR ≤ 60 bpm was predicted using (a) ABP_VS and one minute trend based random forest model, (b) ABP_VS based random forest model, and (c) one minute trend based random forest model.

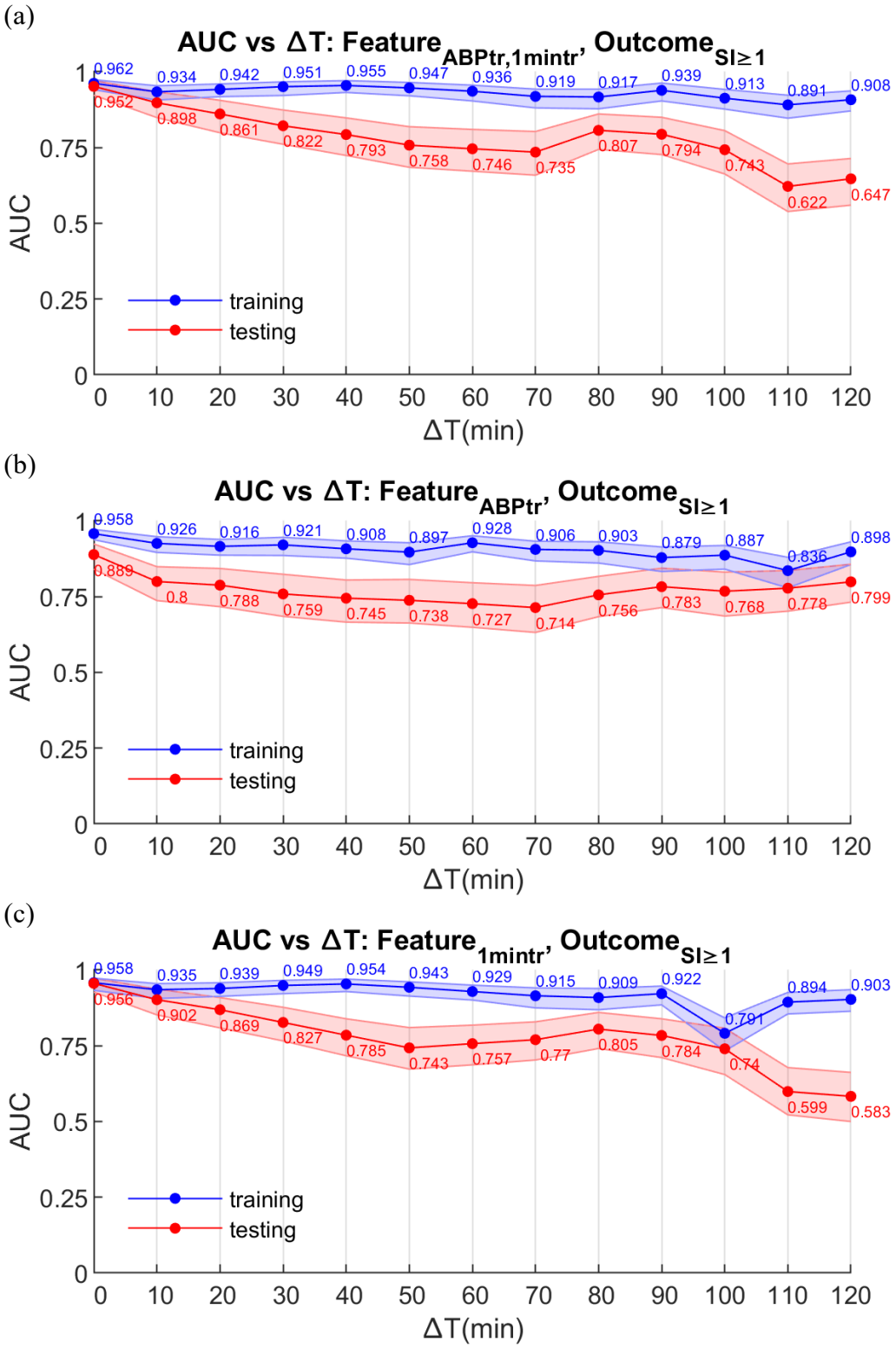

Figure 10. Prediction results of SI ≥ 1
SI ≥ 1 was predicted using (a) ABP_VS and one minute trend based random forest model, (b) ABP_VS based random forest model, and (c) one minute trend based random forest model.

