PHYSIOLOGICAL STRESS DURING FAILED SPOTANEOUS BREATHING TRIALS IN PROLONGED MECHANICAL VENTILATION PATIENTS

By

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To my dearest family

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ICU	Intensive care unit
MV	Mechanical ventilation
SBT	Spontaneous breathing trial
NIP	Negative inspiratory pressure;
ANS	Autonomic nervous system;
HRV	heart rate variability;
PSD	Power spectral density;
HFP	High frequency power;
LFP	low frequency power;
NU	normalized unit;
HPLC	High Performance Liquid Chromatography
RR	Respiratory rate;
RSA	Respiratory sinus arrhythmia;
VD	ventilator dependant;
Vti	Inspired tidal volume
V_E	Minute Ventilation

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PHYSIOLOGICAL STRESS DETECTION DURING FAILED SPOTANEOUS BREATHING TRIALS IN PROLONGED MECHANICAL VENTILATION PATIENTS

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Failing a spontaneous breathing trial (SBT) is a stressful experience for patients requiring prolonged mechanical ventilation (PMV). The objective of this study was to quantify the physiological stress during failed SBT in PMV patients. 10 PMV patients, (50±21 MV support days) who were undergoing weaning were studied. Heart rate variability (HRV) indices, plasma catecholamines and arterial blood gases (ABG) were measured while the patients received MV support and at the point of SBT failure. Breathing variables were compared at the first and last 5 min of SBT. SBT failure was defined by standard criteria.

Average duration of SBT was 67± 65 minutes. At SBT failure, normalized high frequency variability decreased from 67±12 to 37±16 ($p \leq 0.001$) while normalized low frequency variability increased from 33±12 to 63±16 ($p \leq 0.001$). Additionally, norepinephrine increased from 837± 618 to 1666 ± 954 pg/ml ($p \leq 0.001$) and epinephrine increased from 92±35 to 174 ±103 pg/ml ($p \leq 0.01$)]. Minute ventilation increased from 8.07±2.8 to 9.2±3 L/min ($p \leq 0.05$) and peak inspiratory flow increased

from 33.1±7 to 36.7±8 L/min ($p \leq 0.05$)]. ABG values were not different between MV support and at SBT failure.

HRV changes at the point of SBT failure suggest a high level of sympathoadrenal stimulation, which was confirmed by the elevated catecholamines. Thus, SBT failure is associated with high levels of sympathetic stimulation and respiratory drive, but not necessarily ABG alterations. We believe that in PMV patients the high levels of physiological stress might be responsible for making spontaneous breathing unsustainable, leading to the eventual failure in the SBT. HRV can be used in PMV patients as a non-invasive tool for monitoring patient's tolerance during SBT.

CHAPTER 1
SPECIFIC AIMS

Difficulty weaning patients from mechanical ventilation (MV) is a growing clinical and economic problem in the United States health care system (1). The vast majority of patients supported by MV are quickly weaned, but a minority (~10%) of these patients experience difficult weaning and require prolonged mechanical ventilation (PMV) support, often for months (2). Furthermore, PMV is associated with increased morbidity and mortality. As a consequence, PMV patients incur substantial health care costs (1). Therefore, the process of weaning is instituted as soon as the precipitating disease process is significantly improved or is resolved (3).

One common method for weaning patients from MV is having the patient perform daily spontaneous breathing trials (SBT) of progressive duration until weaning is accomplished (4). However, during SBT, the abrupt switch in the intrathoracic pressure from positive (MV) to negative (spontaneous breathing) significantly affects intrathoracic hemodynamics leading to cardiovascular stress (5, 6). Additionally, the underlying pathophysiological processes may affect a critically ill patient's ability to compensate for these alterations to maintain homeostasis (5-7). Previous studies report the occurrence of tachycardia, myocardial ischemia, pulmonary edema and gut ischemia during transition from MV to SBT, indicative of cardiovascular compromise (5, 6). Furthermore, weaning- associated ECG and thallium cardiac blood flow scan-related signs of ischemia have been reported in both subjects with known coronary artery disease (8) and in otherwise normal patients (9).

Moreover, inspiratory muscle load-capacity imbalance has been identified as a crucial contributor to ventilator dependence. Patients who fail weaning trials may

experience inspiratory pressure loads that approximate up to 40% of maximal trans-diaphragmatic pressure (10). Workloads of this magnitude are unsustainable in healthy adults who undergo breathing or extremity loading tasks (10-12). Furthermore, the role played by psychological factors in the outcome of SBT is not very well understood. A qualitative study of the patients' perception of weaning from MV concluded that the patients' dominant feeling was generalized stress (13). The fear of loss of the life support system may be responsible for the stress response. Psychological stress is difficult to measure objectively in critically ill patients and even more so in mechanically ventilated patients (13). Few studies have evaluated the psychological state of critically ill patients and its effect on physiological response.

The pathophysiology of MV weaning failure is multifactorial (4). Additionally, there is no consensus on which physiological variable to monitor in PMV patients during the SBT to decide whether to continue a SBT for an initially planned duration, prolong it, or curtail it (3). In this case, the heart rate variability (HRV) analysis offers a simple, noninvasive bedside measure to detect the fluctuations in the autonomic control mechanisms that compensate for environmental and physiological changes (14, 15).

In a recent study, Frazier et al. (16) compared heart rate variability measures and plasma catecholamine levels during MV support and continuous positive airway pressure (CPAP) trials in patients on MV support for short durations (11.7 $\pm$11.3 days). The study showed that two thirds of the patients demonstrated abnormal autonomic nervous system (ANS) function and this dysfunction was more severe in patients who failed the CPAP trial (16). However, a possible limitation to studies comparing HRV in two groups of patients is the confounding influence of concurrent factors like age,

gender (17) and diseases such as diabetes mellitus(14, 18), congestive heart failure and various neurological diseases which constitute major co-morbidities in ICU patients (14, 18). Additionally, medications like beta blockers acting directly or indirectly on the ANS potentially influence HRV (18). Therefore in these studies the difference found could be the result of intrinsic differences between groups, rather than the difference between outcomes (success or failure in the SBT) within a subject.

However, there is no consensus on which physiological variable to monitor in PMV patients during the SBT to decide whether to prolong or curtail a SBT trial. The objective of this research study is to quantify the physiological stress during failed SBT in PMV patients using a within subject design. The study was designed to achieve the following specific aims.

Specific Aim # 1: To compare the physiological stress level during mechanical ventilation and at the point of failure during spontaneous breathing trial in prolonged mechanically ventilated patients using heart rate variability analysis

Hypothesis # 1: We hypothesize that in prolonged mechanically ventilated patients during failed spontaneous breathing trials heart rate variability analysis will indicate higher physiological stress level at the point of failure as compared to mechanical ventilation support.

Specific Aim # 2: To compare plasma catecholamine levels during mechanical ventilation and at the point of failure during spontaneous breathing trial in prolonged mechanically ventilated patients.

Hypothesis # 2: We hypothesize that in prolonged mechanically ventilated patients during failed spontaneous breathing trials plasma catecholamine analysis will indicate

higher physiological stress level at the point of failure as compared to mechanical ventilation support.

Specific Aim # 3: To compare the breathing pattern variables at the first and last five minutes of the spontaneous breathing trial in prolonged mechanically ventilated patients.

Hypothesis # 3: We hypothesize that in prolonged mechanically ventilated patients during failed spontaneous breathing trials breathing pattern variables will be significantly different comparing the start and the end of the spontaneous breathing trial.

Rationale:

This will be the first study to quantify the physiological stress during spontaneous breathing trials in prolonged mechanically ventilated patient. Using a within subject design this study will also help validate the use of heart rate variability analysis as a non-invasive bedside tool to evaluate the physiological stress during weaning trials.

CHAPTER 2
REVIEW OF LITERATURE

Prolonged Mechanical Ventilation and Weaning Failure

Prolonged Mechanical Ventilation Healthcare Implications

Mechanical ventilation (MV) is clinically used to maintain adequate alveolar ventilation in patients who are unable of maintaining it on their own. The indications for mechanical ventilation, as derived from a study (19) of 1638 patients in eight countries are acute respiratory failure (66 percent of patients), coma (15 percent), acute chronic obstructive pulmonary disease exacerbation (13 percent), and neuromuscular disorders (5 percent). The disorders in the first group include acute respiratory distress syndrome, heart failure, pneumonia, sepsis, complications of surgery, and trauma (with each subgroup accounting for about 8 to 11 percent of the overall group). The objectives of mechanical ventilation are primarily to decrease the work of breathing and reverse life-threatening hypoxemia or acute progressive respiratory acidosis. (20) As the conditions that warranted placing the patient on the ventilator stabilize and begin to resolve, the time comes to consider the discontinuation of mechanical ventilation; a process commonly referred to as weaning (21, 22). At any given time, 30-70% of patients in the intensive care unit (ICU) are receiving mechanical ventilatory support; 70-80% of them are rapidly weaned off this support, often within a few days. (2) However, weaning is more problematic in the remaining 20-30% of patients leading to prolong mechanical ventilation (PMV) support. (2)

A recent international consensus conference recommended that PMV should be defined as need for at least 21 consecutive days of MV for at least 6 hours/day (3). Approximately 10% of all critically ill patients and up to 34% of those ventilated for more

than two days require PMV support (23-25). Importantly, ~45% of the time the patient spends on mechanical ventilation is dedicated to the weaning process (2). Annually in the US, approximately 250,000 patients experience difficult weaning and the estimated annual cost of providing care during these PMV support episodes is 16 billion dollars. (1) Early survival from acute respiratory failure in the ICU has increased during the past two decades and the number of patients experiencing PMV is growing 5 times as rapidly as the number of hospital admissions (26). Additionally, persons aged 65 and older presently account for over half of all intensive care unit days in the US (27). This age group, whose members also have the highest baseline risk of respiratory failure and subsequent PMV, is expected to double in number as the “Baby-Boom” generation approach the age of 65 years (28, 29). However, this increase is accompanied by significantly fewer discharges to home, more discharges to nursing homes, with a greater burden of comorbidities (24). Thus, compared with other ICU patients, those on long-term MV consume a disproportionate amount of critical care resources, in view of the small fraction of the ICU population that they represent (30-32).

Despite receiving such a high level of care fewer than 50% of PMV hospital survivors survive more than one year (23, 33, 34). Furthermore, most PMV patients who survive 1 year report significant deficits in cognitive functioning, physical functioning, energy and sleep (33). Consequently, the survivors often suffer significant disability in performing basic daily functions, experience reduced quality of life, and possess significant long-term care-giving needs (23, 33, 35).

Pathophysiology of Mechanical Ventilation Weaning Failure

The pathophysiology of weaning failure in PMV patients is complex and multifactorial. The main reasons are respiratory pump failure, hemodynamic instability and psychological dependence on the ventilator (4, 36-38).

Respiratory load capacity imbalance

The vast majority of patients who fail a spontaneous breathing trial do so because of an imbalance between respiratory muscle capacity and the load placed on the respiratory system (37, 38). The increase in work of breathing may be due to an increase in elastic or resistive loads, or both. Elastic workload increases when there is a reduction in compliance of the lungs and/or a reduction in the compliance of the chest wall. Additionally, numerous studies indicate that MV-induced diaphragmatic weakness, due to both atrophy and contractile dysfunction, is an important contributor to weaning difficulties. Baseline passive respiratory mechanics are unable to reliably differentiate patients who fail a weaning trial from those who pass (39). However, patients with respiratory muscle weakness can exhibit deterioration of pulmonary mechanics during periods of unassisted breathing.

A number of investigations reported dynamic hyperinflation during failed SBT. The presence of dynamic hyperinflation implies that alveolar pressure remains positive throughout expiration. At the end of the expiration, this positive pressure is termed auto positive end-expiratory pressure (auto PEEP) or intrinsic positive end-expiratory pressure (PEEPi) (40). During SBT most notably PEEPi increases, which may occur due to active expiratory muscle contractions and early termination of exhalation (41, 42). Progressive hyperinflation is accompanied by increased airway resistance and decreased pulmonary compliance (12, 43). In the presence of dynamic hyperinflation,

tidal breathing occurs over a less-compliant region of the pressure-volume curve as end-expiratory lung volumes expand. In result, increased pressure is required to generate a tidal inhalation (43). Excessive resistive ventilatory loads may occur due to airway obstruction by edema, bronchoconstriction, or mucus plugging. Increased elastic loading occurs with pulmonary congestion, effusion, ascites (excess fluid in the peritoneal cavity), or skeletal injury. Chronic comorbid diseases such as chronic obstructive pulmonary disease may exacerbate acute resistive and elastic ventilatory loads. Patients who repeatedly fail weaning trials may experience inspiratory pressure loads that approximate up to 40% of maximal trans-diaphragmatic pressure (10). Workloads of this magnitude are unsustainable in healthy adults who undergo breathing or extremity loading tasks (10-12). Thus, high airway resistance (bronchospasm and excessive airway secretions) (44, 45) and low respiratory system compliance (stiff chest wall, stiff lungs, edematous or atelectatic alveoli) (46, 47) contribute to the increased work of breathing and can make spontaneous breathing unsustainable.

Inspiratory weakness has been identified as a crucial contributor to ventilator dependence (10, 48, 49). Numerous animal models have confirmed that periods of controlled MV between six and 48 hours results in diaphragmatic atrophy and contractile dysfunction referred to as ventilator induced diaphragm dysfunction (VIDD) (50-53). Atrophy of the inactive diaphragm occurs in conjunction with rapidly down-regulated protein synthesis (54, 55), followed shortly thereafter by a heightened, sustained state of proteolysis (54, 56, 57). Controlled MV is thought to initiate atrophy signaling cascades in the diaphragm up to eight times faster than in the limb muscles (55, 58), suggesting that this chronically active muscle may be more susceptible to

disuse atrophy (59). Recent research by Levine (60) illustrated that passively ventilated adults, free from active pulmonary or infectious diseases, exhibited rapid and profound diaphragmatic atrophy. In this study, organ donors with terminal brain injuries experienced 57% atrophy of type I fibers and 53% atrophy in type II fibers with a median 34 hours of controlled MV, compared to the diaphragms of adults who underwent thoracic surgeries for 4-6 hours.

Additional factors in critical care practice may influence the development of VIDD. Medications such as neuromuscular blocking agents and corticosteroids may impair excitation-contraction coupling and accelerate the development of critical illness myopathy (61). Hyperglycemia, systemic inflammatory response syndrome, and multiple-system organ failure each place patients at greater risk for intensive care unit (ICU) acquired weakness of the diaphragm (62). Inspiratory muscle weakness is associated with delayed weaning (63). Thus, it is likely that several factors (e.g., underlying disease state, infection, drug therapy, etc.) can converge with VIDD to exacerbate diaphragmatic weakness in critically ill patients leading to reduced capacity of the respiratory muscles (64). The factors that lead to weaning failure due to respiratory load capacity imbalance are summarized in Table 2-1 (adopted with permission from (65).

Hemodynamic imbalance

The heart and lungs interact during each ventilation cycle because of their anatomic position in the closed thoracic cavity. Ventilation can profoundly alter cardiovascular function via complex, conflicting, and often opposing processes (66). Figure 2-1 summarizes the potential cardiopulmonary interactions with changes in intrathoracic pressure and lung volume [adopted with permission from (67)]. Positive-

pressure ventilation generates positive intrathoracic pressure on inspiration. This is in contrast to spontaneous inspiration, whereby a sub-atmospheric intrathoracic pressure is produced by diaphragm contraction and a pressure gradient is formed between the atmosphere and the alveoli, and gas flows into the alveoli along the gradient.

The transition from mechanical ventilation to independent spontaneous ventilation induces alterations in intrathoracic pressure that influence thoracic blood volume and flow (68-71). Abrupt removal of mechanical ventilation and reinstitution of spontaneous ventilation typically increases the venous return. An increase in the venous return may produce right ventricular dilation. Right ventricular dilation will shift the intra-ventricular septum toward the left ventricle, impede left ventricular filling, and decrease subsequent cardiac output (72). In addition, right ventricular dilation may augment right ventricular intra-chamber pressure and influence the pressure gradient for coronary blood flow. These responses may be even greater in individuals who exhibit increased breathing work because of the significantly greater change in intrathoracic pressure necessary to produce gas flow into the lungs (73). Thus, application and discontinuation of mechanical ventilation can alter both myocardial oxygen supply and demand (73).

Most published criteria (4, 74, 75) require stable hemodynamic status to initiate the spontaneous breathing trial without further definition or description of specific criteria. In addition, many investigators who have suggested that cardiac dysfunction may prevent successful discontinuation of mechanical ventilation studied patients with known cardiac disease (6, 66, 72, 73, 76, 77). However, many critically ill patients may have undetected cardiac dysfunction. The underlying pathophysiological processes inherent to the critical illness may also induce alterations in cardiac function and affect a patient’s

ability to compensate. Thus, many critically ill patients may be unable to respond to hemodynamic changes produced by ventilator discontinuation making the weaning from mechanical ventilatory support a cardiovascular stress.

Cardiovascular instability during discontinuation of mechanical ventilation was first described more than 30 years ago by Beach et al. (1973) in postoperative cardiac surgery patients (78). Patients who had decreased cardiac output in response to ventilator discontinuation had a concurrent increase in central venous pressure, pulmonary vascular resistance, and systemic vascular resistance. Fifteen years later, Demling et al. (79) found that 32% of surgical and burn ICU patients (n=22) required reintubation because of unstable hemodynamic status and pulmonary edema. In a similar study, nearly one fourth of all medical ICU (MICU) patients who did not achieve spontaneous ventilation (n = 18) required reinstitution of mechanical ventilation because of congestive heart failure (80). Other investigators have described the need for significantly longer periods of mechanical ventilation in patients with left ventricular dysfunction (81, 82). In ventilator dependent patients with chronic cardiopulmonary disease (n=15), left ventricular responses to the discontinuation of mechanical ventilation included the development of acute heart failure concurrently with significant elevations in plasma levels of catecholamines (83). In another study, patients with chronic obstructive pulmonary disease (COPD) without diagnosed coronary artery disease had a significant decrease in left ventricular ejection fraction during T-piece breathing (84).

Additionally, myocardial dysfunction (85-87) and myocardial ischemia (73, 88) were identified as mechanism causing failure of weaning from mechanical ventilation.

Frazier et al. (16) recommended that clinicians must be aware of the potential for silent myocardial ischemia during the stress of liberation from mechanical ventilation.

Moreover, previous studies report occurrence of pulmonary edema, and gut ischemia, during the transition from MV to SBT, indicative of cardiovascular compromise (5, 6). Furthermore, weaning- associated ECG and thallium cardiac blood flow scan-related signs of ischemia have been reported in both subjects with known coronary artery disease (8) and in otherwise normal patients (9). This indicates that the failure in the weaning process may be secondary to cardiovascular decompensation. Therefore analysis of cardiovascular variables, before and during weaning has been proposed as an important determinant of weaning outcome (36). Autonomic tone influences thoracic hemodynamics because of its effects on heart rate, ventricular filling time, vascular tone, and degree of ventricular contractility.

Psychological factors

The psychological factors may be among the important non-respiratory factors contributing to unsuccessful liberation from mechanical ventilation and leading to ventilator dependence (4, 89-91). Psychological stress is difficult to quantify objectively in critically ill patients and even more so in mechanically ventilated patients.

