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# CARDIAC RHYTHM DURING MECHANICAL VENTILATION AND WEANING FROM VENTILATION

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ABSTRACT OF DISSERTATION

Muna Hassan Hammash

The Graduate School

University of Kentucky

2010

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# CARDIAC RHYTHM DURING MECHANICAL VENTILATION AND WEANING FROM VENTILATION

ABSTRACT OF DISSERTATION

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the College of Nursing
at the University of Kentucky

By
Muna Hassan Hammash

Lexington, Kentucky

Director: Dr. Debra K. Moser, Professor of Nursing

Lexington, Kentucky

2010

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ABSTRACT OF DISSERTATION

CARDIAC RHYTHM DURING MECHANICAL VENTILATION
AND WEANING FROM VENTILATION

The transition from mechanical ventilation (MV) to spontaneous ventilation during weaning is associated with hemodynamic alterations and autonomic nervous system (ANS) alterations (reflected by heart rate variability [HRV]). Although cardiac dysrhythmias are an important manifestation of hemodynamic alterations, development of dysrhythmias during MV and weaning and subsequent impact on length of MV has received little attention.

The purposes of this dissertation were to 1) evaluate the relationship of heart rate variability (HRV) during weaning to the development of cardiac dysrhythmias and 2) determine the relationship of cardiac dysrhythmias to length of MV.

A convenience sample of 35 patients (66.7% men; mean age 53.3 years) who required MV was enrolled in this study. Continuous 3-lead electrocardiographic data were collected for 24 hours at baseline during MV and for the first 2 hours during the initial weaning trial. HRV was evaluated using spectral power analysis.

Twenty- seven patients out of 30 were exposed to a combination of pressure support (8-15 cm $H_2O$) and continuous positive airway pressure 5 cm $H_2O$ during weaning trial. Three patients self- extubated and received supplemental oxygen through either a partial rebreathing or non-rebreathing mask. Low frequency (LF) power HRV decreased, while high frequency (HF) and very low frequency (VLF) power HRV did not change during weaning. Multiple regression analyses showed that LF and HF HRV were significant predictors of occurrence of ventricular and supraventricular ectopic beats during weaning, while VLF power predicted occurrence of ventricular ectopic beats only. The mean of occurrence of supraventricular ectopic beats per hour during weaning was double the mean at baseline, while the mean of ventricular ectopic beats per hour did not change. Mean number of supraventricular ectopic beats per hour during weaning was a significant predictor of length of MV.

This dissertation has fulfilled an important gap in the evidence base for cardiac dysrhythmias during weaning from MV. Cardiac dysrhythmias and HRV alterations

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should be systemically evaluated during MV and weaning trials in order to decrease length of MV.

KEYWORDS: Cardiac Dysrhythmias, Mechanical Ventilation, Weaning, Heart Rate Variability, Length of Ventilation

Muna Hassan Hammash

Student's Signature

06/24/2010

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# CARDIAC RHYTHM DURING MECHANICAL VENTILATION AND WEANING FROM VENTILATION

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DISSERTATION

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A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the College of Nursing at the University of Kentucky

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This dissertation is dedicated to
the soul of my late father Hassan,
my husband Ali,
and my daughters Jaineen and Sarah

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I would like to gift this dissertation to the soul of my late father Hassan, who inspired me since my childhood and who was the reason for my achievements throughout my life. I would like to thank my mom, sister, brothers, nieces, nephews, parents-in-law, brothers-in-law and sisters-in-law. My final and most heartfelt acknowledgment must go to my husband Ali and my daughters Jaineen and Sarah for their love, care, and support in happiness and sorrow.



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# CHAPTER I:
# CARDIAC RHYTHM DURING MECHANICAL VENTILATION AND WEANING FROM VENTILATION

## Significance of Problem

Mechanical ventilation (MV), a well established intensive care unit (ICU) strategy, is used increasingly often to support pulmonary function in critically ill patients. [1, 2] In critical care units, as many as 90% of patients require MV.[1, 3-5] Despite its lifesaving potential, MV is associated with a wide variety of risks including ventilator-associated pneumonia, barotrauma, cardiovascular compromise, and diaphragm fatigue.[6, 7] Prolonged MV increases the possibility of occurrence of these complications.[7] Reintubation following accidental or intentional premature extubation is also associated with high morbidity, mortality, health care costs, longer ICU and hospital stay, and a greater chance to transfer to a rehabilitation institution. [1, 8, 9] Thus, the goal for mechanically ventilated patients is to transition back to spontaneous ventilation as rapidly as feasible, a process called weaning.[3] Liberation from MV may be easily achieved in most patients who require routine postoperative ventilator support or those with overdose of sedatives. However, weaning is often difficult and the chance of failure is higher in patients who have chronic pulmonary disease, heart failure, central nervous system dysfunction, renal failure, hepatic failure or sepsis. [8-10]

During weaning, different modes of spontaneous ventilation can be used that result in different hemodynamic responses that are dependent on intrathoracic pressure (ITP) changes inherent to each[12, 13] and the individual's underlying cardiac function. [12, 14, 15] Unfortunately, about one third of mechanically ventilated patients exhibit significant difficulty weaning from MV [9, 16, 17] and consequently have a longer duration of MV and a longer hospital stay. The Collective Task Force of the American College of Chest Physicians, the American Association for Respiratory Care, and the American College of Critical Care has identified weaning from MV as a research priority.[18]

Multiple investigators have examined the impact of oxygenation failure, respiratory muscle dysfunction and cardiovascular dysfunction as major factors in weaning outcomes.[19-28] Although dysrhythmias are an important manifestation of cardiovascular dysfunction, the development of dysrhythmias during weaning and subsequent impact on length of MV has received little attention.



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The transition from MV to spontaneous ventilation during the weaning process can induce hemodynamic alterations [14, 29-32] as a result of changes in intrathoracic blood volume. Altered autonomic nervous system (ANS) response (reflected by decreased heart rate variability [HRV]) [33, 34] to hemodynamic alterations can cause dysrhythmias.[35-45] Dysrhythmias subsequently may increase the length of MV as suggested in the study proposed model (Figure 1).

## Model for Testing Hypotheses

Changes in intrathoracic pressure (ITP) and lung volume that occur during weaning may induce significant hemodynamic changes that influence thoracic blood volume and flow.[12, 27, 33] The autonomic nervous system responds to the hemodynamic alterations inherent to different weaning modes in order to maintain adequate cardiac output and oxygen delivery. Compensatory ANS alterations include changes in heart rate, ventricular afterload, contractility, and filling time. However, altered ANS tone (reflected by decreased HRV) in response to hemodynamic alterations during weaning could be arrhythmogenic [46] depending on the magnitude of hemodynamic alterations, underlying cardiovascular function, and the adequacy of compensatory mechanisms.[7, 14, 15] Patients who develop cardiac dysrhythmias during weaning may have inadequate cardiac output and oxygen delivery required for metabolic needs and consequently fail weaning attempts.

In this study, we hypothesized that there is a relationship between the occurrence of dysrhythmias during initial weaning attempt and length of MV (Figure 1.1). Patients with underlying cardiovascular dysfunction and impaired compensatory mechanisms for hemodynamic changes in response to weaning attempts may experience significant cardiac dysrhythmias.[17] Patients with cardiac dysrhythmias may fail to wean from MV and require longer support from MV.

## Purpose of the Study

The purposes of this study were to 1) evaluate the relationship HRV (as a noninvasive reflection of ANS tone) during weaning to the development of cardiac dysrhythmias and 2) determine the relationship of cardiac dysrhythmias during weaning to length of MV. Clinically significant cardiac dysrhythmias (i.e., ventricular ectopy, ventricular tachycardia/fibrillation, atrial fibrillation/flutter, and supraventricular tachycardia) were the focus of this study because of their potential negative consequences



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in patients who are undergoing weaning trials. Studying and identifying cardiac dysrhythmias that occur during MV and weaning, and determining the role that dysrhythmias might play in length of MV are vital in order to provide appropriate care and management for mechanically ventilated patients.

## Specific Aims

The specific aims of the study were the following:

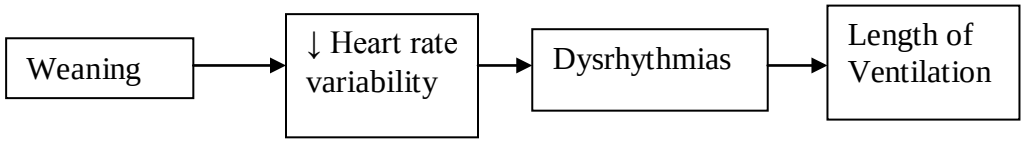
1: To determine the relationship of HRV (measured in the frequency domain) during weaning to the development of cardiac dysrhythmias after controlling for baseline HRV measured during MV.

Hypothesis 1**:** HRV measured in the frequency domain during weaning will be related to the occurrence of cardiac dysrhythmias. That is, in patients with cardiac dysrhythmias during weaning compared to those without dysrhythmias, HRV will demonstrate higher power in the low frequency (0.04 to 0.15 Hz range) and very low frequency (< 0.04 Hz), and decreased power in the high frequency range (0.15 to 0.40 Hz).

2: To determine the relationship of the occurrence of dysrhythmias during weaning to length of MV after controlling for Acute Physiology and Chronic Health Evaluation (APACHE) IV score.

Hypothesis 2: Rate of dysrhythmias per hour during weaning will be an independent predictor of length of MV.

**Figure1.1: Conceptual model of the relationship between heart rate variability, dysrhythmias and length of ventilation**

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# CHAPTER II
# REVIEW OF LITERATURE

Transition from MV to spontaneous ventilation during the weaning process produces hemodynamic alterations and autonomic nervous system (ANS) dysfunction (reflected by decreased HRV) especially in patients with underlying cardiovascular dysfunction. Autonomic nervous system alterations can cause cardiac dysrhythmias depending on underlying cardiovascular function and adequacy of compensatory mechanisms. Although dysrhythmias that develop during weaning are often clinically significant, there is paucity of research on expression of dysrhythmias during weaning and its impact on length of MV.

Management of dysrhythmias that develop during weaning from MV is vital because dysrhythmias can induce myocardial ischemia, impair myocardial contractility and decrease cardiac index, eventually leading to weaning failure and longer time of MV. Prolonged MV is associated with a variety of risks and complications such as ventilator-associated pneumonia, lung barotrauma, and cardiovascular compromise.[6, 7]

The purpose of this chapter is to provide a physiological background of factors that contribute to occurrence of cardiac dysrhythmias during weaning. The focus is on physiology of cardiac action potential, underlying mechanisms of cardiac dysrhythmias, and physiology of HRV. Cardiovascular effects of mechanical ventilation and weaning; relationship between HRV to the development of cardiac dysrhythmias during weaning, process of weaning from MV, measurement of HRV are reviewed and presented in this chapter also.

## Heart- lung interaction during mechanical ventilation and weaning from ventilation

Cardiac and pulmonary systems interact with each other during spontaneous and mechanical ventilation. This interaction involves mechanical, neural, and humoral mechanisms.[14, 30, 47] Intrathoracic structures including the heart, pericardium, great vessels and veins are affected by changes in the surrounding pressure, which are the pleural pressure and ITP.[14] Changes in pleural pressure, ITP, and lung volume associated with spontaneous ventilation and MV affect the determinants of stroke volume—preload, afterload and myocardial contractility. [14, 15, 32, 47-49]



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***Cardiovascular effects of spontaneous ventilation.***

During spontaneous inspiration, negative ITP induces a decrease in right atrial pressure and an increase in RV transmural pressure (i.e., the difference between cardiac intramural and extramural pressure). The decrease in right atrial pressure and the increase in right ventricular (RV) transmural pressure subsequently increase the pressure gradient between vana cava and right atrium for venous return to the heart. The result of increased venous return to the right heart is an increase in intrathoracic vascular volume and RV diastolic filling volume.[50] The increase in intrathoracic vascular volume and RV diastolic filling volume increases RV end- diastolic volume, which results in an increase in stroke volume by the Frank-Starling mechanism. Changes in left ventricular (LV) preload tend to follow RV preload within 1-2 beats.[50]

An increase in RV end- diastolic volume results in a decrease in LV diastolic compliance and end-diastolic volume through ventricular interdependence and leftward septal shift. LV afterload increases secondary to the increased LV transmural pressure. As a result, LV stroke volume decreases and a fall (<10mmHg) in systolic blood pressure during inspiration is observed. [51, 52] The decrease in systolic blood pressure stimulates the baroreceptor reflex, which consequently increases sympathetic outflow to the heart and a slight increase in heart rate occurs.

In summary, negative ITP that occurs during spontaneous inspiration causes increased venous return, RV preload and LV afterload, leading to a small fall in systolic blood pressure and a slight increase in heart rate.

***Cardiovascular effects of mechanical ventilation.***

Unlike spontaneous breathing, positive pressure MV results in an increase in ITP during inspiration and throughout the respiratory cycle if positive end expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) are used. [49]

During inspiration, positive ITP is associated with decreases in venous return and RV transmural pressure, causing a reduction in RVEDV (preload).[53, 54] Also, positive ITP and expanding lung volume compress vena cava and RV, which in turn cause a reduction in RV preload. At peak lung inflation, especially in severe obstructive pulmonary disease with lung hyperinflation, or when PEEP is applied, pulmonary vascular resistance (PVR) is elevated and RV ejection is impeded. [7, 55, 56] In critically ill patients (e.g., patients with



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adult respiratory distress syndrome), increases in PVR may markedly increase RV afterload, and induce acute cor pulmonale and cardiovascular collapse secondary to excessive RV dilation, RV ischemia, and compromised LV filling. [56, 57]

Right ventricular output directly influences left atrial and LV filling volume and output. Decreased RV end- diastolic volume and RV ejection decrease pulmonary venous flow, LV end- diastolic volume,[58] LV stroke volume, and cardiac output. Positive ITP reduces LV afterload by decreasing transmural LV systolic pressure.[59] Reduction in LV afterload facilitates ventricular ejection and helps maintain cardiac output (CO), although sometimes at a lower level than normal, during MV.[2]

Given the tendency toward a lower CO in some patients receiving MV and to increase blood pressure and maintain adequate cardiac output, the neurohormonal system responds to these hemodynamic alterations by secreting catecholamines, vasopressin and rennin. Activation of rennin- angiotensin system induces increases in angiotensin II and aldosterone levels. The result of increases of these neurohormones includes tachycardia, vasoconstriction, oliguria, and retention of sodium and water, and subsequently increases in blood pressure. An increase in heart rate occurs as an initial response to lower CO. This can be seen in the beat-to-beat variations in heart rate that compensate for cyclical differences in RV and LV output. Lung inflation mediates these instantaneous cardiovascular alterations by modulating autonomic tone. The lungs are highly innervated with autonomic fibers. Normally, lung inflation with tidal volume <10ml/kg induces vagal tone withdrawal and increases heart rate, producing the phenomenon of respiratory sinus arrhythmia. Lung inflation of >15ml/kg tidal volume induces both increased vagal tone and sympathetic withdrawal, which produces heart rate decreases.[7]

In summary, positive ITP that is associated with positive pressure ventilation causes decreases in venous return, RV end- diastolic volume, and LV afterload. Decreases in preload and afterload cause a dramatic decrease in CO in patients with hypovolemia.[60] Decreases in preload and afterload may improve CO and decrease oxygen demand in patients with hypervolemic heart failure, or impaired cardiac function.