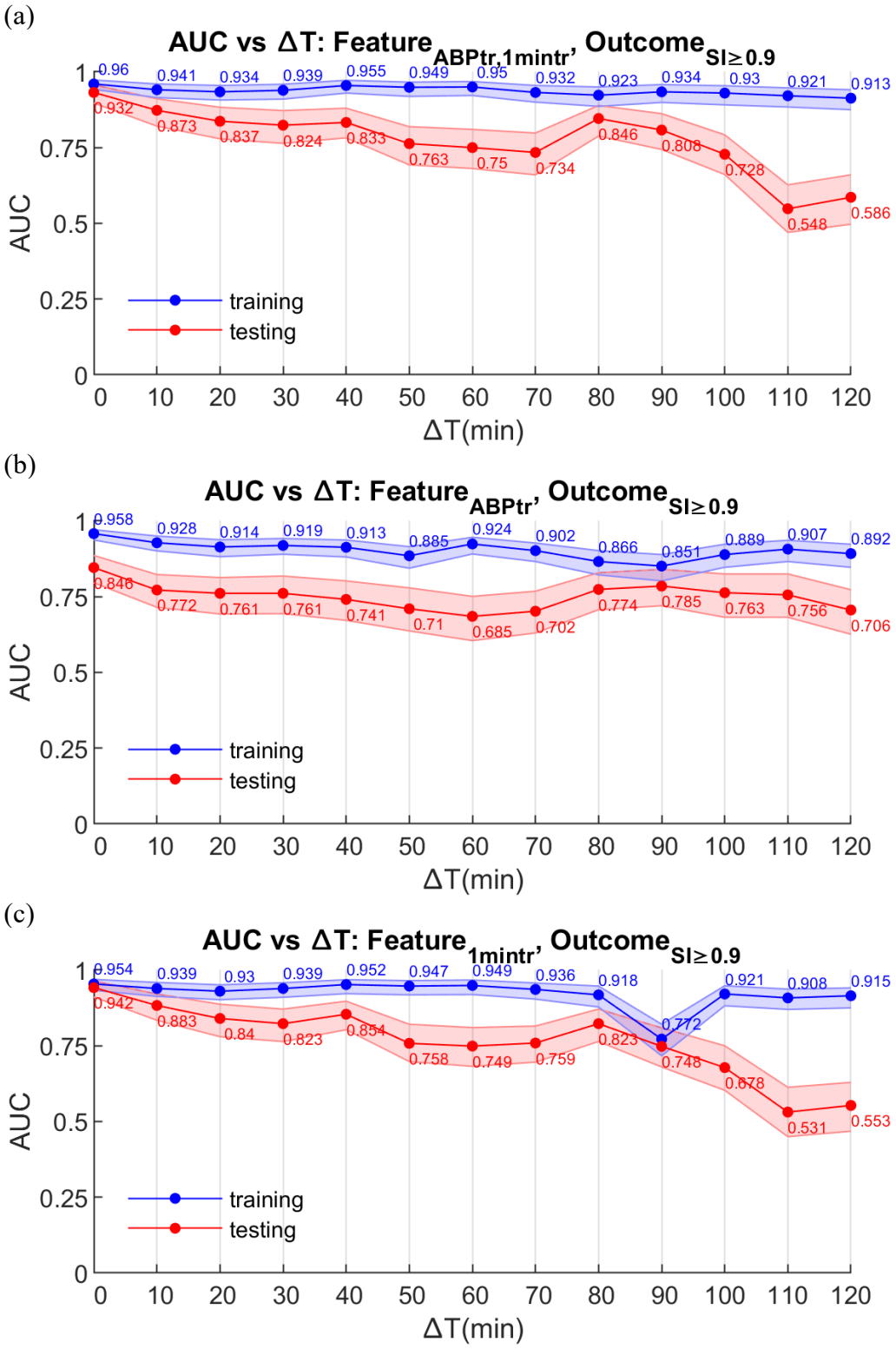

Figure 11. Prediction results of SI ≥ 0.9.
SI ≥ 0.9 was predicted using (a) ABP_VS and one minute trend based random forest model, (b) ABP_VS based random forest model, and (c) one minute trend based random forest model.

