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RIGHT HEART HEMODYNAMICS DURING WEANING FROM MECHANICAL VENTILATION

DISSERTATION

Presented in Partial Fulfillment of the Requirements for
the Degree Doctor of Philosophy in the Graduate School of
The Ohio State University

By
Susan K. Frazier, B.S.N., M.S.

* * * *
The Ohio State University
1996

Dissertation Committee:
K. S. Stone
D. K. Moser
E. R. Schertel

Approved by
Kathleen L. Stone
Adviser
College of Nursing
To My Family
ACKNOWLEDGEMENTS

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Fields of Study

Major Field : Nursing

Minor Field : Cardiopulmonary Physiology
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<td>ANOVA-RM</td>
<td>repeated measures analysis of variance</td>
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<td>ANP</td>
<td>atrial natriuretic peptide</td>
</tr>
<tr>
<td>ARDS</td>
<td>adult respiratory distress syndrome</td>
</tr>
<tr>
<td>biPAP</td>
<td>biphasic pulmonary airway pressure</td>
</tr>
<tr>
<td>CABG</td>
<td>coronary artery bypass graft</td>
</tr>
<tr>
<td>Cl</td>
<td>cardiac index</td>
</tr>
<tr>
<td>CO</td>
<td>cardiac output</td>
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<tr>
<td>CO2</td>
<td>carbon dioxide</td>
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<td>COPD</td>
<td>chronic obstructive pulmonary disease</td>
</tr>
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<td>CPAP</td>
<td>continuous positive airway pressure</td>
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<td>CT</td>
<td>computerized axial tomography</td>
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<td>CVP</td>
<td>central venous pressure</td>
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<td>EDV</td>
<td>end-diastolic volume</td>
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<tr>
<td>EDVI</td>
<td>end-diastolic volume index</td>
</tr>
<tr>
<td>EELV</td>
<td>end-expiratory lung volume</td>
</tr>
<tr>
<td>f</td>
<td>respiratory rate</td>
</tr>
<tr>
<td>FEV1</td>
<td>forced expiratory volume at one second</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>ratio of forced expiratory volume at second to forced vital capacity</td>
</tr>
<tr>
<td>FiO2</td>
<td>fraction of inspired oxygen</td>
</tr>
<tr>
<td>FRC</td>
<td>functional residual capacity</td>
</tr>
<tr>
<td>FVC</td>
<td>forced vital capacity</td>
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<td>HCO3-</td>
<td>bicarbonate</td>
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<td>HPV</td>
<td>hypoxic pulmonary vasoconstriction</td>
</tr>
<tr>
<td>HR</td>
<td>heart rate</td>
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<tr>
<td>IMV</td>
<td>intermittent mandatory ventilation</td>
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<tr>
<td>ITP</td>
<td>intrathoracic pressure</td>
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<tr>
<td>IVS</td>
<td>intraventricular septum</td>
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<td>left anterior descending coronary artery</td>
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<td>LV</td>
<td>left ventricle</td>
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<tr>
<td>LVEDV</td>
<td>left ventricular end-diastolic volume</td>
</tr>
<tr>
<td>LVEF</td>
<td>left ventricular ejection fraction</td>
</tr>
<tr>
<td>LVSWI</td>
<td>left ventricular stroke work index</td>
</tr>
<tr>
<td>MEF</td>
<td>maximum expiratory flow</td>
</tr>
<tr>
<td>MIGET</td>
<td>multiple inert gas elimination technique</td>
</tr>
<tr>
<td>MPAP</td>
<td>mean pulmonary artery pressure</td>
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<td>MV</td>
<td>mechanical ventilation</td>
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<tr>
<td>Pab</td>
<td>pressure in the abdomen</td>
</tr>
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<td>PaCO₂</td>
<td>arterial partial pressure of carbon dioxide</td>
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<tr>
<td>PaO₂</td>
<td>arterial partial pressure of oxygen</td>
</tr>
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<td>PaO₂/FiO₂</td>
<td>ratio of arterial oxygen to inspired oxygen</td>
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<td>PAOP</td>
<td>pulmonary artery occlusion pressure</td>
</tr>
<tr>
<td>PAP</td>
<td>pulmonary artery pressure</td>
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<td>Pₐw</td>
<td>pressure in the airway</td>
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<td>PEEP</td>
<td>positive end-expiratory pressure</td>
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<td>Pes</td>
<td>pressure in the esophagus</td>
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<td>Pfv</td>
<td>pressure in the femoral vein</td>
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<tr>
<td>Pra</td>
<td>pressure in the right atrium</td>
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<td>PRSW</td>
<td>preload recruitable stroke work</td>
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<td>PS</td>
<td>pressure support</td>
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<td>PTP</td>
<td>pressure time product</td>
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<td>PVR</td>
<td>pulmonary vascular resistance</td>
</tr>
<tr>
<td>PVRI</td>
<td>pulmonary vascular resistance index</td>
</tr>
<tr>
<td>RAP</td>
<td>right atrial pressure</td>
</tr>
<tr>
<td>RAPₘₜ</td>
<td>transmural right atrial pressure</td>
</tr>
<tr>
<td>RCA</td>
<td>right coronary artery</td>
</tr>
<tr>
<td>RF</td>
<td>residual fraction</td>
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<td>RV</td>
<td>right ventricle</td>
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<td>DESCRIPTION</td>
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<tr>
<td>RVEDV</td>
<td>right ventricular end-diastolic volume</td>
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<tr>
<td>RVEDVI</td>
<td>right ventricular end-diastolic volume index</td>
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<tr>
<td>RVEF</td>
<td>right ventricular ejection fraction</td>
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<td>RVESV</td>
<td>right ventricular end-systolic volume</td>
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<td>RVSW</td>
<td>right ventricular stroke work</td>
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<td>right ventricular stroke work index</td>
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<td>SIMV</td>
<td>synchronous intermittent mandatory ventilation</td>
</tr>
<tr>
<td>SpV</td>
<td>spontaneous ventilation</td>
</tr>
<tr>
<td>SV</td>
<td>stroke volume</td>
</tr>
<tr>
<td>SVI</td>
<td>stroke volume index</td>
</tr>
<tr>
<td>SvO₂</td>
<td>mixed venous oxygen saturation</td>
</tr>
<tr>
<td>SVR</td>
<td>systemic vascular resistance</td>
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<tr>
<td>SWI</td>
<td>stroke work index</td>
</tr>
<tr>
<td>TLC</td>
<td>total lung capacity</td>
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<tr>
<td>V_A/Q</td>
<td>ventilation perfusion ratio</td>
</tr>
<tr>
<td>V_d/V_t</td>
<td>proportion of dead space volume</td>
</tr>
<tr>
<td>V_E</td>
<td>minute ventilation</td>
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<td>V_t</td>
<td>tidal volume</td>
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<tr>
<td>VC</td>
<td>vital capacity</td>
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<tr>
<td>VO₂</td>
<td>oxygen consumption</td>
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<tr>
<td>WOB</td>
<td>work of breathing</td>
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CHAPTER I
RIGHT HEART HEMODYNAMICS DURING WEANING FROM
MECHANICAL VENTILATION

Significance of Problem

It is estimated that 9 to 37% of all mechanically ventilated patients have significant difficulty during the transition from mechanical ventilation (MV) to spontaneous ventilation (SpV) or weaning (Aldrich, Karpel, Uhrlass, Sparapani, Eramo, & Ferranti, 1989; Nett, Morganroth, & Petty, 1984; Stoller, 1991). A significant number of these individuals have chronic obstructive pulmonary disease (COPD) and require prolonged ventilator care because of their inability to make this transition (Cordasco, Sivak, & Perez-Trepichio, 1991; Indihar, 1991; Menzies, Gibbons, & Goldberg, 1989). Preexisting vascular and hemodynamic abnormalities inherent to COPD, in addition to hemodynamic instability produced by the transition from positive to negative intrathoracic pressure, may significantly contribute to this difficulty (Bastien, Durand, George, Gurbala, & Estanove, 1988; Beydon, Cinotti, Rekik, Radermacher, Adnot, Meignan, et al., 1991; Teboul, Abrouk, & Lemaire, 1988; Torres, Reyes, Roca, Wagner, & Rodriguez-Roisin, 1989).

Hemodynamic instability during the transition to spontaneous ventilation is one of the four proposed causes of weaning failure (Marini, 1991). Prior investigations suggest that changes in intrathoracic pressure (ITP) due to the application of mechanical ventilation influence right heart hemodynamic performance (Biondi, Schulman, Soufer, Matthay, Hines, Kay,
et al., 1988; Fessler, Brower, Wise, & Permutt, 1990; Fessler, Brower, Wise, & Permutt, 1991; Fewell, Abendschein, Carlson, Murray, & Rapaport, 1980a; Fewell, Abendschein, Carlson, Rapaport, & Murray, 1980b; Groeneveld, Schreuder, Verneij, & Thijs, 1990; Johnston, Vinten-Johansen, Shugart, & Santamore, 1992; Navarrete-Navarro, Vazquez, Fernandez, Torres, Reina, & Hinojosa, 1989; Schulman, Biondi, Zohgbi, Zaret, & Soufer, 1990; Teboul, et al., 1988; Viquerat, Righetti, & Suter, 1983). Normally, ITP becomes less than atmospheric with diaphragm descent during spontaneous inspiration. Since ITP is reflected on the heart and great vessels within the closed thoracic cavity, spontaneous inspiration augments the pressure gradient between the abdominal vena cava and the right heart. Consequently, venous return is increased during normal spontaneous inspiration. Positive pressure mechanical ventilation produces a positive ITP during inspiration which reduces venous return by decreasing the pressure gradient. The shift from positive ITP during mechanical ventilation to negative ITP with spontaneous ventilation may be a significant factor in the development of hemodynamic instability with weaning, particularly in those individuals with preexisting cardiac dysfunction. Individuals with moderate to severe COPD may have significant preexisting right heart dysfunction because of vascular and hemodynamic changes inherent to the disease process. Hemodynamic changes during the transition from mechanical to spontaneous ventilation, in addition to preexisting right heart dysfunction, may induce cardiac decompensation and overt heart failure. However, there is a paucity of research that examines right heart hemodynamics during weaning from MV.
Purpose of the Study

The purpose of this study was to describe changes in right heart hemodynamics associated with the transition from mechanical to spontaneous ventilation. The findings from this study will assist the critical care team in the optimization of cardiopulmonary function and deterrence of cardiopulmonary complications, provide insight into appropriate hemodynamic monitoring parameters during this transition and aid in the identification of an optimal ventilatory support mode for ventilated individuals during their transition from MV to SpV.

Specific Aims

The specific aims of this study were:

1. To compare right heart hemodynamic changes associated with the transition from mechanical ventilation to spontaneous ventilation in an anesthetized canine model using two groups: Group 1 (normal biventricular function) and Group 2 (propranolol induced acute biventricular failure).

   Hypothesis 1. Changes in right heart hemodynamics during the transition from mechanical ventilation to spontaneous ventilation are the result of changes in ITP which alter right heart preload, afterload and right ventricular contractility.

   This hypothesis was tested in Groups 1 and 2. Right heart hemodynamic and ITP measurements were obtained during MV, SpV and SpV through a resistor.

2. To compare the right heart hemodynamic changes associated with transition from mechanical ventilation to spontaneous ventilation using three modes of weaning: t-piece with supplemental oxygen, continuous
positive airway pressure (CPAP) at 5 cm H\textsubscript{2}O and pressure support (PS) at 5 cm H\textsubscript{2}O in an anesthetized canine model with and without heart failure (Group 1, Group 2, respectively).

Hypothesis 2. The extent of right heart hemodynamic changes will differ based on the degree of change in intrathoracic pressure produced by the three weaning modes (t-piece, CPAP, PS). These variations may also be related to the characteristics of support delivery found with the three modes of weaning (t-piece - no support, CPAP - continuous support; PS - support during inspiration).

This hypothesis was tested in the two groups of canine subjects by measurement of right heart hemodynamics and ITP during each of the three weaning modes (t-piece, CPAP, PS).

**Definitions of Variables**

**Independent Variables**

In this study, the independent variables were the type of ventilation and the level of ITP. The types of ventilation included mechanical ventilation, spontaneous ventilation (t-piece), spontaneous ventilation through a 3mm inner diameter resistor (Resistor), continuous positive airway pressure 5cm. (CPAP) and pressure support 5 cm. (PS). ITP was altered with the different modes of ventilation: positive ITP with MV, PS, CPAP and less than atmospheric ITP with t-piece and Resistor. Esophageal pressure (Pes) was measured as an indirect indicator of ITP.

**Dependent Variables**

The dependent variables for this study were cardiac output (CO) and right ventricular end-diastolic volume (RVEDV) measured by thermodilution, stroke volume (SV), pulmonary vascular resistance (PVR) and right
ventricular stroke work (RVSW) derived from measured volume and pressure variables (systolic, diastolic and mean arterial and pulmonary arterial blood pressure, right atrial pressure, pulmonary artery occlusion pressure) and heart rate (HR) indicated by continuous lead II electrocardiographic recording. Abdominal pressure (Pab) was measured to permit calculation of transdiaphragmatic pressure. The primary dependent variables may be placed in a conceptual framework to facilitate understanding of integral relationships of these variables (Figure 1.). Cardiac output is the product of heart rate and stroke volume. Stroke volume is influenced by the degree of right ventricular preload, afterload and contractility.
Figure 1. Conceptual model of the relationship between the major dependent variables
Chapter II

REVIEW OF LITERATURE

Right Heart Hemodynamics During Weaning from Mechanical Ventilation

There is a paucity of literature reporting investigations of right heart hemodynamics following removal of mechanical ventilation. In an early study of hemodynamic responses to weaning, Beach, Millen and Grenvik (1973) found a differential CO response to the transition from MV to SpV in a group of postoperative cardiac surgical patients (n = 37). One group responded to SpV by increasing CO an average of 19% (Group A, n = 19); while the other group decreased CO 17% on average (Group B, n = 18). Pulmonary vascular resistance (PVR) data was available for only six subjects and documented an overall increase in PVR with SpV, particularly in Group B subjects (A = 35% increase, B = 81% increase). Central venous pressure (CVP) was also elevated in Group B subjects, both with MV and SpV (MV = 12 ± 1.1, SpV = 13 ± 1.6 torr) compared to Group A (MV = 8 ± 0.6, SpV = 8 ± 0.9 torr). Systemic vascular resistance (SVR) significantly increased in Group B with SpV (p < 0.001); while Group A had a slight, but significant decrease in SVR with SpV (p = 0.02). These investigators suggested the presence of biventricular dysfunction in Group B subjects, particularly following removal of MV. A more complete analysis of cardiac function was precluded by lack of measurement sophistication at the time of this study.
A specific analysis of right heart performance during weaning was accomplished when Teboul, Abrouk and Lemaire (1988) measured right ventricular function in seven COPD patients during transition from MV to SpV. Right ventricular ejection fraction (RVEF) and end-diastolic volume (EDV) were measured by the thermodilution technique during MV and 15 minutes after the institution of SpV. Pulmonary artery pressure (PAP) was continuously measured and rose significantly following disconnection from MV (25 ± 4 mmHg to 28.5 ± 4.5 mmHg, p = 0.05). In spite of this elevation in right ventricular afterload, RVEF and EDV were not statistically different from values obtained during MV. The investigators inferred that these subjects were able to maintain forward blood flow in the presence of an increase in afterload by increasing contractility. The augmentation of right ventricular contractility was attributed to an increased catecholamine discharge in response to removal of MV, even though catecholamines were not measured. These subjects were able to maintain tissue oxygenation and were easily weaned from MV. This study is limited by the very small, homogeneous sample, and lack of data regarding baseline extent of pulmonary disease, level of right ventricular function prior to MV and the degree of negative ITp developed during spontaneous inspiration. Although all subjects in their sample were easily weaned from MV, the investigators concluded that measurement of RVEF and EDV could potentially identify “unweanable patients”.

Further investigation of right heart performance occurred when Bastien, Durand, George, Gurbala and Estanove (1988) monitored right ventricular function following coronary artery bypass graft (CABG) surgery (n = 34). Hemodynamic parameters were measured prior to anesthesia induction, 2, 4,
6 and 20 hours post operation during MV; as well as, 1 and 24 hours post extubation. Two postoperative periods with significant hemodynamic changes were identified. Cardiac index (CI) and RVEF decreased significantly the first six postoperative hours (CI from $2.59 \pm 0.4$ to $2.31 \pm 0.4$ liters/min/m², RVEF from $0.48 \pm 0.07$ to $0.37 \pm 0.09$, $p < 0.05$). Subsequently, the second major period of hemodynamic instability occurred during the transition to SpV. Following removal from MV, RVEF decreased without a significant change in CI (RVEF from $0.43 \pm 0.1$ to $0.36 \pm 0.07$, CI from $2.72 \pm 0.5$ to $2.8 \pm 0.5$ liters/min/m²). A depression in right ventricular contractility and/or tachycardia with decreased ventricular filling (heart rate maximum $95 \pm 14$ beats/min) were identified as potential explanations for these reductions. Neither CVP nor pulmonary artery occlusion pressure (PAOP) were significantly different during any of the measurement periods (CVP ranged from $7 \pm 2$ mmHg to $8.5 \pm 3$ mmHg, PAOP ranged from $8.2 \pm 3.3$ mmHg to $10.5 \pm 4.8$ mmHg). However, right ventricular end-diastolic volume index (RVEDVI) decreased significantly during the first six postoperative hours (RVEDVI from $93 \pm 18$ to $72 \pm 21$, $p < 0.05$), then increased significantly following removal from MV (RVEDVI from $78 \pm 22$ to $84 \pm 22$, $p < 0.05$). These investigators identified periods of right ventricular depression post cardiac surgery and proposed RVEDVI as a more sensitive indicator of preload than CVP or PAOP in this population. These subjects exhibited a limited ability to increase contractility in response to an increase in venous return. An increase in right ventricular EDV may shift the interventricular septum to the left and interfere with left ventricular compliance and filling, as well as, increase right ventricular wall stress and reduce coronary blood flow producing myocardial ischemia.
Different MV modes are employed to assist individuals during the transition to SpV; however, right heart performance with these modes has not been thoroughly investigated. Raper and Sibbald (1992) studied the effects of incremental CPAP on right ventricular hemodynamics in an unanesthetized, ovine model with (n = 7) and without sepsis (n = 9). The sheep were instrumented under general anesthesia, then permitted to recover for three days prior to study. CPAP was applied in 4 mmHg incremental levels from zero to a maximum of 16 mmHg. CO, RVEF and right ventricular end-diastolic volume (RVEDV) were measured by the thermodilution method at each level of CPAP in the unanesthetized, spontaneously breathing subjects. Incremental CPAP produced similar results in septic and non septic states. CI was not significantly different with incremental CPAP (0 CPAP, CI = 5.08 ± 0.94; 16 cm CPAP, CI = 5.21 ± 0.94, NS). PVR or right ventricular afterload increased significantly and progressively with CPAP level (0 CPAP, PVRI = 198 ± 49 dynes/s/cm\(^3\)/m\(^2\); 16 cm CPAP, PVRI = 363 ± 77 dynes/s/cm\(^3\)/m\(^2\), p <0.0001); while RVEF decreased significantly (0 CPAP, RVEF = 0.38 ± 0.05; 16 cm CPAP, RVEF = 0.31 ± 0.05, p <0.0001). RVEDVI remained essentially unchanged (0 CPAP, RVEDVI 133 ± 29 ml/m\(^2\); 16 cm CPAP, RVEDVI =140 ± 29 ml/m\(^2\), NS). Transmural right atrial pressure (RAPm) was significantly reduced by incremental CPAP levels (0 CPAP, RAPm = 7.7 ± 1.7 mmHg; 16 cm CPAP, RAPm = 4.8 ± 2.9 mmHg, p <0.0001). The decline in RAPm with concurrent maintenance of RVEDV indicated right ventricular compliance was enhanced by incremental levels of CPAP. The fundamental conclusions of this investigation were that incremental CPAP levels can alter elements of cardiac and vascular performance, while net consequences depend on the effectiveness of
compensatory mechanisms invoked in response to changes in preload and afterload. In these subjects, CO was preserved by increases in heart rate and stroke work.

To the investigators' knowledge, there are no reports that examine right heart function with PS ventilation or compare right heart performance during spontaneous ventilation to that with CPAP and PS. There are some recent studies that investigate global hemodynamics in conjunction with intermittent non-invasive ventilation; however, none of these studies specifically evaluates right heart performance (Ambrosino, Nava, Torbicki, Riccardi, Fracchia, Opasich, et al., 1993; Bradley, Holloway, McLaughlin, Ross, Walters, & Liu, 1992; Genovese, Moskowitz, Tarasiuk, Graver, & Scharf, 1994; Montner, Greene, Murata, Stark, Timms, & Chick, 1994).

During the transition from MV to SpV, right heart hemodynamics may be influenced by the change from positive ITP to negative ITP. Negative swings in ITP influence both right ventricular preload and afterload. Previous studies were often limited by the measurement technology and small sample size. In addition, there has not been a thorough investigation of the effects of weaning support modes on right heart hemodynamics.

**Review of Related Literature**

**Chronic Obstructive Pulmonary Disease**

COPD, the fourth leading cause of death in the United States, was responsible for over 100,000 deaths in 1993 (Hull, 1995). Although mortality from other leading causes of death like heart attack and stroke decreased significantly from 1980 to 1986 (heart attack by 13.2%, stroke by 25.5%), mortality due to COPD increased during this time period by 15.3%. This is considered a conservative estimate, since less than half of warranted death
certificates were found to list COPD as a contributing cause of death (Sherrill, Lebowitz, & Burrows, 1990). The increase in mortality is attributed to the long term effects of cigarette smoking and air pollution.