A qualitative study of patients' perception of weaning from MV concluded that the patients' dominant feeling was generalized stress (13). The fear of loss of the life support system may be responsible for the stress response. In one observational study (92), the psychological status of 43 consecutive patients who had undergone successful weaning 48 to 96 hours earlier was recorded using an 32-item questionnaire. Several difficult experiences were recorded, including an inability to communicate, sleep disorders, diffuse anxiety, depression, and fear of abandonment by staff. Although

patients received no sedation for 48 hours, many could not recall distinguishing between night and day, and they reported being confused during weaning (92). In another investigation (93), 10 alert patients who were receiving mechanical ventilation, and were judged ready to wean, and who had undergone two to five failed weaning attempts underwent extensive psychometric testing. Several instruments were used, including the multidimensional health locus of control scales form, the Hope scale, the Norbeck social support questionnaire, and a scale measuring fear and other responses to mechanical ventilation (93). Mechanical ventilation was reported as a moderately fearful experience. Patients felt as though their locus of control was external to themselves, reflecting the intense dependence they have on the ICU team and on family members (93). As patients were weaned from mechanical ventilation, the locus of control was internalized. Hope increased as time passed following successful weaning, and hopelessness predominated for patients who continued to require mechanical ventilation (93).

Wunderlich et al. (94) measured the patient uncertainty and stress during weaning to determine levels of stress and to determine the helpfulness of information from nurses and to explore patients' perceptions. After extensive pretesting by an expert panel and pilot interviewing, eight open-ended questions were asked of 19 extubated patients. Qualitative data were analyzed for content and were coded into themes. The study reported that most patients experienced extreme uncertainty and stress during weaning. Patients with underlying pulmonary disease (compared to those without underlying disease) and women had worse experiences than men. Patients were afraid because they did not know what to expect and did not understand what was going on,

including whether they would be on the ventilator for the rest of their lives (94). The dominant feeling that patients described was discomfort while weaning from mechanical ventilation (94). The second prominent theme was frustration at the inability to communicate. Patients were very appreciative of information provided by ICU nurses during weaning that promoted patient empowerment. This study highlights the stress and uncertainty of patients undergoing mechanical ventilator weaning (94).

Perceptions of dyspnea during mechanical ventilation and weaning were examined in a small number of studies. In interviews with patients after extubation, Logan et al. (95) found that dyspnea was a primary subjective experience during weaning. In studies by Powers et al. and Knebel et al. patients had moderate to high levels of dyspnea during mechanical ventilation. (96, 97) Connelly et al. (98) and Bouley et al. (99) found low to moderate levels of dyspnea in patients receiving mechanical ventilation. No differences in dyspnea were noted between patients who were weaned completely from mechanical ventilation and those who were not. (98). Knebel et al. (97) and Bouley et al. (99) examined the occurrence of dyspnea during different methods of weaning and found no differences between the methods.

Perceptions of fatigue during mechanical ventilation and weaning were examined in 4 studies (95, 98, 100, 101). In an investigation by Logan and Jenny, patients who were interviewed after extubation reported a lack of energy, extreme fatigue, and exhaustion during weaning that decreased breathing effectiveness and caused discomfort and frustration. Weaning self-efficacy is defined as confidence in one's ability to breathe without ventilatory support (95). However, research that measures perceptions of self-efficacy during weaning is scarce. Moody et al. (102) found that

sense of mastery related to weaning from mechanical ventilation was a significant predictor of complete weaning in a sample of long-term ventilator-dependent patients. Moreover, many patients suffer significant anxiety during their ICU stay and the process of weaning from mechanical ventilation and these memories of distress may remain for years (103). The prevalence of anxiety during ICU is reported to be 30–75%. (92, 104) The anxiety was secondary to dyspnea (105); inability to communicate (106); and sleep disruption (103).

Additionally, Otte et al. (107) found that depressive symptoms were associated with elevated nor-epinephrine (NE) levels in patients with coronary artery disease. Few studies have evaluated the psychological state of critically ill patients and the effect on physiological response. Furthermore, in a recent study Jubran et al. (108) evaluated the prevalence of depressive disorders in PMV patients and found that depressive disorder is diagnosed in 42% of patients who are being weaned from prolonged ventilation. Additionally, the study showed that patients with depressive disorders were more likely to experience weaning failure and death (108).

Despite the qualitative evidence psychological stress is difficult to quantify in critically ill patients and even more so in mechanically ventilated patients. Therefore, heart rate variability measure may be useful in non-invasive monitoring of the patients.

Weaning Predictors in Prolonged Mechanical Ventilation Patients

In an attempt to identify mechanisms of weaning failure and predict its likelihood of occurrence, previous studies contrasted the ventilatory characteristics of patients who were successful from those who failed weaning (10, 36, 43, 49, 109-113). Early weaning readiness trials established the use of the spontaneous breathing trial, a short period of unassisted breathing, to test readiness for extubation (81, 114). However, the

research highlighted that many causes of early extubation failure do not necessarily predict weaning failure in patients who require prolonged MV and weaning failure cannot be explained by weaning predictors based exclusively upon respiratory mechanics (3).

A number of breathing pattern parameters have been reported to be associated with the success or failure of ventilator discontinuation (4, 113, 115, 116). These including vital capacity, tidal volume, respiratory rate, minute ventilation, rapid shallow breathing index (RSBI), calculated by dividing the tidal volume by the respiratory rate and maximal inspiratory pressure (PImax). Moreover, integrated factors also have been employed (4), for example, CROP index [ratio of dynamic compliance × maximum negative inspiratory pressure × PaO2/PAO2) to respiratory rate]). The receiver operating characteristic (ROC) curve is a plot of the sensitivity of a test versus its false-positive rate for all possible cut points.Analyses of ROC have shown none of these indices are sufficiently sensitive and specific to be useful in predicting the success of ventilation discontinuation, especially in the elderly and/or in the PMV patients. (4)

Studies examining the breathing pattern, maximal inspiratory pressure, and lung mechanics in patients being weaned from MV have reported inconsistent findings (38, 82). Del Rosario et al. reported that patients who failed to wean had a higher respiratory rate and RSBI by comparing with successful to wean groups. But, the $P_i$max and dynamic intrinsic positive airway pressure ($PEEP_i$) measured from the oesophageal pressure were similar in both groups. (38) Jubran et al. (82) found that in the early phase of the weaning trial, the failure group developed rapid shallow breathing and a higher value of $PEEP_i$ than the success group. Over the weaning course, the

respiratory resistance increased in the failure group whereas it remains unchanged in the success group. At the end of weaning trials, they found that 13 of 17 failure-to-wean patients increased in $PaCO_2$ whereas 4 showed a decrease in $PaCO_2$. They concluded that the patients who fail to wean developed rapid shallow breathing at the onset of the weaning trial and progressively increased in respiratory resistance and PEEPi, representing an excessive load to the respiratory muscles. This combination of increased mechanical load with rapid shallow breathing led to inefficient CO_2 clearance, which was the dominant determinant of weaning failure in the overall group. However, the observation that a rapid shallow breathing pattern developed at the onset of weaning trials in the failure group is not a universal phenomenon. Capdevia investigated 17 patients receiving PMV (an averaged MV staying > 20 days) and found that at the onset of weaning trials, high respiratory rate and low tidal volume values were observed in both success and failure groups, without significant inter-group differences(49). But, they agreed that PEEPi increased in response to the increased respiratory rate in the failure group throughout the weaning period. (49).

It seems that an excessive inspiratory load imposed on the respiratory muscles is an essential determinant of weaning failure. This excessive load leads to increase in the required breathing energy expenditure with a concomitant breathing pattern alteration (82). Additionally, it is accepted that a high neural drive persists over the weaning period in failure-to-wean patients. (37) The presence of a high neural drive indicates that the respiratory muscles continue to generate large inspiratory pressure to cope with this excessive load rather than a decrease in respiratory motor output. If the mechanical

loads excessive to the capacity that respiratory muscle can generate, this imbalance will lead to respiratory distress and sooner or later weaning failure will ensue.

The importance of the load-capacity balance on the weaning outcome of PMV patients has been highlighted in a study by Purro et al. (10) They showed that in the presence of a high neural drive to breathe, the patients with a high load/capacity index (Pdi/Pdimax > 0.4) were unweanable (where Pdi is the pressure required for tidal breathing and Pdimax is maximal pressure that the respiratory muscles can generate) They also found that a positive linear relationship between the load/capacity index and the effective inspiratory impedance ($P_{0.1}$/tidal volume/inspiratory time and $P_{0.1}$ is the value of airway pressure exactly 100ms after the beginning of the occluded inspiration) (r = 0.61). Therefore, they suggested that non-invasive methods such as breathing pattern and $P_{0.1}$ might help to identify the patients who fail to wean. However, it has been shown that the value of $P_{0.1}$ may be underestimated in the presence of hypercapnia or in the patients with abnormal lung mechanics. (117). Additionally, the ratio of Pdi/Pdimax obtained during the patients receiving on MV support might underestimate the values that would be obtained during spontaneous respiration since it is reported that a progressive deterioration in respiratory mechanics during SBT in the patients who fail to wean and Pdimax probably decreased by the end of the weaning trials(118). Moreover, in clinical settings, it is non possible to measure the ratio of Pdi/Pdimax on a breath-by-breath basis during the weaning trials. Thus, an accessible and alternate index to represent the relationship of the load-capacity balance is needed.

In PMV patients the switch from positive pressure mechanical ventilation to negative pressure spontaneous breathing is a stressful experience. This stress could be

physiological (hemodynamic instability, respiratory load-capacity imbalance), psychological or both. Moreover, the underlying pathophysiological processes inherent to the critical illness may affect the patient's ability to maintain homeostasis during this stressful experience. Furthermore, in PMV patients weaning failure cannot be explained by weaning predictors based exclusively upon respiratory mechanics. Therefore the measurement of physiological stress during SBT would be helpful in monitoring the patient's tolerance to the SBT.

Autonomic Nervous System and Maintenance of Homeostasis

Autonomic Nervous System Basic Physiology

The autonomic nervous system (ANS) is a part of the peripheral nervous system that functions to regulate the basic visceral (organ) processes needed for the maintenance of the normal internal environment of the body in an equilibrium state called as homeostasis. (119) The ANS is responsible for extrinsic regulation of cardiac muscle, smooth muscles (e.g. vascular smooth muscles) and all glandular secretions (e.g. hormones). The autonomic nervous system is traditionally described as a motor system that provides control over visceral functions critical for homeostasis. However, it is not strictly an efferent (motor) nervous system. Almost all visceral nerve bundles have sensory fibers intermixed with motor fibers (approximately 50% of all axons in the splanchnic nerves and 20% of all axons in the vagus nerves) (119). These sensory fibers carry information from receptors to the central nervous system. This information is, in turn, integrated and relayed by multi-neuronal pathways to the brain and/or spinal cord and eventually modulates the autonomic motor outflow. Thus, the ANS provides all the pathways for negative feedback control systems (119).

The ANS is composed of two anatomically and functionally distinct divisions, the sympathetic system and the parasympathetic system. Both systems are tonically active. In other words, they provide some degree of nervous input to a given tissue at all times. Therefore, the frequency of discharge of neurons in both systems can either increase or decrease. As a result, tissue activity may be either enhanced or inhibited. This characteristic of the ANS improves its ability to more precisely regulate a tissue's function.

Parasympathetic division

The preganglionic neurons of the parasympathetic system arise from several nuclei of the brainstem and from the sacral region of the spinal cord (segments S_2-S_4). The axons of the preganglionic neurons are quite long compared to those of the sympathetic system and synapse with postganglionic neurons within terminal ganglia which are close to or embedded within the effector tissues. The axons of the postganglionic neurons, which are very short, then provide input to the cells of that effector tissue. Parasympathetic pre-ganglia fibers run from the brain stem with the cranial nerves to muscles and glands in the head (cranial nerves III, VII, IX) and to the organs in thorax and abdomen (vagus nerve). The preganglionic neurons that arise from the sacral region of the spinal cord exit the CNS and join together to form the pelvic nerves. Because the terminal ganglia are located within the innervated tissue, there is typically little divergence in the parasympathetic system compared to the sympathetic system. In many organs, there is a 1:1 ratio of preganglionic fibers to postganglionic fibers. Therefore, the effects of the parasympathetic system tend to be more discrete and localized, with only specific tissues being stimulated at any given

moment, compared to the sympathetic system where a more diffuse discharge is possible.

Sympathetic division

The preganglionic neurons of the sympathetic system arise from the thoracic and lumbar regions of the spinal cord (segments T_1 through L_2). Most of these preganglionic axons are short and synapse with postganglionic neurons within ganglia found in the sympathetic ganglion chains. These ganglion chains, which run parallel immediately along either side of the spinal cord, each consist of 22 ganglia. The preganglionic neuron may exit the spinal cord and synapse with a postganglionic neuron in a ganglion at the same spinal cord level from which it arises. The preganglionic neuron may also travel more rostrally or caudally in the ganglion chain to synapse with postganglionic neurons in ganglia at other levels. In fact, a single preganglionic neuron may synapse with several postganglionic neurons in many different ganglia. Overall, the ratio of preganglionic fibers to postganglionic fibers is about 1:20. The long postganglionic neurons originating in the ganglion chain then travel outward and terminate on the effector tissues. This divergence of the preganglionic neuron results in coordinated sympathetic stimulation to tissues throughout the body. The concurrent stimulation of many organs and tissues in the body is referred to as a mass sympathetic discharge.

Other preganglionic neurons exit the spinal cord and pass through the ganglion chain without synapsing with a postganglionic neuron. Instead, the axons of these neurons travel more peripherally and synapse with postganglionic neurons in one of the sympathetic collateral ganglia. These ganglia are located about halfway between the CNS and the effector tissue. Finally, the preganglionic neuron may travel to the adrenal

medulla and synapse directly with this glandular tissue. The cells of the adrenal medulla have the same embryonic origin as neural tissue and, in fact, function as modified postganglionic neurons. An important feature of this system, which is quite distinct from the parasympathetic system, is that the postganglionic neurons of the sympathetic system travel within each of the 31 pairs of spinal nerves. Interestingly, 8% of the fibers that constitute a spinal nerve are sympathetic fibers.

The response of the two types of fibers may be either antagonistic (as in the heart) or almost parallel (in salivary glands). Functionally, both divisions act synergically on the controlled organ, i.e. the desired response is brought by simultaneous stimulation of one division and stimulation reduction of the other division, and vice versa. The actions of both divisions of the ANS must be balanced to maintain homeostasis. Table 2-1: summarizes the comparison between sympathetic parasympathetic divisions.

Neurotransmitters

The two most common neurotransmitters released by neurons of the ANS are acetylcholine and norepinephrine. Neurotransmitters are synthesized in the axon varicosities and stored in vesicles for subsequent release. Nerve fibers that release acetylcholine are referred to as cholinergic fibers. These include all preganglionic fibers of the ANS, both sympathetic and parasympathetic systems; all postganglionic fibers of the parasympathetic system; and sympathetic postganglionic fibers innervating sweat glands. Nerve fibers that release norepinephrine are referred to as adrenergic fibers. Most sympathetic postganglionic fibers release norepinephrine.

The cells of the adrenal medulla are considered modified sympathetic postganglionic neurons. Instead of a neurotransmitter, these cells release hormones

into the blood. Approximately 20% of the hormonal output of the adrenal medulla is norepinephrine. The remaining 80% is epinephrine. Unlike true postganglionic neurons in the sympathetic system, the adrenal medulla contains an enzyme that methylates norepinephrine to form epinephrine. The synthesis of epinephrine, also known as adrenaline, is enhanced under conditions of stress. These 2 hormones released by the adrenal medulla are collectively referred to as the catecholamines.

Receptors

The effect caused by any of these neurotransmitters is determined by the receptor distribution in a particular tissue and the biochemical properties of the cells in that tissue, specifically, the second messenger and enzyme systems present within the cell. The neurotransmitters of the ANS and the circulating catecholamines bind to specific receptors on the cell membranes of the effector tissue. All adrenergic receptors and muscarinic receptors are coupled to G proteins which are also embedded within the plasma membrane. Receptor stimulation causes activation of the G protein and the formation of an intracellular chemical, the second messenger. The function of the intracellular second messenger molecules is to elicit tissue-specific biochemical events within the cell which alter the cell's activity. In this way, a given neurotransmitter may stimulate the same type of receptor on 2 different types of tissue and cause 2 different responses due to the presence of different biochemical pathways within each tissue.

Acetylcholine binds to 2 types of cholinergic receptors. Nicotinic receptors are found on the cell bodies of all postganglionic neurons, both sympathetic and parasympathetic, in the ganglia of the ANS. Acetylcholine released from the preganglionic neurons binds to these nicotinic receptors and causes a rapid increase in

the cellular permeability to Na^+ ions and Ca^{++} ions. The resulting influx of these 2 cations causes depolarization and excitation of the postganglionic neurons the ANS pathways. Muscarinic receptors are found on the cell membranes of the effector tissues and are linked to G proteins and second messenger systems which carry out the intracellular effects. Acetylcholine released from all parasympathetic postganglionic neurons and some sympathetic postganglionic neurons traveling to sweat glands binds to these receptors. Muscarinic receptors may be either inhibitory or excitatory, depending on the tissue upon which they are found. For example, muscarinic receptor stimulation in the myocardium is inhibitory and decreases heart rate while stimulation of these receptors in the lungs is excitatory, causing contraction of airway smooth muscle and bronchoconstriction.

There are 2 classes of adrenergic receptors for norepinephrine and epinephrine, alpha (α) and beta (β). Furthermore, there are at least 2 subtypes of receptors in each class: α_1, α_2, β_1 and β_2. All of these receptors are linked to G proteins and second messenger systems which carry out the intracellular effects. Alpha receptors are the more abundant of the adrenergic receptors. Of the 2 subtypes, α_1 receptors are more widely distributed on the effector tissues. Alpha one receptor stimulation leads to an increase in intracellular calcium. As a result, these receptors tend to be excitatory. For example, stimulation of α_1 receptors causes contraction of vascular smooth muscle resulting in vasoconstriction and increased glandular secretion by way of exocytosis.

Adrenal medulla

A mass sympathetic discharge, which typically occurs during the “fight-or-flight” response and during exercise, involves the simultaneous stimulation of organs and

tissues throughout the body. Included among these tissues are the adrenal medullae which release epinephrine and norepinephrine into the blood. In large part, the indirect effects of these catecholamines are similar to and, therefore, reinforce those of direct sympathetic stimulation. However, there are some important differences in the effects of the circulating catecholamines and those of norepinephrine released from sympathetic nerves.

The duration of activity of the catecholamines is significantly longer than that of neuronally released norepinephrine. Therefore, the effects on the tissues are more prolonged. This difference has to do with the mechanism of inactivation of these substances. Norepinephrine is immediately removed from the neuro-effector synapse by way of reuptake into the postganglionic neuron. This rapid removal limits the duration of the effect of this neurotransmitter. In contrast, there are no enzymes in the blood to degrade the catecholamines. Instead, the catecholamines are inactivated by COMT in the liver. As one might expect, the hepatic clearance of these hormones from the blood would require several passes through the circulation. Therefore, the catecholamines are available to cause their effects for a comparatively longer period of time (up to 1-2 minutes as opposed to milliseconds).

Because they travel in the blood, organs and tissues throughout the body are exposed to the catecholamines. Therefore, they are capable of stimulating tissues that are not directly innervated by sympathetic nerve fibers: airway smooth muscle, hepatocytes, and adipose tissue, in particular. As a result, the catecholamines have a much wider breadth of activity compared to norepinephrine released from sympathetic nerves. The third important feature that distinguishes the catecholamines from

neuronally released norepinephrine involves epinephrine's affinity for β_2 receptors. Norepinephrine has a very limited affinity for these receptors. Therefore, circulating epinephrine causes effects that differ from those of direct sympathetic innervation including a greater stimulatory effect on the heart and relaxation of smooth muscle (vascular, bronchial, gastrointestinal, and genitourinary).

Epinephrine and norepinephrine have equal affinity for β_1 receptors, the predominant adrenergic receptor on the heart. However, the human heart also contains a small percentage of β_2 receptors which, like β_1 receptors are excitatory. Therefore, epinephrine is capable of stimulating a greater number of receptors and of causing a greater stimulatory effect on the myocardium.