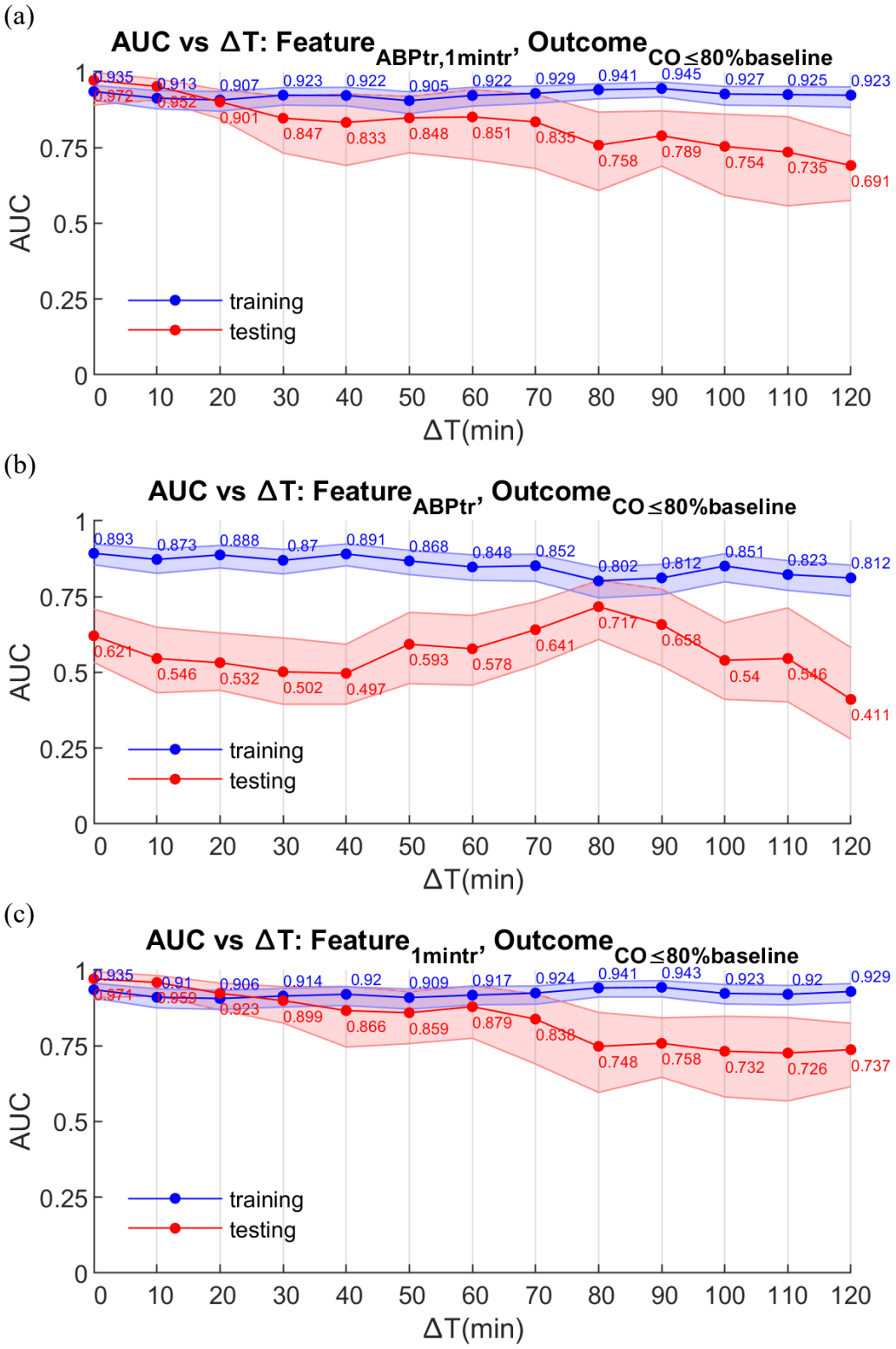

Figure 12. Prediction results of CO ≤ 80% baseline.
CO ≤ 80% baseline was predicted using (a) ABP_VS and one minute trend based random forest model, (b) ABP_VS based random forest model, and (c) one minute trend based random forest model.