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***Cardiovascular effects of weaning.***

Conceptually, "ventilator weaning" represents the period of transition from total ventilatory support to spontaneous breathing. [18, 61, 62] On average, weaning accounts for 40% of the total duration of mechanically ventilatory support.[3, 63] During ventilator weaning, different modes of spontaneous ventilation can be used that result in different hemodynamic responses dependent on ITP changes inherent to each. [12, 13] Up to one third of mechanically ventilated patients fail weaning trial.[9, 16, 17] The hemodynamic responses to weaning include cardiovascular dysfunction, autonomic alteration, cardiac dysrhythmias, and myocardial ischemia.

During weaning, ITP decreases. The degree of ITP reduction depends on the mode used. The decrease in ITP may result in abrupt increases in venous return, RV preload and LV afterload. Also during weaning, hypoventilation and alveolar hypoxia may occur. Hypoventilation and alveolar hypoxia induce hypoxic pulmonary vasoconstriction, profoundly increasing PVR, RV afterload[64] and subsequently decreasing RV ejection. Reduced RV ejection induces RV dilatation, decreases coronary blood flow, and shifts the interventricular septum to the left. Increased LV afterload may impede LV ejection and result in increases in LV end-diastolic volume and pressure. LV dilation, further increase in LV afterload, pulmonary edema secondary to acute heart failure, and coronary blood flow reduction may occur. Alterations in preload and afterload that occur during weaning may induce acute cardiac mechanical changes and ANS alterations that may be arrhythmogenic.

Acute ventricular loading (preload) or dilation that occurs during weaning plays an important role in the development of cardiac dysrhythmias. Mechanical changes (i.e., cardiac chambers loading and stretch) have been shown to induce significant electrophysiological changes (i.e., shortening myocardial action potential and refractoriness) mediated by cardiac myocyte stretch-activated channels and selective-ion channels.[65, 66] This mechano-electrical feedback mechanism induces atrial and ventricular dysrhythmias, predominantly ectopic beats, non-sustained ventricular tachycardia, and atrial dysrhythmias. The risk of dysrhythmia development during



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weaning is higher in patients with impaired ventricular function and congestive heart failure who have chronic regionally or globally impaired dilated hearts and are subject to pressure /volume overload.[65-73]

Changes in ANS tone occur as a result of fluid shifts into the intrathoracic vascular compartment from changes in ITP.[12, 27, 33] The ANS compensates for these fluid shifts by an increase in sympathetic tone and a decrease in parasympathetic tone. The result is a decrease in HRV and further increase in LV afterload. Sympathetic dominance is associated with negative effects on the cardiac myocyte action potential (i.e., decreased ventricular refractoriness, increased myocardial excitability) that may enhance abnormal automaticity, triggered activity and reentry mechanisms of cardiac dysrhythmias. Cardiac dysrhythmias may impair myocardial oxygen delivery and cardiac pumping, resulting in myocardial ischemia and low cardiac index.

Myocardial ischemia results from an imbalance between oxygen supply and demand. During weaning, oxygen supply may be reduced by hypoxemia, inadequate coronary blood flow, and dysrhythmias. Pulmonary edema that may occur during weaning causes ventilation-perfusion mismatching as manifested by hypoxemia. Inadequate coronary blood flow is produced by ventricular dilation, and increased LV end-diastolic pressure and afterload. Cardiac dysrhythmias, particularly ectopic beats, may limit diastolic filling time and oxygen supply and induce myocardial ischemia. Significant cardiac dysrhythmias and myocardial ischemia may cause ventricular hypokinesis or dyskinesis, which in turn decreases ejection fraction and results in low cardiac index. Weaning failure and increased mechanical ventilation time may result.

Overall, patients with cardiovascular dysfunction and impaired compensatory mechanisms for alterations in right and left preload and afterload; and ANS that occur during weaning may experience significant cardiac dysrhythmias. Dysrhythmias can induce myocardial ischemia,[19, 22, 25, 28, 74-76] impair myocardial contractility, [76] decrease ventricular ejection fraction and cardiac index, eventually leading to weaning failure and longer length of ventilation.



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## Cardiac Rhythm

***Normal cardiac rhythm.***

Heart rhythm, the normal occurrence of heart beats in regular intervals, is initiated by intrinsic electrical system composed of modified myocytes. These modified myocytes include the SA node, atrioventricular (AV) node, the bundle of His and Purkinjie fibers.[77-79]

The depolarization of the heart is normally initiated by the SA node "the pacemaker of the heart".[79] The SA node is a cluster of specialized cells that generates the initial electrical impulse of each normal heart beat. Electrical impulses from the SA node stimulate adjacent cells and are transmitted through the atria to the AV node via conducting internodal tracts. The AV node slows conduction velocity and thus delays impulse transmission. Then, a specialized conduction pathway composed of Bundle of His and Purkinjie fibers conduct the wave of depolarization throughout the ventricles to initiate ventricular contraction.[79]

The SA node is considered the pacemaker of the heart because it has the greatest rate of spontaneous firing. If the SA node fails to produce impulses, as seen in heart blocks, the tissue with the next highest automaticity rate, typically the AV node functions as the pacemaker. If the AV node fails to produce impulses, the Bundle of His may function as the pacemaker. However, the rate of depolarization of the Bundle of His is less than the rate of depolarization of the SA and AV nodes.[77-80]

The SA node is innervated by both sympathetic and parasympathetic nerve fibers. At rest, parasympathetic fibers dominate and release acetylcholine that slows rate of depolarization of the SA node and maintains heart rate between 60 and 80 beats/min. During exercise, relative withdrawal of vagal tone and activation of sympathetic nerves occur. The sympathetic nerve fibers release norepinephrine that increases the SA node rate of depolarization resulting in increased in heart rate.[78, 79, 81] In addition to the sympathetic and parasympathetic nervous system, the intrinsic rate of SA depolarization is modulated by baroreceptor activity, the intrinsic cardiac nervous system, cardiopulmonary reflexes, and respiration.



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The phenomenon in which respiration modulates the SA node depolarization rate and cyclical variation stroke volume and consequently cardiac output is referred to as respiratory sinus arrhythmia (RSA). The negative ITP and positive intra-abdominal pressure that occur during spontaneous inspiration enhance RV filling and stroke volume. At the same time, lung expansion that occurs during inspiration causes pooling of blood in the pulmonary circulation and decreases the return of blood to the left ventricle. Consequently, LV stroke volume decreases transiently, vagal efferent stimuli are inhibited and heart rate increases. The reverse occurs during expiration,[77] whereas efferent vagal is stimulated and heart rate decreases.

Overall, withdrawal of vagal tone occurs during inspiration[77] and results in the physiologic phenomenon called respiratory sinus arrhythmia, an observable manifestation of HRV that reflects the ability of the body to make beat-by-beat adjustments in cardiac output.

***Electrophysiology of cardiac excitation.***

Cardiac tissue is excitable and capable of responding to stimulation with a large, rapid shift in membrane voltage.[77, 79, 80] Cyclical depolarization and repolarization of the cell in which changes of the membrane voltage occur is called an action potential. The action potential lasts only for a few hundred milliseconds and triggers a sequence of organized myocardial contraction.[77, 79, 80]

***Physiology of action potential.***

The action potential consists of five phases: rapid upstroke (phase 0), early repolarization (phase1), a plateau (phase 2), repolarization (phase 3), and resting potential (phase 4). Phases of action potentials result from movement of sodium ($Na^{+}$), $Ca^{+2}$ and potassium ($K^{+}$) ions across the cell membrane through various ion channels and exchange pumps.[77, 79, 80]



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***Resting membrane potential.***

The resting membrane potential (phase 4) is generated by differences in ion concentration across the cell membrane. Potassium ions are highly concentrated inside the cell; while $Na^+$ is highly concentrated outside the cell membrane. At resting state, the cell membrane is highly permeable to $K^+$ ions through the inward rectifier channel ($i_{K\ ir}$). Sodium inward movement through the inward background current is very small compared to $K^+$ movement. However, the resting membrane potential remains stable despite the continuous slow exchange of $K^+$ for $Na^+$.[77, 79, 80]

***Types of cardiac action potentials.***

There are two main types of cardiac action potentials: fast and slow response action potentials. The speed of conduction through tissue is a function of the slope and amplitude of phase 0. Fast-response action potential occur in the atrial and ventricular myocytes and purkinjie fibers. These cells depolarize rapidly, conduct stimulation rapidly to the adjacent cell, and have a sustained plateau phase.[77-80] Slow response action potential occur in pacemaker cells, the SA and AV nodes of the heart. These cells depolarize spontaneously, slowly and have a shorter plateau phase. [77, 79, 80]

***Fast- response action potentials.***

The working myocardial cells of the atria and ventricles and Purkinje fibers are examples of fast response action potentials. [77-80] Fast-response cells have a resting membrane potential of approximately -90mv. Excitation of these cells by an action potential from an adjacent cell causes a rapid depolarization to a threshold voltage of about -60 to -65 mV. Once this threshold voltage is reached, the $Na^+$ channels open and a large inward directed, depolarizing $Na^+$ currents ($I_{Na}$) enter the cell and the initial overshoot upstroke (Phase 0) occurs with a peak voltage of +20 to +30 mV. The overshoot is brief because the $Na^+$ channels automatically inactivate after a few milliseconds.

At early repolarization (phase 1), the $Na^+$ channels are spontaneously and rapidly inactivated, but a special type of transient outward $K^+$ channel ($i_{to}$) opens, causing a small, early, rapid but incomplete repolarization of the cell to approximately +10 mV. At Phase 2 (plateau), the increase in inward $Ca^{+2}$ current ($i_{Ca}$) down the electrochemical gradient through L-type calcium channels is nearly counterbalanced by the repolarizing



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effect of the outward $K^+$ current ($I_{K1}$), resulting in a plateau period in the region of 0mV, which lasts 200-400 msec. During this phase, the increase in $Ca^{+2}$ entry has a positive inotropic effect on the myocardial cells during contraction. The increase in cytosolic $Ca^{+2}$ concentration that occurs during plateau activates the $Na^+$-$Ca^{+2}$exchanger. The $Na^+$-$Ca^{+2}$ exchanger allows three extracellular $Na^+$ to enter the cell in exchange for one $Ca^{+2}$ expelled outside the cell. The plateau inward $Na^+$ current created by the $Na^+$-$Ca^{+2}$ exchanger maintains the late plateau. Eventually, at phase 3, the delayed rectifier $K^+$ currents dominate and $Ca^{+2}$ channels becomes inactive, causing rapid repolarization of the cell back to the -90 mV resting membrane potential.

***Physiological and pathological changes in action potential plateau.***

Duration of the action potential plateau is determined mainly by the size of $K^+$ currents.[77-80] In circumstances of tachycardia induced by sympathetic nerve stimulation, action potential shortens due to the increased size of repolarizing $K^+$ currents.

During hypoxia, ATP concentration falls while ADP and $H^+$ concentrations rise, which in turn increases the opening of $K_{ATP}$ channels. The resulting increase in $K^+$ currents not only induces early repolarization and shortens the action potential but also decreases $Ca^{+2}$ entry during action potential. Decreased $Ca^{+2}$ entry has negative inotropic effect. High sympathetic nerve activity in ischemic hearts triggers cardiac dysrhythmias.

In chronic heart disease and heart failure, the action potential lengthens. The genetic abnormality of the delayed rectifier $K^+$ channels (long Q-T syndrome) that occur in chronic heart disease prolongs the action potential plateau and leads to $Ca^{+2}$ overload and afterdepolarization, which may in turn triggers arrhythmia.[77-80]

Antiarrhythmic drugs can alter the action potential of fast-response cells. β-adrenergic agonists increase the duration and amplitude of the plateau by increasing $Ca^{+2}$ currents. Sodium-channel blockers inactivate fast $Na^+$ channels and decrease the slope of phase 0. Potassium-channel blockers delay repolarization (phase 3) by blocking the $K^+$ channels.[77-80]



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***Slow response action potential.***

The slow response action potential is most often found in the SA and AV nodes. These cells have the ability to depolarize spontaneously, a property called automaticity.Unlike non-pacemaker action potentials, the action potential in nodal tissue has only 3 phases. Phase 0 is determined primarily by the currents through T- and L-type slow inward calcium channels.

The SA node does not involve fast $Na^+$ currents. The SA and AV nodal tissues depolarize spontaneously during phase 4 via the funny channels ($I_f$). During phase 4 and when membrane potential is about -60 mV, the funny channels ($I_f$) open and conduct slow, inward $Na^+$ currents causing the membrane potential to depolarize spontaneously. When the membrane potential reaches about -50 mV, the T- and L-type calcium channels open, consequently causing $Ca^{+2}$ influx and the membrane continues to depolarize until an action potential threshold is reached (usually between -40 and -30 mV). Repolarization (Phase 3) occurs as $K^+$ channels ($I_k$) open and the L-type calcium channels become inactivated and close.[77-80]

Although nodal tissue depolarizes spontaneously, its rate of firing is altered by many factors such as the ANS. The SA node is highly innervated by sympathetic and parasympathetic fibers. Parasympathetic (vagal) activation dominates over sympathetic influences at rest, while sympathetic activation dominates during stress and exercise. Acetylcholine released by vagal nerve decreases the SA activation rate by increasing $K^+$ and decreasing slow inward calcium and $Na^+$ currents. Norepinephrine released by sympathetic fibers increases pacemaker rate by decreasing $K^+$ and increasing slow inward calcium and $Na^+$ currents.[77-80]



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***Absolute and relative refractory periods.***

Refractoriness refers to the inability of cardiac tissue to be re-excited. During depolarization, the cell goes through a period in which it becomes refractory to subsequent depolarizing events. This period is generally divided into 2 phases: the absolute refractory period and the relative refractory period. The absolute refractory period involves phases 0, 1, 2, and part of phase 3. During absolute refractory period, no new action potential can be initiated, regardless of the magnitude of the stimulus. The absolute refractory period serves as a protective mechanism against reentry dysrhythmias.[77, 79]

During the relative refractory period, the $Na^{+}$ and $Ca^{+2}$ channels are closed but are capable of activation. Thus, only a stimulus that exceeds the normal threshold can initiate a subsequent depolarization. [77, 79]

Overall, action potential initiates organized sequence of contractions in the heart. The phases of action potential vary from region to region in the heart. The longest duration of these action potentials is found in the cells of Purkinjie fibers, which works as a safeguard against re-entrant dysrhythmias.

## Cardiac dysrhythmias

Cardiac dysrhythmias, any abnormality in normal cardiac rhythmic pattern, are common and important clinical problems in patients receiving MV or undergoing the process of weaning from MV.[17] Cardiac dysrhythmias result primarily from either abnormalities of impulse formation, impulse conduction, or both.[77, 79] Abnormal automaticity, triggered activity and reentry mechanisms are responsible for the most clinically important and potentially malignant dysrhythmias such as ventricular ectopic beats, ventricular tachycardia/fibrillation, atrial fibrillation/flutter, and supraventricular tachycardia. [82, 83] In addition, abnormalities of mechanical loading (i.e., increased intrathoracic vascular volume) can induce dysrhythmias through a mechano-electrical feedback mechanism.[46, 65, 67, 68, 70, 72, 73, 84]



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***Abnormal automaticity.***

Automaticity refers to the ability of cardiac cells to depolarize spontaneously and initiate an electrical impulse without the effect of external stimuli. [77-79, 81] Abnormal automaticity is an abnormal condition generated by sustained ventricular excitability and repetitive afterdepolarization.[77-79, 81] Conditions such as ischemia, hypoxia, acidosis, and hyperkalemia can induce abnormal automaticity.[77-79, 81]

Ischemia and hypoxia mainly interfere with the function of the $Na^+$-$K^+$ pump. Reduction in the amount of oxygen necessary for the pump operation, results in reduction of the resting membrane. When the resting membrane potential is reduced, the cell reach threshold more rapidly and becomes abnormally permeable to $Na^+$ during action potential phase 4, producing spontaneous depolarization.[77-79, 81] Dysrhythmia that may result from abnormal automaticity include premature atrial and ventricular extrasystoles (PACs, PVCs, respectively), and idioventricular rhythms.[77-79, 81]

***Triggered activity.***

Triggered activity is an abnormal condition of pacemaker and myocardial non-pacemaker cells in which the myocyte depolarizes during action potential phase 2, phase 3, or phase 4 after repolarization is complete.[77-79, 81] Resulting beats are called triggered beats as they are triggered by prior beats. Triggered activity is characterized by the occurrence of afterdepolarization. Afterdepolarizations that develop during phase 2 or 3 are called early afterdepolarization (EAD) and those that develop in phase 4 after repolarization is complete are called delayed afterdepolarization (DAD).[77-79, 81]

Early afterdepolarization that occurs during phase 2 or early in phase 3 results from activation of slow calcium channels. While EAD that occur late during phase 3 results from large inward $Na^+$ currents generated by calcium overload. [82, 83] Once an EAD reaches threshold, a second early beat "i.e., triggered beat" arises as result of preceding action potential. Each triggered beat may precede another abnormal impulse resulting in several abnormal beats.