COPD is most predominant in white males and prevalence increases with aging. A COPD risk model constructed to predict an individual's risk of COPD described initial lung function, age, gender and smoking as major determinants in the development of COPD. Additional significant contributors to this model included levels of serum IgE, a familial history of COPD, childhood history of respiratory illness, occupational exposures to inorganic particulate inhalants and socioeconomic status (Sherrill, et al., 1990).

COPD is also the second leading cause of disability in the United States (West, 1987). Dyspnea is the most common symptom experienced with COPD and can significantly interfere with the performance of activities of daily living. This reduction in functional activity is associated with the degree of abnormal pulmonary mechanics, severity of gas exchange impairment, the presence of dyspnea, alterations in central ventilatory control mechanisms, impaired cardiac performance secondary to right heart dysfunction, inadequate nutritional status and respiratory muscle fatigue (Celli, Snider, Heffner, Tiep, Ziment, Make, et al., 1995). In general, COPD induces pathological changes in the structure and function of pulmonary parenchyma and pulmonary vasculature that result in significant morbidity and mortality.

Alterations in Pulmonary Parenchyma with COPD

The diagnosis of COPD is based on the existence of an abnormal expiratory airflow over a period of several weeks to months. This airflow obstruction may be functional or structural, but is not produced by localized upper airway
disease, or pulmonary diseases like bronchiectasis or cystic fibrosis. There may be some degree of bronchial hyperreactivity with COPD; however, the dominant feature is a chronic airflow limitation. Three pathological conditions are included within the syndrome of COPD: emphysema, chronic bronchitis and peripheral airways disease (Celli, Snider, Heffner, Tiep, Ziment, Make, et al., 1995). One or more of these pathological entities may be present to various degrees in individuals with COPD.

Emphysema is “a condition of the lung characterized by abnormal permanent enlargement of the air spaces distal to the terminal bronchiole, accompanied by destruction of their walls, and without obvious fibrosis” (Snider, Kleinerman, Thurlbeck, & Bengali, 1985, pg. 183). Airspace enlargement may be simple airspace enlargement due to congenital or acquired causes, airspace enlargement with fibrosis or emphysema (Snider, et al., 1985). Congenital airspace enlargement is inherent to Down syndrome; while, acquired airspace enlargement occurs during the normal aging process. Airspace enlargement with fibrosis is found with interstitial pulmonary fibrosis and granulomatous pathology following destruction of parenchyma and replacement by fibrous tissue. With emphysema, pulmonary tissue, particularly the alveolar capillary gas exchange surface, is destroyed. The destruction of pulmonary tissue induces airspace enlargement, but fibrous tissue replacement does not occur. Destruction of the gas exchange surface reduces the surface area for gas diffusion. Emphysema is classified by anatomic subtypes as centriacinar, panacinar or distal acinar (Celli, et al., 1995; Snider, et al., 1985; Thurlbeck, 1990).

Centriacinar or proximal acinar emphysema describes pathological changes in the proximal portion of the acinus and is further divided into two
subtypes: centrilobular and focal. Centrilobular emphysema is primarily associated with cigarette smoking and chronic inflammation. The second subtype, focal emphysema, is associated with inhalation of mineral dusts. Dust particles are deposited in the respiratory bronchioles where they are phagocytized by alveolar macrophages. These dust laden macrophages accumulate in large numbers in and around the respiratory bronchioles and eventually dilate the bronchioles. Panacinar emphysema involves all portions of the acinus and is associated with α1 antitrypsin deficiency. A congenital deficiency of this protease inhibitor renders pulmonary tissue susceptible to destruction by super oxide radicals and proteolytic enzymes. Distal acinar emphysema predominantly involves lesions of the distal acinus or the alveolar ducts and sacs. This form of emphysema is uncommon, but is associated with nonspecific airway enlargement and spontaneous pneumothorax. Classification of emphysema into these anatomic subtypes is presumptive in the living individual, since true diagnosis can only be made by postmortem examination. However, some degree of emphysema is generally documented postmortem in individuals with moderate COPD; while in severe COPD, emphysematous lesions are the most prominent component of the pathological process (Thurlbeck, 1990).

The second pathological condition included in COPD is chronic bronchitis which is characterized by an excessive production of mucous for three or more months in a year during two or more consecutive years (Thurlbeck, 1990). Excess mucous production is associated with bronchial mucous gland enlargement and increased mucous production. Smooth muscle hypertrophy and mucosal inflammation thicken bronchial walls which reduces the airway lumen diameter. Cartilage atrophy produces airway collapse,
particularly during expiration.

The third pathological condition is peripheral airways disease which encompasses a variety of histological abnormalities. These include bronchiolar inflammation, fibrosis and narrowing, increased mucous production and mucous plugging of airways and actual obliteration of bronchioles. These changes are postulated to be the consequence of inappropriate inflammatory mediator release (Thurlbeck, 1990). Overall, pathological changes found with COPD produce mechanical instability of the airways, airway lumen reduction and tortuosity, loss of lung elastic recoil and recoil pressure, as well as an increase in resistance to airflow.

Alterations in Pulmonary Vasculature with COPD

COPD not only produces changes in the structure and function of the airways and acinus, but also alters the structure and function of the pulmonary circulation. The pulmonary vasculature is normally a low pressure, high compliance, non-nutritive system that perfuses the pulmonary parenchyma. Following systemic circulation past metabolically active tissues, mixed venous blood is returned to the right ventricle for ejection into the pulmonary vessels. The pulmonary circulation receives the entire right ventricular output, so that mixed venous blood may participate in gas exchange at the alveolar capillary membrane. The main pulmonary artery extends only 5 centimeters from the right ventricle before dividing into the right and left pulmonary arteries (Guyton, 1986). Normally, the walls of these large pulmonary arteries are structurally different from systemic arteries of the same caliber. The walls of the main pulmonary vessels are comprised of eight elastic layers; however, the vessel media contains only a thin layer of smooth muscle, in contrast to systemic arteries of the same caliber (Taylor,
Rehder, Hyatt, & Parker, 1989). The smooth muscle in the thin walled pulmonary arteries inserts into short elastic fibers which allow the vessel to distend easily and accommodate changes in right heart output (MacNee, 1994a). The compliance of the main pulmonary vessels is only one millimeter mercury increase in pressure for each two milliliter increase in blood volume which produces a total pulmonary compliance of approximately 30 ml/mmHg pressure (Guyton, 1986; Taylor, et al., 1989).

Pulmonary artery compliance varies during the ventilatory cycle (Grant, Fitzpatrick, & Lieber, 1991; Grant & Lieber, 1992; Grant & Canty, 1989). The greatest degree of compliance is found at end-inspiration; while the least is found at end-expiration. Theoretically, this time variation in compliance is due to shifts of blood volume between alveolar and extra-alveolar vessels within the ventilatory cycle. At end-inspiration, alveolar vessels are compressed and blood is shifted to extra-alveolar vessels like the main pulmonary vessels. At end-expiration, blood has been propelled into alveolar vessels for gas exchange and pulmonary artery compliance is reduced. With COPD, alveolar vessels are chronically compressed due to air space enlargement and hyperinflation. This increases alveolar pressure and augments resistance to blood flow. With an increase in pulmonary resistance, a greater pressure must be generated by the right ventricle to develop the gradient necessary to propel blood into alveolar vessels for gas exchange.

Normally, the total resistance to blood flow in the pulmonary circulation is approximately one twelfth that of the systemic circulation (1.5 mmHg/L/min. vs 18.3 mmHg/L/min.) (Taylor, et al., 1989). The site of greatest pressure change and greatest resistance to blood flow in the systemic arterial circulation is the precapillary arteriole; however, these same
precapillary vessels are not normally present in the pulmonary vasculature (MacNee, 1994a). Smaller pulmonary arteries (80 to 500 µm diameter) contain increased amounts of muscle and are the primary site of changes in pulmonary vascular tone. The development of airflow limitation and hypoxemia is correlated with changes in vascular structure of these vessels. With COPD, a layer of smooth muscle is longitudinally deposited in the intimal layer of these vessels. Elastic fibers are interwoven with these smooth muscle cells and thickening of the intimal layer reduces vessel lumen (Wilkinson, Langhorne, Heath, Barer, & Howard, 1988). With severe disease, the smooth muscle in the medial layer hypertrophies, further reducing vessel lumen diameter (Magee, Wright, Wiggs, Pare, & Hogg, 1987). Precapillary pulmonary arterioles (< 80 µm diameter) are normally thin walled with an elastic lamina and little or no smooth muscle cells. With COPD, circular muscle is deposited in the medial layer of these arterioles and a second elastic lamina develops. In some instances, a vessel lumen becomes divided into multiple parallel tubes further increasing resistance to blood flow (Wilkinson, et al., 1988). Theoretically, these vascular changes are produced by hypoxia, mechanical stretching of the vessel wall and/or by the pathological processes of COPD (Wilkinson, et al., 1988).

In addition to structural changes in pulmonary vessels, pulmonary vascular tone in COPD is also influenced by several active and passive mechanisms. Active mechanisms include abnormalities in alveolar and arterial concentrations of oxygen and carbon dioxide, abnormalities in arterial pH and pathology in the pulmonary vessels (Des Jardins, 1993; Taylor, et al., 1989). A reduction in alveolar oxygen concentration to less than 90 mmHg produces smooth muscle contraction in the small, muscular pulmonary
arteries (Taylor, et al., 1989). This increase in vascular tone in response to hypoxia is an active reflex known as hypoxic pulmonary vasoconstriction (HPV). HPV reduces blood flow to inadequately ventilated/oxygenated alveoli which improves ventilation perfusion matching. Hypoxia may inhibit the activity of potassium channels in pulmonary vascular smooth muscle cells (Post, Hume, Archer, & Weir, 1992). This inhibition alters membrane potassium currents and induces depolarization of the resting membrane potential. With depolarization, voltage dependent calcium channels are activated and calcium enters the smooth muscle cells producing muscle contraction and increasing vascular tone. HPV may also be stimulated by elevation of alveolar carbon dioxide to greater than 50 mmHg; however, this vascular response is most likely due to a subsequent changes in pH. PVR will increase by 50% for each pH decrease of 0.1 below normal value (7.35) (Taylor, et al., 1989). There is a significant synergistic effect when both hypoxia and hypercapnia/acidosis are present. The HPV response is three times more potent in the presence of alveolar hypoxia and pH reduction by 0.1 to 0.2 units (MacNee, 1994a; Taylor, et al., 1989). COPD with chronic airflow limitation, reduction in alveolar capillary membrane surface area and increased ventilation perfusion mismatch produce hypoxia and hypercapnia. The HPV reflex then further increases vascular resistance.

Because of pathological alterations in vessel structure with COPD, pulmonary thrombosis commonly occurs (Calverley, Howatson, Flenley, & Lamb, 1992). Although partial or total blockage of a pulmonary vessel passively obstructs the flow of blood, pulmonary baroreflexes and vasoactive mediators released in the presence of thrombosis also actively alter pulmonary vascular tone (Elliott, 1992). Baroreceptors located in pulmonary
arteries are stimulated by elevations in pressure within the artery which provoke a reflex vasoconstriction. Also, serotonin and thromboxane A2 are vasoactive amines released in response to thrombosis. When activated, platelets release dense granules containing serotonin (5-hydroxytryptamine), a potent vasoconstrictor (West, 1990). Thromboxane A2, a product of arachadonic acid metabolism, is formed following release of arachadonic acid from platelet membrane phospholipids (West, 1990). In addition, thromboxane A2 is produced by pulmonary endothelial cells in response to the presence of arachadonic acid, serotonin and vessel wall stretch (Katusic & Shepherd, 1991). Thromboxane A2 produces an increase in pulmonary vascular resistance by stimulating vascular smooth muscle contraction. It is hypothesized that the normal, resting pulmonary vascular tone is the result of a balance between the endothelium dependent vasoconstrictor, thromboxane A2, and an endothelium dependent vasodilator, probably nitric oxide (Taylor, et al., 1989; Zapol, Rimar, Gillis, Marletta, & Bosken, 1994).

Passive mechanisms produce changes in pulmonary vascular tone due to a mechanical influence on vessel caliber. These mechanisms include changes in PAP, blood volume, left atrial pressure, lung volume and blood viscosity (Des Jardins, 1993). As pulmonary blood volume and PAP increase, vascular resistance decreases. Because of the degree of pulmonary vessel compliance, right heart cardiac output must normally increase by 2.5 fold before any increase in PAP is detected (MacNee, 1994a). Ordinarily, an increase in right heart output results in the recruitment of underperfused vessels and distension of perfused vessels, so resistance to blood flow decreases. An increase in left atrial pressure will also decrease PVR. The pressure in the pulmonary circuit must remain higher than that in the left atrium to
establish a pressure gradient for forward flow of blood. An increase in left atrial pressure without a concomitant increase in pulmonary pressure will produce distension of pulmonary vessels which reduces vascular resistance. However, vessel distension may increase capillary hydrostatic pressure sufficiently to produce movement of fluid into the interstitium. With COPD, the number of pulmonary vessels is reduced and vessel morphology is altered. Recruitment and distension of pulmonary vessels is no longer an option. This significantly increases the resistance to blood flow in the pulmonary system, particularly during periods of increased right heart ejection as seen with exercise (MacNee, 1994a). The right ventricle must generate a greater pressure to ensure forward blood flow when pulmonary vascular resistance is increased.

Lung volume passively influences PVR. Ordinarily, the relationship between resistance and volume is U-shaped with PVR lowest at functional residual capacity (FRC). As lung volume increases, radial traction on the extra-alveolar vessels increases vessel caliber; while alveolar vessels are compressed. Since the alveolar and extra-alveolar vessels are in series, the total resistance is the sum of these two resistances and PVR increases. At lung volumes below FRC, radial traction on extra-alveolar vessels is significantly reduced, as is vessel diameter; while alveolar vessels have a greater diameter. Again the total resistance increases. With COPD, airspace enlargement, alveolar wall destruction and loss of elastic recoil increases lung volumes throughout the ventilatory cycle. Alveolar vessels are persistently compressed and destruction of alveolar walls and supporting structures reduces the radial traction of extra-alveolar vessels. The product is a consistent increase in total PVR.
An increase in PVR due to active and passive mechanisms coupled with a reduction in the number of pulmonary vessels and alteration in pulmonary vascular structure yields an overall decrease in pulmonary capillary blood volume (Morrison, Abboud, Muller, Miller, Gibson, Nelems, et al., 1990). Ordinarily in a basal state, the lungs accommodate approximately 10% of the total blood volume or about 480 ml. Approximately 180 ml of this volume is contained within the pulmonary microvessels; while the remainder lies within the pulmonary arteries (150 ml.) and veins (150 ml.) (Taylor, et al., 1989). In COPD, significant loss of pulmonary capillaries reduces the volume of blood that contacts the alveolar capillary membrane and participates in gas exchange. Hypoxemia and hypercapnia are the consequence.

Tissue hypoxia is sensed by renal cells that synthesize erythropoietin. Erythropoietin stimulates production of colony forming units-erythrocyte in bone marrow with a subsequent release of immature reticulocytes into circulation (West, 1990). Reticulocyte maturation generates a greater volume of erythrocytes in circulation which intends to augment the oxygen carrying capacity of the blood and reduce tissue hypoxia. There is a basal release of erythropoietin which maintains normal levels of erythropoiesis. However, hypoxemia induces the kidney to release greater amounts of erythropoietin which increases production and release of erythrocytes. This induces a secondary polycythemia which alters the viscosity of blood and influences resistance to flow according to Poiseuille's law \( Q = \Delta P r^4/8\eta \). Flow is inversely proportional to viscosity, so as viscosity increases, flow decreases (Des Jardins, 1993). Because pressure is directly proportional to the viscosity \( P = Q8\eta/r^4\pi \), pressure rises with increased viscosity.
Viscosity is a flow determining property and is defined as the internal friction produced by gas or fluid molecules in response to a change in form or relative position or as the ratio of shear stress to shear rate (Berne & Levy, 1992; Des Jardins, 1993). Shear stress describes the relationship between applied force and area in the movement of molecules through a tube. Shear rate describes the association between the velocity of these molecules and the distance of the molecules from the walls of the tube (Berne & Levy, 1992; West, 1990). The viscosity of blood changes with the hematocrit. With a normal hematocrit of 40-45%, blood viscosity is nearly four times greater than that of water (West, 1990). Secondary polycythemia is a common finding with COPD, since hypoxia stimulates production of erythrocytes. Hematocrit and blood viscosity increase and for each percent increase in hematocrit, the resistance to blood flow increases by 4% (Taylor, et al., 1989). To maintain forward blood flow, pressure must then increase according to Poiseuille's law.

In conclusion, histological changes with COPD may be found in the large airways (chronic bronchitis), small airways (peripheral airways disease), gas exchange unit of the lung (emphysema) and the pulmonary vasculature. In COPD, parenchymal lesions of emphysema, chronic bronchitis and peripheral airways disease are generally found in combination with various degrees of severity. Occasionally, one type of lesion will dominate the pathology; however, this is generally late in the process when end stage disease is present. Pulmonary vascular changes are associated with the severity of hypoxemia (MacNee, 1994a). Pathological lesions associated with COPD produce significant alterations in the physiological functioning of the pulmonary system.
Physiological Consequences of COPD

The primary purpose of the pulmonary system is gas exchange. Ventilation, the movement of gas in and out of the lungs, is produced by pressure gradients developed between the pleural space, the alveolus and the atmosphere. Exchange of oxygen and carbon dioxide occurs at the alveolar capillary membrane. COPD lesions influence pulmonary function by altering gas flow, the mechanics of ventilation, efficiency of gas exchange, pulmonary and cardiac hemodynamics and pulmonary fluid volume and fluid spacing.

With obstructive pulmonary disease, the resistance to gas flow is increased by: 1) cartilage atrophy and subsequent airway collapse, particularly during expiration; 2) destruction of elastic parenchymal tissue with loss of elastic recoil and radial traction; 3) reduction of airway diameter by intimal and medial thickening; and 4) the presence of excess mucous. Maximum expiratory flow (MEF) is particularly affected by these pathological alterations. The loss of cartilage, coupled with a reduction in radial traction and displacement of the surfactant layer renders the peripheral portions of airways unstable. Once the pressure in the pleural space is greater than airway pressure, the airway is compressed and an expiratory flow limitation is reached. The loss of elastic tissue adds to this effect by reducing the recoil pressure of the lung from -25 to -10 cmH₂O (Taylor, et al., 1989). The static compliance of the lung tissue increases. This generates less alveolar pressure for a given volume of gas and further reduces airway pressure which increases the incidence of dynamic compression. The forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), FEV₁/FVC, forced expiratory flow (FEF) and MEF are all reduced; while the total lung capacity (TLC), residual volume, FRC and tidal volume (V₂) are increased (Des Jardins,
Pulmonary function changes indicate expiratory flow is reduced and terminates at a higher FRC volume due to premature airway closure secondary to dynamic airway compression.

Dynamic compression of airways, loss of elastic parenchymal tissue and reduction of elastic recoil produce increased volumes of gas in the alveoli at end-expiration or hyperinflation. Normally at FRC, the elastic recoil of the pulmonary parenchyma and the chest wall are equal. This produces a total static recoil pressure of zero. With alveolar hyperinflation, FRC is increased and the static relaxation volume of the chest wall is not reached (Kimball, Leith, & Robins, 1982). This alters the mechanics of ventilation and increases the elastic work of breathing. With hyperinflation, inspiratory muscles do not return to their resting, optimal length. Less tension is developed during subsequent contraction due to a reduction in actin myosin cross bridge formation (West, 1990). Normally the diaphragm produces the primary mechanical changes in thoracic cavity size which generate pressure gradients and causes gas to flow in and out of the lungs. Inappropriate length tension relationships in the diaphragm reduce muscle efficiency and produce less change in thoracic cavity size for the same or greater energy expenditure. Accessory muscles of inspiration are then recruited to develop the necessary pressure gradients for ventilation; however, hyperinflation also induces an inappropriate length tension relationship in these muscles. A significantly greater negative pleural pressure must be generated to develop pressure gradients for air flow. More energy is consumed with resting levels of ventilation and the work of breathing increases. Elastic work is the primary component of increased work of breathing (WOB) and is required to overcome the recoil force of the hyperinflated chest wall (Shade, Kawagoe,
Brower, Permutt, & Fessler, 1994). Inefficient ventilation due to hyperinflation increases the oxygen consumption of the respiratory muscles.

The oxygen consumption of respiratory muscles is associated with the degree of mechanical inefficiency. Ordinarily, respiratory muscles consume 0.25 to 2.0 ml O\textsubscript{2}/liter of ventilation or 5 to 10 ml/min. which is less than 5% of total O\textsubscript{2} consumption (VO\textsubscript{2}) (Field, Kelly, & Macklem, 1982). At rest, total VO\textsubscript{2} is usually about 250 ml/min. With significant hyperinflation, respiratory muscle O\textsubscript{2} consumption can increase to as much as 25% to 40% of total VO\textsubscript{2} due to muscle inefficiency (Shade, et al., 1994). This reduces oxygen availability for other tissues, particularly in the presence of hypoxemia.