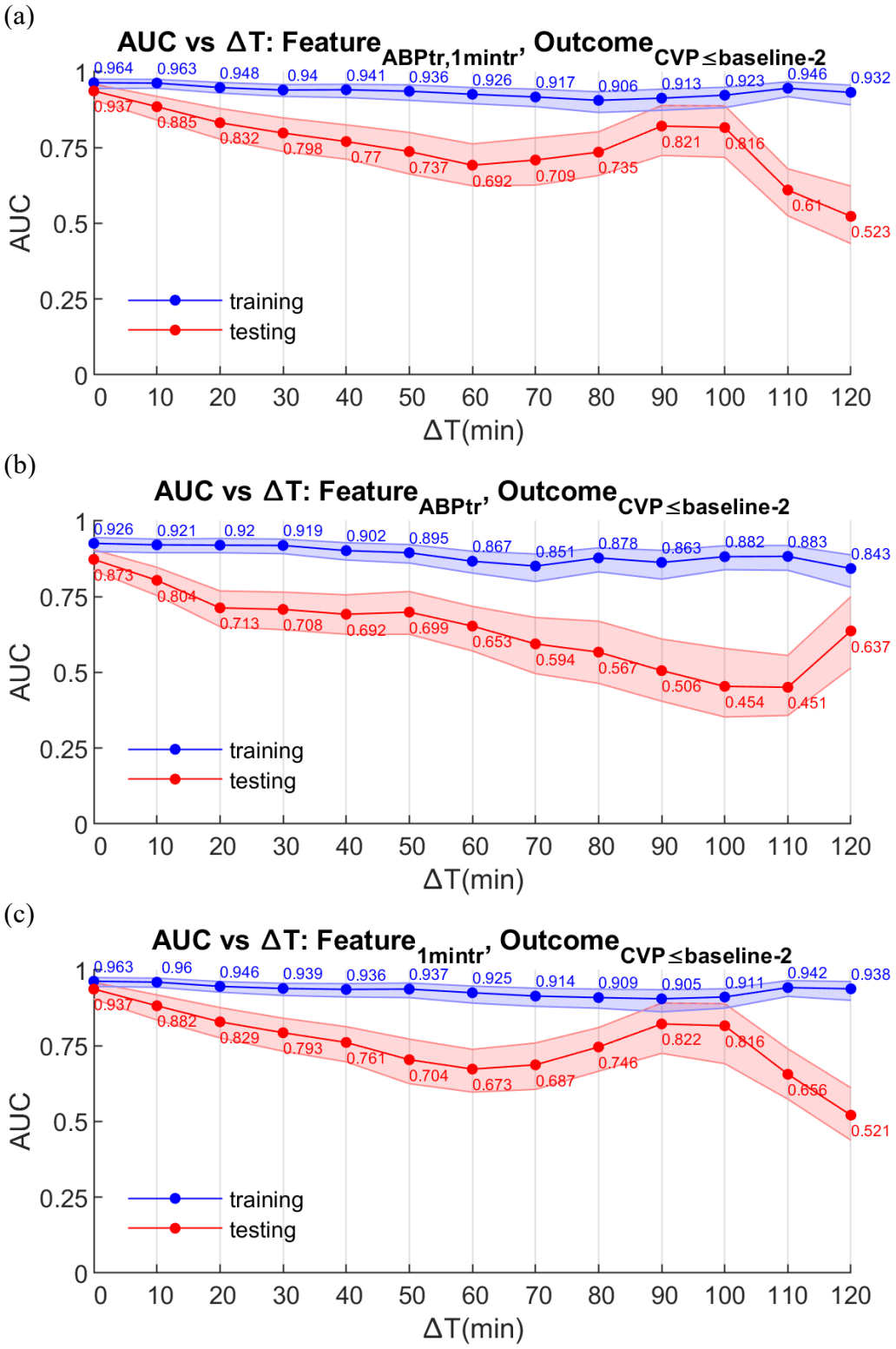

Figure 13. Prediction results of CVP ≤ baseline-2.
CVP ≤ baseline-2 was predicted using (a) ABP_VS and one minute trend based random forest model, (b) ABP_VS based random forest model, and (c) one minute trend based random forest model.