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Early afterdepolarization can develop under conditions of hypoxia, acidosis, hypokalemia, hypomagnesemia, hypothermia, high $PCO_2$, and high concentrations of catecholamines, and develops in areas of stretch or mechanical injury. Early afterdepolarizations are more likely to give rise to serious dysrhythmias such as long QT syndrome, torsades de pointes, and polymorphic ventricular tachycardia.[77-79, 81]

High concentrations of catecholamines, digitalis, and hypokalemia trigger development of DAD and cause serious arrhythmias such as accelerated junctional rhythm and ventricular tachycardia in singles, pairs or paroxysms.[77-79, 81]

***Reentry.***

Reentry, a type of conduction abnormality, occurs when an impulse enters and reenters a previously depolarized area and depolarizes it again. [82, 83] The path over which the impulse travels to excite and re-excite a portion of cardiac tissue is called re-entrant circuit. Reentry is the mechanism of the vast majority of clinically relevant tachyarrhythmias.[77-79, 81] Reentry occurs in areas of unidirectional block, in which impulses conduct in one direction and reenter it again with low velocity to continue propagation in a circular manner, resulting in a run of premature beats or sustained tachycardia.

Conditions that induce reentry can be grouped under: 1) shortening of cell refractoriness caused by sympathetic stimulation, 2) lengthening of the conduction pathway such as in hypertrophy, and 3) slowing of impulse conduction as manifested during ischemia.[77-79, 81] Clinical arrhythmias that are caused by reentry mechanism include ventricular tachycardia, atrial fibrillation, atrial flutter, and Wolff- Parkinson-White syndrome.

***Stretch and mechano-electrical feedback mechanism.***

Mechano-electrical feedback is a term that describes electrophysiological changes caused by regional mechanical stretch or global hemodynamic over-load mediated by stretch- activated ion channels. The mechano-electrical feedback mechanism is characterized by shortening of action potential duration, a decrease in the resting diastolic potential, and development of EAD and ectopic beats.



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The mechano-electrical feedback mechanism may play a role in arrhythmogenesis in patients with impaired ventricular function or in regionally or globally impaired dilated hearts or in hearts subject to pressure /volume overload or failure.[85-89]

In general, arrhythmogenic conditions, such as hypoxemia, hypercarbia, acidosis, hypokalemia, hypomagnesemia, high concentrations of catecholamines and digitalis, myocardial stretch or mechanical injury trigger the mechanisms of abnormal automaticity, triggered activity and reentry.[82, 83, 90, 91]

## Heart rate variability

The autonomic nervous system (ANS) is an important component of the physiology of heart rhythm. A link between ANS alteration, specifically increased sympathetic activity and decreased parasympathetic activity (as reflected by decreased HRV), and the occurrence of dysrhythmias was demonstrated in numerous experimental and clinical studies.[35-42, 44, 92]

Heart rate variability is the analysis of beat-to-beat variation in heart rate. Variability of heart rate results, in large part, from ongoing changes in sympathetic and parasympathetic inputs to the SA node.

Heart rate variability is a noninvasive indicator of autonomic neural regulation of the heart,[93] and is used as a valuable diagnostic and risk stratifying strategy in patients with cardiac diseases as well in normal populations. Decreased HRV has been associated with increased mortality in patients with heart failure,[94] and acute myocardial infarction.[95, 96] In addition, HRV is considered a powerful predictor of sudden cardiac death and dysrhythmic events in patients with underlying cardiac dysfunction.[37, 42, 43, 97, 98]

***Heart rate variability and weaning from mechanical ventilation.***

Respiratory sinus arrhythmia (RSA) is a normal phenomenon that refers to the cyclical variation in heart rate during the respiratory cycle, such that the heart rate accelerates during inspiration and slows during expiration. Sinus arrhythmia is mainly mediated through changes in efferent vagal activity. Vagal activity is influenced by stretch receptors in the lung and by baroreceptors located in the carotid sinuses and aortic arch. Lung inflation that occurs during inspiration stimulates the vagal nerves in the lung and induces a reflex tachycardia. During expiration, increases in blood pressure stimulate baroreceptors and hence reflex bradycardia is seen.[99]



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Weaning, the process of transition from MV to spontaneous ventilation, is associated with alterations in ANS tone, reflected by decreased HRV especially in patients with underlying cardiovascular dysfunction and impaired compensatory mechanisms. Alteration in HRV during weaning and its relation to weaning outcome was investigated in both animals and human subjects. Shen et al.[34] analyzed HRV in 24 patients during transition from pressure support ventilation (PSV) to spontaneous breathing trial (SBT). The investigators found a significant decrease in LF and HF HRV in the group of patients who failed the weaning process, but not in the success group. In animal study, Frazier et al.[33] found a significant increase in VLF power and a significant decrease in HF power with exposure to a combination of pressure support and continuous positive airway pressure (PS+CPAP) in a group of six canines. The reduction in HF power could be explained as a result of the withdrawal of parasympathetic nervous system activity, increased respiratory rate and decreased tidal volume that occur during weaning. Frazier et al.[100] demonstrated that patients who failed their initial weaning trial had reduced HRV during ventilation and further decreased HRV during the weaning trial.

***Heart rate variability and dysrhythmias.***

Numerous investigators have demonstrated a significant relationship between reduced HRV, genesis of malignant ventricular dysrhythmias (Primarily ventricular fibrillation and ventricular tachyarrhythmias), and mortality. [35, 41-43, 45, 101] Clinical researchers have shown reduced HRV with a shift toward sympatho-vagal imbalance (i.e., increased sympathetic and/or reduced vagal tone) to occur before the expression of dysrhythmias.[39, 40]

An increase in parasympathetic tone is considered a protective mechanism for the heart. Increases in sympathetic tone are strongly associated with the genesis of ventricular dysrhythmias caused by the three electrophysiologic mechanisms: reentry, triggered activity, and automaticity.



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Most studies that describe a relationship between reduced HRV and occurrence of cardiac dysrhythmias were limited to patients with cardiovascular diseases especially heart failure, acute myocardial ischemia and myocardial infarction. [35, 36, 102] Studies have shown that imbalances toward adrenergic predominance are associated with susceptibility to dysrhythmia.[35, 36, 102] That is because sympathetic stimulation decreases ventricular refractoriness and increases myocardial excitability.

Numerous investigators reported significant alterations in ANS balance, with a shift toward increased sympathetic activity or decreased parasympathetic activity or both, and initiation of ventricular arrhythmias. Huikuri et al.[103] reported a significant decrease in HF power one hour preceding the onset of the ventricular tachycardia in patients with ischemic heart disease. Fei et al.[39] reported a significant increase in the LF/HF ratio immediately before the onset of ventricular tachycardia episodes. The investigators attributed the increase in the LF/HF to the decrease in parasympathetic activity rather than enhanced sympathetic activity in patients with heart diseases. In contrast, Hayashi et al.[40] reported that the increase in the LF/HF before the onset of ventricular tachycardia was attributed to the sympathetic dominance in patients without structural heart diseases. Several studies have shown a shift toward an increase in sympathetic tone or a loss of vagal tone before occurrence of paroxysmal atrial fibrillation[36, 102] and atrial flutter [104] in patients with underlying heart diseases.

***Heart rate variability measurement.***

The analysis of HRV is usually performed using commercial software. After appropriate confirmation of heart beats obtained with Holter recordings and filtering artifacts, a series of RR intervals (RR tachogram) is used to quantify HRV.[105] The RR interval (sometimes called normal-to-normal [NN] interval) is the time interval between the R waves of two consecutive normal beats. Traditionally, two major approaches are often used to measure HRV, time domain and frequency domain analyses. Several investigators used these two methods as complementary to each other.

***Time domain analysis.***

Time domain analysis is the simplest to perform. It is based on the statistical calculations of standard deviation of NN intervals, coefficient of variance, short-and long-term components of HRV. Time domain measures of HRV are defined in Table 2.1



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according to the recommendations of a Task Force Committee.[106] Commonly used time domain measures include standard deviation of normal RR interval (SDNN), the standard deviation of the average of NN intervals in all 5 min segments of the entire recording (SDANN), the square root of the mean of the sum of the squares of differences between adjacent NN intervals (MSSD), and the percentage of successive normal RR intervals that change by more than 50 ms compared to the total number of RR intervals (pNN50).

**Table 2.1: Time domain measures of heart rate variability**

| Variable | Statistical measures |
|---|---|
| SDNN [ms] | Standard deviation of all NN intervals |
| SDANN [ms] | Standard deviation of the average of NN intervals in all 5 min segments of the entire recording |
| RMSSD [ms] | Square root of the mean of the sum of the squares of differences between adjacent NN intervals |
| SDNN index [ms] | Mean of the standard deviations of all NN intervals for all 5 min segments of the entire recording |
| NN50 count | Number of pairs of adjacent NN intervals differing by > 50 ms in the entire recording |
| pNN50 [%] | NN50 count divided by the total number of all NN intervals |
| Triangular index | Total number of all NN intervals divided by the height of the histogram of all NN intervals measured on discrete scale with bins of 1/128 s |

*Frequency domain analysis.* Frequency domain analysis, or spectral analysis of HRV, is a technique that provides distinct measures of the vagal as well as the sympathetic modulation of the heart. Frequency domain measures of HRV are defined in Table 2.2 according to the recommendations of a Task Force Committee.[106]

**Table 2.2: Frequency domain measures of heart rate variability**

| Variable | Statistical measures |
|---|---|
| Total power [$ms^2$] | Variance of all NN intervals |
| ULF [$ms^2$] | Power in the ultra low frequency range ($\leq$0.003 Hz) |
| VLF [$ms^2$] | Power in the very low frequency range (0.003–0.04 Hz) |
| LF [$ms^2$] | Power in the low frequency range (0.04–0.15 Hz) |
| HF [$ms^2$] | Power in the high frequency range (0.15–0.4 Hz) |

ULF= Ultra low frequency; VLF= Very low frequency; LF= Low frequency; HF= High frequency



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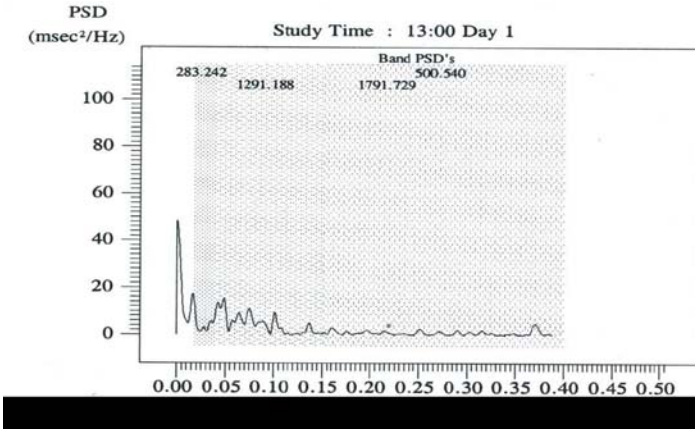
The technique of power spectral analysis involves decomposing the heart rate signal into a sum of sine waves as a function of frequency. The squared amplitude (i.e., power) of spectral components are displayed on a plot in which the power spectral density (PSD) of HRV versus frequency are poltted.[106] The total area under the curve of the PSD versus frequency plot is equal to the total statistical variance, or the power of the signal. These power distributions are calculated for defined frequency bands (Figure 2.1) and are interpreted as an estimate of the variance of the HRV signal within the bands of HF, LF, VLF, and ULF.[44, 106] The HF component (0.15-0.40 Hz) represents the vagal control to the heart,[93] modulated by respiration.[107-109] The LF (0.04-0.15Hz) component is more controversial and has contribution from both, vagal and sympathetic modulation of the heart.[94, 108, 110] But, many investigators proposed the LF as an index of sympathetic modulation.[93] Very low frequency power (0.003–0.04 Hz) represents the sympathetic activity. The ratio of LF to HF (LF: HF) is used as an index of sympatho-vagal balance of the ANS.[93, 106, 111] Short term recordings (up to 5 minutes) yield 3 peaks which are high frequency (HF), low frequency (LF), and very low frequency (VLF). While long term measurement (24 hrs) allows the measurement of ultralow frequency (VLF).

**Figure 2.1: Power spectral analysis of heart rate variability at baseline for one subject enrolled in the study**



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The PSD can be estimated using a parametric (autoregressive [AR]) or a nonparametric (Fast Fourier transform algorithm [FFT]) method.[106] The FFT is easier to use and it requires a priori selection of the frequency range of bands of interest.[112]

In summary, findings from clinical studies suggested that the ANS status is a major determinant and a contributing mechanism in the generation of cardiac dysrhythmias. Sympathetic activation and/or vagal withdrawal reflected as reduced HRV increased the risk of developing lethal dysrhythmias. Measurement of HRV provides significant information concerning the sympatho-vagal balance in the control of cardiovascular function.

## Weaning from Mechanical Ventilation

Mechanical ventilation is widely used to support ventilatory function in critically ill patients. However, prolonged MV is associated with a variety of risks and complications, which are associated with high morbidity and mortality rates, increased hospital and ICU length of stay, and costs.[1, 113] Therefore, weaning from MV as early as possible is an important goal for mechanically ventilated patients.

The appropriate time of weaning should be selected carefully. Needless and long MV increases the risk of ventilator-associated pneumonia, increased ICU length of stay, and mortality. Alternatively, premature weaning imposes severe stress on the respiratory and cardiovascular systems, which is associated with high complication rate, morbidity, and mortality.[8, 114]

Weaning is the process during which MV is gradually withdrawn and spontaneous breathing is resumed. This process represents approximately 41% of the total time spent on MV.[1, 115] At the 5th International Consensus Conference in Intensive Care Medicine, Tobin[116] described the weaning process as a continuum consisting of a series of six stages lasting from intubation until hospital discharge.

As a brief description of this process, weaning from MV begins with treatment of acute respiratory failure (stage 1). When the underlying cause of acute respiratory failure stabilizes or significantly improves, the potential for weaning is considered (stage 2) and daily assessment of the patient's readiness for ventilator discontinuation is considered (stage 3). Patients who meet the criteria for readiness to wean go through a spontaneous breathing trial (SBT) (stage 4). Those who can tolerate the trial and are able to follow



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commands are extubated (stage 5), while those who cannot are returned back to full ventilatory support for at least 24 h before performing a new trial. Patients who are extubated and cannot maintain spontaneous breathing for 24 to 72 hours after extubation are reintubated (stage 6).