Gas exchange efficiency is reduced with COPD due to a loss of alveolar capillary surface area and the presence of ventilation perfusion (VA/Q) abnormalities (West, 1987). Destruction of pulmonary parenchyma reduces the available gas exchange surface area and diffusion capacity of the lung (Taylor, et al., 1989). Carbon monoxide diffusion capacity has been demonstrated to be significantly correlated (n = 34, r = 0.84, p <0.001) with the degree of airspace enlargement and loss of diffusive surface area in patients with chronic airflow limitation (Biernacki, Gould, Whyte, & Flenley, 1989). VA/Q mismatch is the primary mechanism responsible for hypoxemia with COPD and is produced by the development of alveolar dead space units and shunt-effect units (Augusti & Barbera, 1994). Alveolar dead space develops when nonperfused alveoli are ventilated. Alveolar dead space with COPD is the product of capillary destruction, reduction of blood flow through tortuous, reduced diameter vessels and/or thrombosis. Theoretically, collateral ventilation acts as a compensatory mechanism and serves to maintain overall gas exchange by providing communication between
alveolar dead space and normally perfused alveoli. Collateral ventilation provides access to the alveolar capillary membrane for the gas present in dead space alveoli. Ordinarily, resistance to collateral gas flow is high. However, when airway resistance is higher than the collateral resistance, as may be seen with COPD, gas flow through collateral channels (pores of Kohn, channels of Lambert) may preserve gas exchange and reduce the degree of $V_A/Q$ mismatch (Taylor, et al., 1989). In addition, hypercarbia induces dilation of small airways and collateral channels (Swenson, Robertson, & Hlastala, 1994). Pathological changes with COPD increase the degree of collateral ventilation to as much as ten times the normal rate (Morrell, Wignall, Biggs, & Seed, 1994).

Shunt-effect areas are the result of perfusion of poorly ventilated alveoli. Airway collapse secondary to cartilage atrophy and expiratory flow limitation reduces the exchange of gas between the alveoli and the atmosphere. Gas that remains in these alveoli has a reduced oxygen concentration and an elevated carbon dioxide concentration. Normally, this stimulates the HPV reflex in adjacent vessels to maintain a close match between ventilation and perfusion. However, with COPD, intimal thickening modifies the vasoconstrictive response to alveolar hypoxia and produces greater $V_A/Q$ mismatch (Barbera, Riverola, Roca, Ramirez, Wagner, Ros, et al., 1994). This attenuated response is attributed to two mechanisms. First, intimal thickening reduces the elasticity of the vessel wall and diminishes the effectiveness of medial smooth muscle contraction. Second, endothelial remodeling may alter production and/or release of endothelial-derived relaxing factor, nitric oxide (Barbera, et al., 1994; Zapol, et al., 1994). Collateral ventilation again may preserve gas exchange in some of these obstructed
alveoli by providing an alternate path for gas flow. However, the primary consequence of reduced diffusive capacity and $V_A/Q$ mismatch is reduction in arterial oxygen concentration, hypoxemia.

With COPD, pulmonary hemodynamics are influenced by multiple factors which combine to produce pulmonary arterial hypertension and an increase in PVR (MacNee, 1994a). Elevations in PAP due to COPD are positively associated with mortality rate; the higher the PAP, the worse the individual’s prognosis (MacNee, 1994a; Menzies, Gibbons, & Goldberg, 1989; Mols, Huynh, Dechamps, Maeije, Guillaume, & Ham, 1989). However, the degree of pulmonary hypertension may reflect disease severity, rather than directly influence mortality. Structural alterations in the pulmonary vasculature are the primary factor in the development of pulmonary hypertension with COPD. Structural changes reduce elasticity and vessel compliance, so increases in blood volume produce a greater increase in pressure. Recruitment and distension of vessels is limited by the degree of vessel destruction. This is probably not an important factor in resting pulmonary hypertension. It is a substantial component of the exercise induced pulmonary hypertension seen with COPD. Although, HPV secondary to hypoxia, hypercarbia and acidosis probably contributes to chronic elevations in PAP, administration of oxygen with normalization of arterial blood gases does not produce normalization of PAP. This demonstrates that HPV is not the sole component of pulmonary hypertension with COPD. Inhibition of nitric oxide synthesis and/or release from endothelial cells may alter the response of the pulmonary vessels to hypoxia and may also produce significant vascular remodeling with COPD (Dinh-Xuan, 1992). Hyperinflation continually reduces the diameter of alveolar vessels which
chronically elevates total PVR. PAP must be increased to produce the necessary gradient to propel blood forward. Secondary polycythemia due to chronic hypoxemia increases blood viscosity and subsequently pulmonary vascular resistance. According to Poiseuille's law, greater pressure must be generated to move the more viscous fluid through pulmonary vessels. It is probable that various combinations of these factors contribute to elevations in PAP and PVR with COPD. Since the pulmonary vessels and the heart are anatomically positioned in series, alterations in pulmonary hemodynamics influence the function of the heart.

Right ventricular dysfunction is commonly found in individuals with COPD (Dries & Mathru, 1994; Klinger & Hill, 1991) and the presence of right heart dysfunction has been identified as a significant predictor of mortality in this population (Dallari, Barozzi, Pinelli, Meright, Grandi, Manzotti, et al., 1994; Menzies, et al., 1989; Shachor, Liberman, Tamir, Schindler, Weiler, & Bruderman, 1989). The prevalence of right ventricular dysfunction increases as airflow limitation worsens. Right ventricular dysfunction is present in 40% of individuals with an FEV₁ less than one liter and in 70% of individuals with an FEV₁ less than 600 ml (MacNee, 1994a). Right ventricular performance is both preload and afterload dependent. The ventricle is preload dependent since it can only pump the blood volume received. The degree of negative ITP influences the pressure gradient for venous return. Elevations in PAP and PVR with COPD increase afterload. Normally, mean PAP and PVR are approximately one sixth that of the systemic circulation (Dries & Mathru, 1994). As pulmonary hypertension gradually develops with COPD, the right ventricle adapts to the increasing impedance to ejection with an increase in RVEDV and dilatation.
Ventricular dilatation increases the radius of curvature of the chamber, thins the ventricular wall and increases wall stress according to the law of LaPlace ($\tau = Pr/w$) where $\tau$ is wall stress, $P$ is pressure, $r$ is radius of the chamber and $w$ is wall thickness (West, 1990).

Chronic volume overload produces structural and biochemical alterations in myocytes that influence ventricular function. There is a relative imbalance between energy production and use in the overloaded ventricle. Cellular damage and myocyte necrosis induce fibroblast proliferation and replacement of myocytes by connective tissue. Not only is there an increase in collagen, but also the type of collagen synthesized is altered. Initially, a soft collagen is produced. With chronic volume overload, a stiff collagen associated with scar tissue is synthesized that increases wall stiffness and reduces the ability of the ventricle to dilate (Katz, 1992). Although the number of mitochondria and myofibrils increases, the ratio of myofibrils to mitochondria also increases. This results in a decreased availability of ATP (Katz, 1992). Capillary density decreases and less oxygen and nutrients are delivered to the myocytes for energy production. Abnormal gene expression alters myocardial protein synthesis by accelerating the rate of synthesis and modifying the patterns of gene expression. These abnormal genes produce cardiac muscle that is short lived. The structural and biochemical changes induce both right ventricular systolic and diastolic dysfunction (Marangoni, Scalvini, Schena, Vitacca, Quadri, & Levi, 1992; Mols, et al., 1989).

With COPD, there is a decrease in the rate of right ventricular emptying during systole and a significant reduction in the rate of ventricular filling during diastole with relative preservation of right ventricular contractility (MacNee, Wathen, Hannan, Flenley, & Muir, 1983; Marangoni, et al., 1992;
RVEF as an indication of global ventricular performance has been shown to have a variable response to pulmonary artery hypertension with COPD. Significant negative correlations were obtained between PAP and RVEF measured by radionuclide technique by Mols, Huynh, Dechamps, Maeije, Guillaume and Ham (1989) (n = 41, r = -.61, p<0.001) and Brent, Mahler, Matthay, Berger and Zaret (1984) (n = 30, r = -.74, p<0.001). However, Biernacki, Gould, Whyte and Flenley (1989) did not confirm this relationship (n = 32, r = .23, NS). Elevations in RVEDV may shift the interventricular septum to the left and alter left ventricular compliance and filling (Culver, Marini, & Butler, 1981; Pinsky, 1990; Pinsky, 1994; Scharf, 1992; Schertz & Pinsky, 1993). In addition, left ventricular dysfunction has been described in the COPD population (Jardin, Gueret, Prost, Farcot, Ozier, & Bourdarias, 1984; Kohama, Tanouchi, Masatsugu, Kitabatake, & Kamada, 1990; MacNee, 1994b).

Jardin, Gueret, Prost, Farcot, Ozier and Bourdarias (1984) described significant ventricular interaction in 10 COPD patients undergoing two dimensional echocardiographic examination. Left ventricular hypertrophy was identified by estimation of the left ventricular free wall thickness. Left ventricular chamber size was significantly reduced compared to normal subjects (COPD LVEDV = 67.7 ± 24.6 ml, control LVEDV = 103.2 ± 19.9 ml). Volume loading produced septal flattening and an increase in RVEDV with subsequent further reduction in left ventricular chamber size. Left ventricular structural alterations may also contribute to left ventricular dysfunction with COPD. At autopsy, Kohama, Tanouchi, Masatsugu, Kitabatake and Kamada (1990) identified greater myocardial fibrosis and left ventricular hypertrophy in individuals with right ventricular hypertrophy
secondary to COPD. The degree of fibrosis in the right and left ventricles was significantly correlated ($r = 0.54$, $p < 0.01$), as was the diameter of individual myocytes in the right and left ventricle ($r = .91$, $p < 0.01$). Left ventricular dysfunction with COPD is associated with ventricular interdependence and pathological changes in muscle structure.

A state of salt and water retention develops in some individuals with severe COPD. The causative mechanism for the development of edema with COPD has not been fully elucidated and remains controversial. Traditionally, edema with COPD was attributed to right heart failure. More recent theories implicate neurohumoral activation, rather than cardiac failure (Anand, Chandrashekhar, Ferrari, Sarma, Guleria, Jindal, et al., 1992; Skwarski, Lee, Turnbull, & MacNee, 1993). These investigators hypothesized hypercarbia acts as a powerful peripheral vasodilator and attenuates systemic vascular resistance that reduces mean arterial pressure. The decrease in arterial blood pressure stimulates baroreceptors which activate the sympathetic nervous system. Sympathetic activation induces catecholamine release which produces renal vasoconstriction and reduces renal blood flow and glomerular filtration rate causing activation of the renin-angiotensin-aldosterone system. Sodium and water retention are stimulated. In addition, hypercarbia and acidosis amplify exchange of sodium ions for hydrogen ions in the renal tubules further increasing sodium retention. The resultant increased vascular volume intends to preserve systemic blood pressure and organ perfusion. Expanded vascular volume augments intracardiac volumes and produces atrial stretch that stimulates the release of atrial natriuretic peptide (ANP), a vasodilator, diuretic and natriuretic. ANP may serve to protect the right ventricle by reducing preload via diuresis of excess fluid and sodium.
and reducing afterload by stimulating pulmonary vasodilation (Jin, Yang, Chen, Jackson, & Oparil, 1990; Ou, Sardella, Hill, & Thron, 1989; Rogers, Sheedy, Waterhouse, Howard, & Morice, 1994; Skwarski, et al., 1993). ANP may also enhance the barrier function of the endothelial cells during hypoxemia, reducing extravasation of fluid into the interstitium (Westendorp, Roos, Hoeven, Thiong, Simons, Frolich, et al., 1993).

In conclusion, COPD, alters the mechanics of ventilation and increases the work of breathing. Greater oxygen consumption by respiratory muscles necessitates increased oxygen delivery. Increased oxygen demand, reduced gas exchange efficiency and significant pulmonary hemodynamic alterations place a formidable burden on the right heart.

Right Ventricular Hemodynamics

Anatomy of the Right Ventricle

The right ventricle is posterior to the sternum, anterior to the left heart and lies at an oblique angle within the thoracic cavity. The right ventricular chamber is comprised of three walls: the anterior, posterior lateral, and inferior walls which form two separate anatomical and functional regions. The sinus or inflow region and the conus or outflow region produce a shallow U-shaped chamber (Dries & Mathru, 1994; Hurford & Zapol, 1988; Katz, 1992). Contraction of the ventricle begins in the sinus region at both the base and apex of the ventricle. A peristaltic-like motion in the lateral free wall ends at the conus and pulls the tricuspid valve toward the ventricular apex which moves a large portion of the blood volume forward. Contraction of the conus region begins 25 to 50 milliseconds after the initiation of sinus area contraction. The conus area remains contracted well into diastole which serves to buffer the pulmonary artery from pressure elevations in the sinus
region during ventricular filling (Dries & Mathru, 1994; Hurford & Zapol, 1988). End-systole is difficult to identify, since right ventricular ejection continues after peak ventricular pressure is developed. Normally, right ventricular diastolic compliance is high, so end-diastolic pressure is maintained at a relatively low value by ventricular dilation. This compensatory mechanism is effective until the pericardium restrains further dilation.

Nutritive blood flow to the human right ventricle is primarily supplied by the right coronary artery (RCA); however, a small portion of the anterior free wall is supplied by the left anterior descending (LAD) branch of the left coronary artery. The interventricular septum (IVS), which forms the posterior lateral wall of the right ventricle, receives dual nutritive flow from the LAD and either the RCA or circumflex artery (Headley & Von Rueden, 1991). Nutritive flow to the right ventricle is approximately equal during systole and diastole (Dries & Mathru, 1994; Headley & Von Rueden, 1991). The pressure gradient that establishes this nutritive flow is developed between the root of the aorta at the coronary ostia and the arterioles in right ventricular myocardium. Normally, this pressure gradient remains sufficient to maintain flow through both systole and diastole, since low right ventricular systolic pressure generates less wall tension and compression of myocardial arterioles (Headley & Von Rueden, 1991). Optimal right ventricular function relies on a balance between oxygen demand and supply delivered during biphasic perfusion. The myocardial oxygen consumption of the right ventricle is about half that of the left ventricle, but normal oxygen extraction by myocardial tissue is high. Increased oxygen demand must be met by increased perfusion (Dries & Mathru, 1994). Changes in right
ventricular intrachamber pressure may reduce the pressure gradient for coronary flow which can decrease nutritive blood flow, induce ischemia and/or myocardial necrosis and provoke right ventricular dysfunction.

Determinants of Right Ventricular Performance

The right ventricle is preload dependent. Preload is the degree of myocardial fiber stretch prior to the initiation of systole and is traditionally depicted as the end-diastolic volume (Katz, 1992). The relationship between EDV and systolic function is described by the Frank-Starling law of the heart. As EDV increases, myocardial fibers stretch to a greater degree and more myosin crossbridges are available for cycling. The myofilaments also increase their calcium sensitivity. Subsequent contraction is more forceful, so that the increased EDV is matched with an increase in cardiac output (Berne & Levy, 1992). Right ventricular preload is a function of the volume of venous blood returned to the heart.

Venous return is influenced by the pressure gradient developed between the right atrium and the vena cava, the heart rate, the compliance of the ventricle, the volume of blood in the periphery and the level of peripheral vasoconstriction (Jacob, Dierberger, & Kissling, 1992). ITP is reflected on the heart and thoracic vessels within the closed thoracic cavity. Cyclic changes in ITP with ventilation normally produce phasic changes in venous return. Normal ventilatory mechanics produce a negative ITP during inspiration. The right atrium is directly exposed to this pressure change and right atrial pressure decreases in a directly proportional fashion (Tyberg, Taichman, Smith, Douglas, Smiseth, & Keon, 1986). This augments the pressure gradient and increases venous return to the right heart. According to the Frank-Starling relationship, as long as the right ventricle remains on the
ascending portion of the Starling curve, an increase in preload will produce an increase in systolic function, but this mechanism does have a physiologic limit. As right atrial pressure decreases, venous return increases until a plateau is reached at approximately zero pressure. At this point, intraluminal vena caval pressure is exceeded by the surrounding pressure and the extrathoracic vena cava collapses at the site of entry into the thoracic cavity (Berne & Levy, 1992). During expiration, ITP rises. Venous return is reduced as the pressure gradient between the right heart and vena cava diminishes. An ITP increase as slight as 4 mmHg can reduce venous return by 50% for a transient period of time (Dries & Mathru, 1994).

Changes in abdominal pressure, usually as a result of diaphragm descent during inspiration, also influence venous return (Takata & Robotham, 1992; Takata, Wise, & Robotham, 1990). Takata, Wise and Robotham (1990) hypothesized the existence of abdominal vascular zones to explain changes in venous return related to abdominal pressure changes. Experimental canine studies confirmed their predictions that the abdominal venous compartment functions as a capacitor in zone III conditions and a Starling resistor in zone II conditions. In this model, the upstream pressure is that of the femoral vein (Pfv). The abdominal pressure (Pab) surrounds the abdominal vena cava and the downstream pressure is that of the right atrium (Pra). Zone III describes a condition where \( P_{fv} > P_{ra} > P_{ab} \). In this instance, the abdominal compartment functions as a capacitor to store volume. With inspiration, an increase in abdominal pressure due to diaphragm descent, combined with a reduction in right atrial pressure secondary to negative ITP, produces an increase in venous return. Zone II describes a condition where \( P_{fv} > P_{ab} > P_{ra} \). In this instance, the abdominal compartment acts as a Starling resistor and an
increase in abdominal pressure will reduce venous return by collapsing the abdominal vena cava (Takata, et al., 1990). Further investigation by this group supported the theory of abdominal vascular zones and demonstrated the significance of blood volume status (Takata & Robotham, 1992). In a canine model, hypervolemia and increased abdominal pressure during diaphragm contraction induced a functional increase in venous return by optimizing splanchnic venal caval flow. However, increased abdominal pressure in the face of hypovolemia reduced venous return by impeding nonsplanchnic venal caval flow. The investigators hypothesized that abdominal pressure may be differentially distributed, which could significantly influence individual organ system contributions to the volume of venous return. However, in a normal individual, venous return generally increases during inspiration and decreases during expiration.

Heart rate influences venous return by altering diastolic filling time. Diastole consists of isovolumic relaxation, rapid filling, diastasis or slow filling and atrial systole (Berne & Levy, 1992; Katz, 1992). During isovolumic relaxation, ventricular pressure falls rapidly without a change in ventricular volume. The majority of right ventricular filling occurs during the rapid filling phase that immediately follows opening of the tricuspid valve. Diastasis provides a gradual addition of blood volume to the ventricle and atrial systole completes ventricular filling. The average duration of diastole is 0.53 seconds compared to 0.27 seconds for systole (Katz, 1992). Factors that increase heart rate curtail total cardiac cycle time which reduces diastolic filling time. Slow heart rates permit prolonged diastolic filling. The volume of blood ejected during systole is directly dependent on the volume in the ventricle at end-diastole.
Tachycardia may also interfere with ventricular filling by impeding relaxation which reduces ventricular compliance and shifts the pressure volume relationship to the left. A shift of this nature indicates that a given volume of blood will produce a greater pressure in a less compliant ventricle. Myocardial cytosolic calcium concentration is increased during tachycardia. This calcium must be returned to the sarcoplasmic reticulum following systole for relaxation to occur, but diastolic time is reduced during tachycardia. Sarcolemmal calcium pump activity must be accelerated by the phosphorylation of phospholamban to enhance the return of calcium to the sarcolemma and enable the ventricle to relax (Katz, 1992). Relaxation produces a greater degree of compliance which permits optimal filling. Ventricular compliance may also be reduced by changes in the geometry of the chamber and/or alterations in the fibrous structure of the ventricle as seen in ventricular hypertrophy, dilation, ischemia, restrictive cardiomyopathy and myocardial fibrosis (Headley & Von Rueden, 1991; Katz, 1992).

The right ventricle is also afterload dependent (Dries & Mathru, 1994; Headley & Von Rueden, 1991). Right ventricular afterload denotes the resistance or impedance of the pulmonary vasculature to ventricular ejection (Headley & Von Rueden, 1991; Katz, 1992). Right ventricular afterload is determined by right ventricular end-diastolic volume and blood viscosity, right ventricular chamber size and wall thickness, the total cross sectional area of the pulmonary vessels and the degree of total PVR (Des Jardins, 1993; Headley & Von Rueden, 1991). The importance of each of these factors can be explained by Poiseuille's law \( V = \Delta P r^4 \pi / 8\eta \) where \( V = \) flow, \( \Delta P = \) pressure gradient, \( r^4 = \) radius of the vessel to the fourth power, \( \pi / 8 = \) proportionality
constant and $\eta = \text{viscosity of the fluid}$ (Katz, 1992). The size of the pressure
gradient ($\Delta P$) developed between the right ventricle and the pulmonary artery
is a function of the preload or end-diastolic volume, as well as the size of the
ventricular chamber and the wall thickness of that chamber. The end-
diastolic volume preloadsthe muscle or stretches the myofiliments. This
offers more myosin crossbridges for cycling and increases myofiliment
calcium sensitivity. According to the Frank-Starling law, when the ventricle
is on the ascending portion of the curve, an increase in preload will induce an
increase in systolic function. Systole generates the pressure gradient between
the right ventricle and the pulmonary artery.

The impact of chamber size and wall thickness on the driving pressure can
be explained by the law of Laplace ($\tau = Pr/w$, where $\tau = \text{wall tension}$, $P =$
pressure in the chamber, $r = \text{radius of the chamber and } w = \text{wall thickness}$)
(Berne & Levy, 1992). As the myocardial fibers contract, tension developed in
the walls normally produces an increase in chamber pressure. This is the
driving pressure for forward blood flow when the pulmonic valve opens.
The degree of wall tension has a direct impact on the pressure gradient for
nutritive blood flow to the ventricle. As wall tension increases, the pressure
gradient between the coronary ostia and the arterioles in the right ventricular
myocardium decreases. If wall tension is sufficient to reduce right ventricular
myocardial perfusion, the contractile ability of the muscle decreases and the
pressure gradient between the ventricle and pulmonary artery attenuates.