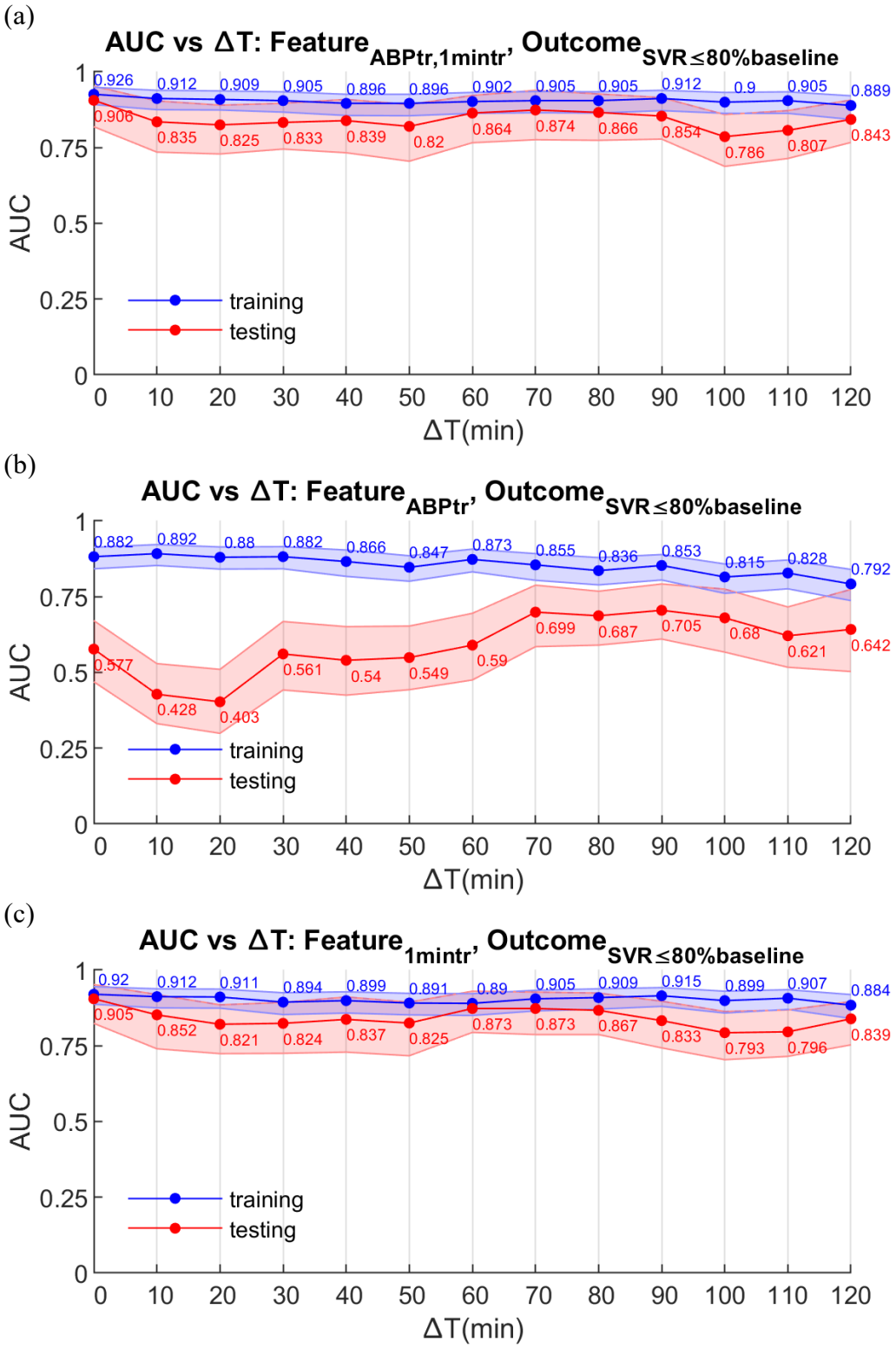

Figure 14. Prediction results of SVR ≤ 80% baseline
SVR ≤ 80% baseline was predicted using (a) ABP_VS and one minute trend based random forest model, (b) ABP_VS based random forest model, and (c) one minute trend based random forest model.