It is well known that vagal nerve stimulation and acetylcholine infusion can result in significant changes in cardiac electrophysiology, including nonuniform effects on atrial refractory periods (120) pacemaker activity and atrioventricular (AV) conduction,(121) and induction of AF (122). Cervical vagal stimulation shortens the atrial effective refractory period primarily in the high right atrium and facilitates induction of AF by a single premature extra-stimulus (123).

Autonomic Control of the Heart

The sinus node has an intrinsic rate of spontaneous depolarization, known as the intrinsic HR (10). The intrinsic HR is the HR measured in the absence of sympathetic and parasympathetic inputs (achieved by denervation or pharmacologic blockade). In healthy human subjects, this is approximately 100 beats/min and is age and gender dependent endurance exercise-trained individuals may have a lower intrinsic HR (124). Other non-autonomic contributions to changes in HR are hypoxia, circadian rhythm and temperature (125, 126). Thus, sympathetic and parasympathetic effects on the intrinsic

HR predominantly determine the actual HR. The heart is innervated by the sympathetic and the parasympathetic nervous systems; their influence on ion channels is manifested as changes in the heart rate, refractoriness, and contractility.

The ventrolateral medulla (VLM) is a functionally identified region within the medulla oblongata that has been shown to be involved in regulation of cardiovascular activity. Anatomically, the VLM has been divided into rostral (RVLM) and caudal (CVLM) divisions (127, 128). The RVLM comprises the nucleus reticularis paragigantocellularis, nucleus reticularis gigantocellularis, nucleus reticularis parvocellularis, the C1 area, and the rostral portion of the nucleus ambiguus (128). The CVLM comprises the A1 region, the caudal portion of the nucleus reticularis gigantocellularis, nucleus reticularis ventralis, lateral reticular nucleus, and the caudal portion of the nucleus ambiguous (127). Electrical or chemical stimulation of the RVLM neurons elicits a pressor response associated with an increase in heart rate and sympathetic activity, RVLM being referred to as the ‘pressor area' (129). In contrast, similar stimulation of the CVLM neurons evokes a decrease in blood pressure, bradycardia, and a reduction in sympathetic nerve activity. This area is commonly known as the ‘depressor area' (127, 128).

The HR control is mainly determined by the outflow from the cardiovagal motoneurons that are located in the nucleus ambiguus and the dorsal vagal nucleus (130, 131). The cardiovagal motoneurons in the nucleus ambiguus are excited by afferent inputs from the peripheral baroreceptors (131), arterial chemoreceptors and unmyelinated cardiac afferents. This excitatory effect is mediated via a direct monosynaptic projection from the nucleus tractus solitarius, which relays baroreceptor afferent inputs, and a supramedullary pathway that may involve the parabrachial

nucleus and the anterior hypothalamus (131). Stimulation of the anterior hypothalamus inhibits the activity of cardiovagal motoneurons in the nucleus ambiguus via direct short-latency inhibition mediated by the gamma-aminobutyric acid-A receptors, disfacilitation due to inhibition of the neurons of the nucleus tractus solitarius activated by baroreceptor afferents, and an increase in inspiratory drive (131). Respiration affects the basic discharge of cardiovagal motoneurons and their sensitivity to central and reflex inputs (132), causing hyperpolarization during inspiration. It is the main determinant of respiratory sinus arrhythmia, which is an important clinical index of vagal innervation to the heart (133). Individual neurons of the nucleus ambiguus and the dorsal vagal nucleus innervate either the sinoatrial or the atrioventricular node, but not both. Therefore, the CNS may selectively influence the sinoatrial or atrioventricular node together or independently. The nucleus tractus solitarius integrates the inputs from peripheral visceral receptors with those from higher control centers like the prefrontal cortex, the central nucleus of the amygdala, the hypothalamus and the periaqueductal gray matter, and modifies the gain of baroreflexes and other cardiorespiratory responses during exercise and other adaptive conditions (134). Most cardiac branches of the vagal nerve separate in the thorax and innervate several cardiac ganglion cells, using acetylcholine as transmitter(135). The vagal inputs produce mainly fast excitatory postsynaptic potentials via nicotinic receptors and to a lesser extent slow inhibitory potentials via muscarinic receptors (136). Acetylcholine, activating the M_2 subtype of muscarinic receptors, mediates the parasympathetic influence on the heart. The activation of these receptors leads to an increase in potassium conductance and a

decrease in cyclic adenosine monophosphate via G-protein mediated mechanisms (136).

Parasympathetic stimulation

Stimulation of the parasympathetic nerve to the heart, the vagus nerve, causes the hormone acetylcholine to be released at the vagal endings. This hormone has two major affects on the heart. First it decreases the rate or rhythm of the sinus node and second, it decreases the excitability of the A-V junctional fibers between the arterial musculature and the A-V node, thus slowing transmission of the cardiac impulse into the ventricles. Moderate stimulation can slow the rate of the heart pumping to as little as one-half of the normal rate. Strong vagus stimulation can stop the rhythmical excitation of the sinus node or block transmission of the cardiac impulse through the A-V junction. In either case, rhythmical impulses are no longer transmitted into the ventricles. The ventricles usually stop beating for 5-20 seconds, where after the Purkinje fibres develop a rhythm of their own and cause ventricular contraction at a rate of 15-40 beats per minute. This phenomenon is called ventricular escape (137).

During rest, the cardio motor centre continuously discharges impulses via the vagus to the heart. The resultant cardio-inhibitory effect of the vagus is called “vagal tone”, and is quite considerable during rest. Effective physical training increases vagal tone, and fit athletes have therefore a slower stroke rate but a greater stroke volume than unfit persons (137-139). The acetylcholine released at the vagal nerve endings binds to muscarine (N2) receptors and greatly increases the permeability of the fiber membranes to potassium, which allows rapid leakage of potassium out of the conductive fibers. This causes an increased negative potential inside the fibers. This effect is called hyper-polarization, which makes the tissue much less excitable (137,

140, 141). In the sinus node, the state of hyper polarization decreases the “resting” membrane potential of the sinus nodal fibers to a level more negative (-65 to -75 millivolts), than the normal level of -55 to -60 millivolts. Therefore the drift of the resting membrane potential caused by sodium leakage takes longer to reach the threshold potential for excitation. This greatly slows the rate of rhythmicity of these nodal fibers. If the vagal stimulation is strong enough, it is possible to stop the rhythmical self-excitation of this node. In the A-V node, the state of hyper polarization makes it difficult for the minute junctional fibers, which can generate only small quantities of current during the action potential, to excite the nodal fibers. Therefore, the safety factor for transmission of the cardiac impulses through the junctional fibers and into the nodal fibers decreases. A moderate decrease simply delays conduction of the impulse, but a decrease in safety factor below unity (so low that the action potential of a fiber cannot cause an action potential in the successive portion of the fiber), blocks conduction (137, 140, 141).

Sympathetic stimulation

Sympathetic stimulation causes essentially the opposite effects on the heart to those caused by vagal stimulation. First it increases the rate of sinus nodal discharge. Secondly, it increases the rate of conduction as well as the level of excitability in all portions of the heart. Thirdly, it greatly increases the force of contraction of all the cardiac musculature, both arterial and ventricle. In short: sympathetic stimulation increases the strength of heart contraction up to two fold. In contrast to the parasympathetic fibers, the sympathetic discharge occurs at a low level during rest and increases sharply during stress (physical, mental, and traumatic stress) (137, 138).

The permeability of the fiber membrane to sodium and calcium increases upon sympathetic stimulation. In the sinus node, an increase of sodium permeability causes a

more positive resting potential and an increased rate or upward drift of the membrane potential to the threshold level for self excitation. This accelerates the onset of self-excitation and therefore the heart rate. In the A-V node, increased sodium permeability makes it easier for the action potential to excite each succeeding portion of the conducting fiber, thereby decreasing the conduction time from the atria to the ventricles. The increase in permeability to calcium ions is at least partially responsible for the increase in contractile strength of the cardiac muscle under the influence of sympathetic stimulation because calcium ions play a powerful role in exiting the contractile process of the myofibrils (137-139, 142, 143).

Reflex control of heart rate

The reciprocal association between sympathetic and vagal nerve control forms the basis for several cardiac reflexes.

Baroreceptor reflex. Baroreceptors are pressure sensors comprising of pressure sensitive nerve **endings**. They are located in the elastic segments of arterial walls and respond to stretching. Baroreceptors detect vessel stretch caused by pressure increases, codifying this information into bursts of action potentials (proportional to pressure changes), which are then sent to the nucleus tractus solitarii (NTS) in the dorsal brainstem, the primary termination site for the cardiovascular afferents. Second-order NTS glutamatergic neurons (as well as higher-order NTS neurons) excite both parasympathetic preganglionic cell bodies (in the dorsal motor nucleus of the vagus and nucleus ambiguus) and the sympathetic cell groups in the caudal ventrolateral medulla (CVLM; GABAergic inhibitory neurons) that project to and inhibit rostral ventrolateral medulla (RVLM) glutamatergic neurons, thus decreasing sympathetic preganglionic neuronal outflow. During unloading of baroreceptors, increased sympathetic and

decreased parasympathetic outflows (regulated by this simple reflex loop integrated within the brainstem), cause a marked bradycardic response, diminished cardiac output, increased venous capacitance and decreased total peripheral resistance (144, 145). Opposite autonomic effects, i.e. reduced parasympathetic and increased sympathetic drive, are observed during loading of the baroreceptors (145, 146). Oscillations in blood pressure accompany self-oscillations in the vasomotor part of the baroreflex loop and are termed Mayer waves. These are mediated by the interaction between the sympathetic and parasympathetic nervous system. Mayer waves are oscillations of arterial pressure occurring spontaneously in conscious subjects at a frequency lower than respiration (~0.1 Hz in humans) (137, 138, 147). Mayer waves are tightly coupled with synchronous oscillations of efferent sympathetic nervous activity and are almost invariably enhanced during states of sympathetic activation. For this reason, the amplitude of these oscillations has been proposed as a surrogate measure of sympathetic activity (148-150).

Bainbridge reflex. High-pressure sensitive receptors in the left ventricle and low-pressure responsive elements in the atria and right ventricle consist of stretch-induced mechanoreceptors that respond to pressure or volume changes. These receptors activate myelinated vagal afferent fibers that project to the nucleus solitarius and increase sympathetic nerve activity to the SA node but not to the ventricles, thereby increasing heart rate but not contractility (151-153). Distention of these mechanoreceptors also increases renal excretion of free water by inhibition of antidiuretic hormone secretion from the posterior lobe of the pituitary gland (137, 138, 147, 154, 155). It appears highly likely that the Bainbridge reflex may be mediated by

distention of these mechanoreceptors. Second, a diffuse receptor network is distributed throughout the cardiac chambers that projects via unmyelinated vagal afferent neurons to the nucleus tractus solitarius. These receptors behave like the carotid and aortic mechanoreceptors and produce a vasodepressor response consisting of vagus activation concomitant with a simultaneous increase in venous capacitance (151-153).

Respiratory centre reflex of the medulla A third reflex occurs during excitation of the respiratory centre in the medulla. Impulses “spill-over” from the respiratory centre into the vasomotor centre, with effects on the sympathetic and parasympathetic nervous systems activity(138).

Respiratory sinus arrhythmia (RSA) RSA causes rhythmical variations in the heart at the respiration frequency. The RSA is based on the simultaneous influence of the three above-mentioned physiological reflexes on the heart rate. Stimulation of the Bainbridge reflex results in a corresponding stimulation of the baroreceptor reflex aimed at decreasing the heart rate. The combined action of the Bainbridge and baroreceptor reflexes, plus the third reflex that occurs in the respiratory centre of the medulla, has the effect that normal respiration may increase and decrease heart rate by approximately 5% during inspiration and expiration respectively (137, 138, 147).

Heart rate fluctuation is thus a result of various factors, which are often difficult to discern from total behavior, which combine different wave forms. Thus, by studying heart rate variability, we have an opportunity to study the cardiac dynamic behavior influenced by a variety of endogenous and exogenous factors. It is possible to obtain information about the nature of the perturbations to which the cardiovascular system is

exposed as well as the regulatory responses to these perturbations. Figure 2-1 summarizes the influences on the heart rate.

Techniques that are available for the study of autonomic nerve activity in humans do not allow any direct exploration of vagal efferent activity. Earlier research suggests the use of heart rate variability as a surrogate measure of vagal control of the sinoatrial node (156). With regard to sympathetic nerve activity, several studies have indicated the interesting capabilities of two of the most widely used techniques plasma catecholamine levels and muscle sympathetic neural activity (157).

Heart Rate Variability Analysis

Measure of Autonomic Tone

Heart rate variability (HRV), the variation over time of the period between consecutive heartbeats, is predominantly dependent on the extrinsic regulation of the heart rate. HRV is thought to reflect the heart's ability to adapt to changing circumstances by detecting and quickly responding to unpredictable stimuli. HRV analysis is the ability to assess overall cardiac health and the state of the autonomic nervous system (ANS) responsible for regulating cardiac activity.

It is known that the vagus nerve is primarily responsible for momentary short term changes in heart rate. It follows that quantification of the beat-to-beat, high frequency variability of heart rate is an index of vagal/parasympathetic influence on the heart. Parasympathetic control is related to central vagal outflow to the heart, mean level of vagal effect on the heart (cardiac vagal tone), phasic variation of vagal influence on the heart associated with respiration, and dynamic vagal responses that influence RR-interval, including the parasympathetic baroreflex response. In a normal, healthy heart the rate is restrained by parasympathetic tone. This means that the heart rate can rise

by 40-50% when the vagal supply is compromised. That is from average 70 to 100 beats per minute (158). A lower frequency heart rate variation is considered to be influenced by both sympathetic and parasympathetic (vagal) nervous system(159).

High frequency and low frequency (HF and LF) variation is thus derived from at least partly distinct, although overlapping physiologic mechanisms. Very low and ultra low frequencies have been reported for circadian rhythms, changes in activity, posture, periodic breathing, autonomic outflow, state of arousal, thermoregulatory cycles and fluctuations in plasma renin activity (159). The mechanisms are, however still somewhat unclear. During this study only high and low frequencies variations were studied.

The timing of dynamic and steady state effects differ between vagal and sympathetic heart rate control. The parasympathetic nervous system is able to modulate heart rate at all frequencies, while the sympathetic system modulates heart rate at lower frequencies (160-163). Cardiovascular health in general has been associated with higher variability at all frequencies. It is this ever-changing rhythm that acts as a buffer against internal and external stresses to maintain homeostasis. The sympathetic and parasympathetic autonomic branches are tonically active to maintain this steady internal environment. Under resting conditions (“rest and digest”), vagal tone prevails but can be swiftly replaced by the “fight or flight” reaction from the sympathetic division (164-166). The autonomic branches can, depending on the external and internal demands, be controlled reciprocally, independently, or be co-activated or co-inhibited (167).

Heart Rate Variability Autonomic Nervous System Testing

HRV analysis has been used for the assessment of ANS responses during standard autonomic tests, in which a selective stimulus elicits sympathetic (rest to tilting,

cold pressure test, etc.) or parasympathetic (deep breathing, valsalva maneuver) responses (168, 169). The pronounced, acute changes after the stimulus are important for grading the autonomic performances and for evaluating neuroregulatory disorders. Early responses to tilt have shown both vagal and sympathetic changes: the almost instantaneous disappearance of the HF component was accompanied by a slower, progressive increase in the LF components (170, 171). The response was dependent on the amplitude of the stimulus: a faster (and larger) sympathetic response was observed for more pronounced tilt angels (172). When the tilt was prolonged, oscillations and non-stationarity characterized the trend of the LF components, being more evident in patients with syncope (173). Autonomic unbalance before syncope has also been assessed using the time-varying method (172, 173). documenting a sympathetic withdrawal preceding syncope, which may be either sudden or progressive. This withdrawal has also been confirmed by the analysis of MSNA variability analysis (174).

Heart Rate Variability Frequency Domain Analysis

The time intervals between consecutive heart beats are customarily measured in the electrocardiogram from the beginning of a QRS complex to the beginning of the next QRS complex, so these intervals might be called QQ intervals, but they are conventionally named RR intervals. Although custom dictates using the beginning of the QRS complex as the reference (fiducial) point, it should be noted that this point can be difficult to locate in noisy or low amplitude ECGs, leading to measurement error. Many investigators prefer to measure inter-beat intervals using the R-wave peak as the reference point, reasoning that this measurement can be made with smaller errors. If the measurements are being made for the purpose of studying RR or heart rate

variability, it is appropriate to make such a choice in order to obtain more accurate measurements of intrinsic variability.

Definition: Physiological data collected as a series in time, as with any time series, may be considered a sum of sinusoidal oscillations with distinct frequencies. Conversion from a time domain to frequency domain analysis is made possible with a mathematical transformation developed almost two centuries ago (1807) by the French mathematician Jean-Babtiste-Joseph Fourier (1768–1830). Other transforms exist (e.g. wavelet, Hilbert), but Fourier was first and his transformation is used most commonly. The amplitude of each sine and cosine wave determines its contribution to the biological signal; frequency domain analysis displays the contributions of each sine wave as a function of its frequency. Facilitated by computerized data harvest and computation, the result of converting data from time series to frequency analysis is termed spectral analysis because it provides an evaluation of the power (amplitude) of the contributing frequencies to the underlying signal.

Frequency domain analysis yields information about the amount of the overall variance in heart rate resulting from periodic oscillations of heart rate at various frequencies. Because heart rate (or, more accurately, heart period) is measured in milliseconds, variance, which is referred to as the “power” in a portion of the total spectrum of frequencies, is measured in milliseconds squared. Some investigators report spectral “amplitude,” which is the square root of power and is measured in milliseconds. Fig. 2-3 represents a hypothetical analysis in the frequency domain. In this drastically simplified example, total variability is assumed to be a result of only three frequencies, shown superimposed in Fig. 1 (top left): a “high” frequency of 0.25 Hz (15

cycles per minute), a “low” frequency of 0.1 Hz (6 cycles per minute), and a “very low” frequency of 0.016 Hz (1 cycle per minute). Fig. 1 (top right) shows the signal that results when the underlying frequencies in Fig. 1 (top left) are combined. Finally, Fig. 1 (bottom left) shows the result of a Fourier analysis on the signal in Fig. 1 (top right).

Calculation: Frequency domain measures use spectral analysis of a sequence of R-R intervals and provide information on how power (variance) is distributed as a function of frequency. Short-term recordings (5 min) yield up to 3 peaks in very low (0.003 to 0.04 Hz; VLF), low (0.04 to 0.15 Hz; LF), and high (0.15 to 0.4 Hz; HF) frequency ranges. One reason for the association of each limb of the autonomic nervous system with a different frequency range stems from the fact that the timing of the HR response to autonomic nerve activity is not identical for each limb. Although a burst of vagal nerve activity has a maximal effect at 0.6 s with a return to baseline within 1 s, a sympathetic burst has no effect for 1 s, a maximal effect at 4 s, and a return to baseline within 20 s (175, 176). Both cardiac and peripheral sympathetic responses have a similar time delay (175, 176). The short delay of the vagal cardiac responses allows the parasympathetic nervous system to modulate HR at all frequencies between 0 and 0.5 Hz, although the sympathetic system has significant gain only below 0.15 Hz (177). Muscle sympathetic nerve activity has been shown to fluctuate every 10 s (178) a period long enough for vascular smooth muscle and sinus node effectors to respond to released norepinephrine and modulate blood pressure and HR (179). This period corresponds to the LF range observed in HRV. The absolute and normalized LF powers have therefore been used as an index of sympathetic modulation of the heart rate, and the ratio of absolute LF to HF power has been used as an index of “sympathovagal

balance” (179, 180). The third main spectral component in the frequency domain is the very low frequency power (VLF, ≤0.04 Hz). Its physiological explanation is less defined and the existence of its physiological background might even be questioned. Total power (TP, ≤0.4 Hz) expresses variance of RR intervals over the measured period (181). The measurement of VLF, LF, and HF is usually made in absolute values, but LF and HF can also be calculated in normalized units, which represent the relative value of each power component in proportion to the total power minus the VLF component (181). The low frequency power (LFP) (0.04 to 0.15 Hz) and high frequency power (HFP) (0.15 to 0.4 Hz) were derived from the sum of area within specific frequency range under the power spectrum density curve and expressed in absolute units (ms2) and normalized units (n.u.) (181).