The pulmonary vasculature normally offers low resistance to forward
flow because of its large cross sectional area. Poiseuille's law indicates that
flow is directly influenced by the cross sectional area ($r^4$); as the area increases,
flow increases in a proportional fashion. Total cross sectional area increases and PVR remains low with elevations in driving pressure because of vessel recruitment and distensibility. Low resting pulmonary vascular tone influences the overall cross sectional area, as well as, the radius of individual pulmonary vessels (West, 1990). Total cross sectional area is also influenced by lung volume and arterial concentrations of vasoactive agents (oxygen, carbon dioxide, hydrogen ions, norepinephrine, serotonin). Reduction in vessel radii reduces total area and increases resistance to forward flow. Poiseuille's law also states that viscosity (\( \eta \)) is inversely proportional to flow. Blood viscosity is determined primarily by the hematocrit, so as viscosity/hematocrit increases, flow decreases unless a compensatory mechanism is invoked. In summary, the integration of preload, blood viscosity, right ventricular chamber structure and the degree of pulmonary vascular resistance determine the afterload of the right ventricle.

The final determinant of right ventricular performance is contractility. Contractility is the inherent ability of cardiac muscle to shorten, independent of preload and afterload (Berne & Levy, 1992; Headley & Von Rueden, 1991; Katz, 1992). Contractility is primarily influenced by the amount of cytosolic calcium available to bind to myocardial contractile proteins (Katz, 1992). The ability of the right ventricle to augment contractility is more limited than the left due to the smaller, thinner right ventricular muscle mass (Headley & Von Rueden, 1991). Analysis of the right ventricular pressure-volume relationship obtained with a conductance catheter provides estimates of ventricular preload, afterload and contractility (Kass, Yamazaki, Burkhoff, Maughan, & Sagawa, 1986; McKay, Spears, Aroesty, Baim, Royal, Heller, et al., 1984; Solda, Pantaleo, Perlini, Calciati, Finardi, Pinsky, et al., 1992). An
increase in contractility shifts the right ventricular pressure-volume relationship upward and to the left, so the volume of blood ejected is greater and end-systolic volume decreases. Although pressure-volume loops offer important information about right ventricular performance, their clinical applicability is limited at this time (Solda, et al., 1992).

Evaluation of Right Ventricular Performance

The critical importance of the right ventricle in the maintenance of normal cardiopulmonary physiology has only recently been illustrated (Dries & Mathru, 1994; Vincent & Lenaers, 1989). Prior to this, the right ventricle was conceived solely as a conduit for blood as it entered the pulmonary circuit. Early studies concluded that destruction of the right ventricular free wall produced negligible hemodynamic consequences, as long as pulmonary vascular resistance remained low (Hurford & Zapol, 1988; Vincent & Lenaers, 1989). However, the primary purpose of the right ventricle is to adapt to changes in venous return and prevent substantial fluctuation in systemic venous pressure. Cardiac output is generally not maintained for a prolonged period without a functioning right ventricle (Vincent & Lenaers, 1989).

Evaluation of right ventricular function has been difficult due to the location of the right ventricle with respect to other structures in the thoracic cavity, the complex geometric shape of the chamber and the nonuniformity of right ventricular contraction (Hurford & Zapol, 1988; Vincent & Lenaers, 1989). Contrast angiography was the accepted clinical technique for evaluating right ventricular function until recently and is still considered the “gold standard” by many (Dries & Mathru, 1994). At the present time, multiple techniques are available to assess right ventricular performance including echocardiography, contrast angiography, radionuclide ventriculography and thermodilution
Echocardiography uses a beam of ultrasound pulses to indirectly visualize structures within the path of this beam. Ultrasound pulses are emitted from a transducer which also serves to capture pulse echoes from the underlying structures. The echocardiography unit measures the time interval between the emission of the pulse and the return of the echo to identify the depth of the structure (Jawad, 1990). Echocardiography may be particularly problematic in individuals with COPD. Hyperinflation interferes with sound wave transmission and image quality may be poor. Determination of right ventricular volumes and identification of right ventricular hypertrophy by echocardiography is limited by the ability to differentiate the right ventricular wall from other cardiac structures and the ability to obtain images of adequate quality in a significant proportion of COPD patients (MacNee, 1994a). Serial bedside echocardiographic examinations in ventilated individuals are precluded by the cost of each examination and the utility of right ventricular information obtained by this type of examination, particularly in individuals with pulmonary pathology which induces hyperinflation.

Contrast angiography employs an injection of contrast media into the circulation with subsequent computer analysis of the images produced as the contrast medium fills the right heart. With this technique, the estimation of right ventricular volume and ejection fraction require assumptions about the geometry of the chamber and the nature of right ventricular contraction (Dries & Mathru, 1994; Hurford & Zapol, 1988). Reliability of this technique may be questionable if these assumptions are not met. With this technique, ventilated individuals must be transported to an area with fluoroscopic
facilities and repeated measures of right ventricular volume/ejection fraction require subsequent injections of contrast material.

Radionuclide ventriculography uses radioactive isotopes to evaluate right heart performance. Two techniques currently in use are the first pass and gated pool techniques. In first pass studies, an isotope with a short half life is injected and sequential images are obtained as the isotope passes through the heart. This technique identifies the shape of the right ventricle. End-diastolic volume and ejection fraction can be calculated by analysis of time activity curves (Dries & Mathru, 1994; Headley & Diethorn, 1993; Hurford & Zapol, 1988). Gated pool or equilibrium multiple-gated blood pool studies require injection of an isotope with a longer half life. Sequential images are obtained and gated to the R wave of the electrocardiogram. Right ventricular volumes and ejection fraction can be calculated by analysis of the distribution of radioactivity during the cardiac cycle. This technique is particularly problematic with studies of the right ventricle, since the right atrium lies in a posterior position. Radioactivity in the right atrium cannot easily be separated from that in the right ventricle with this technique. Again, these techniques are expensive and require transport of the ventilated individual to an area with radionuclide scanning equipment. Although the half life of the radioactive substances employed in these studies is short, frequent, serial determinations of right ventricular function are not possible with these techniques.

Thermodilution determination of right ventricular volumes and ejection fraction use similar technology and technique as thermodilution cardiac output measurements. The pulmonary artery catheter employed to measure right ventricular volumes and ejection fraction is a 110 cm, radiopaque, six
lumen, flow directed catheter constructed of polyvinylchloride. Once properly positioned, two intracardiac electrodes, one in the pulmonary artery (distal - 6 cm from tip) and one in the right ventricle (proximal - 16 cm from tip), detect R waves and identify successive systoles. A rapid response thermistor (95 milliseconds) is located at the distal catheter tip and senses beat by beat changes in temperature. The proximal injectate port consists of three openings with each orifice angled differently to optimize mixing of the cold injectate with the blood. This port is located at either 21 cm or 24 cm from the distal tip. Ideally, the injectate port should be located in the right atrium within 2 to 5 cm of the tricuspid valve. Iced solution is injected into the proximal injectate port with steady force over a period of four seconds or less. The injectate is given at end expiration to ensure reproducibility of results and to minimize the influence of ventilation. Three to five consecutive measures are taken with a minimum of one minute between each to allow blood temperature to return to basal value. Three measures within 10% of the median value are averaged to obtain cardiac output; while three measures within 15% of the median value are averaged to obtain right ventricular ejection fraction (Headley & Diethorn, 1993). This technique offers the ability to perform frequent serial determinations of right ventricular performance and examine trends in this performance without transporting the ventilated individual to other areas within the hospital. Although, the pulmonary artery catheter necessary for these measures is somewhat costly and requires invasion of the cardiovascular system, the overall cost for thermodilution measurement of right ventricular volumes is considerably less than the other available techniques.
Right Ventricular Volume as an Indicator of Preload

Traditionally, the end-diastolic volume of the heart or preload has been inferred from measurements of pressure. Right atrial pressure (RAP) or CVP is used to estimate right ventricular end-diastolic filling pressure and PAOP approximates left ventricular end-diastolic filling pressure (Berne & Levy, 1992). End-diastolic pressure values are used to estimate EDV; however, the end-diastolic pressure volume relationship of the right ventricle is not linear. The right ventricular pressure volume relationship is influenced, not only by the volume filling the ventricle, but also by the lusitropic state of the ventricle (Katz, 1992). Lusitropic state depends on the degree to which actin and myosin have been dissociated following contraction, the structure of the connective tissue cardiac skeleton, the influence of the pericardium and the geometry and thickness of the ventricular walls. Actin myosin dissociation is regulated by the magnitude of initial calcium release during systole, the affinity of troponin for calcium and the rate and extent of calcium uptake into the sarcoplasmic reticulum. Estimation of right ventricular end-diastolic volume from right atrial pressure may be inaccurate when the lusitropic state of the right heart is altered.

In an early study, Martyn, Snider, Farago and Burke (1981) compared the predictive value of traditional indicators of adequate fluid resuscitation (CVP, PAOP, mean arterial pressure and urinary output) with thermodilution measures of RVEDV and RVEF during the initial four days of treatment for 16 acutely burned subjects (mean burn surface area 75.2%). RVEDVI was identified as the best predictor of CI. RVEDVI explained 56.3% (r = 0.75) of the variance in CI; while PAOP explained 10.2% (r = 0.32) and right ventricular end-diastolic pressure explained only 7.3% (r = 0.27). The
multiple regression equation with the highest predictive ability explained 91% of the variance \( r = 0.95 \) and included RVEDV, RVEF and heart rate. The investigators hypothesized changes in airway and ITP, elevated catecholamine concentrations and commonly used pharmacological therapies may alter ventricular compliance and influence the pressure volume relationship in these acutely injured individuals. In this type of population, evaluation of filling pressure alone could provide an inaccurate evaluation of the individual’s preload status.

In 1990, Reuse, Vincent and Pinsky described right ventricular function during fluid challenge in 41 acutely ill subjects (76% mechanically ventilated, 51% receiving catecholamine infusion). Fluid challenge consisted of 300 ml of 4.5% albumin administered in response to systolic blood pressure less than 90 mmHg, CI less than 2.5 liters/min/m², heart rate greater than 120 beats/minute and/or urinary output less than 25 ml/hour. Hemodynamic evaluation was performed at end-expiration prior to and following fluid challenge. Subjects were divided into two groups based on their CI response to fluid challenge. Responders \( n = 26 \) significantly increased CI and RVEDVI (responders CI pre = 3.0 ± 1.1, post CI = 3.5 ± 1.2 L/min/m², RVEDVI pre = 104 ± 27, post = 115 ± 30 ml/m², p <0.01); while CI decreased and RVEDVI remained unchanged in nonresponders \( n = 15 \) (CI pre = 3.2 ± 1.4, post 3.0 ± 1.3 L/min/m², RVEDVI pre = 117 ± 46, post = 121 ± 44, NS). RVEF remained relatively constant (responders pre = 27% ± 8%, post = 28 ± 8%, nonresponders pre = 27 ± 12%, post = 25 ± 11%, NS). Subjects were then divided into two groups based on their initial RVEDVI value. Between these groups, there were no significant differences in PAOP or RAP either before or after fluid challenge. Subjects with an initial RVEDVI >140 ml/m² \( n = 8 \) did
not increase RVEDVI and significantly decreased left ventricular stroke work index (RVEDVI pre = 163 ± 22, post = 160 ± 38 ml/m², NS, LVSWI pre = 44.4 ± 16.3, post = 39.7 ± 16 g·m·m², p <0.05); while subjects with an initial RVEDVI <140 ml/m² (n = 33) significantly increased both RVEDVI and left ventricular stroke work index (RVEDVI pre = 95 ± 23, post = 107 ± 26 ml/m², LVSWI pre = 39.2 ± 20.4, post = 47 ± 23.6 g·m·m², p <0.01). The investigators proposed a significant difference in ventricular compliance between groups and concluded fluid challenge is most effective in increasing CO with individuals having a RVEDVI <140 ml/m². Fluid administration to individuals with a RVEDVI >140 ml/m² may produce ventricular distension and negatively influence right ventricular wall stress, myocardial blood flow and systolic function. Right ventricular distension may also cause a septal shift to the left and reduce left ventricular compliance, chamber size and cardiac output.

In a similar study, Diebel, Wilson, Tagett and Kline (1992) determined the value of PAOP, CVP and RVEDVI as indicators of preload status in 29 critically ill subjects (69% mechanically ventilated, 31% receiving low dose catecholamine infusion). Univariate regression analysis detected significant relationships between CI and all three variables (PAOP r = .42, CVP r = .51, RVEDVI r = .61, p <0.001). Multiple regression analysis determined RVEDVI was the best predictor of CI (β = 2.5 ± 0.15, p <0.001); while PAOP was not found to be significant in the equation (β = 0.069 ± 0.06, p = .23). CVP was a significant predictor of CI (β = -.32 ± .05, p <0.001); however, RVEDVI and CVP were only weakly correlated (r = .42, p <0.001). In 52% of these subjects, PAOP indicated a preload state in direct opposition to RVEDVI. Eight subjects were diagnosed with fluid overload by a PAOP value greater than 18 mmHg;
however, only one of these subjects had a RVEDVI that was greater than 140 ml/m². In 19 other subjects, measured PAOP was less than 12 mmHg, but eight of these subjects had a RVEDVI greater than 140 ml/m². Twenty two sets of hemodynamic measures were completed in subjects who received a fluid bolus. Subjects were divided into responders (n = 13) and nonresponders (n = 9) based on their CI response to fluid bolus. The two groups were significantly different prebolus (responders: PAOP = 14 ± 7 mmHg, RVEDVI = 83 ± 21 ml/m², CI = 3.8 ± 1.8 l/min/m², HR = 109 ± 23 beats/min, nonresponders PAOP = 7 ± 2 mmHg, RVEDVI = 142 ± 11 ml/m², CI = 4.7 ± 0.7 l/min/m², HR = 90 ± 12 beats/min). When prebolus RVEDVI was greater than 140 ml/m² (n = 8), CI remained unchanged or decreased in all subjects. The inaccuracy of PAOP in the prediction of preload is identified by inspection of the PAOP values in the nonresponders group. The prebolus (7 ± 3 mmHg) and postbolus (9 ± 3 mmHg) PAOP values obtained in this group were not significantly different and both indicated a low preload state (p < 0.01); however, RVEDVI both prebolus (142 ± 11 ml/m²) and postbolus (156 ± 15 ml/m²) indicated excessive preload. CI rose by at least 10% in the responders following fluid bolus indicating preload recruitable work. These investigators suggested RVEDVI was a much better indicator of preload recruitable work than either CVP or PAOP.

Right ventricular preload may not be accurately described by traditional hemodynamic measures like CVP. Inadequate preload will decrease cardiac output; while right ventricular volume overload can produce myocardial ischemia and necrosis. Both conditions are detrimental to right and left ventricular performance and eventually reduce tissue oxygen delivery.
Right Ventricular Function in Pathological States

Although the right ventricle was previously thought to have little importance in cardiopulmonary function during illness, over the past decade and a half investigators have identified the significance of right ventricular function during a variety of pathological conditions. During an early investigation, right ventricular dysfunction was described following thermal injury (Martyn, et al., 1981). This finding stimulated analysis of right ventricular function in other trauma populations. Hoffman, Greenfield, Sugerman and Tatum (1983) investigated right ventricular function following resuscitation from shock (n = 16). Shock was defined as systolic blood pressure less than 80 mmHg produced by either hypovolemia (n = 7) or sepsis (n = 9). Biventricular performance was evaluated within 24 hours of resuscitation. A postoperative control group (n = 7) required minimum fluid replacement of 6 liters, but did not experience hypovolemia. Control subjects were evaluated within 24 hours of operation. When compared to the control group, right ventricular dysfunction was identified following resuscitation from both septic and hypovolemic shock. RVEF was significantly reduced (Control RVEF = 0.52 ± 0.07, hypovolemia RVEF = 0.31 ± 0.05, p <0.001, sepsis RVEF = 0.35 ± 0.16, p <0.02); while end-diastolic volume was significantly increased (Control EDVI = 55.8 ± 7.4 ml/m², hypovolemia EDVI = 106.5 ± 22 ml/m², p <0.001, sepsis EDVI = 143 ± 28 ml/m², p <0.001). Right ventricular stroke work index (RVSWI) was also significantly greater in the shock subjects compared to controls (Control RVSWI = 3.70 ± 2.6 gm m/m², hypovolemia RVSWI = 6.99 ± 2.5 gm m/m², p <0.05, sepsis RVSWI = 7.77 ± 2.5 gm m/m², p <0.01), while left ventricular stroke work index was essentially the same in both groups. The investigators postulated a decrease
in coronary blood flow during shock produced right ventricular dysfunction following resuscitation. Large fluid loads administered during resuscitation then increased right ventricular radius of curvature, wall stress and myocardial oxygen demand. In this group of subjects, improvement in right ventricular function was associated with survival; while a further decline in right ventricular performance occurred in those who subsequently died.

Since right ventricular dysfunction was found to be associated with increased mortality, Martyn, Wilson and Burke (1986) evaluated the efficacy of low dose dopamine infusion in improving right ventricular performance in subjects (n = 26) with thermal injury (mean burn 54.9 ± 8.4%). Dopamine dose ranged from zero to 9 ± 0.7 μg/kg/min. This investigation did not document any benefit from dopamine infusion in this patient population. RVEF, RVEDVI and PVR were not significantly different with dopamine infusion (zero infusion RVEDVI = 99.4 ml/m², RVEF = 41%, PVR 1.6 units, 6.8 μg/kg/min infusion RVEDVI = 90.7 ml/m², RVEF = 42%, PVR = 1.5 units). However, PAP was significantly elevated with dopamine infusion (zero dopamine PAP = 22.3 mmHg, 6.8 μg/kg/min PAP = 25.1, p <0.05). The investigators concluded low dose dopamine infusion did not significantly alter right ventricular function post severe trauma; however, elevations in PAP increased right ventricular afterload. This may further reduce the ability of the ventricle to eject blood into the pulmonary vessels.

In an investigation of the evolution of right ventricular performance following severe, multiple trauma, Eddy, Rice and Anardi (1988) monitored thermodilution indices of right ventricular performance for 24 hours following injury in 17 subjects. Initial examination of hemodynamic data indicated an early elevation of PAP, in conjunction with a depression of
RVEF, particularly in nonsurvivors (survivors PAP = 22.1 torr, RVEF = 28%, nonsurvivors PAP = 31.7 torr, RVEF = 18%). RVEDV increased post trauma, especially in nonsurvivors (survivors RVEDV = 158 ml, nonsurvivors RVEDV = 195 ml). Traditional measures used to monitor hemodynamic status in trauma patients (CO, PAOP, CVP, BP) did not reflect depressed right ventricular function. Severe right ventricular dysfunction identified by thermodilution measures was obvious well before decreases in CO. Ejection fraction improved to nearly normal values over the 24 hour period in trauma survivors (n = 12); while nonsurvivors exhibited deterioration of right ventricular function over the same 24 hour period. These investigators proposed increased PAP/afterload following multiple trauma impeded right ventricular ejection. The ventricle dilated within the pericardium to accommodate the larger volume which increased curvature of the ventricle and myocardial oxygen demand. In this state, right ventricular dysfunction secondary to subendocardial ischemia precluded obligatory increases in CO necessary for adequate oxygen delivery.

Right ventricular dysfunction has also been described in other pathological states which increase afterload/pulmonary vascular resistance and/or depress myocardial contractility (Dries & Mathru, 1994; Reuse, Frank, Contempre, & Vincent, 1988). In sepsis, endothelial cell functions are altered, microemboli formed and cytokines and mediators released. The result is pulmonary hypertension, depressed myocardial contractility and right ventricular dysfunction. Dhainaut, Lanore, de Gournay, Huyghebaert, Brunet, Vilemam and Monsallier (1988) monitored the evolution of right ventricular function in septic shock subjects (n = 23). Shock was defined as mean arterial pressure less than 60 mmHg, peripheral cyanosis and a urinary
output less than 20 ml/hr. Thermodilution hemodynamic measures were obtained within 6 hours of shock onset following volume expansion with a plasma protein solution. Volume was administered until PAOP was greater than 12 mmHg and additional volume did not improve CO. Hemodynamic values were compared with those obtained during diagnostic cardiac catheterization in 10 control subjects. Generally, septic subjects exhibited tachycardia, reduced systemic vascular resistance and hypotension. Mean PAP was significantly elevated when compared with control (+ 40%, p < 0.05). RVEF was significantly lower in septic subjects, in conjunction with an elevated RVEDVI (RVEF -39%, p < 0.05, RVEDVI + 38%, p < 0.05). RVEF continued to be reduced in septic subjects compared to control; however, 48 hours after initial measurement, there was a significant difference between subjects who survived their illness and those who did not (RVEF survivors = 0.31 ± 0.12, RVEF nonsurvivors = 0.22 ± 0.11, p < 0.05). The investigators attributed this mortality difference to reduction in right ventricular contractility, in conjunction with increased afterload in nonsurvivors.

Right ventricular dysfunction has also been described following cardiac surgery (Dorman, Spinale, Kratz, Alpert, & Ford, 1992; Dries & Mathru, 1994). Coronary artery disease is frequently treated with CABG. Hypoxic pulmonary vasoconstriction appears to be heightened following cardiac surgery and may significantly augment right ventricular afterload. Since small increases in carbon dioxide tension were shown to produce large increases in PVR post CABG operation. Viitanen, Salmenpera and Heinonen (1990) evaluated the effect of changes in arterial carbon dioxide tension on right ventricular function in postoperative CABG patients (n = 18). Thermodilution hemodynamic measures were obtained with normocarbia (PaCO₂ = 38.3 ±
2.5mmHg), hypocarbia (PaCO₂ = 33.2 ± 2.8) and hypercarbia (PaCO₂ = 49.8 ± 2.9 mmHg). There were no significant changes in hemodynamics during hypocarbia; however, hypercarbia significantly increased PAP (normocarbia PAP = 18.1 ± 3.4 mmHg, hypercarbia PAP = 24.2 ± 2.8 mmHg, p < 0.001) and PVR (normocarbia PVR = 205 ± 70 dyne·sec·cm⁻⁵, hypercarbia PVR = 315 ± 137 dyne·sec·cm⁻⁵, p < 0.001). RVEF was significantly reduced with a concomitant increase in RVEDV (normocarbia RVEF = 0.40 ± 0.10, RVEDV = 123 ± 37 ml, hypercarbia RVEF = 0.32 ± 0.10, RVEDV = 153 ± 36 ml, p < 0.001). Stroke volume remained unchanged due to preload augmentation, but the increase in right heart afterload necessitated a 45% increase in RVSWI to maintain forward blood flow. There were no significant differences in CI, heart rate, mean arterial pressure or SVR evident between normocarbia and hypercarbia states. These investigators hypothesized subjects with little compensatory reserve might be unable to maintain adequate pulmonary blood flow in the presence of hypercarbia post CABG operation.