6.0 DISCUSSION AND CONCLUSION

Based upon the need for cardiac support (VA) in addition to respiratory support alone (VV) in the critically ill or injured patient, VA or VV ECMO would be chosen to provide support for patients with severe respiratory and cardiac disease [35]. Regardless of modality, hemodynamic changes during ECMO need to be monitored closely with high-resource and cognitive load is required to maintain homeostasis. With this project, we have sought to begin the process of developing machine learning models to predict the physiologic status changes during the earliest stages of decompensation during ECMO. We proposed that these models could be used to not only detect these changes, but then act on them utilizing closed-loop physiologic control.

As stated in [36], it takes an interprofessional team to take care of a patient on ECMO. In addition to the critical care needs of a severely critically ill patient on mechanical ventilation, ECMO patients require further monitoring including observing and managing all mechanical an physiologic parameters impacted by the ECMO circuit including: oxygenation, ventilation, coagulation cascade, circuit failure/degradation, neurologic function, cardiac output monitoring, etc. Our machine learning model may be able to help the monitoring and clinical decision process, as described in the results section, by alerting providers to the need for intervention early in their decompensation/degradation. Specifically, we showed that we could predict physiologic status changes (including hypotension, tachycardia, bradycardia, shock index (mortality or the need of transfusion)) at least 30 minutes before the actual event using the continuous collected vital signs. In other words, with the ability of early prediction for physiologic status changes, we could alarm the corresponding team in advance, and they could perform any precaution accordingly. Furthermore, we investigated the status of the subject's CO, SVR and CVP; importantly, if the provider could predict these biomarkers early, physicians could start preparing for any necessary interventions in advance. Additionally, the predictions also provide the initial inputs for the closed loop control of the physiologic monitoring system. Hence, by continuously predicting any future physiologic changes with our machine learning model using the continuously collected vitals, we could ease some of the workload of the interprofessional team by monitoring the patient status.

The foundation established in this study supports future research on continuously monitoring patient status on ECMO, which could be expanded to several topics. First, we provide the foundation for the ability of using different waveforms to predict the patient status. In this study, besides the one-minute trend data listed in Table 1, we only built models with features generated from the ABP waveform. However, there are another eight waveforms that were collected, as listed in Table 1. We are interested in investigating these other 8 waveforms to determine if we could improve the prediction power by including this data. Second, besides the one-minute trend and waveform data, we also collected information on the medication given to the swine. We could add this information to the model, which could give us more insight into the patient condition and moreover, building a more refined closed loop control physiologic monitoring system. In conclusion, it is crucial to investigate techniques that could strengthen the capacity of our model's prediction power as it could help us to carry out a successful ECMO and lead to improved positive patient outcomes.

There are some limitations to our study. We simplified the modeling by using one assumption that, given the recent physiologic status, the future physiologic status is independent of other factors. The predictive models only considered physiologic variables, while ignoring other potentially relevant variables, such as past treatments and the response to those treatments. However, with other treatment information and their interaction with the recent physiologic

conditions, the prediction accuracy may be further improved. Another limitation is that the number of collected data cases is small. Although the amount of data points is large due to the high-fidelity waveform measurement, there are less than 20 individual subjects observed for the study. More experiments may gather more evidence for understanding how the physiologic status changes with the conditions and the various treatments.

For future work, we could study the physiologic changes (expected and observed). Such physiologic response after an external action (treatment) that could help us develop the closed loop control algorithm, such as a proportional-integral-derivative (PID) controller. In other words, the predictive models could provide early feedback to the closed loop control algorithm. For the controlled variables, we could understand how the manipulated variables impact them. Specifically, if we need to design or implement Multiple-Input and Multiple-Output (MIMO) controllers, we should collect data to estimate how the combination of treatment may have impact on physiologic change. Another important future work could be the design and integration of portable ECMO devices with closed loop control system. The portable devices would allow easier and faster deployment of the ECMO system in far-forward environments. The mobility of the ECMO system could enhance care-providers' ability in handling multiple casualties.