Until recently, the decision to wean was based on physician's judgment and clinical experience. In the last few years, numerous clinical trials were conducted to establish evidence-based protocols to standardize the process of weaning. In some ICUs, protocols driven by respiratory therapists or ICU nurses are used for daily assessment to determine when patients are ready to start the weaning process. Compared to traditional care, weaning protocols resulted in better outcomes in some studies, such as significant decreases in the duration of MV, ventilator-associated pneumonia, weaning time, complication rate, ICU length of stay, costs, reintubation rate, and use of sedative infusion.[9, 117-120]

***Spontaneous breathing trials.***

Implementing an evidence-based weaning protocol involves two major steps: 1) daily assessment of readiness to wean; and 2) performing a SBT (Figure 2.2).

A SBT is an assessment test to determine if a patient needs to be continued on MV or can be successfully extubated.[18] A SBT should be considered as soon as the patient meets the criteria for readiness to wean.

Clinical criteria to determined readiness for weaning were recommended by the multisociety-sponsored evidence- based task force [18] and include (1) evidence of lung injury resolving or stabilizing; (2) adequate oxygenation, ($SpO_2 \geq 90\%$ with PEEP <5 to 8 $cmH_2O$, $FiO_2$ <0.4 to 0.5); (3) stable hemodynamics with minimal or no pressor treatment; and (4) ability to initiate spontaneous breathing effort.

Patients who meet the criteria of readiness to wean, undergo a SBT. The SBT can be conducted using low levels of pressure support (5 to7 $cmH_2O$), continuous positive airway pressure (CPAP), or a T-piece with supplemental oxygen [9, 10, 18, 121, 122] and lasts for at least 30 minutes, but no longer than 2 hours.[18, 122]



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During the SBT, the patient's respiratory pattern, hemodynamic status and comfort are monitored continuously. Although not all weaning protocols have the same guidelines, Many protocols consider the SBT successful if the patient has a PaO2/FiO2 ≥ 150 to 200, PEEP ≤ 6 cm H20, rapid shallow breathing index (RSBI) < 105, and stable hemodynamics with no or minimal vasopressors. Patients who successfully complete a SBT are considered for extubation if they are awake, able to protect their airway, demonstrate effective coughing strength and have minimal need for suctioning.122 Weaning success is defined as extubation, and spontaneous breathing with no ventilatory support for 48 hours following extubation.

Conversely, the SBT is defined as a failure if the patient experiences sustained tachypnea (RR > 35 breaths/min), respiratory distress, decreased oxygen saturation ($SpO_2$ < 90% with $FiO_2$ > 50%), RSBI >105, increase of heart rate > 20 beats/minute above baseline or systolic BP > 20 mmHg above baseline, new dysrhythmias, respiratory acidosis, agitation, diaphoresis, and depressed mental status.[122, 123] Those patients who fail a SBT are returned to full ventilatory support for at least 24 hours for respiratory muscle rest. Causes that contributed to weaning failure are identified and treated before performing another trial. Weaning failure is defined as a failed SBT and/or reintubation within 24-72 hours following planned extubation.[122]

Reintubation is considered if patients experience a decline in mental status, respiratory failure, or significant hemodynamic instability.[123, 124] Unfortunately, extubation failure and reintubation are associated with high risk of nosocomial pneumonia,[123] hospital mortality, prolonged ICU and hospital stays, increased need for tracheostomy and long term acute care.[8, 114, 115]



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***Modes of weaning from Mechanical Ventilation.***

Several modes and techniques are used to facilitate weaning including synchronized intermittent mandatory ventilation (SIMV), T-piece, CPAP and pressure support ventilation (PSV).[115] Synchronized intermittent mandatory ventilation is a ventilatory and weaning mode in which a preset of volume or pressure mandatory breaths are delivered in coordination with patient's spontaneous breaths effort (i.e., patient triggered). If the ventilator was not triggered by the patient, mandatory breaths are delivered according to the set rate. The goal of SIMV weaning is to gradually decrease the number of breaths delivered by the ventilator, allowing the patient to take more breaths of his or her own.[7]

Pressure support ventilation is a form of assisted ventilation, often used to decrease work of breathing. With PSV, the patient triggers the ventilator and the ventilator delivers a preset pressure of gas. Weaning using PSV consists of setting the inspiratory pressure and PEEP to achieve a spontaneous tidal volume of 10-12 ml/Kg; and the patient regulates the respiratory rate and tidal volume. During weaning, the pressure support level is decreased gradually according to patient's tidal volume and respiratory rate.[7] Pressure support ventilation is used during the weaning process in around 26% of patients.[115]

T-piece trials consist of alternating intervals of time on the ventilator with intervals of spontaneous breathing. A T-piece circuit consists of a T-shaped tube that is attached to the endotracheal or tracheostomy tube. One end of the tube is attached to an oxygen flow meter and the other end is open. The goal of using a T-piece is to administer supplemental oxygen while gradually decreasing the amount of time spent off the ventilator.[7]

Several investigators reported and compared the rate of weaning success, length of ventilation and duration of weaning attempts using different weaning modes. Brochard et al.[125] randomly assigned 456 patients to be weaned with PSV or SIMV, or T-piece. They found that patients exposed to PSV had shorter duration of weaning compared to the patients in the other two groups. Matic et al.[63] randomly assigned 260 patients to a 2-hour weaning trial using T-tube (n=110) or PSV (n=150). The investigators reported that 80 (73%) patients in the T-tube group and 120 (80%) patients in PSV group were



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successfully weaned and extubated. In patients with weaning difficulties, length of ventilation, time of weaning, and length of stay was significantly shorter ($p<0.001$) in patients who underwent a PSV trial. Esteban et al.[9] found that one daily trial or multiple daily trials of weaning using T-piece in 130 patients who failed the initial SBT considerably reduced the duration of weaning than either SIMV or PSV. Applying CPAP during spontaneous breathing improves right and left ventricular performance by decreasing its afterload, and improves oxygenation. Squadrone et al. [126] observed in a multicentre randomized controlled trial, that patients who developed severe hpoxemia after abdominal surgery and received CPAP plus oxygen therapy had lower rate of reintubation, occurrence of pneumonia, infection, and sepsis compared to oxygen supplementation alone. In conclusion, there is no better weaning mode. Weaning mode should be selected by physicians and respiratory therapists according to patient's status and needs.

***Predictors of weaning outcome.***

A number of parameters have been found to be associated with success or failure of ventilator discontinuation.[127] Some of these parameters were considered as predictors by several investigators. Predictors include age, medical diagnosis, hemodynamics, lung mechanics, gas exchange, severity of illness, duration of ventilation prior to weaning, and symptoms of diaphoresis and agitation. The relevance and significance of these predictors vary among different patient populations.

Several investigators reported some measurable parameters as significant predictive indices of weaning outcome. Some of these indices include $PaO_2/FiO_2$, respiratory system static compliance, maximum inspiratory pressure (MIP), mixed venous oxygen saturation ($SvO_2$),[75] work of breathing (WOB), gastric mucosal pH,[128] rapid shallow breathing index (RSBI), acute physiology and chronic health evaluation (APACHE score), and arterial blood gases.[122] For the purposes of this study, we focused on RSBI and severity of illness upon ICU admission as measured by APACHE score. That is because some investigators reported that RSBI >100 breaths/min/L [129, 130] and high APACHE score[129, 131] are significant predictors of weaning failure.



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The RSBI is the ratio of respiratory frequency to tidal volume ($f/V_T$) calculated during spontaneous breathing. The RSBI is affected by patient's underlying cardiovascular and respiratory status. Several investigators studied the significance of RSBI as a predictor of weaning outcome in different patient populations and controversial results were found. Some investigators reported that RSBI value <100–105 breaths·min$^{-1}$·L$^{-1}$ predicts a successful SBT with a reported sensitivity of 0.97 and specificity of 0.64.[132] while a value of >100 breaths/min/L[129, 130] predicts failed weaning trials. Other investigators reported that RSBI was not a significant predictor of weaning failure.[122, 133, 134]

The APACHE is a severity-adjusted methodology that predicts outcomes for critically ill adult patients. Twenty seven variables are collected for each patient. These variables include the diagnosis, age, vital signs (temperature, mean arterial pressure, heart rate, respiratory rate), and laboratory values (such as serum potassium, creatinine, albumin, bilirubin, white blood cell count, and hemtocrit). These data, in conjunction with comorbidities, are combined and used to formulate a predictive equation for each individual patient. These predictions are made for mortality (both ICU and hospital), length of stay (both ICU and hospital), ventilatory days, and the need for active treatment.[135-138]

The APACHE IV score (range 0-299) is formed by the sum scores of the acute physiology score (range from 0-252), chronic health score (range from 0-23) and age score (range from 0-24). The acute physiology score is the total number of points that the patient earns from disturbed physiology alone. Chronic health includes more than thirty chronic health items that affect the immune system. Some of these chronic health items include AIDS, acute or chronic myelogenous or lymphocytic leukemia, multiple myeloma, non-Hodgkin's lymphoma, solid tumor with metastasis, presence of an immunocompromised state (secondary to chemotherapy, radiation, or drug therapy), hepatic failure with cirrhosis and jaundice and ascites, UGI bleeding, encephalopathy, or coma, and diabetes mellitus.



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***Physiological determinants of weaning outcome.***

Weaning success is defined as extubation and spontaneous breathing with no ventilatory support for 48 hours following extubation.[9] Conversely, weaning failure is defined as a failed SBT and/or reintubation within 24-72 hours following extubation.[122, 139] Weaning failure occurs as a result of respiratory drive failure, impaired lung mechanics, diaphragmatic dysfunction, hypoxemia,[75] cardiovascular dysfunction, sepsis, and positive fluid balance in the 24 hours before weaning,[130] in addition to airway obstruction or excessive secretions and pneumonia.[123] Extubation failure may also be related to the same reasons.

Unfortunately, failed weaning trials and failed extubation, ultimately prolong the duration of MV. Up to one-third of patients experience difficult and prolonged weaning. Prolonged MV is defined as patients' need to ventilatory support for >72 hours or even more.[139, 140] Patients with difficult and prolonged weaning have higher incidence of ICU mortality than those patients who wean easily. The high mortality rate results from the underlying disease and/or complications associated with MV, especially ventilator-associated pneumonia.

## Summary

Up to 90% of patients admitted to ICUs require MV. The use of MV is associated with increased morbidity, mortality and greater financial costs. Thus, it is important to discontinue MV as soon as feasible. However, weaning from MV can produce hemodynamic alteration (i.e., intrathoracic vascular volume and flow), and alterations in ANS (reflected by decreased HRV). Decreased HRV can cause dysrhythmias especially in patients with underlying cardiovascular disease. Cardiac dysrhythmias can decrease cardiac output, induce myocardial ischemia, worsen respiratory failure and thus negatively affect length of MV.

There is paucity of research about cardiac dysrhythmias during weaning from MV and its impact on length of MV. Studying and identifying cardiac dysrhythmias that occur during MV and weaning, and determining the role that dysrhythmias might play in length of MV are vital in order to provide appropriate care and management for mechanically ventilated patients.

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CHAPTER III:
MATERIALS AND METHODS

## Design

In this longitudinal, repeated measures design, we collected data to evaluate the impact of changes in HRV during weaning from MV on the development of cardiac dysrhythmias and the impact of cardiac dysrhythmias on length of ventilation. Data were collected on the following variables: 1) HRV (measured by examination of the beat-to-beat variability of heart rate continuously collected using Holter recording techniques and evaluated in the frequency domain); 2) dysrhythmias (measured by continuously collected ECG data using Holter recording techniques); and 3) length of MV. Data were measured for each subject at baseline during MV and during the initial weaning trial from MV. Comparison of each subject's baseline data with weaning data allowed each subject to serve as their own control.

## Sample and Setting

A convenience sample of 35 adult patients was enrolled from the medical intensive care unit (MICU), surgical intensive care unit (SICU), cardiac care unit (CCU) and trauma intensive care unit (TICU) at the University of Kentucky Chandler Medical Center (UKMC), Lexington, Kentucky.

The MICU is an 8-bed unit. It provides care for a mean monthly census of 40 patients. About 67% of these patients required MV support during their ICU stay. The CCU is an 8-bed unit. An average of 37 patients per month is admitted to the CCU. Approximately, 44% of admitted patients required MV for an average of 6.1 days. The SICU is a 6-bed unit. An average of 33 patients per month is admitted to the SICU. Around 67% of admitted patients required MV for an average of 11.7 days. The TICU is an 8-bed unit. An average of 35 patients per month received care in TICU. Around 64% of admitted patients require MV for an average of 6.5 days.

Patients of both genders and all races/ethnicities who were 18 years of age or older and received MV for a minimum of 24 hours via endotracheal tube were eligible to be included. The exclusion criteria for this study were patients who: 1) had a myocardial infarction within the past 3 months or were admitted with a myocardial infarction; 2) were undergoing cardiac surgery or underwent cardiac surgery within the last 3 months; 3) had neurological trauma or stroke within the last 3 months or were admitted with



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neurological trauma or stroke; 4) were in atrial fibrillation or had bouts of atrial fibrillation; 5) had a pacemaker or implanted cardioverter defibrillator; or 6) had a pulmonary artery catheter or central venous catheter that was not in proper position as confirmed by radiography. These exclusion criteria make patients more vulnerable to develop dysrhythmias and induce changes in HRV because of their underlying disease process, and not because of the effect of MV or weaning process.

## Ethical Review

This study was approved by the Institutional Review Board (IRB) at the University of Kentucky (Appendix A).

## Measures

### *Dysrhythmias*

The number of times the heart beats each minute and the rhythm of these beats, were evaluated by analysis of cardiac electrical activity using a 3-lead, 24-hour ECG Holter recorder (459 Del Mar, Irvine, CA) with leads I, II, and $V_2$. Holter recordings were scanned using a Del Mar Holter Analysis System (453A, Irvine, CA) in semiautomatic mode with operator confirmation of all beat types. The timing of QRS complex onset, as well as all beat types and artifact, were manually confirmed. Data about the number of ventricular, and supraventricular ectopic beats; and number of episodes of ventricular tachycardia/fibrillation, and atrial fibrillation/flutter were collected.

These dysrhythmias were chosen because of their potential for serious impact upon hemodynamics and oxygen delivery and potential effect on weaning outcome and length of MV. Number of occurrences of each type of dysrhythmias, with the exception of atrial fibrillation/flutter and ventricular tachycardia, were referenced as beats per hour. Episodes of atrial fibrillation/flutter and ventricular tachycardia/fibrillation were referenced as present or not, and occurring after initiation of weaning or not.

### *Heart rate variability (HRV)*

Heart rate variability refers to beat-to-beat fluctuations in heart rate and is a noninvasive indicator of autonomic tone. Heart rate variability is a predictor of risk of sudden cardiac death in patients with diabetes and myocardial infarction.[141] For this study, frequency domain measures were used to reflect HRV. Frequency domain analysis or power spectral analysis decomposes a signal into a sum of sine waves of different



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amplitudes and frequencies, and then presents the squared amplitudes of the sine waves as a function of frequency. The following spectral components were measured in this study: high frequency (0.15 to 0.40 Hz) which represents an index of parasympathetic activity; low frequency (0.04 to 0.15 Hz) which represents parasympathetic and sympathetic inputs, and very low frequency component (< 0.04 Hz), which represents sympathetic activity.