In an analysis of the evolution of right ventricular performance following CABG, Dorman, Spinale, Kratz, Alpert and Ford (1992) tracked right ventricular function for 48 hours post operation (n = 10). Prebypass measures served as comparison values. Postoperative thermodilution values were obtained at 30 and 60 minutes and 6, 24 and 48 hours postbypass. There was significant depression of RVEF at 24 and 48 hours postbypass (control RVEF = 45 ± 2 %, 24 hours post RVEF = 36 ± 3%, 48 hours post RVEF = 31 ± 2%, p < 0.05). EDV did not vary significantly. These investigators suggested right ventricular dysfunction may be common following CABG; however, the causative etiology has not been clearly elucidated. Hypothesized mechanisms include reperfusion injury due to oxygen free radicals and right ventricular
subendocardial ischemia secondary to elevated afterload post CABG.

Acute increases in PAP and right ventricular afterload are found following pulmonary embolism (Schulman & Matthay, 1992). Gold and Bache (1982) described right ventricular subendocardial ischemia produced by systolic overload following pulmonary artery occlusion in a canine model (n = 18). By administering adenosine during pulmonary artery occlusion, this investigation determined subendocardial ischemia developed before RCA vasodilator reserve is exhausted. Priebe (1990) measured the hemodynamic effects of pulmonary embolization in canines (n = 8) with RCA stenosis. Embolization increased mean PAP and PVR fourfold and reduced pulmonary artery blood flow by 18%. There was a 58% reduction in RCA blood flow following embolization. Priebe inferred from these results that underlying RCA disease may produce severe regional ischemic changes with moderate elevations of right heart afterload.

Acute respiratory failure is accompanied by elevations in PVR due to hypoxic pulmonary vasoconstriction. Subsequent right ventricular dysfunction secondary to pressure overload and myocardial ischemia may be the consequence. Sibbald, Driedger, Cunningham and Cheung (1986) described right ventricular function in 28 subjects with acute respiratory failure due to sepsis, aspiration, fat embolism, pulmonary contusion or drug overdose. These investigators described a significant inverse linear relationship between mean PAP and RVEF (r = -0.61, p <0.001). CO was maintained by an increase in right ventricular preload, although the lack of a concomitant increase in stroke work indicated contractile depression. The fundamental conclusion of this study was acute respiratory failure elevated right ventricular afterload. In most cases, pulmonary blood flow was
maintained by compensatory mechanisms, while increases in mean PAP to a level of 40 mmHg or more produced acute right heart failure.

Brunet, Dhainaut, Devaux, Huyghebaert, Villemant and Monsallier (1988) compared right ventricular function in 36 subjects with acute respiratory failure to that of 10 control subjects. Respiratory failure was defined as the presence of bilateral opacification on chest roentgenographic examination, arterial hypoxemia, shunt fraction greater than 25% with a fraction of inspired oxygen of .50 and a PAOP less than 10 mmHg. All subjects required MV support. Hemodynamic parameters were evaluated by multigated blood pool imaging. Initial hemodynamic measures in the acute respiratory failure group were made during the first 24 hours prior to the initiation of MV with positive end-expiratory pressure (PEEP) (average PEEP 10 cm H2O). Followup measurements were obtained at 5 and 10 days post acute illness. Values for the control group were obtained once during diagnostic cardiac catheterization. At the initial measurement time, subjects with acute respiratory failure had a 21% greater RVEDV than those in the control group (p <0.05), in conjunction with a 16% lower RVEF. There was a also a significant negative correlation between RVEF and PAP (PAP) (r = -0.67, p <0.001). At the recovery measurement time, there were no significant differences in hemodynamic variables between control subjects and the 15 acute respiratory failure subjects who survived. Those who later died from refractory hypoxemia, in conjunction with severe pulmonary artery hypertension (n = 21), demonstrated a progressive increase in RVEDV (59% > control group, p <0.01), with a concomitant decrease in ejection fraction (41% <control, p <0.01). At day 5 following diagnosis of acute respiratory failure, the 8 subjects who died of septic shock exhibited decreases in both right and
left ventricular ejection fractions (RVEF 37% <control, LVEF 35% <control, p <0.01), in combination with a 26% increase in RVEDV (p <0.05). Subjects who died of cardiogenic shock (n = 4) exhibited drastic decreases in biventricular ejection fraction (RVEF 59% <control, LVEF 60% <control) with increases in biventricular volumes indicating biventricular dilatation (RVEDV 32% >control, LVEDV 35% >control). These results suggested biventricular function was maintained in those subjects surviving acute respiratory failure; while those subjects unable to augment ejection fraction in the presence of increased EDV did not survive their illness. These subjects were on the plateau portion of the Starling curve, so additional volume loading would not increase systolic function. Measures of RV performance during weaning from MV were not reported in this study.

Acute lung injury also elevates right ventricular afterload. Calvin and Quinn (1989) determined that right ventricular ischemia produced ventricular dysfunction with acute lung injury in a canine study (n = 15). Pulmonary artery hypertension was produced by doubling, then tripling the PAP. Right ventricular ischemia occurred with acute lung injury; however, study data suggested ischemia was due to inadequate augmentation of coronary blood flow, in relation to an increased oxygen demand, rather than a decreased RCA flow. These subjects also decreased left ventricular filling and reduced CO in response to elevated afterload.

Individuals with COPD commonly have elevations in right ventricular afterload (Klinger & Hill, 1991; MacNee, 1994a). Pulmonary hypertension develops gradually as pathology develops in the pulmonary parenchyma. The ventricle adapts to the additional workload by increasing the number and density of mitochondria in each myocyte, as well as, increasing the number of
myocytes. Hypertrophy increases wall thickness, which reduces wall stress according to the LaPlace relationship. Clinically, this compensatory response to pulmonary hypertension is known as cor pulmonale. The actual incidence of cor pulmonale in the COPD population is unknown, since clinical predictors are relatively insensitive; however, estimates derived from postmortem examination range from 25% to 50% of individuals diagnosed with COPD (Klinger & Hill, 1991). Brent, Mahler, Matthay, Berger and Zaret (1984) found that 63% of their 30 stable subjects had elevated PAP at rest; while, 83% had a concurrently depressed RVEF (<45%). PAP had a significant negative association with RVEF (r = -0.74, p <0.001). In general, elevations in right ventricular afterload are thought to be multifactorial. One primary factor, hypoxemia, may be amenable to treatment.

MacNee, Wathen, Flenley and Muir (1988) examined the effect of oxygen therapy on ventricular function in two groups of COPD subjects. Eight subjects with cor pulmonale were clinically stable without peripheral edema at time of measurement; while the remaining six subjects presented acutely with decompensated cor pulmonale and peripheral edema. Mean PAP and PVR were not significantly different in the two groups; however RVEF was significantly lower in the edematous group (0.47 ± 0.10 versus 0.23 ± 0.11 respectively, p <0.05). Edematous subjects also demonstrated a significantly greater RVEDVI (68 ± 26 ml/m² versus 218 ± 166 ml/m² respectively, p <0.05). Oxygen therapy reduced mean PAP in both groups (nondematous on room air PAP = 30 ± 8 mmHg, on oxygen 25 ± 6 mmHg, edematous on room air PAP = 33 ± 6 mmHg, on oxygen 28 ± 6 mmHg, p <0.01), but there were no significant changes in RVEF or RVEDVI. In this study, oxygen acted as a mild pulmonary vasodilator, but did not have a significant impact on right
ventricular function. However, this study supported the hypothesis right ventricular afterload is multifactorial.

The increase in right ventricular afterload in COPD is primarily produced by vascular changes related to pathology. The degree of emphysematous changes in pulmonary parenchyma could indicate the severity of pulmonary vascular changes and predict pulmonary and right heart hemodynamic abnormalities. Biernacki, Gould, Whyte and Flenley (1989) attempted to correlate the severity of emphysema as determined by computerized tomography (CT) with changes in pulmonary hemodynamics (n = 32). At rest, the RVEF of these subjects was depressed (mean RVEF = 0.33 ± 0.08); while the mean PAP ranged widely from 10 to 51 mmHg (mean PAP = 21.3 ± 8.9). This study did not find a significant relationship between RVEF and the extent of emphysema measured by CT scan (r = 0.38, NS), however, pulmonary vascular abnormalities with COPD may progress differently from pulmonary parenchymal changes.

More recent investigations attempted to noninvasively predict cardiopulmonary hemodynamic status in individuals with COPD. Machraoui, von Dryander, Hinrichsen, Jager, Lemke, Ulmer and Barmeyer (1993) used two dimensional echocardiography to diagnose right ventricular pressure overload (n = 44). Echocardiographic measures were compared with hemodynamic measures obtained during right heart catheterization. PAP was moderately correlated with right ventricular area index (r = 0.78, p <0.001), right ventricular area to body weight ratio (r = 0.76, p <0.001) and right ventricular area (r = 0.72, p <0.001). PVR was also moderately correlated with right cardiac area index (r = 0.71, p <0.001), right atrial area index (r = 0.73, p <0.001), right ventricular area index (r = 0.74, p <0.001) and right-to-left cardiac
area ratio ($r = 0.71, p < 0.001$). Mean PAP in this sample of COPD subjects was $28.88 \pm 5.91$ mmHg. Marangoni, Scalvini, Schena, Vitacca, Quadri and Levi (1992) used pulsed Doppler echocardiography to assess right ventricular diastolic function in three groups of subjects (group 1 - COPD subjects with previously diagnosed pulmonary hypertension $n = 35$, group 2 - COPD subjects without pulmonary hypertension $n = 32$ and group 3 - healthy control group $n = 18$). Although pulmonary function measures indicated similar degrees of pulmonary function in groups 1 and 2 ($\text{FEV}_1 42.9 \pm 14\%$ versus $44.5 \pm 16.5\%$ respectively), mean PAP was significantly different (group 1 mPAP = $27.5 \pm 6.1$ mmHg, group 2 mPAP = $14.3 \pm 4.6$ mmHg, $p = 0.05$). Diastolic function was also significantly different in group 1 subjects. An increase in right ventricular end-diastolic diameter, the ratio between peak atrial filling velocity, deceleration half time, the interval between pulmonary valve closure and tricuspid valve opening; in conjunction with, a reduction in peak early filling velocity and atrial filling velocity indicated diastolic dysfunction in group 1 ($p < 0.001$). Systolic dysfunction was also detected in this group by a prolonged right pre-ejection period ($p < 0.05$), a decreased right ventricular ejection time ($p < 0.01$), a prolonged ratio of pre-ejection period to ejection time ($p < 0.005$), reduced acceleration time ($p < 0.0001$) and reduced ratio of acceleration time to ejection time ($p < 0.0001$). These studies identified a number of non-invasive indicators of right ventricular dysfunction in the COPD population.

The development of pulmonary artery hypertension with COPD is gradual. The right ventricle adapts to the increased workload with hypertrophy, but significant right ventricular dysfunction may be induced by moderate to severe disease. Acute exacerbations of COPD which produce
hypoxemia and hypercapnia are commonly treated with mechanical ventilation. The change from negative ITP with S_{P}V to positive ITP with MV alters cardiopulmonary hemodynamics and underlying right ventricular dysfunction may be exacerbated by resultant changes in right ventricular preload and afterload.

**Right Heart Hemodynamics During Mechanical Ventilation**

Mechanical ventilation produces a positive ITP with inspiration, rather than the normal negative ITP. With the addition of PEEP, a positive ITP is present during the entire duty cycle. Since the heart, vena cava and pulmonary vessels are surrounded by this ITP, the effects of PEEP on right heart function have been a major focus of investigation (Baigorri, de Monte, Blanch, Fernandez, Valles, Mestre, et al., 1994; Biondi, Schulman, Soufer, Matthay, Hines, Kay, et al., 1988; Brienza, Dambrosio, Bruno, Lagioia, Marucci, Belpiede, et al., 1988; Dhainaut, Devaux, Monsallier, Brunet, Villemant, & Huyghebaert, 1986; Fessler, Brower, Wise, & Permutt, 1990; Fessler, Brower, Wise, & Permutt, 1991; Groeneveld, Schreuder, Verneij, & Thijs, 1990; Johnston, Vinten-Johansen, Shugart, & Santamore, 1992; Martin, Saux, Albanese, Bonneru, & Gouin, 1987; Neidhart & Suter, 1988b; Pinsky & Guimond, 1991; Potkin, Hudson, Weaver, & Trobaugh, 1987; Ranieri, Giuliani, Cinnella, Pesce, Brienza, Ippolito, et al., 1993; Road, Leeners, & Grassino, 1991; Schulman, Biondi, Latthay, Zaret, & Soufer, 1989; Schulman, Biondi, Matthay, Barash, Zaret, & Soufer, 1988; Schulman, Biondi, Zohgba, Zaret, & Soufer, 1990; Singer, Vermaat, Hall, Latter, & Patel, 1994; Viquerat, Righetti, & Suter, 1983). An early study of the hemodynamic effects produced by MV identified a decrease in CO as a primary consequence of positive pressure ventilation (Beach, et al., 1973). Since reductions in CO decrease
oxygen delivery to tissues, much research has focused on the mechanisms responsible for this effect.

Fewell, Abendschein, Carlson, Murray and Rapaport (1980a) investigated the potential mechanisms responsible for the decrease in CO with PEEP ventilation. In a canine study (n = 7), indices of ITP, myocardial perfusion, contractility, preload and afterload were recorded during MV with 0 PEEP, during MV with PEEP 12 cmH2O and again following removal of PEEP. MV with PEEP significantly reduced right and left ventricular end-diastolic volumes (RVEDV control = 51.3 ± 12.3 ml, RVEDV with PEEP = 33.8 ± 10.17 ml, LVEDV control = 57.4 ± 8.5 ml, LVEDV with PEEP = 40.2 ± 12.53 ml, p = 0.05), CO (CO control = 3.2 ± 5.2 liters/min, CO with PEEP = 2.36 ± 7.9 liters/min) and stroke volume (SV control = 23.9 ± 5.08 ml, SV with PEEP = 16.1 ± 5.41 ml); while significantly increasing PAP (PAP control = 15.7 ± 2.11 mmHg, PAP with PEEP = 19.3 ± 3.55 mmHg, p = 0.05). Indices of myocardial blood flow and contractility were unchanged with PEEP ventilation. From these data, the investigators hypothesized that reduction in preload induced by continuous positive pressure ventilation was responsible for the decline in CO.

This group of investigators next examined the mechanisms responsible for reduced preload during MV in 16 instrumented, canine subjects (Fewell, Abendschein, Carlson, Rapaport, & Murray, 1980b). Hemodynamic variables were obtained during control periods (MV with 0 PEEP closed chest, MV with 3 cm H2O open chest) and 5-20 minutes following an increase in PEEP (MV with PEEP 12 cm closed chest, MV with PEEP 10 cm open chest). Epicardial pressure was measured on the lateral and posterior surfaces of the heart to determine the effect of expanded lung parenchyma on the heart. Lateral
pleural pressure was also measured. FRC was determined by helium dilution and enabled the investigators to ensure consistent lung volumes between open and closed chest conditions. During this experiment, PEEP increased lateral and posterior epicardial pressures significantly more than lateral pleural pressure (lateral pleural pressure with 0 PEEP = -2.5 ± 0.9 mmHg, with PEEP 12 cm = 0.7 ± 0.7 mmHg, lateral epicardial pressure at 0 PEEP = -1.3 ± 1.3 mmHg, with PEEP 12 cm = 3.6 ± 1.2, posterior epicardial pressure at 0 PEEP = 0.0 ± 1.4 mmHg, with PEEP 12 cm = 5.2 ± 1.1 mmHg, p = 0.05). With the open chest condition, EDVs and CO could be preserved during MV with PEEP by moving the lungs away from the heart. The investigators hypothesized that positive ITp produced by MV with PEEP was directly reflected on the heart and thoracic vessels which reduced diastolic filling and EDVs. This subsequently decreased CO.

Investigations of cardiac function during PEEP ventilation expanded to study diverse patient populations. Viquerat, Righetti and Suter (1983) investigated biventricular volume and RV performance changes produced by 12 cmH2O PEEP in patients with adult respiratory distress syndrome (ARDS) (n = 11). Overall, the addition of PEEP produced a 14% reduction in CO due to a decrease in biventricular EDVs (RVEDVI 0 PEEP = 83 ± 8 ml, RVEDVI with PEEP = 71 ± 7 ml, LVEDVI 0 PEEP = 56 ± 5 ml, LVEDVI with PEEP = 48 ± 4 ml, p <0.0025). A ratio between RVEDVI and LVEDVI was calculated to assess relative ventricular volumetric response to PEEP. Baseline RVEDVI/LVEDVI was >1.5 in 7 subjects which indicated right ventricular enlargement. With the addition of PEEP, this ratio decreased in four of these subjects; while the remaining three evidenced a further increase. Following removal of PEEP, volume and performance indices returned to higher levels,
with the exception of RVEF and RVEDVI/LVEDVI. RVEF decreased from 49% ± 3.1 to 46% ± 2.8; while RVEDVI/LVEDVI increased from 1.48 to 1.62. These investigators suggested changes indicative of right ventricular dilation followed removal of PEEP. They inferred from these data that PEEP induced reduction in CO was secondary to decreases in biventricular volumes.

These findings were supported and further clarified by Dhainaut, Devaux, Monsallier, Brunet, Villeman and Huyghebaert (1986). This group also investigated alterations in CO with the addition of PEEP in ARDS patients (n = 8). PEEP was incrementally increased from zero to a maximum value of 20 cmH₂O. CO gradually decreased with incremental PEEP and at 20 cmH₂O PEEP, the average reduction in CO was 25% (CO 0 PEEP = 4.47 ± 0.7 L/min, CO 20 cmH₂O PEEP = 3.37 ± 0.53 L/min). A curvilinear relationship was identified between PEEP level and CO with a greater reduction in CO at higher PEEP level. RVEDV and LVEDV significantly decreased with PEEP (RVEDV 0 PEEP = 97.6 ± 7.2 ml, RVEDV 20 cmH₂O PEEP = 74.5 ± 6 ml, LVEDV 0 PEEP = 61.2 ± 4.7 ml, LVEDV 20 cmH₂O PEEP = 43.8 ± 3.9, p <0.01); however, biventricular ejection fractions were unchanged. At 20 cm H₂O PEEP, volume expansion was administered to normalize the CO and this therapy restored biventricular volumes to prePEEP levels. This group of investigators concluded the fundamental reason for the reduction in CO with PEEP is a decline in venous return with a subsequent decrease in biventricular end-diastolic volumes and stroke volume.

Potkin, Hudson, Weaver and Trobaugh (1987) lent support to these conclusions in another study of ARDS patients (n = 9). Changes in right ventricular volume and contractility were evaluated by radionuclide angiography modified to improve RV imaging during incremental PEEP.
application (0 up to 25 cm H₂O PEEP). Right and left ventricular counts on average, progressively decreased 38% and 27% respectively with incremental PEEP (p <0.001). CO and stroke volume also progressively decreased on average 27% and 33% respectively. A slight increase in biventricular ejection fraction was observed with incremental PEEP level. These data supported the hypothesis that reduced CO with PEEP ventilation is secondary to a decrease in biventricular EDVs. However, these investigators propose that this may be due to a reduction in venous return or secondary to alterations in ventricular configuration produced by compression of the heart by the pulmonary parenchyma.

In 1988, Schulman, Biondi, Matthay, Barash, Zaret and Soufer hypothesized a variable response of the right ventricle to PEEP ventilation. This group studied right ventricular pressures, volumes, RVEF and CO in a diverse patient population (n = 36). In this sample, PEEP ventilation was instituted as a therapy for cardiogenic pulmonary edema (n = 8), ARDS (n = 11), postoperative support (n = 9) and multilobar pneumonia (n = 8). Hemodynamic measures were obtained during incremental PEEP application (0 to 20 cmH₂O). Right ventricular contractile function was evaluated by examination of the slope of the systolic pressure-volume relationship. These investigators identified a significant differential response. Subjects with severely depressed right ventricular performance as indicated by an ejection fraction less than 30% increased end-diastolic (RVEDV 0 PEEP = 270 ± 74 ml, 20 cm H₂O PEEP = 391 ± 76 ml, p <0.05) and end-systolic volumes (RVESV 0 PEEP = 210 ± 70 ml, 20 cm H₂O PEEP = 321 ± 70 ml, p <0.05) and reduced contractility (slope of systolic pressure-volume 0.12 to 0.04 mmHg/ml, 0 to 15 and 15 to 20 cm H₂O PEEP respectively, p <0.05). Subjects with normal or
moderately depressed RV performance evidenced no significant difference in RV volumes or contractility with incremental PEEP level. Based on these data, the investigators suggested that baseline right ventricular performance is a fundamental determinant of the right ventricular response to PEEP ventilation in diverse patient populations.