In conclusion, the study described herein showed that key physiologic instability during ECMO could be predicted up to 120 minutes (about 2 hours) ahead of the event. This early-events-detection process could be used to alert care providers to critical physiologic instability. Additionally, this could serve as a key decision point in the development of a close loop or human-in-the-loop semiautomatic ECMO control system with obvious implications for the application of this technology to the transport, prehospital, and prolonged field care settings.

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LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMS

711 HPW/RHBAM	Air Force Research Laboratory, 711th Human Performance Wing, Airman Systems Directorate, Airman Biosciences Division, Product Development Branch, Enroute Care Section
%	percent
A2AD	anti-access area denial
ABG	arterial blood gas
ABP	arterial blood pressure
ACT	activated coagulation time
AETC	Air Education and Training Command
AFMS	Air Force Medical Service
AMC	Air Mobility Command
ARDS	acute respiratory distress syndrome
APRV	airway pressure release ventilation
AUC	area under the receiver operating characteristic curve
BP	blood pressure
bpm	beats per minute
CBC	complete blood count
CCATT	USAF critical care air transport teams
CCO	continuous cardiac output
CESAR	conventional ventilation or ECMO for severe adult respiratory failure
CHEER	mechanical CPR, hypothermia, ECMO and early reperfusion
cm	centimeters
CO	cardiac output
CO2	carbon dioxide
COAG	coagulation
CRS	static compliance of the respiratory system
CSTARS	Center for the Sustainment of Trauma and Readiness Skills
CVP	central venous pressure
^{o}C	degrees Celsius
ΔP	driving pressure

DBP	diastolic blood pressure
DVP	invasive diastolic blood pressure
ECLS	extra-corporeal life support
ECMO	extracorporeal membrane oxygenation
E-CPR	extracorporeal cardiopulmonary resuscitation
EEG	electroencephalography
EJ	external jugular
EKG	electrocardiogram
ELCS	Extracorporeal Life Support Systems
ELSO	extracorporeal life support organization
EPR	emergency preservation and resuscitation
ERC	en route care
ETCO2	end-tidal carbon dioxide
FFP	fresh frozen plasma
FIO2	fraction of inspired oxygen
H2O	water
HB	hemoglobin
HR	heart rate
Hz	hertz
ICU	intensive care unit
IM	intramuscular
Kg	kilograms
L	liters
LR	lactated Ringer’s solution
LV	left ventricle
MAP	mean arterial pressure
mcg	micrograms
min	minutes
MIMO	Multiple-Input and Multiple-Output
ml	milliliters
mmHg	millimeters of mercury

MV	mechanical ventilation
PaCO2	partial pressure of carbon dioxide
PaO2	partial pressure of oxygen in the arterial blood
PA	pulmonary artery
PAP	pulmonary artery pressure
PC	pressure control
PEA	pulseless electrical activity
PEEP	positive end-expiratory pressure
PID	proportional-integral derivative
POC	point-of-care
POI	point of injury
Pp	plateau airway pressure
PP	pulse pressure
PT	prothrombin time
PTT	partial thromboplastin time
PVCO2	partial pressure of carbon dioxide in venous blood
RF	random forest
ROTEM	rotational thromboelastometry
RR	respiration rate
rScO2	regional cerebral oxygen saturation
SAAP	selective aortic arch perfusion
SAMU	Service d'Aide Médicale Urgente
SBP	systolic blood pressure
SPO2	oxygen saturation
SO2	sulfur dioxide
STAR	University of Maryland Shock Trauma and Anesthesiology Research
STO2	skeletal muscle oxygen saturation
SVR	systemic vascular resistance
SVO2	venous oxygen saturation
SVP	invasive systolic blood pressure
TH	therapeutic hypothermia

UMB	University of Maryland Baltimore
USAFSAM	U.S. Air Force School of Aerospace Medicine
VA-ECMO	venoarterial extracorporeal membrane oxygenation
VV-ECMO	venovenous extracorporeal membrane oxygenation
VO2	oxygen uptake
VT	tidal volume
vWF	von Willebrand factor