Using the Del Mar HRV analysis software, the recording periods were divided into consecutive, non-overlapping 5-min epochs. Artifacts, atrial fibrillation/flutter and abnormal complexes along with the preceding and succeeding R-R intervals were excluded from the analysis and linear interpolation was used to estimate the instantaneous heart function. Segments in which more than 80% of its R-R intervals were not normal were excluded and a Hanning window applied. A fast Fourier transformation was then done. Heart rate variability changes during weaning were assessed by averaging and comparing power spectra from the 5-min epochs during 24 hour baseline period of MV, and during the first two hours of the weaning process.

***Length of ventilation***

Length of MV was measured as the number of days the patient required MV. It started upon intubation and ended with MV discontinuation either by extubation or by receiving oxygen supplementation through tracheostomy. Data about length of ventilation were abstracted from patient medical record and respiratory therapy records.

***Socio-demographic characteristics and clinical data***

Demographic data including age, gender, marital status, type of insurance, ethnicity, height and weight were abstracted from the patient medical record .

Clinical data including the past and current history of MV, history of cardiac diseases and dysrhythmias, reason of hospitalization, hospital and ICU length of stay before intubation were collected at baseline upon enrolling the patient into the study. Data about APACHE IV score, physiological status, pulmonary status, cardiovascular status, and intake and output status were collected from the medical record twice, for baseline during MV and for the weaning day (Appendix B).



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The institutional review board approval was obtained from the University of Kentucky Medical Institutional Review Board for the conduct of this study. Each morning, the PI evaluated all patients receiving MV for inclusion criteria. Candidate patients who met the inclusion criteria were approached and recruited. The study purpose, data collection protocol, risks and benefits were explained and discussed with a patient surrogate. In this study, the patient surrogate provided the informed consent. The patient was assessed daily for competence to provide informed consent during the study period. Once the patient became competent, the study purpose, data collection protocol, risks and benefits were explained for the patient in the presence of his/her surrogate, and oral consent was obtained.

The data collection timeline is described in Figure 3.1. At baseline, upon enrollment in the study, demographic and baseline clinical data were abstracted from the medical record. Skin on the chest was prepared to attach the electrodes for Holter monitoring. Preparation included carefully clipping of hair in areas where electrodes were to be placed if needed and/or cleaning the skin with alcohol to remove skin oils.[142] Holter monitor electrodes for 3-leads were placed in the appropriate configuration as follows: (1) left anterior axillary line, $6^{th}$ rib; (2) two centimeters right of the xiphoid process on the rib; and (3) left mid- clavicular line, $6^{th}$ rib). Following visual confirmation of an adequate signal, a 24-hour continuous ECG recording was started.

All patients enrolled in the study were evaluated every morning for readiness to wean by respiratory therapists and an attending physician. Readiness to wean was determined based on the following criteria: (1) resolution of the reason for which the patient was intubated; (2) adequate oxygenation, ($SpO_2 \geq 90\%$ with PEEP <5 to 8 $cmH_2O$); (3) stable hemodynamics with minimal or no pressor treatment; (4) pH > 7.35; (5) patient temperature < 102 F; and (6) minimal to no sedation. Once the first weaning trial was prescribed by the attending physician, the PI attached a Holter monitor device as described earlier. ECG was continuously recorded during the weaning trial. Clinical data collected at baseline were collected again during weaning from the medical record. All data collection records and ECG records were coded by a subject number and stored in a locked file cabinet at the College of Nursing research area.



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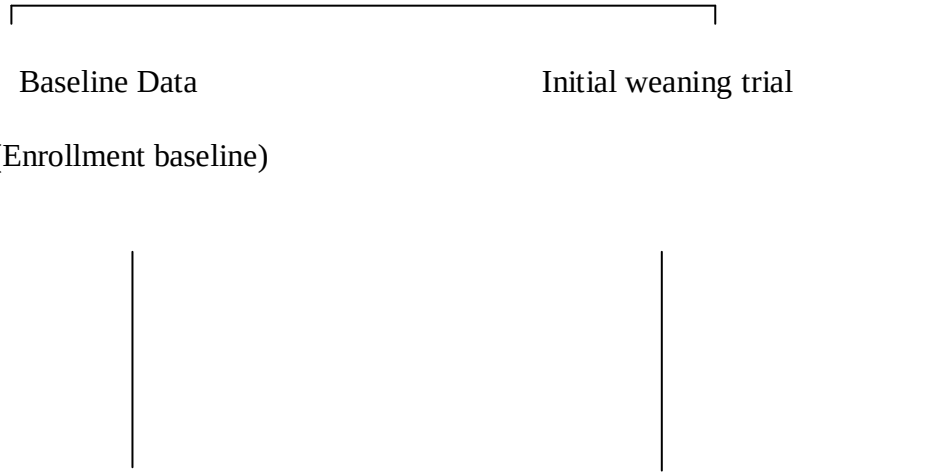
The PI reviewed all data forms for completeness and legibility to decrease missing data and possible erroneous entries and other problems. All data were collected on data forms developed by a team of researchers studying MV and weaning. All data collected were kept in password-protected files, entered and organized in dated folders stored on the College of Nursing secure server.

**Figure 3.1: Data Collection Timeline**




HRV = Heart rate variability



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## Data Analysis

Before conducting analyses to test specific aims, data were cleaned. Frequency distributions were developed for all variables to detect and correct erroneous codes. Extreme, but possible codes were verified. Skewness and kurtosis were computed to identify those variables that might benefit from transformation to reduce any marked deviations from the normality assumptions of linear model analyses. Data analyses were performed using SPSS for Windows, version 16.0 (Chicago, IL). Descriptive statistics were used to characterize the sample. To further characterize the sample, repeated-measures analysis of variance was used to determine differences across time in the variables of interest measured at baseline and during weaning. Differences were considered significant at an a priori $\alpha$ level of .05 or less.

Specific Aim 1: To determine the relationship of ANS tone (reflected by HRV) during weaning to the development of cardiac dysrhythmias after controlling for baseline HRV measured during MV.

Multiple linear regression was used to determine the relationship of HRV during weaning to the development of cardiac dysrhythmias. In order not to violate the assumptions of multiple regression analysis, ratio scores of independent variables were used to narrow the number of variables forced in each model. The ratio scores (i.e., average score at weaning divided by average score at baseline) of high frequency (HF), low frequency (LF), and very low frequency (VLF) were regressed separately on the mean score of occurrence of ventricular and supraventricular ectopic beats during weaning after controlling for APACHE IV score during weaning. In previous published studies, investigators used the value of APACHE score upon admission. In this study, the value of APACHE IV score during weaning was used to evaluate its impact on data collected during weaning. However, it is worthy to mention that there were no differences in results obtained using either the value of APACHE score on admission or during weaning. Separate models were developed to test the relationship of HRV during weaning in the frequency domain (HF, LF, and VLF frequencies) with each of the following outcomes: 1) number of ventricular ectopic beats per hour; and 2) number of supraventricular ectopic beats per hour. No stepping procedure was used to test these models.



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Specific Aim 2**:** To determine the relationship between the occurrence of dysrhythmias during weaning and length of MV. Pearson correlation coefficients were computed length of MV, APACHE score at weaning, rapid shallow breathing index (RSBI), cumulative fluid balance based on 24 hour intake and output, and $PaO_2/FiO_2$. The length of MV was only correlated with APACHE score during weaning. Therefore, the value of APACHE score during weaning was controlled for in multiple regression models as described below.

Multiple linear regression was used to evaluate the predictive power of cardiac dysrhythmias for length of MV, controlling for APACHE IV score during weaning. Variables were entered in two blocks: 1) the first block contained the variable to be controlled (APACHE IV score during weaning); and 2) the second block contained the number of ventricular ectopic beats per hour, and the number of supraventricular ectopic beats per hour separately. No stepping procedure was used to test these models.

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# CHAPTER IV: RESULTS

## Sample Characteristics

A total of 35 patients with a mean age of 53.3 years were enrolled in the study. Of the sample, 23 (66.7%) were men, 34 (97%) were Caucasian, 17 (49%) were married, 23 (65%) were supported with government insurance, 11(31%) had a history of chronic pulmonary disease, 12 (38%) had received MV during a previous hospital admission and 17 (49%) had a history of cardiovascular disease. Of those patients who reported the presence of underlying cardiovascular disease, 16% had a history of cardiac dysrhythmias. Patients enrolled in the study had different medical diagnoses upon admission such as neoplasms, pulmonary diseases, gastrointestinal conditions, liver and kidney diseases. Characteristics of the sample are summarized in Table 4.1.

The majority of patients (72%) were mechanically ventilated for pulmonary conditions (e.g., acute respiratory distress syndrome, acute respiratory failure, pneumonia, and aspiration). Of the 35 patients enrolled in this study, 3 patients (8.6%) died, and 2 patients (5.7%) required tracheostomy without a weaning trial. Two-thirds of the 30 patients 23 (77%) failed the initial weaning trial and underwent an average of 2.8 weaning attempts (range 0-11 trials) before successful weaning. Patients were mechanically ventilated an average of 11.6 ± 8.4 days and stayed in ICU an average of 15.6 ± 9.2 days.



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**Table 4.1: Characteristics of the sample (n=35)**

| Characteristic | Frequency (%) | Mean± SD OR Median ($25^{th}$, $75^{th}$ percentile) |
|---|---|---|
| Age, yr | | 53.3 ±14.6 (Range 22-84) |
| Sex | | |
| Male | 23 (66.7) | |
| Female | 12 (34.3) | |
| Ethnicity | | |
| Caucasian | 34 (97.1) | |
| African- American | 1 (2.9) | |
| Marital status | | |
| Married | 17 (48.6) | |
| Single/divorced/widowed | 18 (51.4) | |
| Type of insurance | | |
| Government | 23 (65.7) | |
| Commercial and HMO | 10 (28.6) | |
| Self | 2 (5.7) | |
| History of pulmonary diseases | | |
| Yes | 11 (31) | |
| No | 24 (69) | |
| History of mechanical ventilation | | |
| Yes | 12 (37.5) | |
| No | 20 (62.5) | |
| History of cardiovascular disease | | |
| Yes | 17 (49) | |
| No | 18 (51) | |
| History of cardiac rhythm disturbances | | |
| Yes | 5 (16) | |
| No | 26 (84) | |
| Admission Diagnosis | | |
| Pulmonary diseases | 6 (17.4) | |
| Cardiac diseases | 1 (2.9) | |
| Liver and kidney conditions | 5 (14.5) | |
| Gastrointestinal conditions | 9 (26.1) | |
| Nervous system conditions | 4 (11.6) | |
| Trauma | 4 (11.6) | |
| Other | 6 (17.4) | |



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**Table 4.1 (Continued): Characteristics of the sample (n=35)**

| Characteristic | Frequency (%) | Mean± SD OR Median ($25^{th}$, $75^{th}$ percentile) |
|---|---|---|
| Hospital length of stay prior to ICU admission, days | | 1 (0, 2)<br>(Range 0-52) |
| Hospital length of stay prior to intubation, days | | 0 (0, 1)<br>(Range 0-52) |
| Reason for current ventilation | | |
| Pulmonary | 25 (72.5) | |
| Neurologic | 4 (11.6) | |
| Surgical | 6 (17.4) | |
| Results of initial weaning trials (n=30)<br>Success<br>Failure | <br>7 (23)<br>23 (77) | |
| Number of weaning trials (n=30) | | 2.8 ± 2.6<br>(Range 0-11) |
| Length of mechanical ventilation, days | | 11.6 ± 8.4<br>(Range 2-33) |
| Length of hospital stay, days | | 28.9 ± 21.9<br>(Range 9-101) |
| Length of ICU stay, days | | 15.6 ± 9.2<br>(Range 3-46) |
| Length of ICU stay prior to tracheostomy (n=7), days | | 13.3 ± 6.9<br>(Range 5-23) |

## Changes in Clinical Characteristics

Clinical characteristics at baseline during MV and at the initial weaning trial were compared using repeated measured ANOVA and are summarized in Table 4.2. Of the 35 patients enrolled in this study, 5 patients (3 died, and 2 required tracheostomy before receiving any weaning trial) were excluded from further data analysis. In addition, because some laboratory data were not ordered similarly, numbers of patients available for baseline and weaning data points were different across the variables.

Of those clinical variables compared (Table 4.2), the Glasgow coma score (GCS), arterial oxygen saturation ($SaO_2$), levels of calcium and magnesium, RBC count, hemoglobin and hematocrit, and cumulative fluid balance on weaning day differed significantly from those measured at baseline. The mean GCS increased significantly from 8.7 at baseline to 10.3 at the time of weaning ($p = 0.001$), indicating an



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improvement in level of consciousness. The mean APACHE IV score at baseline was 69.8, demonstrating a high severity of illness in this sample. The mean APACHE IV score on the weaning day (60.97) was not different of the value measured at baseline (p= .07). The mean $SaO_2$ increased significantly from 95.93% at baseline to 97.67% at the time of weaning (p = 0.02). The baseline mean level of calcium (7.56 mg/dl) and magnesium (1.83mg/dl) increased significantly to 7.89 mg/dl and 2.02 mg/dl, respectively, at weaning time (p < 0.05). Also, RBC count, hemoglobin, and hematocrit decreased significantly by the time of weaning trial (p = 0.05). On weaning day, mean positive fluid balance was significantly higher than at baseline (15340 ± 13765 mL versus 12364 ± 10559 mL, p < 0.05).