Brienza, Dambrosio, Bruno, Lagioia, Marucci, Belpiede and Giulianai (1988) supported this hypothesis in their study of incremental PEEP in subjects with acute respiratory failure (n = 8). In general, PEEP produced a reduction in CI, stroke volume index (SVI) and RVEF with a concomitant increase in RVEDVI, PAP, PAOP, RAP and PVR. Further investigation identified two subgroups based on RVEDVI with zero PEEP (Group A RVEDVI >120 ml/m², Group B RVEDVI <120 ml/m²). With incremental PEEP application, Group A subjects exhibited a linear decrease in RVEF (RVEF at 0 PEEP = 48% ± 3.5, at PEEP 15 cm = 38.3% ± 7.5) and an increase in RVEDVI (RVEDVI at 0 PEEP = 131.5 ± 4.9 ml/m², at PEEP 10 cm = 150.7 ± 31.4 ml/m²). Group B subjects manifested an increase in RAP with PEEP application (RAP at 0 PEEP = 8.7 ± 3.1 mmHg, at PEEP 14 cm = 15 ± 1 mmHg) and a subsequent reduction in RVEDVI (RVEDVI at 0 PEEP = 79 ± 15 ml/m², at PEEP 15 cm = 62 ± 2 ml/m²). In this sample, the reduction in CO seen with PEEP application was secondary to either a decrease in venous return or an increase in right ventricular afterload. These investigators proposed the global response of the right ventricle (RV) to PEEP application is a function of pre-existing RVEDVI. In those subjects with an initial RVEDVI above 120 ml/m², the afterload effect predominated; while those with a RVEDVI less than 120 ml/m² predominantly exhibited reduction of preload.
Neidhart and Suter (1988) also found two responses to PEEP application in their sample of CABG patients (n = 13). Overall, with MV and PEEP application, CI decreased on average by 23% ± 9% via a decrease in stroke volume without a subsequent increase in heart rate. In 77% of the subjects, PEEP also produced an average 18% decrease in EDV; while the remaining subjects increased end-diastolic and end-systolic volumes by 25% and 50% respectively. In those subjects who increased right ventricular volumes, RVEF decreased by 29%. This group of investigators concluded two different mechanisms were responsible for the reduction in CI in this group of subjects. The majority of subjects responded to PEEP with a reduction in venous return; while the remaining subjects reduced RV performance and dilated the RV.

Further inquiry into the differential CO response was reported by Schulman, Biondi, Zohgbi, Zaret and Soufer in 1990. This group studied the effect of PEEP on right ventricular performance and myocardial perfusion before and after occlusion of the RCA in a canine model (n = 16). With intact RCA flow, incremental PEEP significantly reduced CO (CO 0 PEEP = 2.6 ± 0.7 L/min, PEEP 20 cm = 1.0 ± 0.3 L/min, p < 0.05), primarily by a reduction in SV (SV 0 PEEP = 18 ± 3 ml, PEEP 20 cm = 7 ± 1 ml, p < 0.05). RVEF also progressively decreased with incremental PEEP (RVEF 0 PEEP = 37 ± 5%, PEEP 20 cm = 19 ± 6%, p < 0.05); however, end-diastolic and end-systolic volumes were unchanged. RCA occlusion alone reduced CO via a decrease in both stroke volume and heart rate (CO PEEP 20cm = 1.8 ± 0.5 L/min). The addition of PEEP following RCA occlusion produced further decline in CO (1.1 ± 0.5 L/min). RCA occlusion reduced RVEF (baseline EF = 37 ± 5%, post occlusion = 27 ± 4%, p < 0.05) without a change in EDV; however, end-systolic volume
increased. The addition of PEEP further reduced RVEF (27 ± 4% to 15 ± 5%) and significantly increased end-systolic volume (39 ± 8 ml to 49 ± 10 ml, p < 0.05). Myocardial perfusion was not significantly reduced by the addition of PEEP (transmural flow baseline = 0.53 ± 0.17 ml/min/g, with PEEP 20 cm = 0.49 ± 0.16 ml/min/g); however, RCA occlusion significantly reduced myocardial flow (to 0.33 ± 0.13 ml/min/g) and the addition of PEEP produced a further significant decline in transmural blood flow (to 0.20 ± 0.06 ml/min/g). Analysis of the slope of the pressure-volume relation for the RV documented that with normal myocardial perfusion, the addition of PEEP produced no change in the slope of this relationship (0.42 ± 21 units to 0.39 ± 19 units, NS). However, with RCA occlusion, the addition of PEEP produced a significant reduction in the slope of this relationship (RCA occlusion slope = 0.20 ± 0.06 units, RCA occlusion plus PEEP = 0.14 ± 0.05 units, p <0.05). In this experiment RV contractile performance was negatively influenced by the addition of PEEP in the presence of pre-existing RCA blood flow limitation. These investigators concluded that patients with coronary artery disease may be susceptible to right ventricular ischemia with the application of PEEP.

Nutritive coronary vessels on the epicardial surface of the heart are exposed to the effects of ITP. Since MV produces a positive pressure around the heart, Fessler, Brower, Wise and Permutt (1990) investigated the effects of increasing juxtacardiac pressure on coronary blood flow in an isolated canine heart-lung preparation (n = 17). Left atrial transmural pressure, circumflex artery blood flow and arterial and venous blood lactate levels were measured with each 10 mmHg incremental pressure increase to a maximum of 60 mmHg; while venous return, arterial pressure and lung volume were held constant. Increased juxtacardiac pressure reduced left atrial transmural
pressure significantly (up to 1.28 ± 0.31 mmHg decrease, p <0.001) which indicated reduction in left ventricle (LV) afterload; however, with juxtacardiac pressure of >30 mmHg, transmural pressure exhibited a sustained increase. Circumflex artery blood flow decreased as juxtacardiac pressure increased (p <0.01). When the artery was maximally dilated by adenosine infusion, the effects of increased juxtacardiac pressure were accentuated. At 60 mmHg juxtacardiac pressure, arterial-venous blood lactate difference significantly decreased (0.71 ± 0.09 mM to 0.10 ± 0.21 mM, p <0.001) indicating myocardial ischemia. These investigators concluded that increased juxtacardiac pressure mechanically impedes myocardial perfusion. MV may significantly increase juxtacardiac pressure, reduce myocardial flow and generate myocardial ischemia and cardiac dysfunction, particularly in individuals with arterial hypotension and/or coronary artery disease.

Johnston, Vinten-Johansen, Shugart and Santamore (1992) further explored the effects of positive F T P on right ventricular myocardial perfusion. These investigators studied the effects of 0 PEEP and 15 cm H₂O PEEP on infarction size in a canine model (n = 24). RV perfusion and segmental shortening were measured during a 90 minute ischemia period, then during a 120 minute reperfusion period. Mean arterial pressure was maintained > 90 mmHg during this experiment. PVR increased by 79% with the addition of 15 cm H₂O PEEP (p <0.05). During ischemia, greater RV oxygen demand was observed with PEEP application (rate pressure product 0 PEEP = 1909 ± 94 mmHg/beat/min⁻¹, PEEP 15 cm rate pressure product = 2403 ± 174 mmHg/beat/min⁻¹). The RV area at risk during ischemia was greater with PEEP (0 PEEP = 60 ± 3.9%, PEEP 15 cm = 68.5 ± 2.4%, p = 0.08) and collateral perfusion to this area was significantly reduced with PEEP (0 PEEP = 18.3 ± 3.6
ml/min-1/100g⁻¹, PEEP 15 cm = 9.0 ± 1.7 ml/min-1/100g⁻¹). Consequently, PEEP ventilation produced a significantly greater ischemic area (0 PEEP = 21.8 ± 5.3%, PEEP 15 cm = 58.1 ± 8.4%, p <0.05). This group proposed PEEP of 15 cm H₂O may increase the degree of RV infarction by reducing myocardial collateral perfusion, in spite of maintenance of systemic perfusion pressure. Clearly, these studies indicate myocardial perfusion may be significantly altered by the application of positive ITP.

Although numerous studies identified decreased venous return as one of the primary mechanisms which reduce CO with PEEP, a more recent investigation is questioning this hypothesized mechanism. Positive pressure reflected on the right atrium is proposed to reduce the pressure gradient for venous return to the right heart. Fessler, Brower, Wise and Permutt (1991) studied changes in this gradient with PEEP ventilation in a canine model (n = 18) and found no significant change between 0 PEEP and 15 cm H₂O PEEP (RAP 0 PEEP = 3.89 ± 0.26 mmHg, PEEP 15 cm = 4.13 ± 0.29 mmHg, NS). PEEP increased mean systemic pressure and RAP equally, so did not influence the size of the gradient. Investigation of the venous return gradient with and without PEEP ventilation, during abdominal binding, open abdomen, carotid sinus and vagal denervation and total spinal anesthesia with epinephrine infusion, led the investigators to conclude that PEEP increased mean systemic pressure by both reflex changes in vessel capacity and mechanical vessel compression independent of increased abdominal pressure. PEEP decreased the pressure gradient for venous return only with the abdomen bound, due to a relatively greater increase in RAP and during total spinal anesthesia with epinephrine infusion, due to a relatively lesser increase in mean systemic pressure. In this study, alterations in the venous return gradient did not
occur with application of PEEP as expected. Further investigation is required to fully explicate the mechanisms that reduce CO during positive pressure ventilation.

In conclusion, review of this literature clearly indicates that mechanical ventilation with PEEP application can significantly influence the function of the right ventricle. Previous research supports the hypothesis that PEEP produces a positive intrathoracic pressure which reflects on the pulmonary vessels, increases right ventricular afterload and alters RV myocardial oxygen supply-demand balance. Positive juxtacardiac pressure, particularly in the presence of coronary artery disease, may produce ischemia and necrosis by mechanical compression of nutritive vessels. During RV dysfunction, sufficient systolic performance cannot be generated to eject blood into the pulmonary artery and RVEDV increases, further compromising oxygen supply-demand balance. Globally, reduced RV ejection attenuates perfusion of the pulmonary vasculature and decreases oxygen delivery to metabolically active tissues throughout the body. The occurrence of hemodynamic changes during weaning from MV has not been fully explored.

**Weaning From Mechanical Ventilation**

Clinically, the removal of MV and return to SpV is termed weaning, regardless of the method(s) employed or the length of time required to achieve successful spontaneous breathing. Although the majority of ventilated individuals (80-90%) are separated from MV without difficulty; the remaining 10-20% actually require weaning or the gradual withdrawal of MV (Aldrich, Karpel, Uhrlass, Sparapani, Eramo, & Ferranti, 1989; Goodnough Hanneman, Ingersoll, Knebel, Shekleton, Burns, & Clochesy, 1994; Nett, Morganroth, & Petty, 1984; Stoller, 1991). Weaning has been conceptualized
as a dynamic continuum consisting of three phases: preweaning, weaning process and weaning outcome (Knebel, Shekleton, Burns, Clochesy, Goodnough Hanneman, & Ingersoll, 1994b). Progression through these phases is influenced by environmental factors, multiple physiological and psychological factors inherent to the ventilated individual and clinical decisions made by health care professionals. The primary goal is a successful transition to SpV. Appropriate clinical decision making during weaning is vital, since prolonged ventilator dependence, as well as premature weaning may significantly influence morbidity, mortality and health care costs (Marini, 1991; Rosen & Bone, 1988).

Significance of Prolonged Ventilation and Premature Extubation

Morbidity and mortality rates related to intubation and mechanical ventilation have been a focus of investigation since MV developed into a ubiquitous therapy. In an early controlled study, Quasha, Loeber, Feeley, Ulliot and Roizen (1980) compared morbidity rates with early extubation (2 ± 2 hours) and delayed extubation (18 ± 3 hours) following CABG (n = 38). These groups experienced significantly different rates of morbidity and exhibited different requirements for sedatives and narcotics. The group randomized to delayed extubation required significantly greater morphine and diazepam than those extubated early (morphine 15 ± 6 versus 9 ± 5 μg/kg/hr, p <0.02, diazepam 7 ± 5 versus 2 ± 2 μg/kg/h, p <0.005). Sixty five percent of those in the delayed extubation group experienced morbid events including acute myocardial infarction, dysrhythmias, atelectasis, cerebrovascular accident and cardiac tamponade. Twenty eight percent of those extubated early suffered morbid events which primarily consisted of dysrhythmias requiring therapy and one reintubation. Early extubation
produced fewer and less severe morbid events in this small group of patients.

Prolonged ventilator dependence was found to be associated with a reduction in functional capacity, in addition to, an increased mortality by Spicher and White (1987). These investigators performed a retrospective analysis of long term MV patients (>10 days) and assessed mortality rates and functional status. Only 39.2% of the 250 subjects survived to hospital discharge, while 28.6% were alive at one year and 22.5% at two years following prolonged MV. Survival rates were found to be different between diagnostic categories. Individuals requiring MV due to reversible neurological diseases like encephalitis or Guillain-Barre syndrome were more likely to be weaned, extubated and discharged from the hospital than those with cardiac dysfunction or pulmonary diseases like COPD, pneumonia and ARDS (p <0.05). The neurological group also had greater one and two year survival rates (1 year = 52%, 2 year = 37%, p <0.05). In this study, morbidity was described by functional level following hospital discharge. Nearly 28% of those individuals discharged following prolonged MV sustained either a mild deficit or evidenced no functional deficit. Approximately 40% of those discharged had severe deficits requiring institutionalization; while 32.7% were housebound. Prolonged ventilation is not a determinant of survival, but an indicator of the severity of illness.

A similar retrospective review described the postoperative course of open-heart surgery patients who required MV for more than 72 hours after surgery (LoCicero, McCann, Massad, & Joob, 1992). The incidence of prolonged MV (>72 hours) in this group (n = 581) of surgery patients was 9.9%. Mortality rate for this subgroup of 58 patients was 43%, with a 28% mortality rate within the first 14 postoperative days. Morbidity directly related to intubation was high
with a complication rate of 65% for those ventilated long term via an endotracheal tube and 37% for those ventilated via a tracheostomy. Complications of endotracheal intubation were self-extubation, cuff leaks, sinusitis, vocal cord paralysis, endobronchial intubation and oropharyngeal ulceration. Complications of tracheostomy included tracheostomy stoma erosion, subcutaneous emphysema, accidental extubation and tracheoesophageal fistula formation. These investigators described cardiac surgery patients requiring long term MV as a “desperately ill subset of cardiac surgery patients” (LoCicero, et al., 1992, p. 990).

In a prospective study, Ingersoll and Grippi (1991) attempted to identify preoperative factors related to delayed extubation following elective cardiac surgery (n = 47). Nearly 75% of this group was extubated without problem within 24 hours of surgery. The remaining 25% experienced delayed extubation with greater morbidity and mortality rates. Mortality for the entire sample was 6.4% and all of these subjects were in the delayed extubation group. Individuals in the delayed extubation group had a significantly longer ICU and hospital stay compared to those extubated within 24 hours of surgery (ICU 1.5 ± 0.8 days versus 3.9 ± 2.6 days, p = 0.01; post-ICU 8.4 ± 3.5 days versus 10.6 ± 7.8 days, p <0.05). Although a variety of risk factors were assessed including preoperative smoking status, abnormal lung sounds, presence of COPD, use of accessory muscle of respiration; the only factor associated with early extubation was a preoperative positive affect (p = 0.02). Delayed extubation again identified an unstable group of patients with higher mortality and morbidity.

In a similar study in 1993, Jayr, Matthay, Gladstone, Gold and Wiener-Kronish investigated factors associated with prolonged MV following major
abdominal vascular surgery (n = 51). Twenty four percent of these patients required MV for more than 24 hours. Seven subjects included in the prolonged ventilation group were extubated during the first 24 hours, but required reintubation and MV for rapid respiratory rate and increasing hypoxemia. Subjects in this delayed extubation group exhibited greater mortality (25% versus 3%) and a longer ICU and post-ICU hospital stay (ICU 12 ± 8 days versus 3 ± 2 days, post-ICU 24 ± 12 days versus 14 ± 10 days, p <0.05). Morbidity in the form of bilateral atelectasis (83%), bilateral pleural effusion (83%) and pulmonary consolidation (17%) were evident in the subjects requiring prolonged MV. Three factors found to be associated with prolonged ventilation following abdominal vascular surgery included history of heavy cigarette smoking (72 ± 45 pack years versus 44 ± 25 pack years, p <0.05), preoperative hypoxemia (PaO₂ 68 ± 12 mmHg versus 77 ± 10 mmHg, p <0.05) and greater intraoperative blood loss (3.6 ± 2.5 liters versus 1.7 ± 1.1 liter, p <0.05).

Morbidity in the form of nosocomial pneumonia is more likely to occur in patients receiving MV. Buccal and airway epithelial cells in critically ill patients have an increased availability of bacterial receptor sites with subsequent enhanced binding. There may also be a loss of interbacterial inhibition and changes in pH that influence the growth of bacteria. Gastric bacterial colonization occurs within 24 to 48 hours following alkalization therapy, a commonly used treatment in critically ill patients. Endotracheal intubation violates the protective mechanisms of the upper airway and aspiration of colonized oropharyngeal and gastric secretions is the primary mechanism responsible for infection of the lower airway (Pingleton, 1988). Craven, Kunches, Kilinsky, Lichtenberg, Make and McCabe (1986) found a
nosocomial pneumonia rate of 21% in 233 consecutively ventilated patients. The mortality rate for this subgroup of patients was 55% and the duration of MV therapy was a significant predictor of nosocomial pneumonia ($p < 0.005$). Torres, Aznar, Gatell, Jimenez, Gonzalez, Ferrer, Celis and Rodriguez-Roisin (1990) further examined predictive characteristics in a group of 322 patients requiring MV for more than 48 hours. Nearly one quarter of this group of patients developed nosocomial pneumonia. The overall mortality for the entire group was 23%, while mortality for those with nosocomial pneumonia was significantly higher (33%, $p < 0.01$). Multivariate analysis of patient characteristics identified the use of PEEP ventilation, more than one intubation during MV experience and the duration of MV as significant predictors for the development of nosocomial pneumonia. In a similar study, Rello, Quintana, Ausina, Castella, Luquin, Net and Prats (1991) prospectively assessed the incidence and outcome of 1000 consecutive ICU admissions. Slightly more than a quarter of these subjects required MV for more than 48 hours ($n = 264$). Nosocomial pneumonia occurred in 25.7% of this group after a mean of 7.9 days of MV. Mortality rates were not statistically different for subjects with and without nosocomial pneumonia (with 42%, without 37%); however, mortality was directly attributed to nosocomial pneumonia in 21% of the cases. ICU length of stay was significantly different for survivors (without pneumonia 16.7, with pneumonia 26.2 days, $p < 0.01$). Clearly, increases in morbidity and mortality due to nosocomial pneumonia are a significant problem in ventilated patients.

Controlled MV for 72 hours or more induces significant changes in respiratory muscles (Marini, 1991). Oxidative enzymes necessary for energy
production and endurance are depleted, followed closely by breakdown and resorption of respiratory muscle sarcomeres. A recent controlled investigation using a rat model described a significant reduction in the ability of the diaphragm to generate force following only 48 hours of MV (n = 18). Actual muscle mass was significantly reduced in the ventilated group in both costal and crural portions of the diaphragm when compared to a control group (costal 644.1 ± 29.1 mg versus 748.2 ± 30.1, p <0.05; crural 277.3 ± 8.9 mg versus 346.1 ± 13.9 mg, p <0.005). Peak twitch tension and peak rate of force development were also significantly reduced in the ventilated rats (peak twitch 0.43 ± 0.11 Newtons/cm² versus 0.84 ± 0.15 Newtons/cm²; peak force 0.008 ± 0.002 Newtons x ms/cm² versus 0.018 ± 0.002 Newtons x ms/cm², p <0.05). Force frequency curves documented significant reductions in force generation, with maximum reduction of 41.5% at optimal stimulation (100 Hz). Further investigation is necessary to determine the etiology of this force reduction and determine the extent to which this phenomenon occurs in humans receiving MV.

Premature extubation with subsequent reintubation and resumption of MV may also increase morbidity and mortality rates. Few studies have adequately described reintubation rates in relation to the physiologic rationale for extubation failure. Torres, Aznar, Gatell, Jimenez, Gonzalez, Ferrer, Celis and Rodriguez-Roisin (1990) found reintubation was a predictor of nosocomial pneumonia in their group of 322 patients requiring MV for more than 48 hours. Demling, Read, Lind and Flanagan (1988) prospectively investigated extubation failure in 700 consecutive patients in two critical care units (surgical and burn). Standardized criteria were employed to determine readiness for extubation. Thirty two extubation failures in 30 patients
produced an overall reintubation rate of 4%. The primary rationale for reintubation was different for the two units. Patients in the burn ICU required reintubation to maintain airway patency, to protect the lower airway from aspiration, to provide adequate pulmonary toilet and to administer positive pressure ventilation as therapy for hypoxemia secondary to impaired gas exchange. Patients in the surgical ICU primarily required reintubation to administer positive pressure ventilation as therapy for impaired gas exchange; however, nearly one third of these patients were reintubated due to cardiovascular instability producing pulmonary edema and/or progressive metabolic acidosis. Morbidity in this group consisted primarily of new pulmonary infiltrates, atelectasis and nosocomial pneumonia. Morbidity rate in those patients requiring reintubation was nearly 50%. Mortality rate in patients requiring reintubation was 30%. A comparison rate for those patients with a successful extubation was not offered. These investigators could not identify consistent predictors of extubation failure in their sample.

In summary, increased morbidity and mortality rates are found in individuals who experience prolonged MV and/or require reintubation secondary to premature extubation. This group of patients consumes huge quantities of increasingly scarce health care resources. The need for prolonged ventilation is primarily indicative of the severity of illness; however, prolonged ventilation can also be directly related to the development of nosocomial pneumonia, altered respiratory muscle function and complications due to intubation and prolonged MV.