Table 2-1 summarizes the description and normal values of frequency domain measures of heart rate variability. Figure 2- 2 [adopted with permission from (18)] represents the interval tachogram in a normal subject at supine rest (a) and after head-up tilt (b). The HRV spectra are shown calculated by parametric autoregressive modeling (c and d) and by a fast Fourier transform–based nonparametric algorithm (e and f). For c and d, VLF, LF, and HF central frequency, power in absolute value and power in normalized units (n.u.) are also indicated. In e and f, the peak frequency and the power of VLF, LF, and HF were calculated by integrating the power spectral density (PSD) in the defined frequency bands.

Summary and Significance

In summary, PMV is associated with a high risk of mortality, morbidity and healthcare cost. Weaning trials are recommended for the patients who are ready-to-wean. There is growing evidence that transition from mechanical ventilation support to

spontaneous breathing causes hemodynamic instability. Moreover, the underlying pathophysiological processes inherent to the critical illness may affect a patient's ability to compensate making the weaning from mechanical ventilatory support a cardiovascular stress. Furthermore, psychological factors secondary to the apparent loss of the life support may also contribute to the overall physiological stress. Failing a spontaneous breathing trial is an extremely stressful experience for the patients and monitoring the stress level during the spontaneous breathing trial can help to stop the trial at an early stage. There are no data examining the physiological stress level during SBT in PMV patients. This will be the first study to quantify the physiological stress during SBT in PMV patient. Using a within subject design this study will also help validate the use of heart rate variability analysis as a bedside tool to evaluate the physiological stress during weaning trials.

Table 2-1Respiratory load capacity imbalance factors causing weaning failure

Factors that result in decreased neuromuscular competence

Decreased drive	Muscle weakness	Impaired neuromuscular transmission
Drug overdose	Electrolyte derangement	Critical illness polyneuropathy
Brain-stem lesion	Malnutrition	Neuromuscular blockers
Sleep deprivation	Myopathy	Aminoglycosides
Hypothyroidism	Hyperinflation	Guillain-Barré syndrome
Starvation/malnutrition	Drugs, corticosteroids	Mysthenia gravis
Metabolic alkalosis	Sepsis	Phrenic nerve injury
Myotonic dystrophy		Spinal cord lesion

Factors that result in increased respiratory load

Increased resistive loads	Increased chest wall elastic loads	Increased lung elastic loads
Bronchospasm	Pleural effusion	Hyperinflation (intrinsic positive end-expiratory pressure)
Airway edema, secretions	Pneumothorax	Alveolar oedema
Upper airway obstruction	Flail chest	Infection
Obstructive sleep apnea	Obesity	Atelectasis
Endotracheal tube kinking	Ascites	Interstitial inflammation and/or oedema
Secretions encrustation	Abdominal distension	
Ventilatory circuit resistance		

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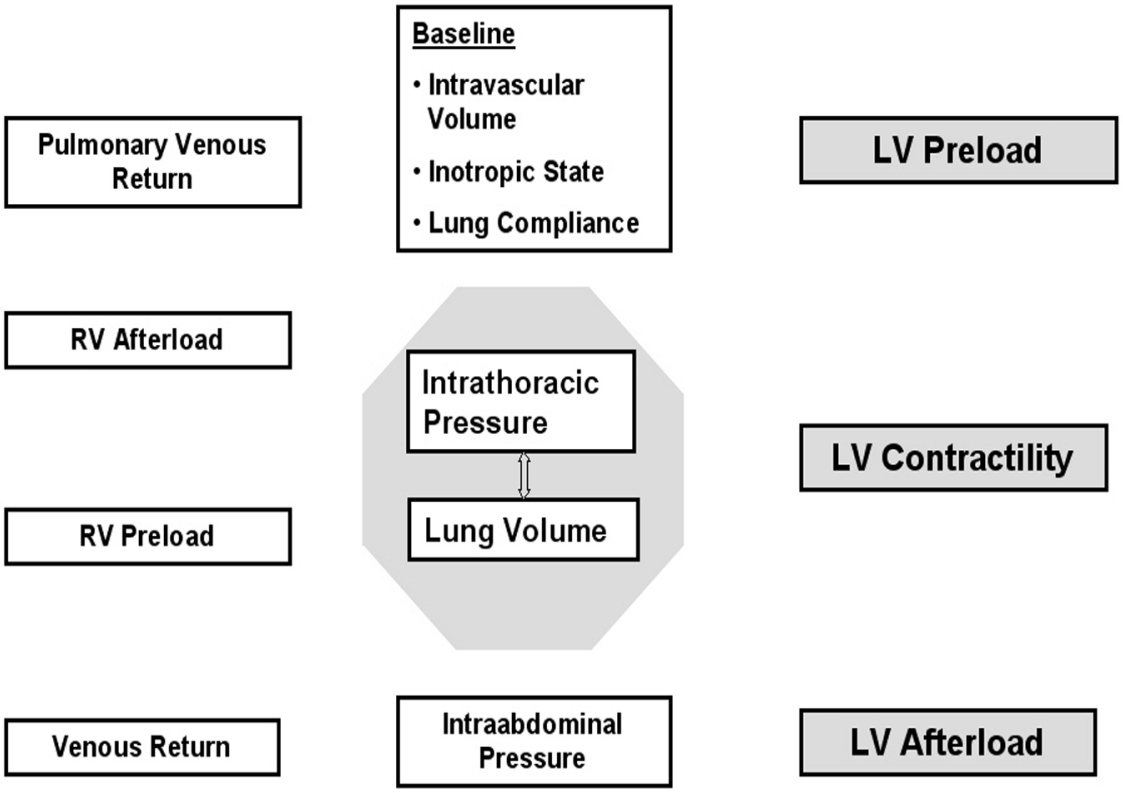
Table 2-2 Comparison sympathetic parasympathetic division

Sympathetic System	Parasympathetic Systems
Originates in thoracic and lumbar regions of the spinal cord (T1-L2)	Originates in brainstem (cranial nerves III, VII, IX, and X) and sacral region of spinal cord (S2-S4)
Ganglia located in paravertebral sympathetic ganglion chain or collateral ganglia	Terminal ganglia located near or embedded within target tissue
Short cholinergic preganglionic fibers; long adrenergic postganglionic fibers	Long cholinergic preganglionic fibers; short cholinergic postganglionic fibers
Ratio of preganglionic fibers to postganglionic fibers is 1:20	Ratio of preganglionic fibers to postganglionic fibers is 1:3
Divergence coordinates activity of neurons at multiple levels of spinal cord	Limited divergence
Activity often involves mass discharge of the entire system	Activity normally to discrete organs
Primary neurotransmitter of postganglionic neurons is norepinephrine	Primary neurotransmitter of postganglionic neurons is acetylcholine
Predominates during emergency ‘‘fight-or-flight’’ reactions and exercise	Predominates during quiet resting conditions

Table 2-3 Frequency domain analysis of Heart rate variability

Variable (Unit)	Description	Normal Values
Total power (ms2/Hz)	The total area under the curve in a power spectrum plot. The ms2/Hz unit is considered an absolute unit of measure.	3466 ± 1018 ms2/Hz
ULF (ultra low frequency)	The peak frequency found in this defined range; obtained from 24-h recordings and may be a graphical representation of direct current (DC).	0.00-0.003 Hz
VLF (very low frequency)	The peak frequency found in this defined range. The physiological significance is unknown but may correspond to thermoregulation. VLF power affected by mathematical algorithms of trend (baseline) removal.	0.003-0.04 Hz
LF (low frequency)	The peak frequency found in this defined range. Both parasympathetic and sympathetic activity influences this component, which may reflect baroreflex-mediated modulatory activity.	0.04-0.15 Hz
LF power (ms2/Hz)	The area under the spectral curve within this frequency range.	1170 ± 416 ms2/Hz
LF power (nu)	Measure represents relative proportional value of LF power to total power; calculated as (LF power/(total power – VLF power)) × 100.	54 ± 4 nu
HF (high frequency)	The peak frequency found in this defined range, which is influenced by both respiratory and parasympathetic activity.	0.15-0.4 Hz
HF power (ms2/Hz)	The area under the spectral curve within this frequency range.	975 ± 203 ms2/Hz
HF power (nu)	Measure represents relative proportional value of HF power to total power; calculated as (HF power/(total power – VLF power)) ×100	29 ± 3 nu
LF/HF ratio	Calculated as LF power/HF power. This controversial measure is considered an assessment of sympathovagal balance.	1.5-2.0

Figure 2-1Schematic representation cardiopulmonary interactions



Adopted from Luecke and Pelosi Clinical review: Positive end-expiratory pressure and cardiac output *Critical Care* 2005 9:607 (67)

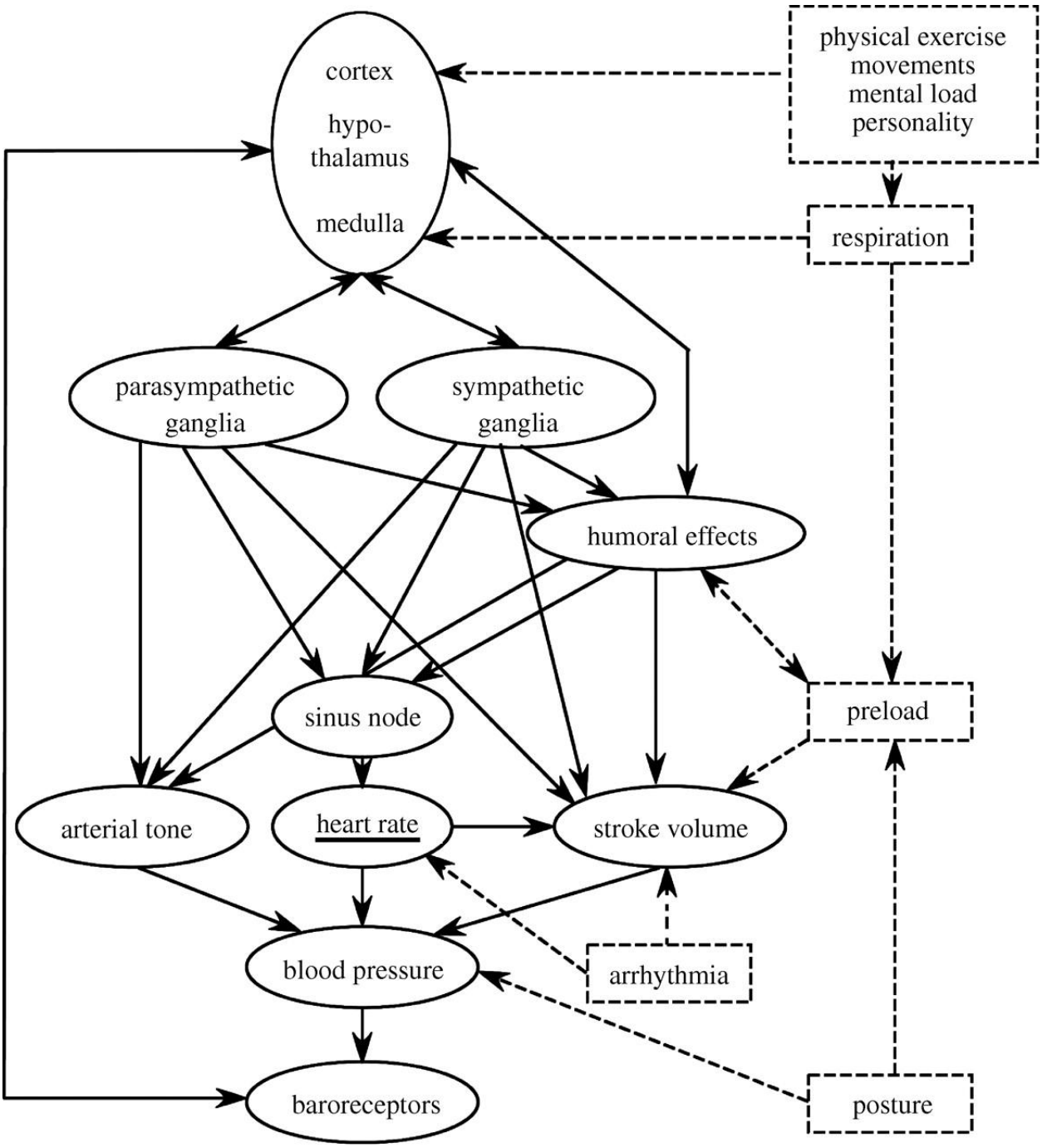


Figure 2-2 A simplified model of heart rate regulation

Additional factors influencing considerably the HR are shown within the dashed boxes. [adopted with permission from (182)].

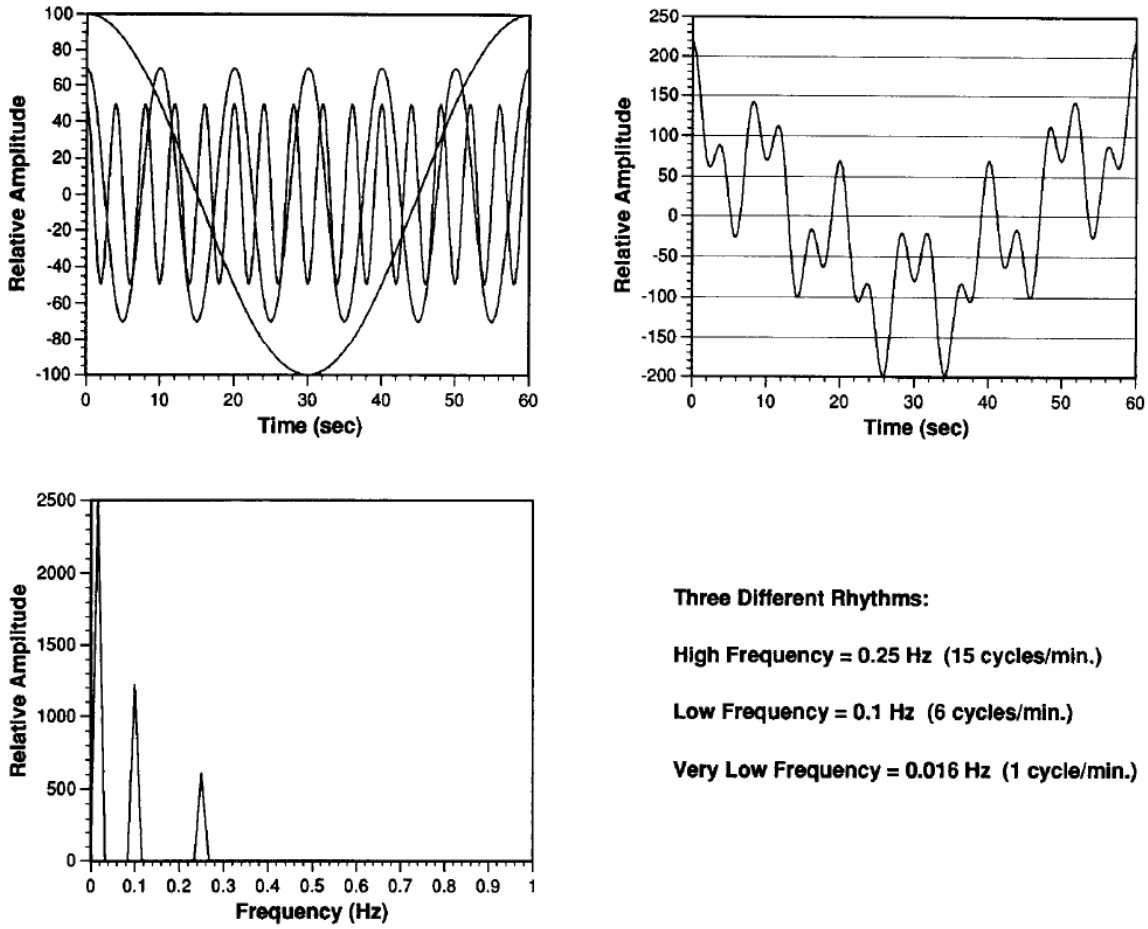


Figure 2-3 Frequency Domain Analysis

(Top left) Three sinusoidal signals: 1 cycle/min, 6 cycles/min, and 15 cycles/min shown superimposed on the same scale. (Top right), Same three signals combined into one signal. (Bottom left), Power spectral analysis of signal shown top right. [adopted with permission from (183)].

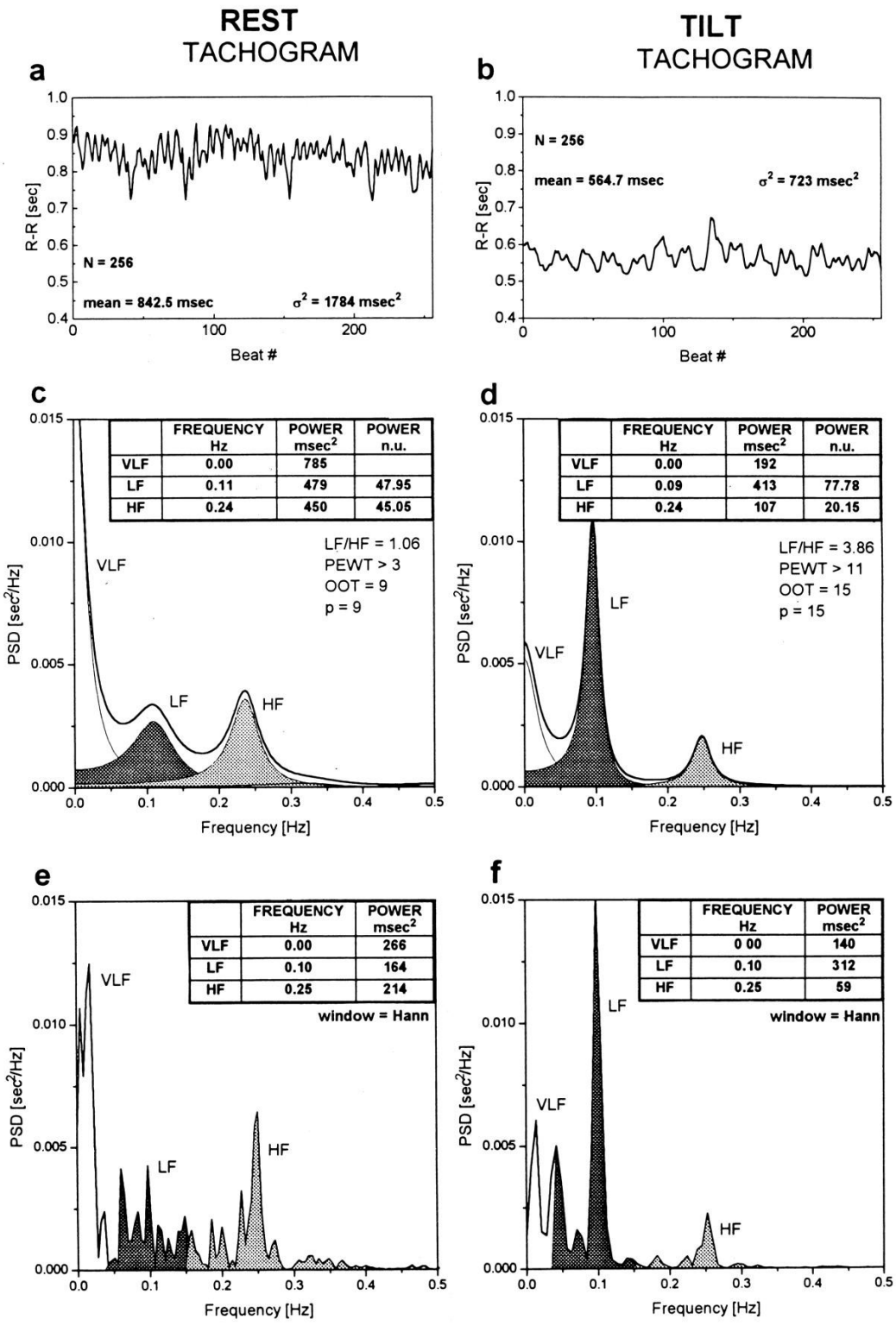


Figure 2-4 Heart Rate Variability Frequency Domain Analysis

[adopted with permission From (18)]

CHAPTER 3
MATERIALS AND METHODS

Research Design

This prospective, observational study was conducted in the Surgical and Intermediate Care Unit at Shands Hospital at the University of Florida. The study protocol was approved by the University of Florida Institutional Review Board and informed consent was obtained from each subject prior to participation in the study.