**Table 4.2: Comparison of patient clinical data at baseline during MV and on the day of initial weaning trial**

| Variable | n | Baseline MV | | Weaning day | | p |
|---|---|---|---|---|---|---|
| | | Mean ± SD | Range | Mean ± SD | Range | |
| Patient's temperature, F | 30 | 98.99 ± 1.41 | 96.2-101.8 | 98.96± 1.72 | 95.9-103.4 | 0.94 |
| Glasgow Coma Score | 30 | 8.7 ± 2.28 | 3-11 | 10.3 ± 1.26 | 6-14 | 0.001 |
| APACHE IV score | 30 | 69.8 ± 25.7 | 26-125 | 60.97 ± 20.36 | 16-111 | 0.07 |
| ABGs | | | | | | |
| pH | 28 | 7.4 ± 0.08 | 7.21-7.55 | 7.41 ± 0.07 | 7.26-7.58 | 0.21 |
| $PaO_2$, mmHg | 28 | 97.3 ± 39.00 | 34-243 | 109.52 ± 35.59 | 34-179 | 0.12 |
| $PaCO_2$, mmHg | 28 | 35.3 ± 10.08 | 23-71 | 35.44 ± 10.26 | 18-69 | 0.93 |
| Bicarbonate, mmol/L | 28 | 21.22 ± 6.05 | 11-43 | 21.96 ± 5.71 | 12-42 | 0.25 |
| $SaO_{2,\%}$ | 28 | 95.93 ± 3.66 | 87-100 | 97.67 ± 1.92 | 93-100 | .02 |
| Serum glucose, mg/dl | 30 | 106.9 ± 17.81 | 77-155 | 121.10 ± 47.47 | 62-282 | .12 |
| Serum sodium, mmol/L | 30 | 138.97 ± 5.54 | 127-150 | 139.03 ± 4.14 | 131-148 | .93 |



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**Table 4.2 (Continued): Comparison of patient clinical data at baseline during MV and on the day of initial weaning trial**

| Variable | n | Baseline MV | | Weaning day | | p |
|---|---|---|---|---|---|---|
| | | Mean ± SD | Range | Mean ± SD | Range | |
| Serum pot assium, mmol/L | 30 | 3.92 ± 0.61 | 2.9-5.7 | 3.9 ± 0.65 | 3-6.2 | .83 |
| Serum calcium, mg/dl | 30 | 7.56 ± 0.77 | 5.3-9.3 | 7.89 ± 0.84 | 5.3-9.3 | .02 |
| Serum magnesium, mg/dl | 19 | 1.83 ± 0.44 | 1.3-3.6 | 2.02 ± 0.42 | 1.4-3.1 | .007 |
| Serum phosphorus, mmol/L | 18 | 3.93 ± 1.97 | 1.1-10.1 | 3.46 ± 1.18 | 1.9-6.2 | .26 |
| Serum chloride, mmol/L | 29 | 109.68 ± 8.08 | 90-129 | 108 ± 7.21 | 91-120 | .47 |
| Serum creatinine, mg/dL | 30 | 1.86 ± 2.05 | .43-9.80 | 1.55 ± 1.25 | .44-5.89 | .14 |
| Blood urea nitrogen, mg/dL | 29 | 27.65 ± 28.02 | 5-138 | 27.17 ± 19.70 | 5-80 | .41 |
| Serum albumin, g/L | 11 | 1.80 ± 0.50 | .9-2.7 | 1.96 ± 0.59 | 1-3.8 | .28 |
| Serum total bilirubin, g/dL | 11 | 2.69 ± 1.82 | .3- 7.6 | 2.15 ± 1.44 | .4- 5 | .21 |
| White blood cells, K/uL | 30 | 14.6 ± 7.55 | 1.5-32 | 12.77 ± 5.53 | 3.5-23.9 | .09 |
| Red blood cells, M/uL | 30 | 3.36 ± 0.54 | 2.05- 4.68 | 3.18 ± 0.30 | 2.64- 3,78 | .04 |
| Platelets, K/uL | 30 | 180.07 ± 114.22 | 34-483 | 205.83 ±180.62 | 18-962 | .44 |
| Hemoglobin, g/L | 30 | 10.11 ± 1.68 | 6.9-14 | 9.60 ± 0.94 | 7.8-11.4 | .05 |
| Hematocrit, % | 30 | 29.07 ± 4.75 | 20.3- 41.5 | 28.04 ± 2.64 | 24- 33.2 | .05 |
| Cumulative fluid balance, mL | 30 | 12364.39 ± 10558.67 | -1431.40- 42406.00 | 15340.06 ± 13764.52 | -528.40- 52804.00 | .03 |



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## Changes in Respiratory Mechanics

In this study, 27 patients out of 30 were exposed to a combination of PS (8-15 cm $H_2O$) and CPAP 5 cm $H_2O$ (PS+CPAP) during weaning trial. Three patients self-extubated and received supplemental oxygen through either a partial rebreathing or non-rebreathing mask.

Respiratory mechanics were measured at baseline during MV and during weaning trial. Respiratory rate (total and spontaneous), peak and mean airway pressures were significantly different from baseline values (Table 4.3). There was no differences in RSBI for patients who failed weaning (57.05± 36.25), and patients who had successful weaning trial (24.00± 7.94); t (21) = 1.54, p= .14.

**Table 4.3: Comparison of respiratory characteristics at baseline during MV and during the initial weaning trial**

| Variable | n | Baseline MV Mean± SD | Weaning (PS+CPAP) Mean± SD | P |
|---|---|---|---|---|
| $V_t$, ml/min | 25 | 526 ± 192.47 | 476.32 ± 151.26 | .26 |
| $FiO_2$, proportion of 1.0 | 29 | 0.47 ± 15.38 | 0.42 ± 12.22 | .14 |
| Total RR, breaths/min | 30 | 17.57 ± 4.85 | 21.73 ± 7.52 | .01 |
| Spontaneous RR, breaths/min | 30 | 3.63 ± 5.68 | 21.73 ± 7.52 | < 0.001 |
| PEEP, cm $H_2O$ | 27 | 6.74 ± 4.71 | 5.00 ± 0.00 | .06 |
| Airway pressure | | | | |
| Peak | 24 | 29.38 ± 8.88 | 18.13 ± 6.40 | < 0.001 |
| Mean | 24 | 14.60 ± 9.17 | 9.34 ± 3.20 | .007 |

$V_t$ = Tidal volume; $FiO_2$= Fraction of inspired oxygen; RR= respiratory rate; PEEP= Positive end-expiratory pressure.

## Changes in Cardiac Rhythm

Cardiac rhythm data were collected at baseline for 24- hours. During the initial weaning trial, cardiac rhythm data were continuously recorded 1- hour before and during weaning trial up to 24 hours. For the purpose of this study, data of cardiac rhythm was reported for the first 2 hours after initiation of the first weaning trial. All subjects (n=35) had complete electrocardiographic data at baseline. Two data records obtained during weaning could not be analyzed because of high T wave amplitude. Electrocardiographic data during weaning were collected from 25 patients only because 3 patients died, 2 patients had tracheostomy before weaning and 3 patients self extubated. In addition,



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weaning trials for another 2 patients were missed by the investigator. One patient had a single episode of ventricular tachycardia during weaning; none had ventricular or atrial fibrillation. All patients experienced either ventricular or supraventricular ectopic beats or both. The mean supraventricular ectopic beats per hour during weaning was significantly higher than the mean at baseline; the mean of ventricular ectopic beats per hour did not change (Table 4.4).

**Table 4.4: Comparison of cardiac rhythm at baseline during MV and during the initial weaning trial (n=25)**

| Cardiac Rhythm | Baseline Mean ± SD | Weaning Mean ± SD | p |
|---|---|---|---|
| Mean supraventricular beats/hour | 40 ± 82.16 | 366± 1726.32 | < 0.001 |
| Mean ventricular beats/hour | 15 ± 37.4 | 14 ± 27.24 | .68 |

Comparisons of the mean of supraventricular ectopic betas at baseline and during weaning for all patients and per individual patients (n=25) are shown in Figures 4.1and 4.2 respectively. Comparisons of the mean of ventricular ectopic betas per hour at baseline and during weaning for all patients and per individual patients (n=25) are shown in Figure 4.3 and 4.4 respectively.

**Figure 4.1: Comparison of mean supraventricular ectopic at baseline and during weaning for all patients (n=25)**

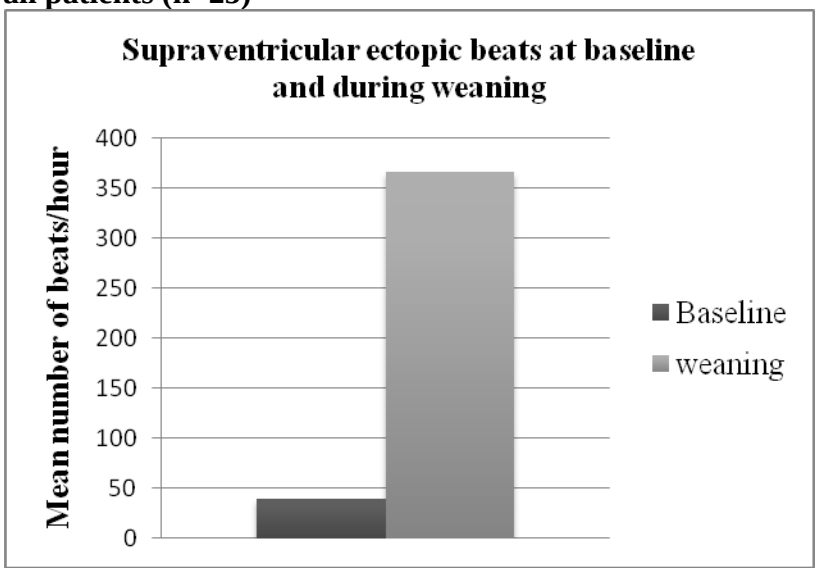




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**Figure 4.2: Comparison of mean supraventricular ectopic at baseline and during weaning per individual patients (n=25)**

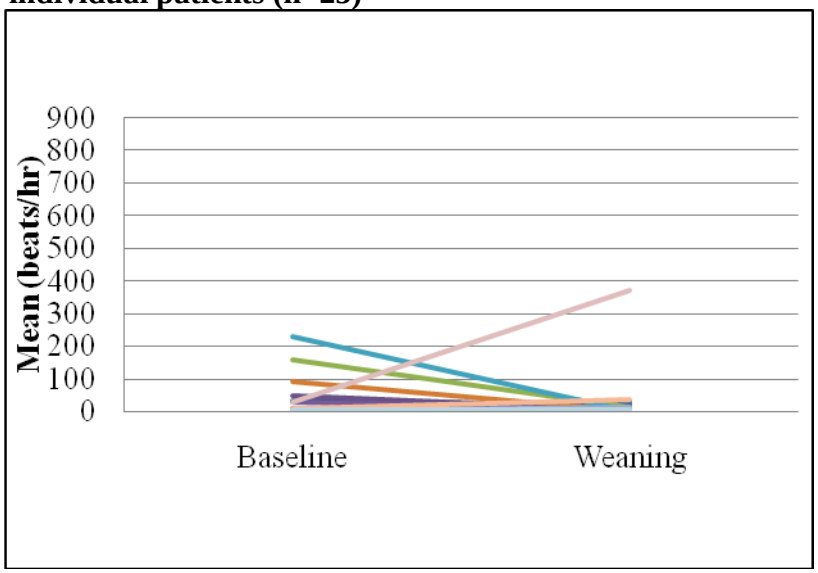


**Figure 4.3: Comparison of mean ventricular ectopic at baseline and during weaning for all patients (n=25)**

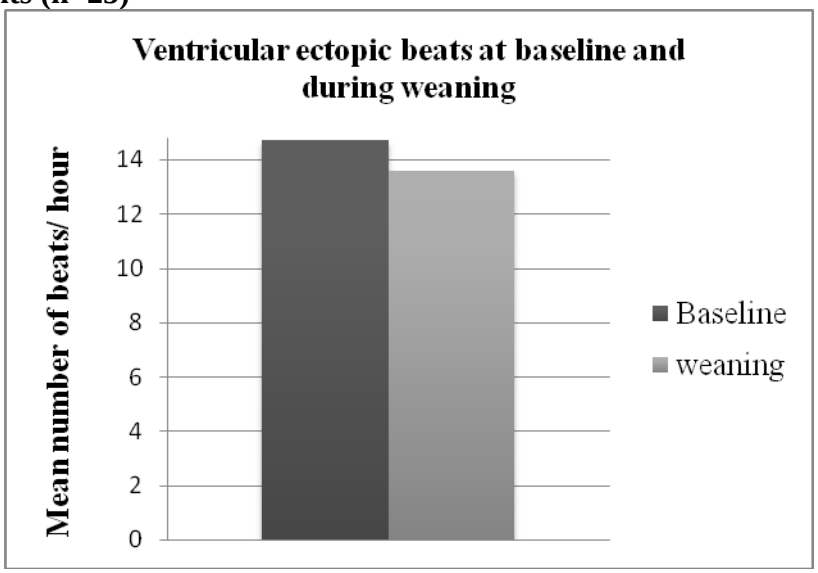




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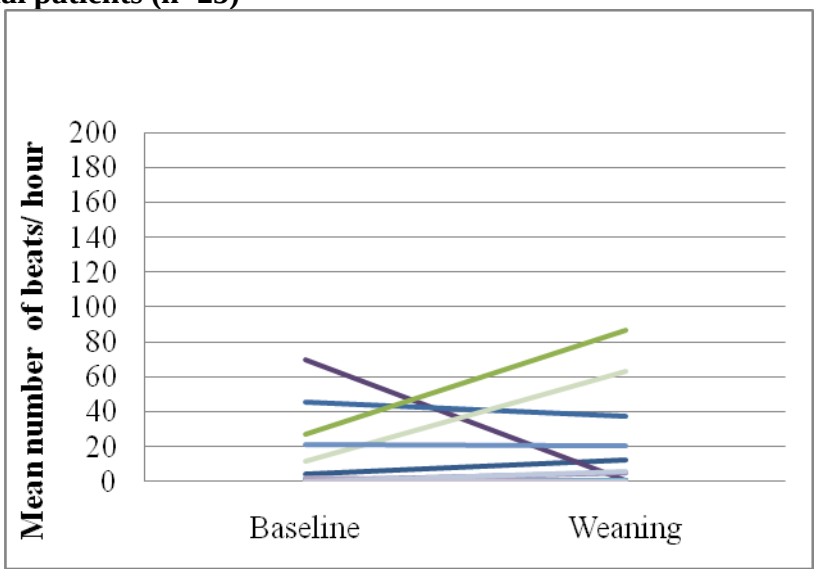
**Figure 4.4: Comparison of mean ventricular ectopic at baseline and during weaning per individual patients (n=25)**




## Changes in Heart Rate Variability (HRV)

The 5-min segments in which 80% of R-R intervals were normal were analyzed for 22 patients at baseline during MV and during the initial weaning trial. Out of the 22 patients, 5 patients had a successful weaning trial and 17 patients failed the trial.

Compared to baseline values, there were no changes in very low frequency (VLF) power and high-frequency (HF) power; but significant increases in low-frequency (LF) with exposure to PS + CPAP during weaning trial ($p \leq 0.05$) as shown in Table 4.5.

**Table 4.5: Heart rate variability at baseline and during the initial weaning trial (n=22)**

| Variable | Baseline Mean± SD | Weaning Mean± SD | p |
|---|---|---|---|
| VLF | 79.41 ± 109.97 | 111.09 ± 139.64 | .06 |
| LF | 82.86 ± 126.43 | 202.62 ± 391.27 | .04 |
| HF | 78.84 ± 108.99 | 50.16 ± 71.85 | .18 |

VLF= Very low frequency; LF= Low-frequency; HF= High-frequency



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Patients who had a successful weaning trial had no change in VLF, LF, and HF power (Table 4.6). Patients who had a failed weaning trial had significant increases in LF power and significant decreases in HF power (Table 4.7).

**Table 4.6: Heart rate variability of patients who had successful weaning trial at baseline and during weaning trial (n=5)**

| | **Baseline Mean ± SD** | **Weaning Mean ± SD** | **P** |
|---|---|---|---|
| VLF | 105.56 ± 142.66 | 63.46 ± 57.88 | .39 |
| LF | 151.45 ± 221.09 | 109.98 ± 97.92 | .62 |
| HF | 55.1 ± 55.54 | 104.49 ± 137.13 | .33 |

VLF= Very low frequency; LF= Low-frequency; HF= High-frequency

**Table 4.7: Heart rate variability of patients who failed the initial weaning trial at baseline and during weaning trial (n=17)**

| | **Baseline Mean ± SD** | **Weaning Mean ± SD** | **P** |
|---|---|---|---|
| VLF | 72.88 ± 103.76 | 122.99 ± 152.24 | .06 |
| LF | 66.96 ± 91.63 | 230.78 ± 433.92 | .04 |
| HF | 107.81± 141.15 | 45.30 ± 55.08 | .04 |

VLF= Very low frequency; LF= Low-frequency; HF= High-frequency



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Comparisons of HRV at baseline and during weaning for the whole sample (n=22), and per individual patients are displayed in Figures 4.5 - 4.8.