**Physiologic Determinants of Ventilator Dependence**

MV is a therapy primarily aimed at altering alveolar ventilation and/or the work of breathing (Shapiro, Kacmarek, Cane, Peruzzi, & Hauptman, 1991).
Once the underlying physiologic disturbance has been corrected, MV should be discontinued to prevent morbidity from the therapy. However, in 9-37% of patients this may not be easily accomplished for a variety of reasons. Four primary reasons for ventilator dependence have been proposed: hemoglobin desaturation, psychological dependence, an imbalance between ventilatory demand and capability and cardiovascular instability (Marini, 1986). The current study investigated cardiovascular instability during weaning from MV.

Cardiovascular instability during weaning may be manifested by dysrhythmias and/or hemodynamic changes. Hypoxemia due to inadequate gas exchange can induce cardiac dysrhythmias; while, the return to normal ITP during ventilation alters preload and afterload of both ventricles. Research findings about the right ventricle during weaning have been previously reviewed. Left ventricular performance may be influenced by increased afterload and ventricular interdependence, so that reduced filling and/or reduced ejection may occur with resumption of SpV. In their investigation of extubation failure, Demling, Read, Lind and Flanagan (1988) found that 32% of subjects (n = 22) required reintubation secondary to pulmonary edema and/or metabolic acidosis originating from cardiovascular instability. In a retrospective analysis, Clochesy, Daly and Montenegro (1995) found that chronically ill subjects with left ventricular dysfunction were ventilated for significantly longer periods of time (p <0.05) and those that were weaned received more pharmacologic treatment for heart failure. Lemaire, Teboul, Cinotti, Giotto, Abrouk, Steg, Macquin-Mavier and Zapol (1988) described acute left ventricular dysfunction during weaning in a group of subjects with chronic cardiopulmonary disease (n = 15). PAOP and transmural pressure
significantly increased with the transition to SpV (PAOP 7.5 ± 5 mmHg to 24.5 ± 13 mmHg, p <0.05; transmural pressure 8 ± 5 mmHg to 25 ± 13 mmHg, p <0.001). Left and right ejection fractions were unchanged; however, EDVI increased in both ventricles (LVEDVI 65 ± 24 ml/m² to 83 ± 32 ml/m², RVEDVI 83 ± 33 ml/m² to 103 ± 39 ml/m², p <0.05). Subjects developed progressive ventilatory failure requiring return to MV. Following aggressive nutritional and diuretic therapy with reduction of total blood volume (123 ± 22 % of predicted to 102 ± 19% of predicted, NS), 60% of these subjects were successfully weaned. Reduced ventricular compliance with increased left ventricular filling pressure and augmentation of left ventricular afterload were implicated in weaning failure in this group of subjects.

Ventricular compliance can be reduced by the development of myocardial ischemia. Using thallium scintigraphy, Hurford, Lynch, Strauss, Lowenstein and Zapol (1991) investigated myocardial perfusion during weaning in a small group of MV dependent subjects (n = 15). In 47% of these subjects, thallium scan identified redistribution of left ventricular myocardial perfusion and/or left ventricular dilation. These investigators concluded that the transition to SpV produced increases in left ventricular preload and afterload which were sufficient to produce myocardial ischemia in a nearly half of their subjects. Elia, Liu, Hilgenberg, Skourtis and Lappas (1991) also studied myocardial perfusion during weaning from MV in a group of postoperative CABG patients (n = 17). Coronary hemodynamics and the presence of anaerobic myocardial metabolism were evaluated by a dual port coronary sinus-great cardiac vein thermodilution catheter and measurement of myocardial lactate, respectively. Measurements were obtained during weaning with synchronous intermittent mandatory ventilation (SIMV) and
CPAP 5 cm. Although all subjects were easily weaned and demonstrated no significant changes in myocardial blood flow or oxygen consumption, nearly half of the subjects produced lactate at some point during weaning. Subjects who produced lactate demonstrated significantly greater increases in systemic blood pressure and vascular resistance ($p < 0.05$). Although myocardial revascularization had been performed prior to study, a significant portion of this group manifested anaerobic myocardial metabolism indicative of ischemia during weaning from MV. Clinical signs indicating ischemia were absent during these episodes.

In a more recent study, Abalos, Leibowitz, Distefano, Halpern and Iberti (1992) investigated the incidence of silent myocardial ischemia during weaning in a group of high risk cardiac patients following non-cardiac operation ($n = 62$). Subjects met one or more inclusion criteria which identified them as high risk for morbidity/mortality secondary to cardiac disease. Once judged ready to wean by standard weaning criteria, each subject was randomized to one of three weaning modes: SIMV 4 breaths/min, t-piece or CPAP 4 cmH$_2$O. Continuous two lead ST segment monitoring (leads V$_5$, III) quantified the extent of silent ischemia during three monitoring phases: prewean, wean and postwean. Ischemia was defined as more than 1 millimeter ST depression occurring 60 milliseconds after the J point. During baseline or prewean phase, 16% of subjects were found to have ST depression >1 mm. Nineteen percent of those subjects with normal baseline ST segments developed ST depression during the study. Silent myocardial ischemia was more prevalent during wean and postwean phases ($p = 0.001$), but primarily occurred during weaning. In those subjects who exhibited ischemia, ST depression occurred on average, 6.4% of their total monitoring
time; while ST depression was detected during 13.7% of their weaning time. There were no significant differences in rate of ischemia between the three modes of weaning. None of the subjects experienced symptoms indicative of myocardial ischemia. These investigators described weaning from MV as a high risk period for silent myocardial ischemia in subjects with preexisting cardiac disease.

In conclusion, cardiovascular instability is one of four proposed causes of ventilator dependence. The transition from MV to SpV alters right ventricular preload and afterload which may induce ventricular dysrhythmias and/or significant hemodynamic alterations. Failure to wean from MV with increased morbidity/mortality may be the consequence.

**Modes of Weaning from Mechanical Ventilation**

In current clinical practice, weaning from MV is accomplished by a variety of techniques. These include t-piece with SpV, CPAP, IMV or SIMV and PS (Weillitz, 1991). The most traditional technique, t-piece, consists of alternating periods of MV with SpV supplemented by oxygen delivered by a t-shaped piece attached to the proximal endotracheal tube. CPAP incorporates SpV with the addition of a positive airway pressure preset above atmospheric pressure throughout the duty cycle. PS provides positive pressure during spontaneous inspiration. No single weaning mode has been proven to be superior and little is known about the decision process clinicians use to select the weaning mode for a particular patient. Schuster (1990) suggested weaning mode be selected based on the physiological rationale for the MV therapy. He proposed that individuals with oxygenation deficits benefit from CPAP; while, those with ventilatory failure benefit from IMV or PS. In an earlier study, Venus, Smith and Mathru (1987) surveyed hospitals in the United
States to determine the most frequently employed weaning modes. In the responding hospitals, IMV was the most frequently used weaning mode (90.2%), with IMV to t-piece used by 63.8% and IMV to CPAP by 26.4% of respondents. However, this survey received only a 28% response rate which may have significantly biased these results. In a more current investigation, Esteban, Alia, Ibanez, Benito, Tobin and the members of the Spanish Lung Failure Collaborative Group (1994) performed a cross sectional multicenter study of 47 Spanish ICUs to determine weaning modes currently used in practice. T-piece was the most common (24%), with SIMV (18%), PSV (15%) and SIMV with PS (9%) also in use. Some combination of two or more weaning modes was implemented in 33% of cases. Use of a combination of SIMV and PS required a significantly longer time to achieve successful weaning (t-piece 5.1 ± 1.4 days, SIMV 4.9 ± 1.2 days, PS 4.8 ± 1.0 days, SIMV and PS 17.8 ± 3.9 days, p <0.01). More significantly, in the overall sample, weaning required 41% of total time spent on the ventilator; while patients with COPD spent 59% of their total ventilator time in the process of weaning. Since reduction in weaning time could reduce morbidity and mortality related to MV, the “best” mode of weaning is a prime focus of research. Studies comparing the effects of different weaning modes on length of weaning time, work of breathing, oxygenation, $V_A/Q$ distribution and breathing comfort have been performed to identify the most efficacious weaning mode.

Length of weaning time and weaning success using IMV and t-piece modes were prospectively evaluated by Tomlinson, Miller, Lorch, Smith, Reines and Sahn (1989). This group randomized 165 consecutive patients requiring MV into weaning by IMV or t-piece and found weaning time was
not significantly different (IMV 5.3 ± 1.2 hours, t-piece 5.9 ± 1.4 hours, NS). Eighty eight percent were successfully weaned on their first attempt; while, 7% required two attempts and 3% needed three attempts. The remaining three patients required three days to achieve successful weaning. Neither method proved superior in this sample. Brochard, Rauss, Benito, Conti, Mancebo, Rekik, Gasparetto and Lemaire (1991a) performed a randomized trial using t-piece, SIMV or PS (n = 109). The mean duration of weaning was significantly less using PS (PS 5.7 ± 3.7 days, pooled t-piece and SIMV 9.3 ± 8.2 days, p <0.05) and the number of weaning failures was also found to be significantly less (PS 8%, SIMV 33%, t-piece 39%, p <0.05). The probability of continuing to require MV was significantly less with PS when compared to either SIMV or t-piece (p <0.03); so in this sample of patients, PS offered a significant advantage when compared to SIMV and t-piece weaning.

Considerable effort has been expended investigating the effect of weaning modes on the work of breathing. Sassoon, Light, Lodia, Sieck and Mahutte (1991) found that t-piece, CPAP and PS weaning had differential effects on the pressure-time product, an index of metabolic work of respiratory muscles, in a group of 10 patients. Low levels of CPAP and PS significantly decreased the pressure-time product when compared with t-piece weaning (p <0.01). In a similar study, Calzia, Lindner, Witt, Schirmer, Lange, Stenz and Georgieff (1994) compared biphasic CPAP (biPAP) and PS with PEEP 5cm (n = 19). BiPAP delivers continuous positive airway pressure at two set levels during SV, one during inspiration and the other during expiration. Both pressure-time product and measured work of breathing were significantly less with PS plus PEEP weaning in this group (PTP biPAP 136 ± 44.0 cmH₂O·s/min, PTP PS and PEEP 104.2 ± 27.6 cmH₂O·s/min, p <0.01; biPAP work 4.4 ± 1.9 J/min,
PS and PEEP work 4.1 ± 1.6 J/min, p <0.01). PS required less work output of the respiratory muscles when compared to biphasic CPAP. In contrast, Kreit, Capper and Eschenbacher (1994) found that work of breathing during PS was dependent on the degree of support provided. In some instances, work was greater with PS than with assisted MV. Petrof, Legare, Goldberg, Milic-Emili and Gottfried (1990) found that three levels of CPAP (5, 10, 15 cm) reduced total work and pressure-time product in a group of COPD patients during weaning (n = 7). Inspiratory work of breathing was significantly less than SpV, the control condition, at all three levels of CPAP and work progressively reduced as CPAP level was increased (5 cm - 17.27 ± 1.92 J/min versus 14.47 ± 1.34 J/min, p <0.05; 10 cm - 17.47 ± 1.91 J/min versus 12.28 ± 1.19 J/min, p <0.01; 15 cm - 19.94 ± 2.78 J/min versus 10.81 ± 1.78 J/min, p <0.005). This decrease in work was attributed to a reduction of the inspiratory threshold load that was imposed by dynamic hyperinflation in this population. In a more recent investigation, Branson, Campbell, Davis and Johnson (1994) found that CPAP with flow triggering was more effective than CPAP with pressure triggering in the reduction of both measured work and pressure-time product in a group of 10 patients (work - 0.58 ± 0.3 J/L versus 0.84 ± 0.2 J/L, p <0.01; pressure-time product 148 ± 50 versus 206 ± 41 cmH2O/s/min, p <0.05). Traditionally, pressure triggering delivered inspiratory gas flow when a pressure drop in the system was sensed and flow ceased when airway pressure attained a preset value. The newer flow triggering delivers a low continuous flow and when inspiration reduces this flow to a preset level, inspiratory flow is delivered. Flow triggering improves the responsiveness of the CPAP system and may be useful in weaning.
A second area of investigation related to weaning modes and work of breathing focuses on compensation for the added inspiratory work generated by the endotracheal tube. Fiastro, Habib and Quan (1988) evaluated the effectiveness of PS in compensating for inspiratory work added by the resistance of different sized endotracheal tubes and a CPAP demand valve system in a mechanical simulation. Each 1 mm decrease in endotracheal tube diameter increased inspiratory work by 67-100%, depending on respiratory rate and tidal volume. Half of the work of breathing could be attributed to the CPAP ventilator circuit and a 9 mm endotracheal tube. When the tube size was reduced to a 7 mm diameter tube, 70% of the work of breathing was produced by the tube and circuit. In this study, the addition of PS could compensate for the additional work imposed by the endotracheal tube and ventilator circuit. Brochard, Rua, Lorino, Lemaire and Harf (1991b) measured work of breathing as patients (n = 11) spontaneously ventilated through a t-piece, as they received four levels of PS ventilation and following extubation. The endotracheal tube with or without the ventilator circuit and demand valve increased work of breathing. PS compensated for this additional work; however, the level required differed substantially between individual subjects and ranged from 3.4 to 14.4 cm. Reduction of this additional work could reduce the work of breathing during weaning from MV and improve the likelihood of weaning success.

Modes of weaning have been found to influence diaphragm function when compared with normal ventilation. Torres, Kacmarek, Kimball, Qvist, Stanek, Whyte and Zapol (1993) studied diaphragmatic mechanics in 10 sheep during quiet spontaneous breathing via a tracheostomy tube, during controlled MV, during three levels of CPAP (5, 10, 15 cm), during three levels
of PS (5, 10, 15 cm) and during a combination of CPAP and PS at three levels (5/5, 10/10, 15/15 cm). CPAP increased diaphragmatic pressure, costal and crural electromyographic activity and end-tidal CO$_2$, while decreasing segmental diaphragmatic length. Expiratory gastric pressure increased significantly with CPAP indicating abdominal muscle recruitment. In contrast, during PS, diaphragmatic length remained constant, while diaphragmatic pressure, end-tidal CO$_2$, electromyographic activity and expiratory gastric pressure decreased. PS in combination with CPAP reversed the negative consequences of CPAP, since end-expiratory lung volume was increased without increasing respiratory muscle loading.

Other investigations have focused on oxygenation during weaning. Cason, DeSalvo and Ray (1994) found oxygen saturation measured by pulse oximetry and mixed venous oxygen saturation (SvO$_2$) determined by an optical module to be sensitive indicators of important changes in oxygenation during weaning in their postoperative CABG patients ($n = 10$). These investigators suggested weaning decisions might have been different had SvO$_2$ levels been assessed during the weaning process. Jones, Byrne, Morgan, Fraser and Hyland (1991) compared the effects of t-piece and CPAP administered for one hour prior to extubation in 106 patients. Two patterns of Pa$_O_2$/Fi$_O_2$ ratio were detected. The CPAP group displayed a slight reduction in Pa$_O_2$/Fi$_O_2$ ratio prior to extubation; however, a large sustained decline occurred following extubation. T-piece subjects displayed a decline prior to extubation, then a slight increase following extubation. Extubation success and failure rates were similar for both groups. Neither mode was clearly superior. Santak, Radermacher, Sandmann and Falke (1991) used the multiple inert gas elimination technique (MIGET) to describe changes in the
VA/Q distribution during MV and IMV with PS in postoperative abdominal vascular surgery patients (n = 9). There were no significant alterations in arterial blood gas values, hemodynamic pressures or percent shunt with the use of IMV and PS. The perfusion distribution was essentially unchanged with IMV and PS; however, there was an increase in distribution of ventilation to lung areas with high VA/Q ratios producing an increase in dead space ventilation (VD/Vt) (VD/Vt 37.2 ± 9.2% to 42.5 ± 8.5%, p <0.05). A compensatory increase in minute ventilation (Ve) maintained normal PaCO2 values (Ve 9.5 ± 0.9 L to 11.3 ± 1.2 L, p <0.05). In this small patient group, IMV with PS maintained efficient VA/Q distributions and gas exchange.

An evolving area of research concerns breathing comfort and perceived sensation during weaning. In an early study, Lush, Janson-Bjerklie, Carrieri and Lovejoy (1988) described the incidence and severity of dyspnea in 5 ventilated patients. Dyspnea was experienced by all subjects with a severity range of 0-95 mm on a 100 mm scale. In a pilot study, Knebel (1992) monitored dyspnea in 13 subjects at the start and end of weaning with PS. Dyspnea was not significantly different between these times; however, when the subjects were categorized by physiological rationale for MV, the progression of dyspnea was different. Patients ventilated postoperatively began with lower dyspnea ratings and reported higher ratings at the completion of weaning. In patients with oxygenation or ventilation failure, dyspnea intensity was high initially and remained unchanged during weaning. In a study of 30 healthy subjects, Simon, Schwartzstein, Weiss, Lahive, FencI, Teghtsooian and Weinberger (1989) used varied stimuli to induce dyspnea and determined that dyspnea or breathlessness is comprised of multiple sensations. Since these sensations are most likely mediated by
diverse physiological mechanisms, it is possible that varied sensations of breathlessness may be induced by different weaning modes. Knebel, Janson-Bjerklie, Malley, Wilson and Marini (1994a) compared breathing comfort in 21 subjects during SIMV and PS weaning. All subjects experienced both weaning modes on a single day separated by 1-3 hours. Visual analogue scales were employed to measure anxiety and dyspnea during weaning. Anxiety and dyspnea were positively correlated during both weaning modes (SIMV r = 0.55, PS r = 0.61). In this group of subjects, dyspnea and anxiety remained stable during weaning and were not significantly different between SIMV and PS modes. However, psychological status may play an important role in symptom reporting in this population, since Dales, Spitzer, Schechter and Suissa (1989) found that psychological status is strongly associated with respiratory symptom reporting in a large group of healthy subjects (n = 600) (adjusted odds ratios 1.13-2.15 for each 10% increase in psychological measure score, p <0.05). Psychological distress must be considered when evaluating levels of respiratory symptomatology in ventilated or weaning patients.

Studies to date have not identified a clearly, superior weaning technique for any population and there is little insight into how weaning modes are selected in clinical practice. Further investigation of existing weaning techniques is necessary to determine their optimal utility in diverse populations.

**Conclusion**

During the transition from MV to SV, right heart hemodynamics may be influenced by the change from positive ITP generated by MV to a negative ITP inherent to normal ventilatory mechanics. Negative swings in ITP influence both right ventricular preload and afterload. These effects may be particularly
pronounced in individuals with COPD because of chronic hyperinflation and functional and structural vascular alterations. There are few previous studies investigating the effects of ITP changes on right heart hemodynamics during weaning and these are often limited by the measurement technology available during data collection and small sample size of diverse animal and human subjects. In addition, there has not been a thorough investigation of the effects of weaning support modes like CPAP and PS on right heart hemodynamics.

The current study investigated changes in right heart hemodynamics during the transition from MV to SV in an instrumented, anesthetized canine model with normal ventricular function and with propranolol induced heart failure. The effect of CPAP and PS on right heart hemodynamics was also examined. The current study addressed the paucity of research on right heart hemodynamic changes during weaning from MV and will provide clinicians with fundamental knowledge about right heart hemodynamic changes during weaning. This knowledge will contribute to the clinician's ability to optimize cardiopulmonary function during weaning, reduce cardiopulmonary instability and complications during the weaning process, as well as, increase the probability of weaning success.
CHAPTER III
MATERIALS AND METHODS

Design

This investigation used an experimental, within subjects, repeated measures design (Figure 2). Subjects were randomly placed in one of two groups (Group 1 normal ventricular function, Group 2 propranolol induced biventricular failure). Data were then collected on each subject at baseline on MV, then again following a 5 minute transition period to one of four randomly assigned ventilatory permutations (t-piece, Resistor, pressure support, continuous positive airway pressure). Each subject was exposed to all four ventilatory permutations. Comparison of each subject's baseline measures with permutation measures allowed each subject to serve as their own control.

Random Assignment to Group

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
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<tr>
<td>R O₁ X₁ O₂</td>
<td>R O₁ X₁ O₂</td>
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<tr>
<td>R O₃ X₂ O₄</td>
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<tr>
<td>R O₇ X₄ O₈</td>
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R = random assignment of one of four ventilatory permutations (t-piece, Resistor, PS, CPAP)
X₁, X₂, X₃, X₄ = ventilatory permutation (t-piece, Resistor, PS or CPAP)
O₁, O₃, O₅, O₇ = baseline data collection on MV
O₂, O₄, O₆, O₈ = data collection following 5 minutes of the assigned ventilatory permutation

Figure 2. Research Design
Setting

This study was performed in the Cardiovascular Laboratory of a large, midwestern, state affiliated university.

Subjects

A sample of 20 male, mongrel dogs were studied in this experiment (10 per group). This sample size provided statistical power of .80 at a two tailed alpha level of .05 with a moderate effect size. Premedication for these subjects consisted of buprenorphine (0.05 mg/kg IM), ketamine (5 mg/kg IV) and diazepam (0.2 mg/kg IV). Complete anesthesia was achieved with an initial bolus dose of α chloralose (80 mg/kg IV) followed by hourly titrated doses (40-60 mg/kg/hr). Veterinary care for the animals was monitored by the Ohio State University Animal Care and Use Committee which ensured that all aspects of care met accepted standards. Animal care facilities at the university are accredited by AAALAC. At the conclusion of each experiment, anesthesia was maintained as the animals were euthanized using saturated potassium chloride (5-10 ml IV). This combination provided rapid, painless euthanasia consistent with recommendations of the American Veterinary Medical Association.