Power Analysis & Sample Size Estimation

A power analysis was conducted to determine a sufficient sample size. Because the experimental model was novel, we applied existing data from previous studies.

In the specific aim # 1, we studied the change in the stress level in PMV patients using heart rate variability parameters using a within subject design. A previous study by Shen et al. (184) compared the heart rate variability measures during assist control mechanical ventilation support (ACMV) to pressure support ventilation (PSV) and SBT in patients who failed and patients who were successful. In the patients who failed the weaning trial the low frequency power to the high frequency power ratio was significantly different comparing ACMV to PSV and SBT. The LF/HF ratio decreased from 1.46 ± 0.03 to 1.42 ± 0.03 comparing ACMV to SBT in patients who failed the weaning trial. The power analysis (185) for this work indicated that a sample size of 10 patients was sufficient to yield statistical significance for LF/HF ratio with a power ($1-\beta$ error probability) =0.85 [Figure 3-1].

In the specific aim # 2, we compared the change in the stress level in PMV patients using plasma catecholamine levels using a within subject design. A previous study by Frazier et al. (16) compared the changes in plasma catecholamine during MV support

and at 1 hr after initiation of a CPAP trial in patients who failed with successful patients. The change within subjects in plasma catecholamines over time was compared using a paired *t* tests (baseline, weaning) in failed SBT found a significant increase in the plasma epinephrine level. Those patients who failed the CPAP trial had lower concentrations of catecholamines than the successful group while receiving baseline MV and increased plasma epinephrine from 68$\pm$43 to CPAP 119$\pm$100 (pg/ml). A power analysis (185) of this work indicated that a sample size of 10 patients was sufficient to yield statistical significance for plasma epinephrine with a power (1- β error probability) =0.85 [Figure 3-2]. An important difference between this study and the current protocol is that this protocol will compare the catecholamines during MV support and during SBT failure. However, we expect the stress levels to be higher during completely unassisted SBT as compared to CPAP trials.

Collectively, the power analysis showed that a sample size of 10 patients should be sufficient to yield statistical significance. Additionally, we decided to drop any selected patients if any unforeseen morbidities occurs during the study. However, we suspected that a drop-out rate would be very low since this is a one-time visit observational only study.

Methods and Measurements

Patients

These patients were a subset of patients from the study 'Respiratory Muscle Training in Ventilator Dependent Patients (NIH R01 HD042705). The patients were selected from a pool of candidates recovering from acute respiratory failure of various etiologies in the surgical intensive care unit and the intermediate respiratory Care Unit at Shands hospital. All patients were tracheostomized during their illness and have categorized to prolong mechanically ventilated patients (at least three weaning attempts or require $\geq$ 21 days of weaning). Informed consent was obtained from the patient or an appropriate surrogate for those patients who met inclusion criteria.

Inclusion criteria

- Patient demonstrating an improvement or resolution of the underlying cause of respiratory failure and adequate gas exchange (e.g. PaO2 ≥ 60 mm Hg while breathing with a $FiO_2 \leq 50\%$; PEEP ≤ 8 cm H_2O; while receiving assist control or SIMV/pressure support MV.
- Patient is medically stable and ready to be weaned from the ventilator as determined by the attending physicians.
- Patient has a cardiac rhythm originating from the sinus node.
- Patient demonstrating stable cardiovascular system (eg. HR<140; stable BP)
- Patient demonstrating stable metabolic status (e.g. acceptable electrolytes)
- adequate mental status (arousal, Glasgow Coma Scale score of >13, and no continuous sedative infusions)
- sinus rhythm with only rare episodes of ectopy.

Exclusion criteria

- hemodynamically significant valvular or congenital heart disease, severe hypertension, atrial fibrillation or flutter
- presence of a cardiac pacemaker
- history of a myocardial infarction or cerebrovascular accident within the past 6 months
- β- adrenergic antagonist drugs (Task Force, 1996)(18).
- history of a spinal cord injury or any progressive neuromuscular disease, such as ALS, muscular dystrophy, multiple sclerosis that will interfere with neurologic breathing controller.
- history of diabetes or chronic obstructive pulmonary disease
- patients requiring continuous analgesic agents that would depress respiratory drive were excluded.
- Patients with frequent dysrhythmias were excluded from study.

Spontaneous Breathing Trials

SBT were started between 8:00 am to 9:00 am and lasted until failure or the predetermined duration was reached. During SBT, the patient was disconnected from the ventilator and required to breathe spontaneously while receiving supplemental oxygen to keep SpO2 > 90%. Patients were maintained in a semi-recumbent position (keeping head-end of the bed 30° elevated). During SBT, all patients received routine nursing care, but no rehabilitation services.

A failed SBT was defined as inability to sustain spontaneous breathing effort for the predetermined duration of the trial followed by reinstitution of MV. Criteria for terminating a SBT included:

- oxygen saturation (SPO2) < 85-90%
- respiratory rate > 35 breaths/min
- respiratory rate change > 50%
- heart rate > 140 beats/min,
- blood pressure change > 20%
- change in mental status (e.g. agitation, anxiety)
- signs of increased work of breathing (e.g. use of accessory respiratory muscles, paradoxical breathing movements)
- onset or worsening of discomfort, diaphoresis.

Data Collection

Demographic data and selected clinical data were collected from the medical records. The clinical features included age, gender, weight, BMI, reasons for initiation of ventilator support, duration of MV use prior to SBT and Acute Physiology and Chronic Health Evaluation (APACHE II) Score.

The data were collected at two points, first when the patient was receiving MV support and last at the point of failure during the SBT. On both points the measured parameters included R-R interval tachogram, plasma catecholamines and arterial blood gases. Breathing parameters were measured on MV and during SBT till failure.

Heart rate variability

The Heart Rhythm Scanner was connected to the subject through Biocom Active ECG unit through 3 small electrodes. The ECG electrodes were attached to the left arm, right arm, and left leg.

All intervals between adjacent QRS complexes resulting from sinus node depolarization were recorded for five minute epochs in a continuous EKG record with the Biocom Heart Rhythm Scanner (Active ECG, Biocom Technologies, Seattle, Washington). The Heart Rhythm Scanner conforms to standards set forth by the North American Society of Pacing and Electrophysiology (1996) (186).

For each epoch, noise artifact and irregular heartbeats were manually edited by visual inspection. This included checking each ECG tracing to make sure that accurate ECG R-R intervals are recorded for HRV analysis. Only the beats that had normal morphological characteristics were used for analysis We excluded complete measurement epochs where events such as extra systolic heartbeats, skipped beats, and other arrhythmias comprised greater than 10% of the total epoch. The power spectral density then was calculated using a Fast Fourier transform (FFT).

Breathing variables analysis

A computerized pulmonary monitoring system (CO_2SMO Plus, Novametrix Medical System Inc. Wallingford, Connecticut, USA), incorporating an adult flow sensor placed between the tracheal canula and the T-piece of the breathing circuit, was used to measure the breathing variables. The monitor was calibrated at the beginning of each testing sequence. Respiratory variables were computed during steady-state breathing with a moving average over the last 8 breaths.

These variables, included minute ventilation (V_E), respiratory rate (RR), inspired tidal volume (Vt_i), peak inspiratory flow (PIF), inspiration time (Ti), expiration time (Te), the duty cycle [Ti/(Ti+Te)], and mean inspiratory flow rate (Vt_i/Ti) were recorded electronically with Analysis Plus software (Novametrix Medical System Inc. Wallingford, Connecticut, USA) on a laptop computer.

Blood gas analysis

An arterial whole blood specimen was obtained from each patient by his/her ICU nurse. The blood samples for blood gas analysis were collected anaerobically into 5-ml heparinized cooled glass syringes. The ABG syringe was transported on ice to the hospital core laboratory. Samples were immediately processed within a calibrated Chiron 855 ABG analyzer (Chiron Diagnostics, Medfield, MA, USA) which is calibrated automatically with known standards every 2 hr and with manual controls run twice daily. All blood gas values were corrected to 37°C body temperature.

The following parameters were determined: pH, partial pressure of carbon dioxide ($PaCO_2$, mmHg), partial pressure of oxygen (PaO_2, mmHg), actual bicarbonate contents (HCO_3, mmol/l), total carbon dioxide (TCO_2, mmol/l) and oxygen saturation of hemoglobin (SAT, %).

Physiological dead space ratio

Dead space is defined as the portion of the respiratory system not involved in gas exchange and includes both alveolar and airway dead space. Dead space is often expressed as a ratio of dead space to tidal volume, also known as physiologic dead space ratio (V_d/V_t), and is a clinical measure of the efficiency of ventilation. Recent advances in capnography technology have provided a simplified method for calculating V_d/V_t from single breath carbon dioxide wave forms.

The CO_2SMO Plus is a capnograph, pulse oximeter, and gas flow monitor. An infrared beam splitter continuously detects real-time mixed expired carbon dioxide. It is for single patient use with minimal dead space. The CO_2SMO Plus uses the method originally described by Fowler (187) and validated by Arnold et al. (188) in 1996. The CO_2SMO Plus provides a standard, expired single breath carbon dioxide (CO_2) wave

form that can be divided into three phases [Figure 3-3]. Phase I represents CO_2-free gas expired from large airway and endotracheal tube dead space, phase II represents a mixture of gas from both large airway dead space and alveolar dead space, and phase III (or alveolar plateau) represents alveolar ventilation (188).

To calculate V_d/V_t using a single breath CO_2 wave form, the slope of the phase III capnograph must first be determined [Figure3-4]. A line is then drawn perpendicular to the x axis so that the intercept between this vertical line and the slope of phase III creates two equal areas, labeled a and b, around the carbon dioxide wave form of phase II. When a concurrently drawn $Paco_2$ is plotted on the same capnograph, X, large airway dead space (V_d^{aw}), and alveolar dead space (V_d^{alv}) can be identified (189). The sum of these three areas equals the theoretical volume of CO_2 exhaled from a lung with no dead space. Area X depicts the elimination of CO_2 during an exhaled breath, whereas areas V_d^{aw} and V_d^{alv} depict ventilation that does not eliminate CO_2. The CO_2SMO Plus computes the V_d/V_t for each breath during a 1-minute interval using an accompanying arterial $Paco_2$ and then averages the V_d/V_t values to produce the reported value. Patient's body weight (BW) and arterial PCO_2 obtained separately from an arterial blood gas, was manually entered into the monitor's computer to calculate the various VD components.

Plasma catecholamine levels analysis

Approximately, 5 mL blood was drawn through an indwelling antecubital venous catheter into a green-top Vacutainer (TM). The whole blood sample was kept on wet ice until centrifuge. Centrifuge was used to separate the plasma within 2 hours of venipuncture. After centrifugation, the plasma was transferred to a plastic, leak-proof vial and was immediately refrigerated. Catecholamines were analyzed by high

performance liquid chromatography, at Quest Diagnostics Nichols Institute San Juan Capistrano, CA, using the standard procedure (190-192).

Three- or five-milliliter blood samples were added to prechilled tubes containing antioxidant solution (20 µl/ml blood). The antioxidant solution consisted of 225 mM glutathione, 93 µM EDTA, 1,660 U/ml heparin, and 250 pmol/ml isoproterenol, as an internal standard, in saline. Blood collection tubes were immediately centrifuged at 4°C for 2 min at 15,000 rpm, and the plasma was removed and stored in a covered ice container. Plasma samples were analyzed on the day of the experiment or frozen at −70°C for later analysis.

Plasma catecholamines were adsorbed on powdered alumina (25 mg/ml plasma) after addition of 1 M Tris buffer with 2% EDTA (pH 8.6; 400 µl/ml plasma). The tubes were agitated for 5 min andcentrifuged; the plasma was aspirated; and the alumina pellet was washed twice with 1 ml of distilled water. Catecholamines were eluted from the alumina under acid conditions with 150 µl 0.1 N $HClO_4$ by vortexing the tubes for 2 min. One hundred microliters of the supernatant were analyzed on a Hewlett-Packard 1100 HPLC system and electrochemical detector (HP 1049A). Catecholamines were eluted isocratically at a flow of 0.75-1.0 ml/min using a 125- × 4-mm LiCrospher 100 column. Elution is a term used to describe the emergence of chemicals from the column of a chromatograph. As they elute, the chemicals typically flow into a detector. Predicting and controlling the order of elution is a key aspect of column chromatographic methods. The mobile phase consisted of 20 mM citric acid, 100 mg/l octanesulfonic acid, 0.2 mM EDTA, and 8-10% methanol, and pH was adjusted to 5.0 with NaOH. The electrochemical detector used a glassy carbon electrode at a

potential of 0.6 V. Epinephrine and norepinephrine peaks were identified and quantified by comparison of retention times and peak areas to those of known standards. The detection limit is 0.2 pmol for both catecholamines, which is equivalent to a plasma concentration of ~0.2 nM. Concentrations in each sample were corrected for recovery using the isoproterenol internal standard.

Statistical Analysis

All statistical analysis was performed using SPSS statistical software (release 9.0, SPSS Inc., Chicago, IL). Heart rate variability indices [Total power, High Frequency power (normalized units), and Low Frequency power (normalized units)], Plasma catecholamine levels (epinephrine and norepinephrine), breathing variables, blood gases and respiratory dead space data were analyzed using paired Student's *t*-Test. A *p*-value $\leq$ 0.05 was considered to be significant.

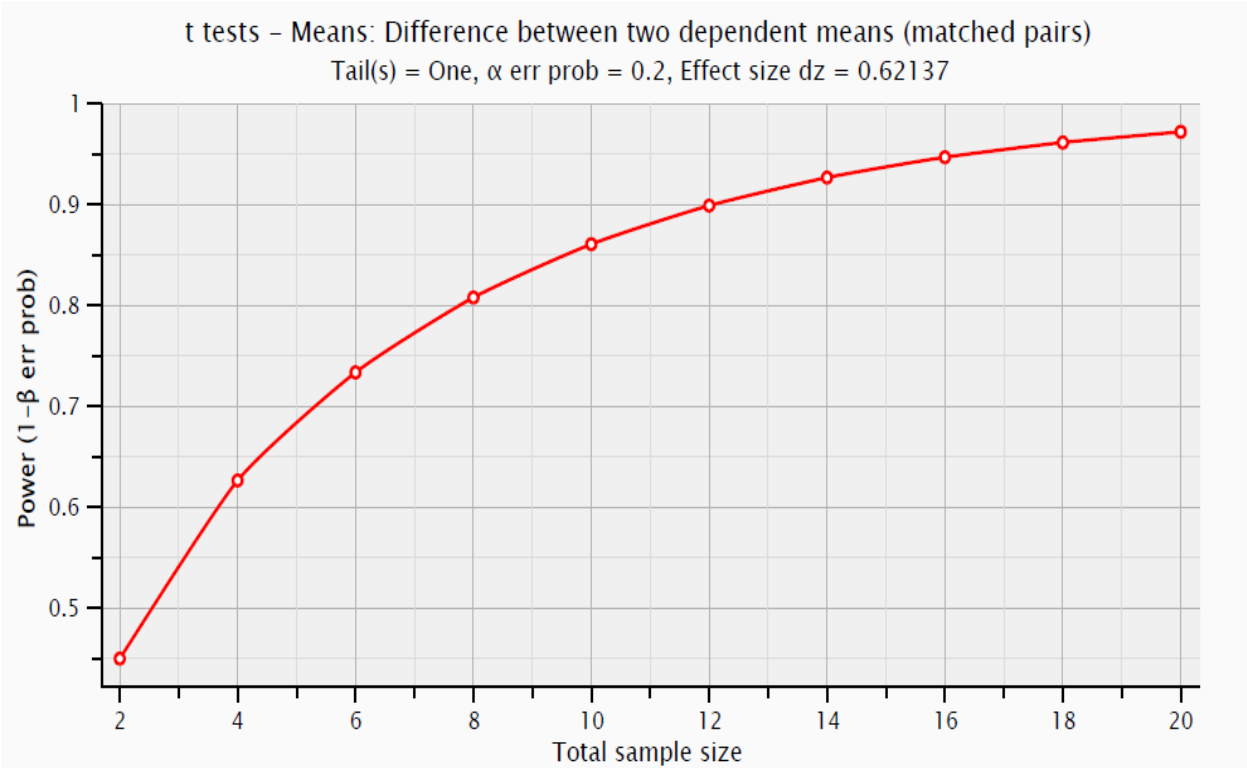


Figure 3-1 Power analysis and sample size estimation (Specific Aim # 1)

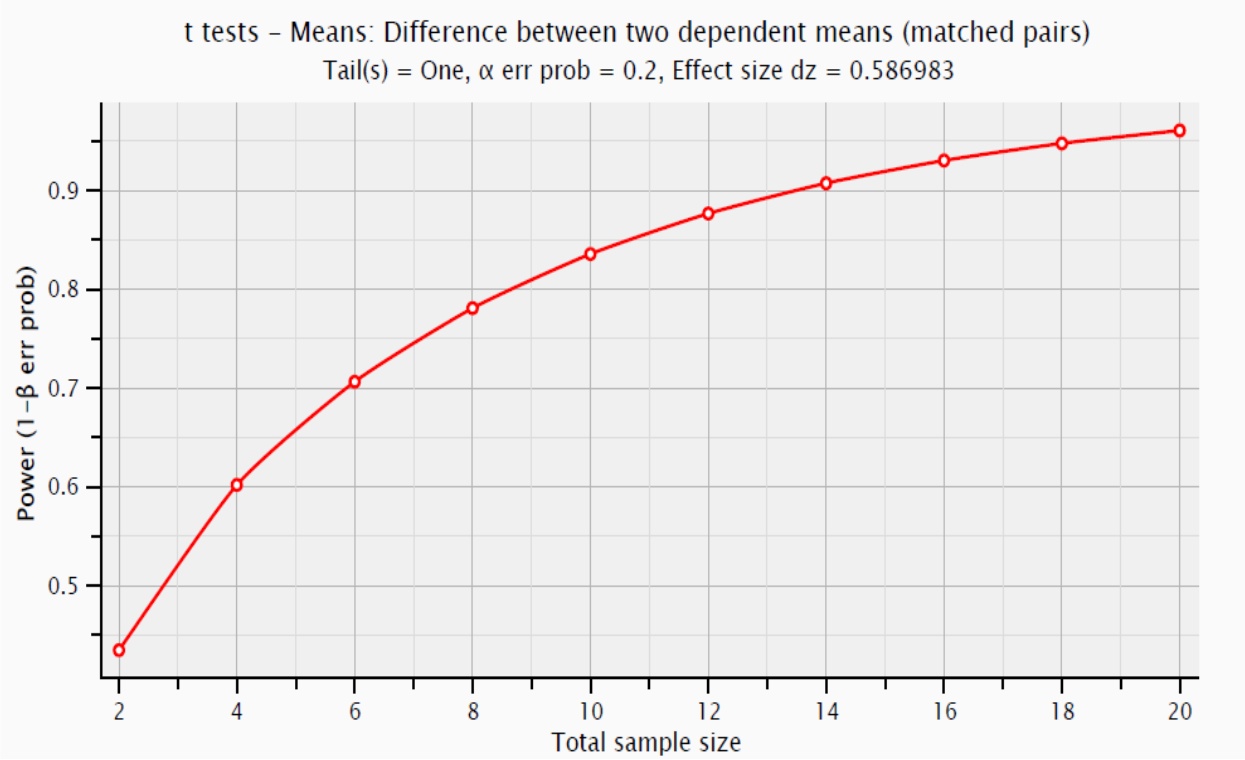


Figure 3-2 Power analysis & sample size estimation (Specific Aim #2)