**Figure 4.5: Comparison of heart rate variability at baseline and during weaning for all patients (n=22)**

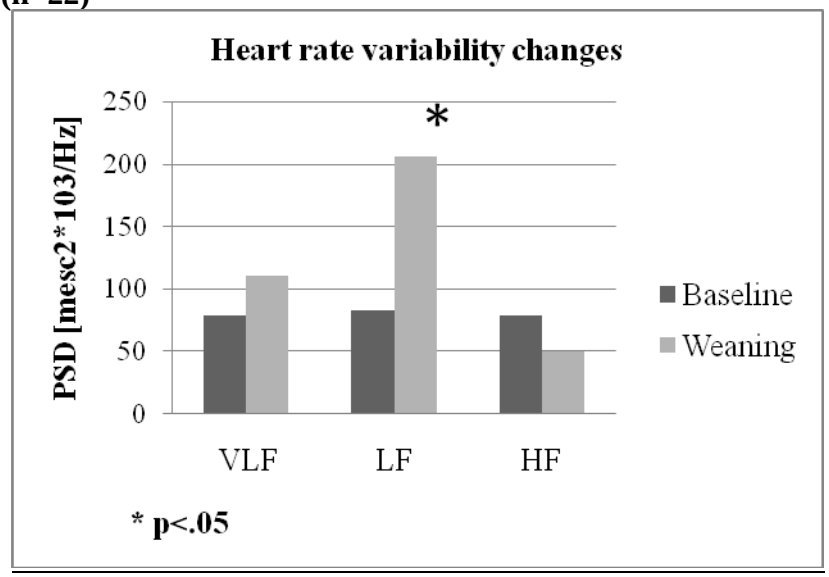


**Figure 4.6: Comparison of VLF at baseline and during weaning per individual patients (n=22)**

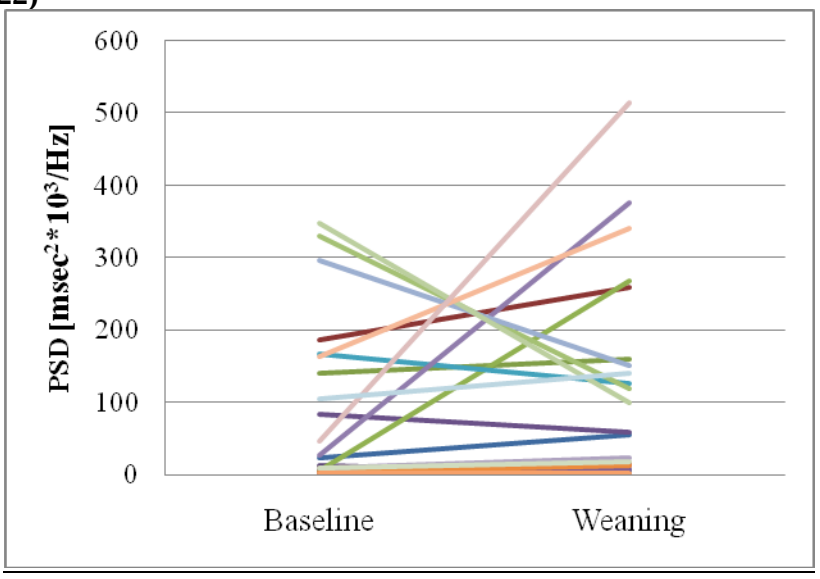




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**Figure 4.7: Comparison of LF at baseline and during weaning per individual patients (n=22)**

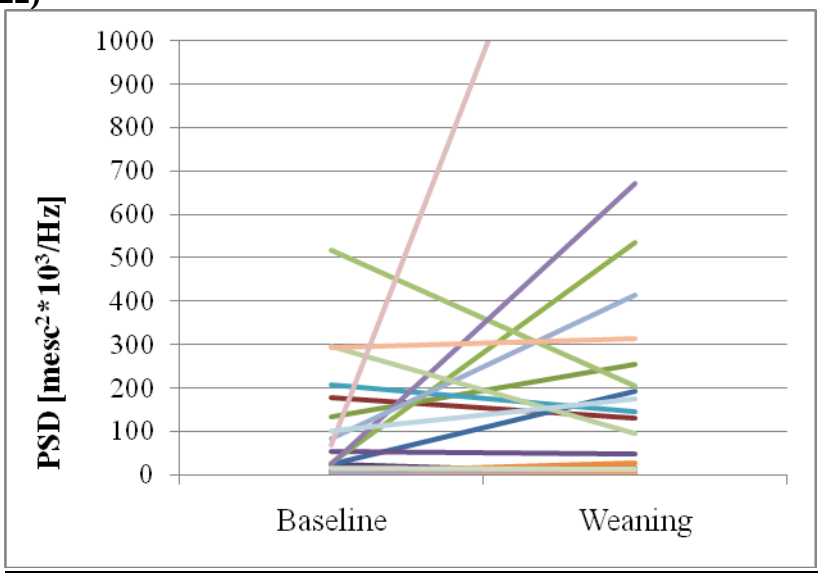
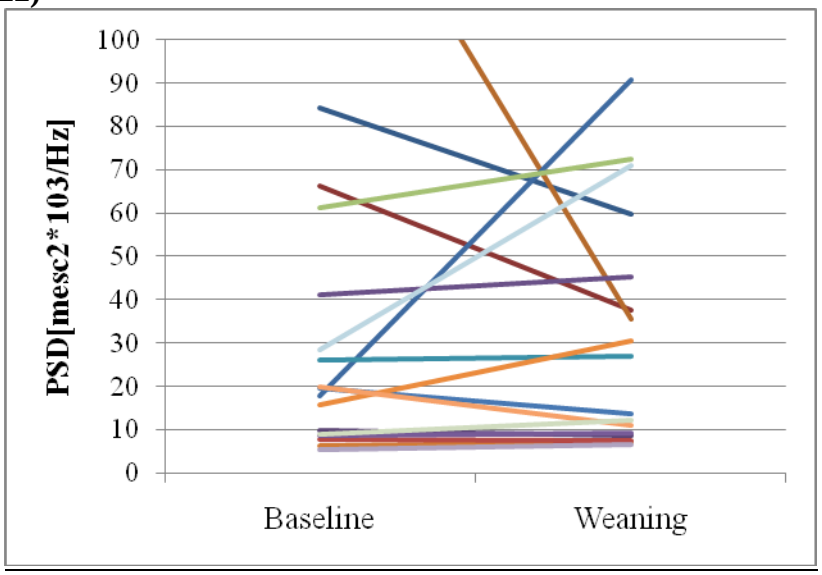



**Figure 4.8: Comparison of HF at baseline and during weaning per individual patients (n=22)**



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**Relationship of heart rate variability (HRV) during weaning to the occurrence of cardiac dysrhythmias**

Multiple regression analyses were separately conducted to test the potential relationship between HRV and occurrence of ventricular and supraventricular ectopic beats during weaning. The ratio scores (i.e., average score at weaning divided by average score at baseline) of HF, LF, and VLF power were regressed separately on the mean number of ventricular and supraventricular ectopic beats during weaning after controlling for APACHE IV score on the day of weaning. In each hierarchical regression, APACHE IV score was entered first, and each of the HRV components was entered last in order to test their unique contribution to prediction.

Multiple linear regression analysis revealed that HRV in the HF power significantly accounted for 68% of the variance in occurrence of ventricular ectopic beats (β = .79, p = < .001) and for 29% of the variance in occurrence of supraventricular ectopic beats during weaning (β = .53, p = .02) as shown in Tables 4.8 and 4.9 respectively. VLF accounted for 63% of the variance in occurrence of ventricular ectopic (β = .776, p = < .001) as displayed in Table 4.10 VLF power was not found to explain a significant amount of the variance in supraventricular beats during weaning (Table 4.11). LF significantly accounted for 41% of the variance in occurrence of ventricular ectopic beats (β = .60, p = .002), and 36% of the variance in occurrence of supraventricular ectopic betas (β =.61, p = .002) during weaning (Tables 4.12 and 4.13).

**Table 4.8: Multiple regression analysis of relationship between HF and occurrence of ventricular ectopic beats during weaning (N=21)**

| **Predictor variable** | $R^2$ | **Adj** $R^2$ | $R^2$ **change** | **F change** | **df** | **Sig. F change** | **Standardized ß** |
|---|---|---|---|---|---|---|---|
| Step 1 APACHE IV | .056 | .006 | .056 | 1.13 | 1, 19 | .302 | .213 |
| Step 2 HF ratio | .684 | .649 | .628 | 35.80 | 1, 18 | < .001 | .793 |

APACHE IV= Acute Physiology and Chronic Health Evaluation IV; HF= High frequency



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**Table 4.9: Multiple regression analysis of relationship between HF and occurrence of supraventricular ectopic beats during weaning (N = 20)**

| Predictor Variable | $R^2$ | Adj $R^2$ | $R^2$ change | F change | df | Sig. F change | Standardized ß |
|---|---|---|---|---|---|---|---|
| Step 1 APACHE IV | .001 | -.055 | .001 | .012 | 1, 18 | .904 | -.042 |
| Step 2 HF ratio | .285 | .201 | .285 | 6.78 | 1, 17 | .02 | .534 |

APACHE IV= Acute Physiology and Chronic Health Evaluation IV; HF= High frequency

**Table 4.10: Multiple regression analysis of relationship between VLF and occurrence of ventricular ectopic beats during weaning (N = 25)**

| Predictor variable | $R^2$ | Adj $R^2$ | $R^2$ change | F change | df | Sig. F change | Standardized ß |
|---|---|---|---|---|---|---|---|
| Step 1 APACHE IV | .056 | .015 | .056 | 1.365 | 1, 23 | .255 | .076 |
| Step 2 VLF ratio | .633 | .599 | .577 | 34.522 | 1, 22 | < .001 | .776 |

APACHE IV= Acute Physiology and Chronic Health Evaluation IV; VLF= Very low frequency

**Table 4.11: Multiple regression analysis of relationship between VLF and occurrence of supraventricular ectopic beats during weaning (N = 24)**

| Predictor variable | $R^2$ | Adj $R^2$ | $R^2$ change | F change | df | Sig. F change | Standardized ß |
|---|---|---|---|---|---|---|---|
| Step 1 APACHE IV | .001 | -.045 | .001 | .015 | 1, 22 | .904 | -.252 |
| Step 2 VLF ratio | .020 | -.073 | .020 | .418 | 1, 21 | .525 | .647 |

APACHE IV= Acute Physiology and Chronic Health Evaluation IV; VLF= Very low frequency

**Table 4.12: Multiple regression analysis of relationship between LF and occurrence of ventricular ectopic beats during weaning (N = 25)**

| Predictor variable | $R^2$ | Adj $R^2$ | $R^2$ change | F change | df | Sig. F change | Standardized ß |
|---|---|---|---|---|---|---|---|
| Step 1 APACHE IV | .056 | .015 | .056 | 1.365 | 1, 23 | .255 | .140 |
| Step 2 LF ratio | .406 | .352 | .350 | 12.96 | 1, 22 | .002 | .600 |

APACHE IV= Acute Physiology and Chronic Health Evaluation IV; LF= Low frequency



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**Table 4.13: Multiple regression analysis of relationship between LF and occurrence of supraventricular ectopic beats during weaning (N = 25)**

| Predictor variable | $R^2$ | Adj $R^2$ | $R^2$ change | F change | df | Sig. F change | Standardized ß |
|---|---|---|---|---|---|---|---|
| Step 1 APACHE IV | .001 | -.045 | .001 | .015 | 1, 22 | .904 | -.126 |
| Step 2 LF ratio | .360 | .298 | .359 | 11.750 | 1, 21 | .002 | .608 |

APACHE IV= Acute Physiology and Chronic Health Evaluation IV; LF= Low frequency

**Relationship of the occurrence of dysrhythmias to length of mechanical ventilation**

Pearson correlation coefficients were computed among length of MV, APACHE IV score at weaning, rapid shallow breathing index (RSBI), cumulative fluid balance based on 24 hour intake and output, and $PaO_2/FiO_2$ (Table 4.14). Length of MV was correlated significantly with APACHE score only ($r = .369$, $p < .05$).

**Table 4.14: Correlation between length of MV, APACHE score, RSBI, fluid status, and PaO2/FiO2 at weaning (n=25)**

| | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| 1. Length of MV | --- | .369* | .004 | .296 | -.019 |
| 2. APACHE score | | --- | -.246 | .077 | .092 |
| 3. RSBI | | | --- | -.149 | -.149 |
| 4. Cumulative fluid balance | | | | --- | .077 |
| 5. $PaO_2/FiO_2$ at weaning | | | | | --- |

MV = Mechanical ventilation; APACHE IV= Acute Physiology and Chronic Health Evaluation IV; RSBI= Rapid shallow breathing index

*$p < .05$, two tailed

The mean number of ventricular and supraventricular ectopic beats during weaning was regressed separately on the mean time the patient received MV after controlling for APACHE IV score on the day of weaning; results are displayed in Tables 4.15 and 4.16.

Multiple linear regression analysis revealed that the occurrence of supraventricular ectopic beats during weaning accounted for 18% of the variance of the time patient spent on MV ($\beta = 2.3$, $p = .032$) as shown in Table 4.15. The occurrence of ventricular ectopic beats during weaning did not explain a significant amount of the variance in time patient spent on MV (Table 14.16).



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**Table 4.15: Multiple regression analysis of relationship between occurrence of supraventricular ectopic beats during weaning and length of MV (N=24)**

| Predictor variable | $R^2$ | Adj $R^2$ | $R^2$ change | F change | df | Sig. F change | Standardized ß |
|---|---|---|---|---|---|---|---|
| Step 1 APACHE IV | .130 | .090 | .130 | 3.275 | 1, 22 | .084 | .863 |
| Step 2 Mean number of SVE/hr | .305 | .239 | .176 | 5.308 | 1, 21 | .032 | 2.304 |

MV = Mechanical ventilation; APACHE IV= Acute Physiology and Chronic Health Evaluation; SVE=Supraventricular Ectopic Beats

**Table 4.16: Multiple Regression Analysis of relationship between occurrence of ventricular ectopic beats during weaning and length of MV (N=26)**

| Predictor variable | $R^2$ | Adj $R^2$ | $R^2$ change | F change | df | Sig. F change | Standardized ß |
|---|---|---|---|---|---|---|---|
| Step 1 APACHE IV | .130 | .094 | .130 | 3.589 | 1, 24 | .070 | 1.929 |
| Step 2 Mean number of VE/hr | .143 | .069 | .013 | .350 | 1, 23 | .560 | .592 |

MV = Mechanical ventilation; APACHE IV= Acute Physiology and Chronic Health Evaluation; VE= Ventricular Ectopic Beats

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CHAPTER V: DISCUSSION

## Discussion of Findings

These data supported the hypotheses that: 1) HRV measured in the frequency domain during weaning was related to the occurrence of cardiac dysrhythmias; and 2) rate of supraventricular ectopic beats per hour during weaning was an independent predictor of length of MV.

Our study results showed that exposing patients (n=22) to a combination of PS10 cm $H_2O$ and CPAP 5 cm $H_2O$ during weaning generated a significant increase in LF power with no change in VLF or HF power compared to baseline. Our study findings were in partial disagreement with Frazier at al. [33] findings. Frazier et al.[33] reported a significant increase in VLF power and a significant decrease in HF power with exposure to a combination of PS 10 cm $H_2O$ and CPAP 10 cm $H_2O$ in a group of six anesthetized canines with normal ventricular function studied in a laboratory setting. The disagreement can be attributed to the underlying cardiac function of subjects enrolled in each study and the degree of positive ITP achieved during weaning. The use of PS+CPAP during weaning produces positive ITP. Positive ITP decreases the pressure gradient between the vena cava and right atrium, which in turn decreases venous return and RV preload. The higher level of positive ITP pressure achieved during weaning is accompanied by further reduction in RV preload in subjects with normal cardiac function as found by Frazier et al.[33] As a result, the ANS compensated by increasing sympathetic tone (reflected by VLF power) and decreasing parasympathetic tone (reflected by HF power) [33] in order to maintain adequate cardiac output and oxygen delivery. The ANS adaptive response can be significantly altered in presence of impaired cardiac function as demonstrated by our findings. In our study, 49% of patients were known to have impaired cardiac conditions. The acute fluid shift during weaning can be challenging for these patients, which explains dominance of sympathetic tone activity in our study demonstrated by increased LF power.