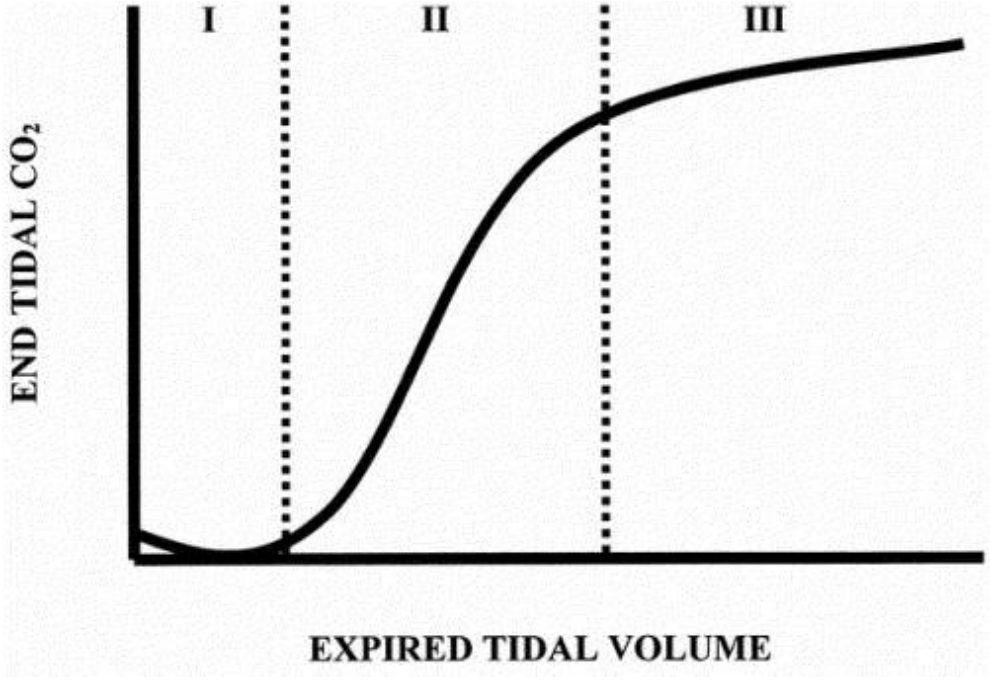


Figure 3-3 Single breath CO_2 waveform

Phase I represents dead space CO_2 expired from large airways. Phase II represents CO_2 mixing from both large airways and alveolar gas. Phase III represents alveolar ventilation alone. Figure adopted from (189)

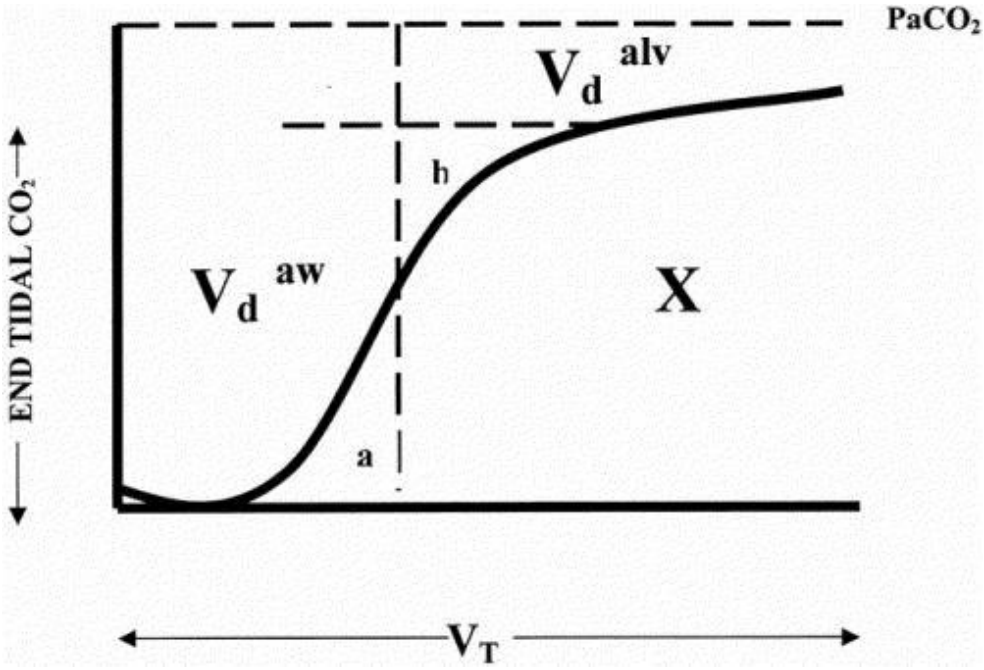


Figure 3-4 Calculation of dead space from single breath CO_2 waveform.

Triangles a and b are created by drawing perpendicular lines. Large airway dead space (V_d^{aw}) is from the start of expiration to the intersection of the perpendicular lines. Area X is the volume of CO_2 in an exhaled breath. Alveolar dead space is represented by V_d^{alv}. The physiologic $V_d/V_t = (V_d^{alv} + V_d^{aw})/(X + V_d^{alv} + V_d^{aw})$. Figure adopted from (189)

CHAPTER 4
RESULTS

Demographic Data

The demographic data for these patients is shown in Table 4-1. Ten patients who had been receiving long-term MV support secondary to respiratory failure were recruited. 3 patients were male while 7 patients were female. Patients exhibited a high severity of illness indicated by an APACHE II score of 19 $\pm$ 9 indicating that on average patients had a 33% chance of mortality during the ICU stay (193).

All the patients experienced respiratory failure following surgical procedures. The average duration of MV before SBT was 50 ± 21 days. Thus all the patients satisfied the minimum criteria of PMV of $\geq$ 21 days of MV support. Typical ventilator setting included intermittent mandatory ventilation rates of 2 to 4 breaths / minute, pressure support of 5 to 15 cm H_2O, continuous positive airway pressure of 3 to 8 cm H_2O, with a FiO_2 of 0.35 to 0.5. All the patients had a tracheostomy performed (tracheal canula size 8 $\pm$ 1 mm ID).

SBT were started between 8:00 am to 9:00 am and lasted until failure. Among the 10 failed trials 8 were terminated when the patients requested to be returned to be MV, and two trials were terminated by staff due to the development of respiratory distress. Average duration of SBT was 67± 65 minutes. Vital signs including heart rate and blood pressure during MV support and at the point of SBT failure are shown in Table 4-2. Although the mean heart rate increased over the duration of the SBT, this increase was not statistically or clinically significant. Additionally, blood pressure did not show a statistically significant difference. Both mean HR and BP were within the SBT

termination criteria. Furthermore, blood chemistry was measured within 24 hrs before SBT start and the values are reported in Table 4-3.

Arterial Blood Gas Analysis

Arterial blood gas values during MV support and at the point of SBT failure are shown in Table 4-4. At the point of SBT failure, the mean PCO_2 was higher while the mean PO_2 and mean PiO_2/FiO_2B were lower as compared to MV support. However, these differences were not statistically significant.

Heart Rate Variability Frequency Domain Analysis

HRV frequency domain indices are shown in Table 4-5. At the point of failure HFnu decreased from 67±12 to 37±16 ($p<0.001$). Additionally, LFnu increased from 33±12 to 63±16 ($p<0.001$). Low HF variability and high LF variability at the point of failure indicates relatively high levels of physiological stress.

Plasma Levels of Catecholamine

Plasma levels of catecholamines during MV support and at the point of SBT failure are shown in Table 4-7. We found NE increased significantly from 837± 618 while the subjects received full MV support to 1666 ± 954 pg/ml ($p<0.001$) at the time of failure, while EP increased from 92±35 to 174 ±103 pg/ml ($p<0.01$)]. Elevated catecholamines indicate high levels of stress.

Breathing Pattern Analysis

Breathing pattern variables during MV support and at the point of SBT failure are shown in Table 4-7. Breathing pattern variables indicated higher respiratory drive at the point of failure during the SBT evident by an increase in V_E from 8.07±2.75 to 9.23±3.08 L/min ($p<0.05$) along with the increase in PIF from 33.1±7.4 to 36.7±8.36 L/min

($p<0.05$)]. Other variables respiratory rate, inspired tidal volume, inspiration and expiration time and mean inspiratory flow rate were not different.

Physiological Dead Space

Additionally, dead space ventilation was compared between MV support and SBT failure. Dead space ventilation was high when the patients were on MV (0.56 ± 0.09) and it increased to 0.62 ± 0.12 however the increase was not significant.

Table 4-1 Demographic Data

Variable (Unit)	Value
Age (years)	73 ± 11
Weight (kg)	66 ± 22
BMI	25.7 ± 4.7
Gender (male/female)	3:7
Acute Physiology and Chronic Health Evaluation (APACHE II) Score	19 ± 6
Mechanical Ventilation (Days)	50 ± 21
Spontaneous Breathing Trial Duration (mins)	67 ± 65

*Data expressed as mean ± SD

Table 4-2 Blood Chemistry Values

Variable	Unit	Reference Range	Result
Serum sodium	mEq/L	135-148	141.9 ± 4.5
Serum potassium	mEq/L	3.5-5	4.24 ± .38
Serum Chloride	mEq/L	98-106	106.30 ± 5.91
Bicarbonate total	mmol/L	23-30	26.21± 2.09
Blood urea nitrogen	mg/dL	7-18	42.02 ± 19.05
Serum creatinine	mg/dL	0.6-1.2	1.42 ± 1.2
White blood cell count	(*10^3)mm^3	3.9 - 10	10.71 ± 5.64
Hemoglobin	gm/dL	13.2 - 16.9	9.89 ± 0.95
Hematocrit	%	38.5 - 49.0	29.62 ± 2.92
Bilirubin	mg/dL	0.2-1.0	0.81 ± 0.52
Serum pre-albumin	mg/dl	20 to 40	10.21± 4.09
Total Protein	gm/dL	6.0 - 8.4	5.45 ± 0.4
Serum albumin	gm/dL	3.5 - 5.0	2.81 ± 0.5

*Data expressed as mean ± SD

Table 4-3 Vital Signs

	On MV	SBT Failure	t-Test (p-value)
Heart Rate	91 + 12.63	97.33 + 14.95	0.16
Blood Pressure			
Systolic	126.33 + 15.44	131.33 + 24.40	0.41
Diastolic	58.50 + 11.60	63.30 + 11.76	0.44

Data expressed as mean $\pm$ SD

*MV: Mechanical ventilation, SBT: Spontaneous breathing trial,

Table 4-4 Arterial Blood Gas Data

	Normal Value	On MV	AT Failure	t-Test (p-value)
pH	7.35 - 7.45	7.4 ± 0.05	7.36 ± 0.07	0.10
$PaCO_2$ (mmHg)	35 - 45	46.88 ± 5.30	50.20 ± 12.19	0.24
PaO_2 (mmHg)	80 - 95	93.39 ± 14.76	81.06 ± 22.72	0.33
HCO_3 (mmol/l)	22 - 26	28.68 ± 1.75	27.78 ± 2.72	0.73
SaO_2 (%)	95-99%	97.25 ± 3.15	95.26 ± 3.26	0.59
PaO_2/FiO_2	≥ 200	241.33 ± 53.56	201.71 ± 60.30	0.26

Data expressed as mean ± SD

* pH: power of Hydrogen, $PaCO_2$: partial pressure of carbon dioxide, PaO_2: partial pressure of oxygen, HCO_3: actual bicarbonate contents, SaO_2: oxygen saturation of hemoglobin, PaO_2/FiO_2: ratio of arterial oxygen partial pressure to fractional inspired oxygen concentration.

Table 4-5 Heart Rate Variability Analysis: Frequency Domain Measures

	On MV	AT Failure	t-Test (p-value)
HF ln (ms2)	6.36±2.3	6.11±1.2	0.22
LF ln (ms2)	7.1±0.3	7.87± 0.9	0.16
HF (n.u.)	67±12	37±16	0.002†
LF (n.u)	33±12	63±16	0.002†
LF/HF	0.6±0.3	2.3±1.8	0.012†

Data expressed as mean ± SD.
HF ln: High Frequency variability, LF ln: Low Frequency variability, HF (n.u.): High Frequency variability normalized units, LF (n.u.): Low Frequency variability normalized units.
† $p \leq 0.05$ between MV support and SBT failure.

Table 4-6 Plasma Catecholamine

	On MV	AT Failure	t-Test (p-value)
NE (pg/ml)	837± 618	1666 ± 954	0.001†
Ep (pg/ml)	92±35	174 ±103	0.001†

NE: Norepinephrine, EP: Epinephrine.
Data expressed as mean ± SD.
† $p \leq 0.05$ between MV support and SBT failure.

Table 4-7 Breathing Pattern Variables

	Early SBT	Late SBT	t-Test (p-value)
VE	8.07 ± 2.8	9.23 ± 3.0	0.05†
RR	27.18 ± 8.9	29.03 ± 8.4	0.37
Vti	316 ± 84	324 ± 102	0.83
PIF	33.11 ± 7.4	36.69 ± 8.4	0.03†
PEF	32.34 ± 7.7	33.56 ± 8.34	0.55
RSBI	90.25 ± 30.8	97.44 ± 32.2	0.52
Ti	0.83 ± 0.19	0.78 ± 0.21	0.36
Te	1.63 ± 0.7	1.51 ± 0.62	0.37
VCO2	169.9 ± 62.1	187.5 ± 74.3	0.17
(Vd/ Vt)	0.56 ± 0.09	0.62 ± 0.12	0.14

Data expressed as mean ± SD

*(Ve) minute ventilation, (RR) respiratory rate, (VT) tidal volume, (PIF) peak inspiratory flow, (PEF) peak expiratory flow, (RSBI) rapid shallow breathing index, (Ti) inspiratory time, (Te) expiratory time, (VCO2) carbon dioxide production rate & (Vd/Vt) dead space ventilation.,

† $p<0.05$ between early SBT and late SBT

CHAPTER 5
DISCUSSION

Principal Findings

Heart rate variability analysis is a novel method of quantification of overall stress. This is the first study that analyzed the overall stress level in PMV patients during MV and at the point of failure during the subsequent spontaneous breathing trial using a within subject design.

Mechanical Ventilator Weaning HRV Changes

In Aim 1, we hypothesized that in PMV patients during failed SBT heart rate variability analysis will indicate higher overall stress level at the point of failure compared to MV support. The frequency domain analysis showed that at the point of failure HFnu which is regarded as the as an index of the level of parasympathetic activity decreased significantly. Moreover, LFnu reflects both sympathetic and parasympathetic activity increased significantly. Additionally the LF/HF ratio is considered to mirror sympathovagal balance and we found a significant increase in the LF/HF ratio at the point of failure in SBT as compared to full MV support. Collectively, these changes indicate relatively high levels of physiological stress when the patients fail the SBT.

There are a number of potential explanations for these changes. HRV may be influenced by a variety of confounding variables. The main factors that influence HRV are age, gender (17) and diseases such as diabetes mellitus, congestive heart failure and various neurological diseases which constitute major co-morbidities in ICU patients(14, 18). Additionally, medications acting directly or indirectly on the ANS potentially influence HRV(18). Therefore in these studies the difference found could be

the result of intrinsic differences between groups, rather than the difference between outcomes (success or failure in the SBT) within a subject.

In our study, as all subjects acted as their own controls, thus the effects of age, gender, and disease were controlled. Additionally, no medication changes occurred during data recording so that medications cannot account for the considerable variability found in our study. HRV is also influenced by circadian rhythms. All SBT were started between 8:00 and 9:00 am; therefore the circadian rhythm variation of HRV was controlled.

Other possible causes of change in HF component are respiratory rate and tidal volume. The HF component of HRV decreases with increased respiratory rate and decreased VT (194, 195). We found no significant changes in RR and tidal volume during MV support and at the point of failure during SBT. Thus, it is unlikely that the lower HRV in the failure group was because of significant differences in respiratory rate and tidal volume. The only differences we found during MV support and at the point of failure during SBT were the PIF and V_E increased significantly at failure.

The concept of LF (n.u.) as a marker of cardiac sympathetic modulation is debatable and the change in LF (n.u.) during SBT may be due to respiratory-autonomic interactions, the pathologic processes of sympathetic modulation of heart beat fluctuations in patients recovering from respiratory failure, or the influence of underlying diseases and medications (196-201).

The critical care environment may also produce significant and chronic sympathetic activation in critically ill patients. Psychological stress is difficult to measure in critically ill patients and even more so in mechanically ventilated patients. However,

Yu et al. (1999) (202) found that anxiety was highly associated with downregulation of β-adrenergic receptors and a blunted ability to respond to further elevation in catecholamines in healthy individuals; and Otte et al. (2005) (107) found that depressive symptoms were associated with elevated NE levels in patients with coronary artery disease. In current study the patients were left undisturbed, and every effort was made to keep the environmental conditions stable throughout data acquisition, suggesting a limited role for environmental factors.

The change of HRV during different ventilator settings was investigated in an animal study by Frazier et al.(203). They found that there were significant increases in very LF power (sympathetic tone) with a concomitant significant reduction in HF power (parasympathetic tone) with exposure to a combination of pressure support and continuous positive airway pressure (203). These changes in HRV were associated with significantly increased heart rate and reduced right ventricular end-diastolic volume.

Additionally, Shen et al. investigated the change of autonomic nervous activity during ventilator weaning by HRV analysis (184). They found that patients who failed a spontaneous breathing trial exhibited a shift to predominant sympathetic control of heart rate during spontaneous breathing in comparison with those who were successfully weaned(184).

Furthermore, in a recent study, Frazier et al. (16) evaluated the autonomic responses of critically ill patients during a 24- hr period of mechanical ventilatory support which included their initial spontaneous breathing trial using continuous positive airway pressure. The autonomic tone was quantified using plasma catecholamine and

heart rate variability indices. The study reported that nearly two thirds of the patients demonstrated abnormal autonomic function and this dysfunction was more severe in those patients who were unable to sustain spontaneous ventilation as illustrated by reductions in time domain and geometric measures of HRV. Plasma catecholamine levels were also elevated at both data points (16). However, patients in the success group exhibited reduced plasma catecholamines in response to the CPAP weaning trial, whereas those in the failure group exhibited increased plasma catecholamines in response to the weaning trial (16).

Prior research has established a substantial link between reduced HRV and poorer outcomes in a variety of critically ill patient populations. Winchell et al. (204) found that reduced total autonomic power was associated with increased mortality in a group of general surgical ICU patients, and in a later study (205), they found that reduced HRV was associated with altered cerebral perfusion and increased mortality in patients with severe head injury. In other critically ill populations, reduced HRV on postoperative Day 1 was an independent predictor of complicated recovery from abdominal aortic surgery (206) and an independent predictor of mortality in patients with multiple organ dysfunction syndrome (207). Additionally, in patients with acute myocardial infarction and heart failure, decreased HRV has been well established as an independent predictor of life threatening dysrhythmias like ventricular tachycardia and of mortality (208, 209). To date, the association between autonomic tone and the success of ventilator weaning has not been a prominent focus of study.

There is currently interest in identifying quantifiable, rapidly attainable measures that may be utilized to recognize ‘at-risk’ patients in a various pathological conditions.

Measurements of HRV have shown promise as such a tool. In the clinical setting of critical illness, methods of collection and interpretation of autonomic nervous system activity with potential utility in real time have been undertaken with some success (210) (204). Several studies have even implied the use of HRV as an additional vital sign in the assessment and care of critically ill patients with the hopes of earlier intervention for those patients deemed at higher risk based on HRV-derived parameter(s) (210) (204, 211).

Mechanical Ventilator weaning Endocrine Stress Response

In aim 2 we hypothesized that in PMV patients during failed SBT plasma catecholamine analysis will indicate higher physiological stress level at the point of failure as compared to MV support. We found that the catecholamine concentrations were significantly elevated from normal values in these patients at both sampling times (laboratory normal range for Epi = supine < 50 pg/ml, NE = supine 110 to 410 pg/ml). These levels increased significantly at the point of failure indicating very high levels of stress during failure.

The most well known physiological response to stress concerns the hypothalamus-pituitary-adrenal (HPA) axis (212). Emotional responses to perceived threat are generated in the limbic system, and signals are sent to subcortical brain centers and the hypothalamus. The hypothalamus, in turn, activates the posterior pituitary to secrete vasopressin and oxytocin, and the adrenal medulla to secrete epinephrine and norepinephrine(212). Catecholamines have a short half life of 2 minutes and, therefore, provide an immediate measure of stress (213). Thus the hormonal stress response may provide an objective method to measure patient comfort during MV.

However, Brinkmann et al. found that catecholamine and stress hormone blood concentrations did not increase following withdrawal of sedation and cessation of MV after abdominal surgery (214). Additionally, Rathgeber et al. used biphasic positive airway pressure, controlled mandatory ventilation, or intermittent mandatory ventilation for weaning after cardiac surgery (215). The hormonal response was not affected by the discomfort of breathing. Calzia et al. (216) compared oxygen consumption (VO_2) , work of breathing (WOB), cardiovascular effects, and the plasma concentrations of catecholamines and other hormones involved in the stress response during weaning using different ventilatory modes, in patients who had aorto-coronary bypass surgery. The study found that during the early stages of weaning from MV after cardiac surgery, switching from passive ventilation to partial spontaneous breathing and interruption of continuous sedation did not alter the postoperative hormonal stress response and VO_2 (216). Furthermore, Quinn et al. (217) compared the effects of synchronized intermittent mandatory ventilation and biphasic positive airway pressure on the stress response, during weaning after cardiac surgery. Neither mode affected postoperative plasma cortisol, epinephrine, or norepinephrine concentrations. In patients who underwent cardiac surgery, Brinkmann et al. (214) and Calzia et al. (216) found no significant differences in plasma epinephrine and norepinephrine levels during weaning.

On the other hand, hormonal stress response has been used successfully in preterm infants to demonstrate the advantage of mechanically supported spontaneous breathing over controlled MV in terms of reduced stress response(217). Additionally, Oh et al. (1991) measured plasma catecholamines in 20 short-term ventilated patients during weaning by synchronized intermittent mandatory ventilation and SIMV and

continuous positive airway pressure (CPAP) (218). The study demonstrated that during the weaning trial plasma epinephrine and non-epinephrine increased significantly as the ventilator assistance was reduced (218). Additionally, studies that evaluated the effects of MV on oxygen consumption in ICU patients during weaning trials have found increased oxygen requirement associated with the rise in catecholamine levels (7, 77). Furthermore, Koksal et al. (219) compared changes in plasma concentrations of insulin, cortisol and glucose, and in urine vanilmandelic acid (VMA), the end product of catecholamine metabolism during weaning and after extubation, using the three different modes of pressure support (PS) ventilation, CPAP and T-piece, in intensive care patients. The study found the greatest changes in measured variables during the 2 hours of weaning occurred in T-piece trial concluding that the weaning via the T-piece caused a greater stress response compared to the PS and CPAP modes (219).

Mechanical Ventilator Weaning: Breathing Pattern analysis

In aim 3 we hypothesized that in PMV patients during failed SBT the breathing pattern will be significantly different between the start and the point of failure. We found a significant increase in V_E and PIF at the point of failure during indicating a higher respiratory drive.

In patients who were ventilated for shorter periods of time a number of breathing pattern parameters have been reported to be associated with the success or failure of ventilator discontinuation (4). Previously, Sahn et al. (115) reported that a $V_E < 10$ l/minute is associated with weaning success. Subsequent studies showed that V_E values > 15–20 l/minute are helpful in identifying patients who are unlikely to be liberated from MV but lower values were not helpful in predicting successful liberation(5,

220-222). Moreover, Martinez et al.(223) showed that the time of recovery of V_E from the end of a 2-hour spontaneous breathing trial to return to baseline after reinstitution of MV is a good predictor of liberation from MV. They concluded that short V_E recovery times (3–4 minutes) may help in determining respiratory reserve and be valuable in predicting the success of extubation (223).

Reported weaning predictors including vital capacity, tidal volume, respiratory rate, minute ventilation, rapid shallow breathing index (RSBI), and maximal inspiratory pressure (Pi_{max}) have been developed and applied in clinical settings. Moreover, integrated factors also have been employed (4), for example, CROP index (CROP = dynamic compliance multiplies by maximal inspiratory pressure by PaO2/PAO2 and divides this product by the respiratory rate). However, analysis of receiver operating characteristics curves (ROC) has shown none of these indices are sufficiently sensitive and specific to be useful in predicting the success of ventilation discontinuation, especially in the elderly and/or in the PMV patients. (4)

Yet few investigators have attempted to examine the breathing variability during weaning protocols (110, 221, 224, 225). Bien et al. reported that breathing pattern variability in the patients who failed to weaning trials was significantly lower than those who passed to weaning trials (110). Accordingly, they also reported that the area under the ROC curves of these breathing variability indices was within 0.73-0.80. Consistently, Wysocki et al. showed that reduced breathing variability, quantified by using CV, during a 60 min SBT was associated with a high incidence of weaning failure in the ICU patients(224). In contrast, EI-Khatib et al. and Engoren found that breathing variability measured by entropy indices was more irregular (higher) in patients who failed

extubation compared to patients who passed extubation trials(221, 225). It is hard to explain the inconsistency of these findings because of the nature of the corresponding populations and different experimental conditions.

Role of Dead Space in Prolonged Mechanical Ventilation Patient

Dead space is usually related to tidal volume and the normal adult dead space to tidal volume ratio is in the range of 0.2 to 0.35 during resting breathing. Dead space is increased in number of disease states associated with abnormalities of gas exchange (226). The patients with a high V_D/V_T ratios (greater than 0.6) are considered as difficult to wean. However, the exception exists. Earlier studies (227) have documented two successful weaning cases whose V_D/V_T ratios were repeatedly in excess of 0.65. They found that V_D/V_T ratios were similar during weaning periods compared with values measured on MV. At the time of successful weaning, the V_D/V_T ratio was still above 0.65. Unfortunately, the explanation for the persistence increases in V_D/V_T ratio remains unclear.

The role of dead space in predicting the outcome of successful weaning from MV is controversial. For example, Hubble et al. have shown that a significant difference in mean V_D/V_T ratio (calculated using a CO2SMO-plus) between successful and failed-to-wean children of MV (0.44+/-0.17 vs. 0.68+/-0.16; p=0.0001) (189). On the other hand, Bousso et al. applied a similar analysis strategy reporting different results; there was no significant difference of the V_D/V_T ratios for patients with successful and failed weaning (0.62+/-0.17 vs. 0.65+/-0.21; p=0.472) (228). The difference in results of these two studies may be reflecting the presence of different populations or measurement errors or both. In the Hubble et al's study most patients were selected from surgical-ICU, with supposedly normal lungs, while the population of Bousso comprised patients with

severe acute respiratory disease such as ARDS. With the lung injury, the dead space is increased and associated with increased ventilation with high V/Q regions and larger anatomic/alveolar dead space. In the Nucton et al. study, they demonstrated that increased V_D/V_T ratio as a consequence of pulmonary vascular injury was observed in patients with ARDS and increased V_D/V_T ratio was an independent risk factor for death among these patients (229). It seems that an increased V_D/V_T ratio in patients with lung injury results from two different mechanisms. First, dead space reflects the efficiency of gas exchange; any alteration in the distribution of pulmonary blood flow will change in dead space. For example, a high V_D/V_T reflects increased ventilation to unperfected areas of lung. Second, dead space reflects the extent of pulmonary vascular injury. Injury to the microcirculation, which is characteristic features of ARDS, increased pulmonary vascular resistance by causing several mechanisms such as vasoconstriction, micro thromboembolism from platelet or endothelial cell swelling (230). All of these mechanisms can increase alveolar dead space, as consequence of increased V_D/V_T ratio.

As mentioned, another explanation is the measurement errors; V_D/V_T ratios in Bousso et al's study may be overestimated. The V_D/V_T ratio is usually derived from the Bohr-Enghof equation (see as above). In this equation the assumption is made that PaCO2 is equal to alveolar carbon dioxide tension (P_ACO2). This assumption can be violated in the presence of a significant anatomical shunt and imbalance of V_A/Q (231). It is stated that if the shunt (Qs) as a proportion of cardiac output (Qt) is greater than 20 percent, this would overestimate V_D/V_T because of a high portion of blood flow from the right side of the heart to the left side of the heart without participating in gas exchange

(231). In turns, carbon dioxide tension in the pulmonary capillaries (PcCO2) must participate in alveolar gas exchange, and P_ACO2 would be lowered than PaCO2, thus increasing the calculated V_D/V_T.

More accurate estimates of V_D/V_T require the multiple inert gas elimination technique (MIGET) but this technique is complicated and clinically impractical in the mechanically ventilated patients. Here is an example to demonstrate the measurement errors; one study (232) compared MIGET to the Bohr-Enghof equation to calculate V_D/V_T in ARDS patients and found markedly overestimated V_D/V_T (0.37+/-0.04 vs. 0.64+/-0.03, respectively), which the latter ignored the effect of anatomic shunt.

Mechanical Ventilation Weaning Arterial Blood gases

Arterial blood gases (ABGs) are used routinely to assess alveolar ventilation during weaning yet surprisingly little is known about their appropriate role during SBTs. Beyond routine bedside monitoring (of heart rate, respiratory rate, blood pressure and subjective parameters), ABGs affect decision making infrequently and may not necessarily lead to a correct decision (233).

Additionally, End-tidal CO_2 ($EtCO_2$; capnography) has be routinely monitored continuously during SBT. It can also be helpful in monitoring dead space in mechanically ventilated patients. Unfortunately, it may be insufficiently sensitive to detect episodes of hypercapnia (234). Some data suggest poor sensitivity detecting less than 10 mm Hg increments of $PaCO_2$, but greater sensitivity for increases of 10 mm Hg or more (233). But accuracy is reduced in patients with parenchymal lung disease, which comprise a majority of medically ill patients (235). False positives (236) (ie,

increments of $EtCO_2$ without significant increments in $PaCO_2$) may also contribute to unnecessary ABGs (234).

Limitations of the Current Project

The major limitation of this study is the absence of successful SBT to compare. The critically ill mechanically ventilated patients undergo standard weaning procedure and undergo SBT as soon as the underlying pathology resolves. 40% of the patient's time on MV is actually spent during weaning (65). By definition PMV patient has undergone > 21 days of MV with the weaning process complicated by multiple SBT failure (3). These PMV patients were recruited for the inspiratory muscle training study. This makes it very rare for the patient to have a successful trial on the first day. In the course of 1 year that this study was conducted we observed a total of 13 patients 10 of which failed the initial SBT while only 3 were successful. These 3 patients did not fail and breathed spontaneously for 48 consecutive hours and were weaned on the first SBT entering the study. The data from these trials is summarized in Chapter 6.

Whether heart rate variability reflects cardiac sympathetic activity is a topic of much debate (26, 33). Microneurographic recordings of muscle sympathetic nerve activity (MSNA) offer a direct measurement of efferent postganglionic sympathetic nerve activity, and as such are considered the gold-standard measurement of global sympathetic outflow to skeletal muscle (237). In the current project although we did measure the plasma catecholamines, we did not measure MSNA recordings during SBT. However, previous studies have compared MSNA and low frequency fluctuations of heart rate variability at rest and shown no relationship in healthy individuals, or in those with chronic disease (238, 239). However, studies employing orthostatic stress or

pharmacologic manipulation of blood pressure have demonstrated significant relationships between MSNA and HRV (178, 240). Additionally, in healthy subjects, parallel increases in MSNA and the ratio of low to high frequency heart rate variability (LF/HF) were observed with orthostatic challenge (241) while experimental changes in blood pressure result in parallel responses in MSNA and LF . These results suggest that MSNA and cardiac sympathetic markers of HRV may change in parallel in response to an autonomic challenge. Importantly, due to the invasiveness and technical complexity associated with this technique, microneurography is generally not practical for repeated measurements or large clinical studies.

Finally, because of the inherited limitation of HRV analysis, (186) the application as a weaning parameter is limited to those without significant arrhythmias. Furthermore, this was a small sample size and needs a larger study to confirm these results.

CHAPTER 6
SUCCESSFUL SPONTANEOUS BREATHING TRIALS

In the course of 1 year that this study was conducted, 13 patients experiencing prolonged mechanical ventilation (PMV) met the inclusion criteria and were studies. 10 of these patients failed the spontaneous breathing trials (SBT) while 3 patients were successful in the SBT. These 3 patients did not show any objective or subjective signs of failure and breathed spontaneously for 48 consecutive hours. These subjects were were classified as successfully weaned . Sample data from the successful SBT is presented. SBT were started between 8:00 am to 9:00 am and lasted until failure or the predetermined duration was reached. During SBT, the patient was disconnected from the ventilator and required to breathe spontaneously while receiving supplemental oxygen to keep SpO2 > 90%. Patients were maintained in a semi-recumbent position (keeping head-end of the bed 30° elevated). During SBT, all patients received routine nursing care, but no rehabilitation services.

Demographic Data

3 (M/F: 2/1) patients did not fail the trial and breathed on their own for 48 hours and were subsequently weaned. The data was obtained at 380 $\pm$ 86.6 minutes during the trial. The average duration of mechanical ventilation (MV) support (54 ± 16 days). Thus all the patients satisfied the minimum criteria of PMV of $\geq$ 21 days of MV support. Typical ventilator setting included intermittent mandatory ventilation rates of 2 to 4 breaths / minute, pressure support of 5 to 15 cm H_2O, continuous positive airway pressure of 3 to 8 cm H_2O, with a FiO_2 of 0.35 to 0.5. The relevant clinical features are summarized in Table 6-1. The blood chemistry on the day of SBT is shown in Table 6-2.

Vital signs including heart rate and blood pressure during MV support and late SBT are shown in Table 6-3. The Heart rate and blood pressure did not show statistically significant difference. Additionally, arterial blood gas values during MV support and during late SBT are shown in Table 6-4. ABG values were not different between MV support and during late SBT.

Heart Rate Variability Frequency Domain Analysis

HRV indices are shown in Table 6-5. High frequency normalized units [HF (nu)], Low frequency normalized units LF(nu) as well as LF/HF ratio were not significantly different.

Plasma Catecholamine Levels at SBT Failure

Plasma levels of catecholamines during MV support and late SBT are shown in Table 6-6. NE as well as EP were not different between MV support and late SBT.

Breathing Pattern Change between Early and Late SBT

Breathing pattern variables during MV support and late SBT are shown in Table 4. Breathing pattern variables including minute ventilation, respiratory rate, inspired tidal volume, inspiratory time, expiratory time as well as peak inspiratory flow rate were not different. Additionally, the dead space ventilation was not different during MV support and during late SBT.

Conclusion

Although HRV indices were low and plasma catecholamine levels were high at both sampling times compared to the healthy norms the values did not change during the successful SBT trial. There is substantive evidence that positive pressure MV itself

generates a complex neurohormonal response because of altered intrathoracic pressure and changes in thoracic hemodynamics and may be responsible for these changes (242). The critical care environment may also produce significant and chronic sympathetic activation in critically ill patients. (16)

Previously, Shen et al. investigated the change of autonomic nervous activity during ventilator weaning by HRV analysis (184). They found that in the success group, the changes of HR, BP, and HRV components were insignificant among the three phases.(184). Furthermore, in a recent study, Frazier et al. (16) evaluated the autonomic responses of critically ill patients during a 24- hr period of mechanical ventilatory support and during the 24 hr that included their initial spontaneous breathing trial using continuous positive airway pressure. Patients in the success group exhibited reduced plasma catecholamines in response to the CPAP weaning trial, whereas those in the failure group exhibited increased plasma catecholamines in response to the weaning trial (16).

Thus, these data from successful SBT demonstrates that the physiological stress did not change during the SBT and the patients could tolerate the SBT well.

Table 6-1 Demographic Data

Variable (Unit)	Value
Age (years)	68 ± 9
Weight (kg)	66 ± 7
BMI	24.3± 1.2
Gender (male/female)	2:1
Acute Physiology and Chronic Health Evaluation (APACHE II) Score	20 ± 6
Mechanical Ventilation (Days)	54 ± 16
Spontaneous Breathing Trial Duration (mins)	380 ± 86

*Data expressed as mean ± SD

Table 6-2 Blood Chemistry Values

Variable	Unit	Result
Serum sodium	mEq/L	153.1 ± 1.5
Serum potassium	mEq/L	4.11 ± 1.38
Serum Chloride	mEq/L	116.87 ± 0.91
Bicarbonate total	mmol/L	24.21± 1.09
Blood urea nitrogen	mg/dL	44.02 ± 7.08
Serum creatinine	mg/dL	1.44 ± 1.1
White blood cell count	$(*10^3)mm^3$	11.71 ± 5. 4
Hemoglobin	gm/dL	10.89 ± 1.05
Hematocrit	%	27.62 ± 2.45
Bilirubin	mg/dL	0.91 ± 0.32
Serum pre-albumin	mg/dl	12.01± 2.09
Total Protein	gm/dL	6.45 ± 1.2
Serum albumin	gm/dL	1.85 ± 0.3

*Data expressed as mean ± SD

Na= Sodium, K = Potassium, CL= Cloride, CO2 = Carbondioxide,BUN = Blood Urea Nitrogen, Cr = Creatinin, WBC= White blood cells, HGB= hemoglobin, HCT = Hematocrit, Billirub = Billirubin, Pre-alb = prealbumin, TP = total protein, Alb = Albumin.

Table 6-3 Vital Signs

	On MV	During SBT	t-Test (p-value)
Heart Rate	91 + 6	92 + 9	0.89
Blood Pressure			
Systolic	119 + 15	130 + 18	0.47
Diastolic	62 + 23	53 + 8	0.44

*MV: Mechanical ventilation, SBT: Spontaneous breathing trial, Data expressed as mean + SD

Table 6-4: Arterial Blood Gas Data

	On MV	During SBT	t-Test (p-value)
pH	7.41 ± 0.02	7.4 ± 0.03	0.70
PCO_2 (mmHg)	44.7 ± 0.3	42.80 ± 3.45	0.71
PO_2 (mmHg)	101.4 ± 1.7	93.6 ± 12.4	0.60
HCO_3 (mmol/l)	27.45 ± 1.05	26.05 ± 4.35	0.74
SaO_2 (%)	99 ± 1.41	97.5 ± 0.71	0.50
PaO_2/FiO_2	296.3 ± 66.5	278.2 ± 106.30	0.64

* pH: power of Hydrogen, $PaCO_2$: partial pressure of carbon dioxide, PaO_2: partial pressure of oxygen, HCO_3: actual bicarbonate contents, SaO_2: oxygen saturation of hemoglobin, PaO_2/FiO_2: ratio of arterial oxygen partial pressure to fractional inspired oxygen concentration. Data expressed as mean ± SD

Table 6-5 Breathing Pattern Variables

	Early SBT	Late SBT	t-Test (p-value)
VE	8.07 + 2.8	8.23 + 3.0	0.6
RR	27.18 + 8.9	28.03 + 8.4	0.37
Vti	316 + 84	324 + 102	0.83
PIF	33.11 + 7.4	34.69 + 8.4	0.51
PEF	32.34 + 7.7	33.56 + 8.34	0.65
RSBI	80.25 + 30.8	87.44 + 32.2	0.52
Ti	0.81 + 0.19	0.78 + 0.21	0.56
Te	1.66 + 0.7	1.54 + 0.62	0.47
VCO2	179.9 + 62.1	177.5 + 74.3	0.54
(Vd/ Vt)	0.55 + 0.09	0.60 + 0.12	0.34

*(Ve) minute ventilation, (RR) respiratory rate, (VT) tidal volume, (PIF) peak inspiratory flow, (PEF) peak expiratory flow, (RSBI) rapid shallow breathing index, (Ti) inspiratory time, (Te) expiratory time, (VCO2) carbon dioxide production rate & (Vd/Vt) dead space ventilation. Data expressed as mean $\pm$ SD, † $p<0.05$ between early SBT and late SBT

Table 6-6: Plasma Catecholamine

	On MV	During SBT	t-Test (p-value)
NE (pg/ml)	742± 574	340 ± 202	0.12
Ep (pg/ml)	60.7±57.9	59.3 ±19	0.5

NE: Norepinephrine, EP: Epinephrine. Data expressed as mean ± SD. † $p \leq 0.05$ between MV support and SBT failure.