Although the potential anxiety and stress that patients experience during weaning from MV was not measured in this study or any previous published studies, stress and anxiety are known to further augment activation of sympathetic tone. The effect of



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emotional stress was removed in Frazier et al. [33] study as their study was conducted in a controlled laboratory setting and the subjects were anaesthetized.

In the current study, patients were separated into two groups based on initial weaning trial outcome. Patients who experienced a successful weaning trial (n=5) exhibited no change in VLF, LF, and HF power, while patients who failed the weaning trial (n=17) exhibited increases in LF power and decreases in HF power compared to baseline. Changes in HRV exhibited by the two groups were in partial agreement with Shen et al.[34] findings. Shen et al.[34] analyzed HRV for 24 patients during weaning from MV during the transition from pressure support ventilation (PSV) to SBT (using a T-piece trial), and found a significant decrease in LF and HF in patients who failed a weaning trial (n=12), but not in the success group. Although Shen and associates study and our study were conducted in ICU settings, differences in HRV findings in patients who failed a weaning trial can be attributed mainly to differences in design of the studies and methodologic factors. Shen and associates started HRV measurement 10- minutes after transition from (PSV) to SBT (T-piece trial), excluded patients who had frequent cardiac arrhythmias (defined as > 10% of nonsinus beats), and excluded the 5-minute segment in which more than 90% of the R-R intervals were not normal-to-normal (N-N) intervals from analysis. In our study, HRV measurement started upon exposure to PS+CPAP trial, only patients with atrial fibrillation/ flutter at baseline were excluded, and the entire 5-minute segment in which more than 80% of the R-R intervals were not normal-to-normal (N-N) intervals were excluded from analysis. In addition, patients enrolled in Shen and associates study were older than patients in our study (69.8 ± 17.8) vs. (53.3 ±14.6). Older age can explain the decrease in ANS adaptive response and the decrease in HRV measurements in Shen and associates study.[143] Medications and underlying disease can have an impact on HRV analysis. However, these two factors were not evaluated in either study.



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Changes in HRV that occurred during weaning may have influenced the occurrence of cardiac dysrhythmias, especially in patients with underlying cardiac dysfunction. Numerous studies have reported a significant relationship between reduced HRV and the genesis of malignant ventricular dysrhythmias, primarily ventricular fibrillation and ventricular tachyarrhythmias, especially in patients with heart failure, myocardial ischemia, and myocardial infarction. [35, 41, 42, 45, 101]

Several studies have shown imbalances that included increased sympathetic activity or decreased parasympathetic activity or both before occurrence of paroxysmal atrial fibrillation [36, 102] and atrial flutter[104] in patients with underlying heart diseases. Huikuri et al.[103] reported a significant decrease in HF power one hour before occurrence of ventricular tachycardia in patients with ischemic heart disease. Fei et al.[38] reported significant changes in HRV immediately prior to the occurrence of tachyarrhythmias in patients with congestive heart failure. Fei et al.[39] reported a significant increase in the LF/HF ratio immediately before occurrence of idiopathic VT episodes. Also, Hayashi et al.[40] reported an increase in the LF/HF before the onset of ventricular tachycardia. Our findings were in agreement with previous published literature. In our study, 49% of patients were known to have cardiac conditions. Increased sympathetic activity (reflected by increased LF power) was found to be arrhythmogenic. The LF power significantly predicted the occurrence of both ventricular and supraventricular ectopic beats during weaning. Although HF and VLF power did not change during weaning compared to baseline, multiple regression analyses showed that HF power measured during weaning was a significant predictor of occurrence of ventricular and supraventricular ectopic beats during weaning; and VLF power measured during weaning was found to be a significant predictor of the occurrence of ventricular ectopic beats but not of occurrence of supraventricular beats during weaning.

All patients in this study demonstrated either ventricular or supraventricular ectopic beats or both during weaning. The mean supraventricular ectopic beats per hour during weaning were double the mean at baseline, while the mean of ventricular ectopic beats per hour did not change. Frazier et al.[17] reported that the number of supraventricular ectopic beats per hour during weaning was almost double the number at baseline, and the number of ventricular ectopic beats per hour decreased by nearly two thirds during



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weaning in 39 patients exposed to CPAP during weaning attempts. Thus, our results mirrored the change in SVEs, but not VEs. This can be attributed to the degree of positive ITP achieved during weaning and data measurements points of time. In our study, we measured cardiac rhythm for 24- hours at baseline and for the first 2-hour after exposing the patients to a combination of PS (8-15 cm $H_2O$) and CPAP 5 cm $H_2O$ during weaning trial. Frazier and associates measured cardiac rhythm for 24- hours at baseline; 1-hour before, during, and up to 24 hours after exposing patients to a combination of PS10 cm $H_2O$ and CPAP 10 cm $H_2O$. The higher the positive ITP applied during weaning, the greater is the impact on acute fluid shift into the intrathoracic vascular component, ANS activity and in turn the greater is the negative effects on myocardial action potential. The underlying disease process of enrolled patients may have an impact on occurrence of ventricular and supraventricular ectopic beats. In our study, the heterogeneous patient population was recruited from MICU, CCU, TICU, CTICU and NICU, while Frazier and associates enrolled a homogeneous patient population from MICU only. Finally, patients enrolled in both studies were critically ill. These patients were subjected to a wide variety of procedures at baseline and during weaning that have varied impact on the occurrence of cardiac dysrhythmias.

In this study, we hypothesized that cardiac dysrhythmias would contribute to difficulty with weaning from MV and thus increase the length of time required for MV. Multiple linear regression analyses revealed that the occurrence of supraventricular, but not ventricular ectopic beats during weaning was a significant predictor of length of MV. This study was the first to evaluate the impact of occurrence of cardiac dysrhythmias during weaning on length of MV. These results advance our understanding of the negative impact of cardiac dysrhythmias on cardiac contractility and myocardial oxygen demand, and in turn weaning outcome. Therefore, cardiac rhythm should be systematically evaluated during MV and weaning in order to decrease length of MV.

## Study Limitations

There are some limitations to this study. First, the sample size is small and that may affect the power of the study to detect differences. Larger sample sizes are recommended for future studies. Second, we did not collect other biomarkers of autonomic activity, such as plasma catecholamine levels and baroreflex sensitivity.



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However, power spectral analysis of HRV is a valid and reliable noninvasive indicator of autonomic nervous system modulation activity. Third, in this study, a heterogeneous patient population with various underlying diseases was included, which might have had considerable effects on the length of MV. The reason of enrolling a heterogeneous patient population was to mirror the actual patient population found in intensive care units, in order to generalize the study findings to include patients with different underlying disease processes. Fourth, the majority of patients were male (67%) and Caucasian (97%), which may affect the generalizability of the study findings. Enrolling patients with approximate numbers of both genders and different categories of ethnicity is recommended for future studies. Fifth, according to the routine care followed in the proposed clinical area, the process of weaning starts once the physician prescribes weaning. This resulted in the PI missing the initial weaning trial for two patients. Sixth, the design of this study is a repeated measures design. So, death or tracheostomy events that occurred before the first weaning trial limited the number of patients with complete data for the two time periods. Therefore, a larger sample size is recommended for future studies.

## SUMMARY AND CONCLUSION

In summary, this study was the first to investigate the relationship of the occurrence of cardiac dysrhythmias during weaning to the length of MV. We demonstrated that changes in HRV measured during weaning significantly predicted the occurrence of cardiac dysrhythmias during weaning and the occurrence of supraventricular ectopic beats during weaning was a significant predictor of the length of MV. Early detection of ANS alterations and effective management of cardiac dysrhythmias during weaning is of paramount importance because these alterations can contribute to longer MV time.

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APPEDICES

## Appendix A: Institutional Review Board

UNIVERSITY OF KENTUCKY
Office of Research Integrity

University Veterinarian, IRB, RDRC, IACUC
315 Kinkead Hall
Lexington, KY 40506-0057
859 257-9428
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Continuation Full Review
Modification approved: revised research description; decreased # of subjects

| Approval Ends | Project Ends | IRB Number |
|---|---|---|
| June 1, 2009 | June 30, 2009 | 07-0405-F1V |

TO: Muna Hammash, MSN, RN
Nursing 5th Floor
509q College of Nursing
Speed Sort 0232
PI phone #: (859)323-4305

FROM: Chairperson/Vice Chairperson
Medical Institutional Review Board (IRB)

SUBJECT: Approval of Protocol Number 07-0405-F1V

DATE: June 2, 2008

On June 2, 2008, the Medical Institutional Review Board approved your protocol entitled:

*Cardiac rhythm during mechanical ventilation and weaning from ventilation*

Approval is effective from June 2, 2008 until June 1, 2009. This approval extends to any consent/assent document unless the IRB has waived the requirement for documentation of informed consent. If applicable, attached is the IRB approved consent/assent document(s) to be used when enrolling subjects. [Note, subjects can only be enrolled using consent/assent forms which have a valid "IRB Approval" stamp unless special waiver has been obtained from the IRB.] Prior to the end of this period, you will be sent a Continuation Review Report Form which must be completed and returned to the Office of Research Integrity so that the protocol can be reviewed and approved for the next period.

In implementing the research activities, you are responsible for complying with IRB decisions, conditions and requirements. The research procedures should be implemented as approved in the IRB protocol. It is the principal investigator's responsibility to ensure any changes planned for the research are submitted for review and approval by the IRB prior to implementation. Protocol changes made without prior IRB approval to eliminate apparent hazards to the subject(s) should be reported in writing immediately to the IRB. Furthermore, discontinuing a study or completion of a study is considered a change in the protocol's status and therefore the IRB should be promptly notified in writing.

For information describing investigator responsibilities after obtaining IRB approval, download and read the document "PI Guidance to Responsibilities, Qualifications, Records and Documentation of Human Subjects Research" from the Office of Research Integrity's Guidance and Policy Documents web page [http://www.research.uky.edu/ori/human/guidance.htm#PIresp]. Additional information regarding IRB review, federal regulations, and institutional policies may be found through ORI's web site [http://www.research.uky.edu/ori]. If you have questions, need additional information, or would like a paper copy of the above mentioned document, contact the Office of Research Integrity at (859) 257-9428.

Robert P. Rapp, Pharm.D., J.D.
Chairperson/Vice Chairperson

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## Appendix B: Data collection instrument

Socio-demographic characteristics and clinical data collection instrument

ID# _____ Date of data collection _____

Date hospital admission _____ Unit _____

Date of ICU admission _____

Part 1: SOCIODEMOGRAPHIC CHARACTERISTICS

1. Sex: 0._____ Male 1._____ Female

2. Age ____ Years old_____

3. Marital Status: 0._____ Single
1._____ Married
2._____ Divorced/Separated
3._____ Widowed
4._____ Co-habitate (living with a good friend or partner)

4. Type of insurance: 1. Government insurance (Medicare, Medicaid, or military medical)
2. Commercial insurance (fee-for service and PPO carriers)
3. HMO (health maintenance organization characterized by coverage that provides healthcare services for members on a prepaid basis).
4. None or self

5. Ethnicity: 1. _____ Black or African-American (not Hispanic or Latino)
2. _____ White or Caucasian (not Hispanic or Latino)
3. _____ Asian
4. _____ Hispanic or Latino
5. _____ American Indian or Alaskan Native
6. _____ Native Hawaiian or other Pacific Islander
7. _____ Other (please specify_____)



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6. What is the highest level of education the patient have completed?

1. _____ Less than high school graduate
2. _____ High school graduate
3. _____ some post high school
4. _____ Some college
5. _____ Associate degree
6. _____ Bachelor's degree
7. _____ Master's degree
8. _____ Professional degree
9. _____ Doctoral degree

7. Patient's Height _____, body weight _____lbs

8. Hospital length of stay prior to ICU admission_____days.

9. Hospital length of stay prior to ICU intubation_____days.

10. Functional limitation prior to admission 0._____ No 1._____Yes.

If yes, describe _____

11. Regular medications prior to admission _____

12. Does the patient have any previous history of mechanical ventilation?

0._____ No 1._____Yes

If yes, a- When?

b- Specify the cause _____

c- Length of previous mechanical ventilation _____ days/hours

d- Complications during previous mechanical ventilation period

13. Does the patient have any history of cardiac rhythm disturbances?

0._____ No 1._____Yes

If yes, a- Specify _____

b- For how long? _____ days

c- What medication used for its management?

14. Medical diagnoses upon admission: _____

15. Reason for current mechanical ventilation:

1. Airway protection 2. Excessive work of breathing

3. Inadequate oxygenation 4. Hypercapnia

5. Other (please specify) _____

16. Length of current MV prior to beginning the study: _____days/hours



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17. APACHE III score _____

Part 2-I: Clinical Data (Baseline) ID# _____

Day # _____ Date _____

| | | | | | |
|---|---|---|---|---|---|
| *Physiological Status* | | WBC / RBC | | Cdyne / Cst | |
| GCS | | Platelets | | Airway resistance | |
| Patient temperature | | Hemoglobin | | WOBv / WOBp | |
| arterial pH | | Hematocrit | | P O.1 | |
| $PaCO_2$ | | *Pulmonary Status* | | Ti / Ttot (cycle time) | |
| $PaO_2$ | | Ventilator mode | | Peak airway / Mean airway pressures | |
| $HCO_3$ | | E.T.T size/location | | RSBI | |
| $SaO_2$ | | Set ventilator rate | | $PaO_2/FiO_2$ | |
| $SpO_2$ | | Total rate | | Self extubation incidence | |
| Glucose / Hgb A1C | | Spontaneous RR | | Re-intubation | |
| BUN | | $Vt_I$( Set) / Vt ( returned) | | *Cardiovascular Status* | |
| Creatinine | | Spontaneous Vt exhaled | | Systolic BP | |
| Sodium | | Pressure control set above PEEP | | Diastolic BP | |
| Potassium | | Pressure support | | Mean arterial pressure | |
| Chloride | | PEEP level | | HR | |
| $CO_2$ | | CPAP level | | CVP | |
| Calcium(tot)/Ionized | | $FiO_2$ | | *I&O Status* | |
| Bilirubin | | Minute Vent total | | Total 24 hour intake | |
| Albumin | | Minute Vent expired | | Total 24 hour output | |
| Magnesium | | Minute Vent inspired | | Cumulative Intake | |
| | | | | Cumulative Output | |
| Phosphorous | | Minute Vent esp | | Cumulative fluid balance | |

Date and description of 12 lead EKGs

Date and description of CXRs

Date and description of cardiac cath/echo



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Current medications and dosages

| Prescribed Drug Name | Dose/Route/Frequency/Dates of Administration | Comments (Total Dose per 24 hours) |
|---|---|---|
| | | |
| | | |
| | | |
| | | |

Part 3: Events summary and patients disposition

1. Total length of stay: Hospital _____ ICU _____
2. Total # ventilator _____ days _____ hours.
3. Number of weaning trials
4. a. Initial weaning trial date and time _____
   b. Mode of weaning _____
   c. Length of weaning trial _____
   d. Weaning outcome: success _____ Failure _____
5. If failed weaning trial, reasons identified in the patient medical record _____
6. Tracheostomy: Yes _____ No _____



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**Publications**

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**Honors and Awards**

American Association of Critical Care Nurse- Philips Medical Research Award, 2009
Southern Nursing Research Society Dissertation Award, 2008

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