Table 6-7 Heart Rate Variability Analysis: Frequency Domain Measures

	On MV	AT Failure	t-Test (p-value)
HF ln (ms2)	6.36±2.3	6.11±1.2	0.22
LF ln (ms2)	7.1±0.3	7.87± 0.9	0.16
HF (n.u.)	66±12	56±16	0.2
LF (n.u)	33±12	43±16	0.12
LF/HF	2.6±0.3	2.3±1.8	0.34

HF ln: High Frequency variability, LF ln: Low Frequency variability, HF (n.u.): High Frequency variability normalized units, LF (n.u.): Low Frequency variability normalized units. Data expressed as mean $\pm$ SD. † $p \leq 0.05$ between MV support and SBT failure.

CHAPTER 7
CONCLUSION AND FUTURE DIRECTIONS

This study is clinically important. Currently, there is no consensus on which physiological variable to monitor in PMV patients during the SBT to decide whether to prolong or curtail a SBT trial. A failed SBT is an extremely distressful experience for the patient, however, it is difficult to quantify physiological stress level during SBT in critically ill patients and more so in PMV patients. There is currently interest in identifying quantifiable, rapidly attainable measures that may be utilized to monitor patient tolerance of SBT. Evaluation of HRV parameters provides an indicator of physiologic status and may yield an earlier indication of impending deterioration or response SBT.

Currently the standard measures of physiological stress are circulating stress hormones and muscle sympathetic nerve activity analysis. However, plasma catecholamine analysis requires blood samples and laboratory analyses and is therefore not suitable for bedside monitoring of intraoperative stress. Whereas, due to the invasiveness and technical complexity associated with this technique, microneurography is generally not practical for repeated measurements or in clinical protocols.

This project demonstrates the feasibility of using heart rate variability analysis as a novel to quantify and monitor in real time the physiological stress associated with a SBT in PMV patients. HRV provides a noninvasive measure of an individual's ability to respond to normal regulatory impulses that influence cardiac rate and rhythm. HRV is a sensitive, tool which can be used bedside to monitor the physiological stress real-time. Additionally, HRV analysis is technically straightforward and an automatically derived

weaning predictor in a busy intensive care setting would be an attractive one. Commercial equipment designed to measure HRV is available which makes this technique far more suitable for studies that involve large samples and/or repeated measures in clinical settings.

Specific suggestions for further study include,

- To study the use of HRV analysis through regular screening during MV support as predictive tool for weaning failure.
- To study the tolerance of different IMST loads in critically ill patients using HRV changes
- To study the tolerance to regular rehabilitation interventions (occupational and physical therapy) in critically ill patients

APPENDIX A
BASIC ELECTROPHYSIOLOGY OF HEART

Cells within the sinoatrial (SA) node are the primary pacemaker site within the heart. These cells are characterized as having no true resting potential, but instead generate regular, spontaneous action potentials. Unlike non-pacemaker action potentials in the heart, and most other cells that elicit action potentials (e.g., nerve cells, muscle cells), the depolarizing current is carried into the cell primarily by relatively slow Ca++ currents instead of by fast Na+ currents. There are, in fact, no fast Na+ channels and currents operating in SA nodal cells. This results in slower action potentials in terms of how rapidly they depolarize. Therefore, these pacemaker action potentials are sometimes referred to as "slow response" action potentials.

SA nodal action potentials are divided into three phases. Phase 4 is the spontaneous depolarization (pacemaker potential) that triggers the action potential once the membrane potential reaches threshold between -40 and -30 mV). Phase 0 is the depolarization phase of the action potential. This is followed by phase 3 repolarization. Once the cell is completely repolarized at about -60 mV, the cycle is spontaneously repeated. The changes in membrane potential during the different phases are brought about by changes in the movement of ions (principally Ca++ and K+, and to a lesser extent Na+) across the membrane through ion channels that open and close at different times during the action potential. When a channel is opened, there is increased electrical conductance (g) of specific ions through that ion channel. Closure of ion channels causes ion conductance to decrease. As ions flow through open channels, they generate electrical currents (i or I) that change the membrane potential.

In the SA node, three ions are particularly important in generating the pacemaker action potential. At the end of repolarization, when the membrane potential is very negative (about -60 mV), ion channels open that conduct slow, inward (depolarizing) Na+ currents. These currents are called "funny" currents and abbreviated as "If". These depolarizing currents cause the membrane potential to begin to spontaneously depolarize, thereby initiating Phase 4. As the membrane potential reaches about -50 mV, another type of channel opens. This channel is called transient or T-type Ca++ channel. As Ca++ enters the cell through these channels down its electrochemical gradient, the inward directed Ca++ currents further depolarize the cell. As the membrane continues to depolarize to about -40 mV, a second Ca++ channel opens. These are the so-called long-lasting, or L-type Ca++ channels. Opening of these channels causes more Ca++ to enter the cell and to further depolarize the cell until an action potential threshold is reached (usually between -40 and -30 mV). During Phase 4 there is also a slow decline in the outward movement of K+ as the K+ channels responsible for Phase 3 continue to close. This fall in K+ conductance (gK+) contributes to the depolarizing pacemaker potential.

Phase 0 depolarization is primarily caused by increased Ca++ conductance (gCa++) through the L-type Ca++ channels that began to open toward the end of Phase 4. The "funny" currents, and Ca++ currents through the T-type Ca++ channels, decline during this phase as their respective channels close. Because the movement of Ca++ through these channels into the cell is not rapid, the rate of depolarization (slope of Phase 0) is much slower than found in other cardiac cells (e.g., Purkinje cells).

Repolarization occurs (Phase 3) as K+ channels open (increased gK+) thereby increasing the outward directed, hyperpolarizing K+ currents. At the same time, the L-type Ca++ channels become inactivated and close, which decreases gCa++ and the inward depolarizing Ca++ currents. During depolarization, the membrane potential (Em) moves toward the equilibrium potential for Ca++, which is about +134 mV. During repolarization, g'Ca++ (relative Ca++ conductance) decreases and g'K+ (relative K+ conductance) increases, which brings Em closer toward the equilibrium potential for K+, which is about -96 mV). Although pacemaker activity is spontaneously generated by SA nodal cells, the rate of this activity can be modified significantly by external factors such as by autonomic nerves, hormones, drugs, ions, and ischemia/hypoxia.

It is important to note that action potentials described for SA nodal cells are very similar to those found in the atrioventrcular (AV) node. Therefore, action potentials in the AV node, like the SA node, are determined primarily by changes in slow inward Ca++ and K+ currents, and do not involve fast Na+ currents. AV nodal action potentials also have intrinsic pacemaker activity produced by the same ion currents as described above for SA nodal cells. Figure A-1 summarizes the automaticity of pacemaker cells of heart.

The cardiac musculature consists of two types of muscle cells (or fibers): (i) cells that initiate and conduct impulses, and (ii) cells that, besides conducting, respond to stimuli by contracting. The cardiac conduction system is composed of the sinoatrial node (SAN), the atrioventicular node (AVN), the HIS bundle, the right and left bundle branches, the fascicles and the Purkinje fibers. The conduction system consists of specialized myocytes. Its atrial components, the SAN (subepicardial) and the AVN

(subendocardial), are in contact with the atrial myocardium. The His bundle goes through the right fibrous trigone (central fibrous body) and runs at the junction of the membranous and muscular septum before it divides into the right and left ventricular bundle branches. The right bundle branch is a cord like structure with a 1 mm diameter, which proceeds along the septal and moderator bands to reach the anterior papillary muscle. In contrast, the left bundle branch forms a broad sheet of conduction fibers that splits along the left side of interventricular septum into three indistinct fascicles [5].

The action potentials generated by the SA node spread throughout the atria primarily by cell-to-cell conduction at a velocity of about 0.5 m/sec. There is some functional evidence for the existence of specialized conducting pathways within the atria (termed internodal tracts), although this is controversial. As the wave of action potentials depolarizes the atrial muscle, the cardiomyocytes contract by a process termed excitation-contraction coupling. Normally, the only pathway available for action potentials to enter the ventricles is through a specialized region of cells (atrioventricular node, or AV node) located in the inferior-posterior region of the interatrial septum. The AV node is a highly specialized conducting tissue (cardiac, not neural in origin) that slows the impulse conduction considerably (to about 0.05 m/sec) thereby allowing sufficient time for complete atrial depolarization and contraction (systole) prior to ventricular depolarization and contraction. The impulses then enter the base of the ventricle at the Bundle of His and then follow the left and right bundle branches along the interventricular septum. These specialized fibers conduct the impulses at a very rapid velocity (about 2 m/sec). The bundle branches then divide into an extensive system of Purkinje fibers that conduct the impulses at high velocity (about 4 m/sec)

throughout the ventricles. This results in rapid depolarization of ventricular myocytes throughout both ventricles.

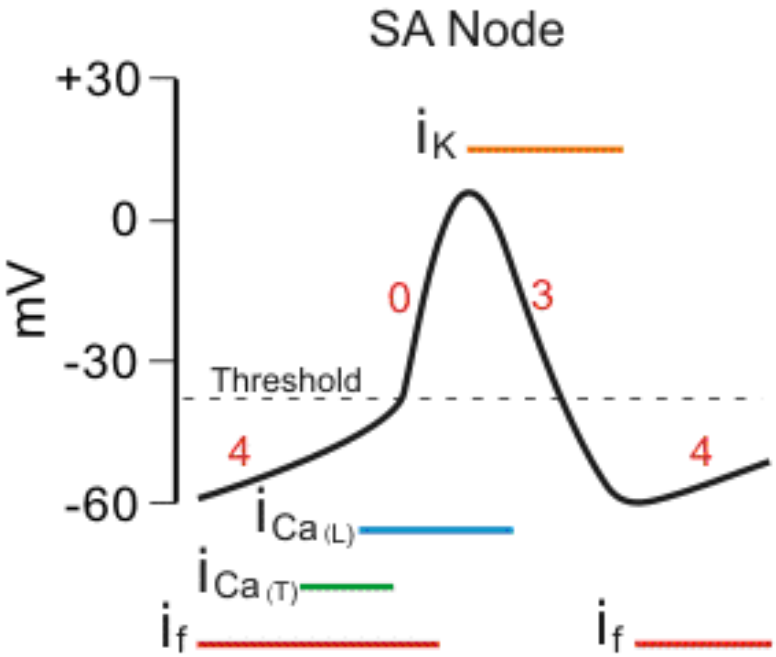


Figure A-1 Sinoatrial Node Action Potentials

APPENDIX B
BASIC ELECTROCARDIOGRAM

The electrocardiogram (ECG) is a tool for evaluating the electrical events in the heart. ECG measurements have been used for diagnostic purposes for more than a century. The action potentials of cardiac muscle cells can be viewed as batteries that cause charge to move throughout the body fluids. These moving charges are caused by all the action potentials occurring simultaneously in many individual myocardial cells, and their result can be detected by recording electrodes on the surface of the skin. The ECG does not provide a direct record of the changes in membrane potential across individual muscle cells. Rather, it is a measure of the currents generated in the extracellular fluid by the changes occurring simultaneously in many cardiac cells.

A conventional three-lead measurement of the ECG is performed by using three leads, placed on the right and left shoulder bones for the first and second leads, and on the left leg or lower left rib bone for the third lead. The resultant ECG signal, recorded in this way, is shown schematically in The P wave is the first deflection and represents the electrical impulse through the atrial musculature (depolarization). The second deflection is the QRS complex and represents the spread of the electrical impulse through the ventricular musculature, which triggers the ventricular contraction. The P–R interval is measured from the beginning of the P wave to the beginning of the QRS complex. It reflects the time taken by impulse to travel the entire distance from the SA node to the ventricular muscle. The final deflection is the T wave and represents the period of recovery for the ventricles (i.e. repolarization).

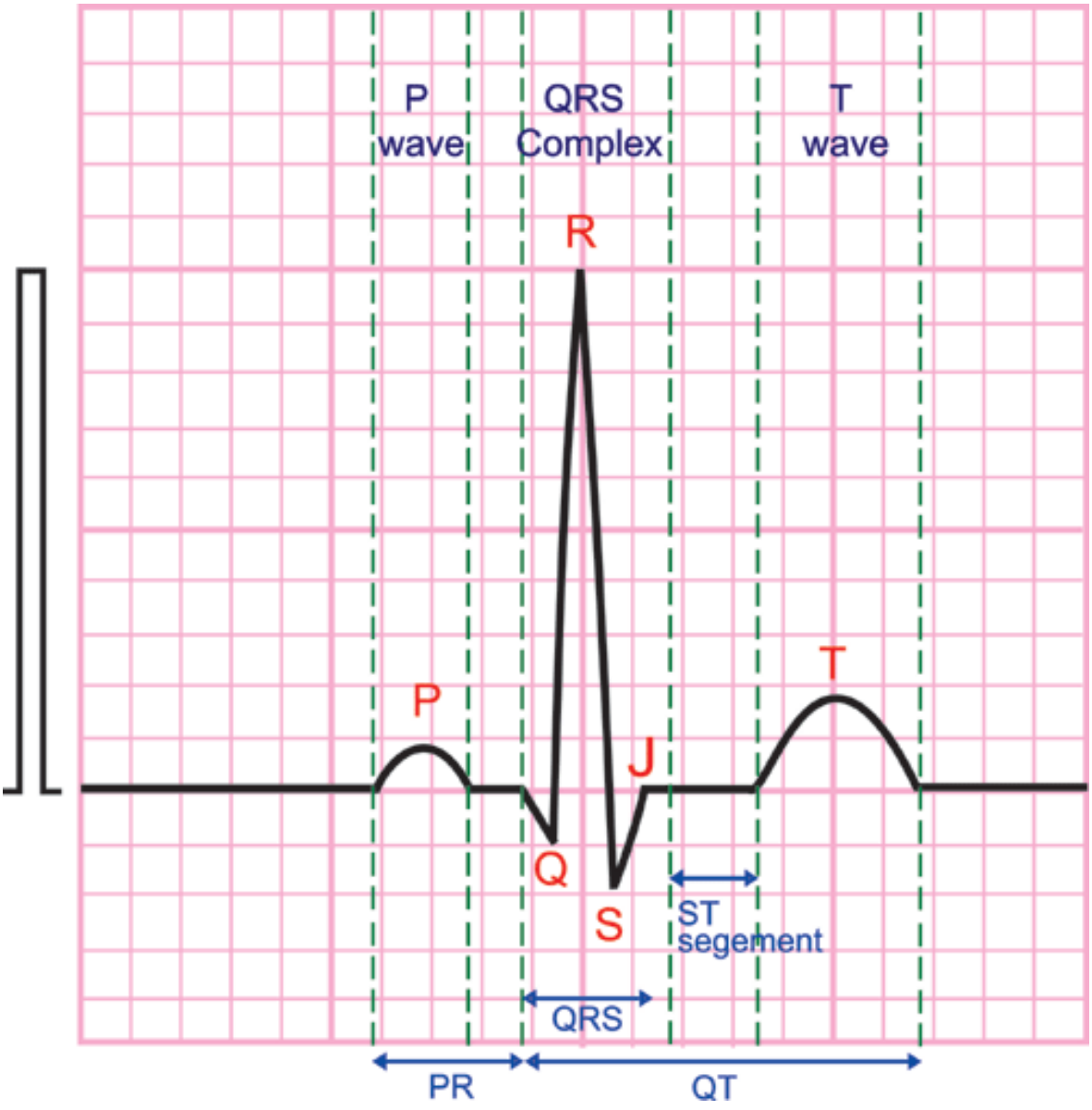


Figure B-1Normal EKG waveform

APPENDIX C
THE POINCARE´ PLOT

Introduction: Variability analysis is essentially a collection of various mathematical and computational techniques that characterize biologic time series with respect to their overall fluctuation, spectral composition, scale-free variation, and degree of irregularity or complexity. A growing exploration of patterns of variation or fluctuations in physiologic time series, particularly heart rate variability (HRV) analysis, has been shown to provide clinically useful and otherwise 'hidden' information about the health of the system producing the dynamics.

The Poincare´ plot is a representation of a time series into a Cartesian plane (or phase space), where the values of each pair of successive elements of the time series define a point in the plot. (1-3) The Poincare´ plot is a very simplified phase space with dimension two and delay or lag of one beat (i.e. each R-R interval is plotted as a function of the previous R-R interval). (243) The 'true' attractor of HRV is certainly not displayed by the Poincare´ plot as the HRV has a higher estimated dimension than two. (244) However, the Poincare´ plot gives a useful visual contact to the R-R data by representing both short- and long-term variations included in the recording. (243) Poincaré HRV plot is a graph in which each RR interval is plotted against next RR interval (a type of delay map).

Points above the line of identity indicate R-R intervals that are longer than the preceding R-R interval, and points below the line of identityindicate a shorter R-R interval than the previous. The quantitative analysis of the HRV attractor displayed by the Poincare´ plot can be made by adjusting it to an ellipse. (243) Using this technique, three indexes can be obtained: the standard deviation (SD) of the instantaneous beat-

to-beat R-R interval variability (minor axis of the ellipse or SD1), the SD of the long term R-R interval variability (major axis of the ellipse or SD2) and the axes ratio (SD1/SD2). (245). The physiological meaning of Poincare´ plot indexes has been explored in different experimental settings (243, 246). It is known that the sympatho–vagal interaction during exercise is reflected by the Poincare´ plot indexes and that the SD1 axis reflects vagal activity in certain specific conditions (247).

At the point of failure SD1 decreased from 24.12+4.22 to 19.06+4.28 ($p<0.001$) while SD2 decreased from 46.42+7.51 to 27.96+9.28($p<0.001$) and SD1/SD2 increased from 0.52+0.56 to 0.68+0.46 ($p<0.001$). Nonlinear analysis of the HRV using a Poincaré plot can reflect the impact of stress situations on short-duration records based on the SD1 parameter (248, 249). Our results indicate a significant inhibition of the parasympathetic activity at the point of failure during SBT, as the SD1 parameter is significantly lower than when the patients were receiving mechanical ventilation. Moreover, the increased SD1/SD2 ratio indicates increased sympathetic tone at the point of failure during SBT compared to mechanical ventilation support.

Thus, because Poincaré plot parameters are easy to compute and because the Poincaré plot is a quantitative visual tool, it could be applied to the analysis of R-R interval data gathered over relative short time periods during mechanical ventilation weaning.

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BIOGRAPHICAL SKETCH

Harshavardhan Deoghare received his bachelor of physical therapy degree from University of Pune in April 2001. He then worked as a consultant physical therapist in National heart Institute, Pune for two years. Deciding to focus his carrier in cardiorespiratory rehabilitation research, Harshavardhan began his doctoral work at the University of Florida in 2004 under the direction of Dr. A.D. Martin. Harshavardhan focused his studies on pulmonary physiology and inspiratory muscle strength training in difficult-to-wean patients. He received his PhD in August 2010.