At the time of transition from MV to SpV, the majority of human ventilator patients no longer require invasive monitoring devices that would permit necessary data acquisition. An animal model was selected for this study because of the invasive nature of dependent variable measurements. An animal model offers the ability to perform sophisticated, invasive measures of cardiovascular function, to manipulate the degree of ITP and to control the mode of ventilation. Previous studies of right heart hemodynamics and mechanical ventilation have been performed in the
canine model presenting the opportunity to compare results within the same species (Fessler, Brower, Wise, & Permutt, 1990; Fewell, Abendschein, Carlson, Murray, & Rapaport, 1980a; Fewell, Abenschein, Carlson, Rapaport, & Murray, 1980b; Johnston, Vinten-Johansen, Shugart, & Santamore, 1992; Schulman, Biondi, Zohgbi, Zaret, & Soufer, 1990). Potential limitations of this model included the administration of a general anesthetic, absence of pulmonary pathology and dysfunction which could potentially alter the transition to SpV, absence of psychological influences during transition and potential species response differences, including postural or position limitations. These limitations must be considered in the interpretation and generalization of the study findings.

**Ethical Review**

This study was part of a larger pilot study entitled "Cardiopulmonary Hemodynamics with Weaning from Mechanical Ventilation" which was approved by the Institutional Laboratory Animal Care and Use Committee at the Ohio State University (Appendix A).

**Instrumentation**

**Right Ventricular Ejection Fraction/Volumetric Oximetry Thermodilution Catheter**

Thermodilution CO and RVEDV were obtained by the use of a 110 cm, heparin coated, pulmonary artery thermodilution catheter (Edwards Laboratories, Model 93A-750H-7.5F, Santa Ana, CA) equipped with a fast response thermistor (95 milliseconds) and two electrodes for intracardiac electrocardiographic detection and beat to beat analysis. This radiopaque, polyvinylchloride catheter is composed of six lumens: the distal pulmonary artery lumen, the proximal injectate lumen (21 cm. from tip), the proximal
monitoring/infusion lumen (31 cm. from tip), the balloon lumen, the thermistor lumen and the lumen that contains the two intracardiac electrodes. When the catheter is in proper position, the distal lumen lies in the pulmonary artery, the proximal injectate lumen lies 2 to 5 cm. proximal to the tricuspid valve and the proximal monitoring lumen is in the right atrium or vena cava. Intracardiac electrodes are positioned in the pulmonary artery (distal, 6 cm. from tip) and the right ventricle (proximal, 16. cm from tip). The multiholed, proximal injectate port consists of three orifices, each at a different angle. This configuration optimizes mixing of the cold injectate with the blood. The rapid response thermistor lies 4 cm from the tip of the catheter and rapidly senses beat by beat changes in pulmonary artery blood temperature. This catheter is interfaced with a computer monitor system (Explorer, Baxter Healthcare Corp, Santa Ana, CA) capable of exponential analysis of the thermal washout curve.

**Explorer Multiple Parameter Hemodynamic Monitor**

The Explorer Multiple Parameter Hemodynamic monitor (Baxter Healthcare Corp., Santa Ana, CA) measured cardiac output, right heart volumes and ejection fraction by the thermodilution technique. To determine cardiac output, the computer analyzed blood temperature changes sensed by the thermistor using the Stewart-Hamilton indicator dilution equation:

\[
CO = 1.08 \text{ CT (60) VI (TB - TI)}/\int \Delta TB(t) \, dt + C
\]

where:

CO is cardiac output in liters/minute, 1.08, CT, 60 and VI are correction factors used to determine the computation constant, TB is the baseline blood temperature, TI is the injectate temperature, \( \tau \) is the variable data acquisition
endpoint that depends on the exponential curve downslope (usually when the curve decreases to 30% peak value), \( \int_{\tau} \Delta T_B (t) \, dt + C \) is the area derived by integration of the time temperature thermodilution curve, and \( C \) is the area beneath the thermodilution curve between \( \tau \) and the end of the curve (Baxter, 1992).

The computation constant is calculated with four correction factors:

\[
\text{computation constant} = (1.08) \, CT \, (60) \, VI.
\]

\( CT \) corrects for the difference in temperature between the injectate and the residual fluid in the catheter prior to injection. This value is a function of the catheter dimensions, the internal volume of the catheter and the temperature of the injectate fluid. The value, 1.08, is the ratio of the density times the specific heat of \( D_5W \) to the density times the specific heat of blood or \( pCp \) \( (D_5W)/pCp \text{ (blood)} = 1.08 \). The value 60 is the seconds in each minute; while \( VI \) is the volume of injectate solution in liters. The Explorer computer determined the appropriate computation constant once information was entered regarding the catheter model in use, the injectate temperature monitoring system and the volume of injectate.

Thermodilution determinations apply the principle of conservation of thermal energy. Following injection of a cold, solution bolus into the right heart, blood rewarming occurs during consecutive systoles. At any point in time, the thermal energy in the right ventricle equals the heat present in the ventricle at the end of the previous systole plus the heat of the blood entering the ventricle during diastole; therefore, the thermal energy in the right ventricle is a function of the blood volume and the blood temperature (Dries & Mathru, 1994; Vincent & Lenaers, 1989). This can be described
mathematically by the following equation:

\[ (T_1 \times ESV \times C) + (TB \times (EDV - ESV) \times C) = T_2 \times EDV \times C \]

where \( T_1 \) and \( T_2 \) are the right ventricular blood temperature during two successive systoles, \( TB \) is the basal blood temperature prior to the iced injection, \( ESV \) and \( EDV \) are the end-systolic and end-diastolic volumes and \( C \) is a constant determined by the specific gravity and thermal capacity of blood.

This equation may be rearranged as:

\[ (T_1 \times ESV) + (TB \times EDV) = (T_2 \times EDV) + (TB \times ESV) \]

which may be further simplified to:

\[ ESV \times (T_1 - TB) = EDV \times (T_2 - TB) \quad \text{or} \quad ESV/EDV = T_2 - TB/T_1 - TB. \]

The ejection fraction equation is further derived as:

\[ EF = (EDV - ESV)/EDV = 1 - (T_2 - TB/T_1 - TB). \]

Two analysis methods may be employed to calculate ejection fraction by thermodilution. Plateau analysis uses the average of five successive thermodilution data points immediately following detection of an R wave. These are averaged to obtain a plateau. Two plateaus are determined, beginning with the R wave first sensed after 80% of the peak temperature change. A second reference point is selected within 15-30% of peak temperature change. Two residual fractions (RF) are calculated, then averaged (\( RF_1 = T_2 -TB/T_1 - TB \) and \( RF_2 = T_3 - TB/T_2 - TB \)). The ejection fraction is then calculated by subtracting the average residual fraction from unity or one. The second method, exponential curve analysis, uses a mathematical model to fit a single, first order, exponential washout curve to indicate the residual fraction of injectate remaining in the ventricle at any point following the injection. The residual fraction remaining in the right ventricle is calculated within each R-R interval. The average residual
fraction is computed, then subtracted from unity to obtain the ejection fraction. This is the method used by the Explorer computer.

To calculate right heart volumes and ejection fraction, the Explorer computer determined the point in the thermal washout curve that was 80% of the peak temperature change. The computer then searched either up to 95% of the peak change or in the opposite direction to locate the nearest R wave. This was designated the first reference point. The second reference point was then located a minimum of two R waves distant to the first reference point and within 15% to 30% of the peak temperature change. Once two reference points were established, an exponential curve was fitted and the slope of this curve determined. The slope was then divided by the number of R-R intervals present between the two reference points to provide the ratio of change per heartbeat or residual fraction. The residual fraction was subtracted from unity to determine the ejection fraction. Once cardiac output, right heart ejection fraction and heart rate were determined, right ventricular end-diastolic and end-systolic volumes and stroke volume were derived from the following equations:

\[ SV = \frac{CO}{HR} \times 1000 \]
\[ EDV = \frac{SV}{REF} \]
\[ ESV = EDV - SV \]

According to the manufacturer, the Explorer system measures cardiac output within the range of 0.1 to 20.0 liters/minute repeatable to ± 2% or ± 0.2 liters/minute from the mean value. The range of right ventricular ejection fraction measured by the Explorer is 0.10 to 0.60 with a repeatability of ± 2%. Repeatability of CO and RVEF was determined by electronically generated standard flow and pulsatile curves. The range of heart rates measured by the
intracardiac electrodes is 40 to 150 beats/minute with an accuracy of $\pm 2$ beats/minute. The blood temperature range of measurement of the system is 17.5 to 43 degrees Centigrade with an accuracy of $\pm 0.5$ degree C between 17.5 to 31 and $\pm 0.3$ degrees between 31 to 43 degrees C. Injectate temperature was measured using the CO set injectate system (Model 93-500) with an in-line temperature probe (Model 93-522). The flow through injectate probe was connected directly to the the CO set injectate system at the site of the proximal injectate lumen. This probe incorporates two resistors and one thermistor organized to generate a curve with linear resistance versus temperature. The probe continuously sampled the injectate and selected the lowest peak temperature (TI) sensed for use in calculation. The injectate temperature range of this system is 0.0 to 27 degrees C with an accuracy of $\pm 0.3$ degrees C from 0 to 25 degrees and $\pm 0.5$ degrees C from 25.5 to 27 degrees C.

Reliability/reproducibility of the thermodilution values was ensured by calibration of the equipment prior to each experiment. An alert system inherent to the Explorer signaled technical measurement problems like premature beats or unstable baseline. Validity/accuracy of these measures was determined by evaluation of catheter placement via waveform and thermal washout curve analysis. Thermodilution values for CO, RVEF and RVEDVI were the average of three to five successive injections of 5 ml iced dextrose solution via the proximal injectate port delivered in less than 4 seconds at end expiration.

Reliability and Validity of the Thermodilution Technique

The primary assumption of the thermodilution technique is complete mixing of the iced solution with the blood. Soon after the thermodilution volumetric technique was introduced the optimal procedure for
thermodilution measurement of right ventricular volumes and ejection fraction was investigated by Kay, Afshari, Barash, Webler, Iskandrian, Bemis, Hakki and Mundth (1983). These investigators assessed the accuracy or validity and reproducibility or reliability of thermodilution measures of right ventricular volumes and ejection fraction in canines (n = 22) and humans (n = 8). In the canine experiment, three levels of ejection fraction were studied: high (55-70%) obtained with volume loading and isoproterenol infusion, normal or steady state (35-40%) and low (17-30%) obtained by increasing afterload with neosynephrine infusion or respiratory acidosis. The three levels of ejection fraction were randomized, as were injectate site (right atrium or right ventricle), injectate volume (3, 5 or 10 ml) and injectate temperature (4 or 24 degrees C). Injection of solution into the right ventricle was found to be significantly less reliable than injection in the right atrium, presumably due to incomplete mixing of the solution within the ventricle. However, even when data from right atrial and right ventricular injection was pooled (n = 329 pairs of ejection fractions), thermodilution ejection fraction was found to be reproducible (± 6%). The injectate volume and temperature had no consequential effect on measured ejection fraction in this study. Accuracy or validity of the thermodilution measures was assessed by multigated equilibrium blood pool imaging performed simultaneously with thermodilution measures. Right ventricular ejection fraction measurements with these two techniques were found to be highly correlated (r = .86, p <0.01). Inspection of a regression analysis led these investigators to conclude that ejection fraction is accurately reflected by either technique.

These same investigators studied the reliability and validity of thermodilution ejection fraction measures in eight cardiac surgical
perioperative subjects (Kay, Afshari, Barash, Webler, Iskandrian, Bemis, et al., 1983). The thermodilution catheter was inserted post anesthesia induction and prior to operation. Thermodilution measurements were obtained during the operation and intermittently over the succeeding three postoperative days. Again, injection site (atrium vs ventricle), injectate temperature (4 or 24 degrees C) and volume (3, 5 or 10 ml) were randomized. A total of 372 pairs of consecutive ejection fraction measures documented reproducibility of ±5%. Right atrial injection generated more reproducible measures than right ventricular injection. Again, injectate temperature and volume had no consequential effect on these measurements. First pass radionuclide angiography was performed on the third postoperative day and compared with simultaneous thermodilution ejection fraction and volume measures. Thermodilution and radionuclide values were found to be highly correlated (r = .90, p <0.01). Discrepancies between thermodilution and first pass results were greater at ejection fractions below 30%. These investigators concluded that thermodilution volumetric and ejection fraction measurements are accurate and reproducible even with extreme high and low ejection fractions.

Since these early studies, thermodilution volumetric measures have been compared to other measurement techniques in a variety of animal and human studies. In 1985, Jardin, Gueret, Dubourg, Farcot, Margairaz and Bourdarias reported a comparison of thermodilution right ventricular volumes and ejection fraction with those obtained by two dimensional echocardiography in 18 subjects with ARDS receiving controlled MV. Measures of ejection fraction, end-diastolic and end-systolic volumes were obtained simultaneously and compared. Right ventricular end-diastolic and end-systolic thermodilution volumes correlated significantly with two
dimensional echocardiographic end-diastolic and end-systolic areas (end-diastolic r = .70, p <0.001. end-systolic r = .78, p <0.001). Ejection fraction values obtained by the two methods were also significantly correlated (r = .74, p <0.001). The 13% coefficient of variation for thermodilution right ventricular ejection fraction was partially attributed to measurement of thermodilution volumes throughout the ventilatory cycle, rather than consistently at one point during the duty cycle. Variability was further ascribed to the hemodynamic instability of these subjects, as well as rapid changes in pulmonary blood temperature and cardiac output due to controlled mechanical ventilation. The investigators found no correlation between end-diastolic pressure and echocardiographic end-diastolic area (r = .25, NS) in this group of critically ill subjects. They concluded thermodilution volumetric assessment permits valid measures of right ventricular volumes and ejection fraction and may be superior to right atrial pressure values as an indicator of right ventricular preload.

A later study by Vincent, Thirion, Brimioulle, Lejeune and Kahn (1986) compared thermodilution ejection fraction and volumetric measures with gated first pass radionuclide measures in 14 acutely ill, spontaneously ventilating subjects. First pass radionuclide measures were considered the "gold standard" reference and thermodilution and first pass measurements were made simultaneously, then compared to determine the validity of the thermodilution technique. Analysis of the thermal washout curve was performed using both plateau and exponential curve analysis. Significant correlations were found between radionuclide ejection fraction and thermodilution ejection fraction determined by both plateau analysis (r = 0.61, p = <0.05) and exponential curve analysis (r = .67, p <0.01). A highly
significant correlation was also found between the two thermodilution analysis techniques ($r = .97$, $p < .001$). The variability coefficient for thermodilution values obtained by plateau analysis was 12.1%; while the variability coefficient for exponential curve analysis was 7.6%. These investigators concluded that thermodilution right ventricular volumetric measures provide results with acceptable variability using exponential curve analysis.

Another validity investigation was undertaken by Morrison, Stovall, Sensequa and Frielfeld (1987). This study compared thermodilution measurement of RVEF with gated first pass and gated blood pool radionuclide ventriculography and single plane contrast right ventricular angiography in 41 stable subjects (normal volunteers $n = 7$, atypical chest pain with normal evaluations $n = 4$, resting pulmonary hypertension $n = 10$, tricuspid regurgitation $n = 10$, coronary artery disease, mild cardiomyopathy and COPD with neither pulmonary hypertension or tricuspid regurgitation $n = 10$). In all subjects, the two radionuclide studies were performed within 30 minutes of each other immediately before cardiac catheterization. Thermodilution measurements were completed during cardiac catheterization and within 2 hours of the radionuclide measurements. Contrast right ventriculography was performed at the end of the cardiac catheterization. Radionuclide measures correlated highly with angiography (gated first pass and angiography, $n = 21$, $r = .90$, gated blood pool and angiography, $n = 21$, $r = .84$), highly with each other (gated first pass and gated blood pool, $n = 37$, $r = .94$) and moderately with thermodilution (gated first pass, $n = 36$, $r = .65$, gated blood pool, $n = 40$, $r = .69$). Thermodilution RVEF correlated poorly with angiographic determinations of ejection fraction ($n = 21$, $r = .29$). These
investigators concluded that the thermodilution technique is not an accurate measurement of RVEF. They hypothesized that incomplete mixing of the injectate in the ventricle produced consistently underestimated ejection fractions; however, they did not address the significant time lags between the measures or report their method of separating overlapping cardiac structures with the other measurement techniques.

Dhainaut, Brunet, Monsallier, Villemant, Devaux, Konno, DeGournay, Armaganidis, Iotti, Huyghebaert and Lanore (1987) also compared the two thermodilution analysis techniques and values obtained with radionuclide first pass and gated techniques in 34 acutely ill, spontaneously ventilating subjects (acute respiratory failure = 13, acute myocardial infarction = 12, septic shock = 5, cardiac failure = 4). First pass and thermodilution measures were obtained immediately prior to and following the nuclear count collection cycle. Gated blood pool imaging followed. Thermodilution measures were again obtained during the count collection for the gated technique. The two thermodilution analysis techniques (plateau and exponential curve) were highly correlated (r = .98); however, the coefficient of variation was lower for exponential curve analysis (7.1% versus 12%) indicating greater reliability of this analysis method. Thermodilution ejection fraction was highly correlated with both first pass (r = .92) and gated techniques (r = .81) in these acutely ill subjects. These investigators described thermodilution RVEF as a reliable and valid means of obtaining serial measures of global right ventricular function in acutely ill, spontaneously ventilating subjects.

In 1988, Eaton validated the thermodilution RVEF using a pulsatile flow bench. This microprocessor controlled, flow bench elicited pulsatile flows between 1 and 6 liters/minute with simulated heart rates up to 115
beats/minute. Ejection fractions produced by this device ranged from 15% to 60%. Thermodilution measurement of ejection fraction correlated highly with the pulsatile flow model (adjusted $R^2 = .94$). Thermodilution cardiac output values obtained during the ejection fraction measurement were also very highly correlated with the pulsatile flow model (adjusted $R^2 = .99$). High reproducibility was indicated by small standard deviations for both measures ($EF = \pm 1.56\%$, $CO = \pm 0.14$ liters). This investigator proposed thermodilution RVEF as a reliable measure of global ventricular function.

Dries and Mathru (1994) compared thermodilution ejection fraction measures with values obtained from biplane ventriculography in 10 subjects with documented cardiac disease (coronary artery disease, congestive heart failure, aortic insufficiency, mitral insufficiency, acute myocardial infarction, and/or cardiomyopathy). Although these investigators found a significant difference ($p < 0.05$) in ejection fraction values obtained with thermodilution ($37.4\% \pm 2.9$) and ventriculography ($49.1\% \pm 4.0$), there was no statistically significant difference in right ventricular end-diastolic (thermodilution $86.5 \text{ ml/m}^2 \pm 7.3$, biplane $103.7 \text{ ml/m}^2 \pm 12.8$) and end-systolic volume (thermodilution $60.8 \text{ ml/m}^2 \pm 7.1$, biplane $55.6 \text{ ml/m}^2 \pm 8.7$) indices by these methods in this small sample. Dries and Mathru suggested thermodilution may be a valid measure of right ventricular volumes and ejection fraction in individuals with a normal sized right ventricle; however, abnormal right ventricular size and geometry found with various cardiac disease may influence the validity of thermodilution measures.

Investigations of parameters that influenced the reliability and validity of thermodilution RVEF followed these earlier studies. Voelker, Gruber, Ickrath, Unterberg and Karsch (1988) placed a pulmonary artery catheter via
the femoral route and compared thermodilution RVEF measures with those obtained by biplane cineventriculography in 22 subjects undergoing cardiac catheterization for suspected coronary artery disease. Thermodilution measurements were obtained 20 minutes after coronary angiography, then non-ionic contrast medium was injected into the right ventricle. Right ventricular end-diastolic and end-systolic silhouettes were collected for off line analysis. Overall, ejection fractions obtained by these two methods were highly correlated ($r = .80$, SEE $\pm 5\%$, $p < 0.001$); however, EDV was found to be a significant factor in the validity of the thermodilution method. For those subjects with a normal EDV ($<160$ ml) the correlation was quite high ($n = 13$, $r = .91$, SEE $\pm 5\%$, $p < 0.001$), but in those subjects with a greater than normal EDV ($>160$ ml) no correlation was found ($n = 9$, $r = .11$, SEE $\pm 7\%$, NS). Heart rate and CO were also found to affect the degree of correlation between these methods. Subjects with a heart rate less than 65 beats/minute had a better correlation than those with a heart rate greater than 65 beats/minute ($n = 12$, $r = .84$, SEE $\pm 6\%$, $p < 0.001$ versus $n = 10$, $r = .71$, SEE $\pm 6\%$, $p < 0.05$). Subjects with a CO $<5.5$ liters/minute also had a greater correlation between methods than those with a CO $>5.5$ liters/minute ($n = 11$, $r = .88$, SEE $\pm 6\%$, $p < 0.001$ versus $n = 11$, $r = .53$, SEE $\pm 5\%$, NS). The investigators disclosed difficulty in positioning the catheter with the injection port in the right atrium via the femoral route. They inferred that differences in ejection fraction between the two methods were due to incomplete mixing of the injectate in the right heart and concluded thermodilution measures of ejection fraction are sufficiently valid if the catheter is correctly placed and the injectate adequately mixed in the right ventricle.
Spinale, Smith, Carabello and Crawford (1990) investigated the influence of volume status on thermodilution RVEF. These investigators compared RVEF obtained by thermodilution with biplane ventriculography in 10 Yorkshire swine. Ejection fraction was measured during steady state, during infusion of isoproterenol, at half of baseline mean arterial pressure induced by hemorrhage and with infusion of isoproterenol during hypovolemia. One thermodilution value was obtained immediately prior to the ventriculogram and two more were acquired immediately following. Overall, thermodilution and ventriculography ejection fraction values were significantly correlated over a range of 17% to 70% ($r = 0.74, p = 0.004$). During hypovolemia and during infusion of isoproterenol with hypovolemia, thermodilution ejection fraction values were significantly lower than ventriculography values ($p < 0.05$). Right ventricular stroke volume values obtained by both techniques were highly correlated over a range of 9 to 56 ml ($r = .91, p < 0.001$); however, RVEDVs were not significantly correlated ($r = .56, p = 0.15$). There were no significant differences in the three successive measures of thermodilution ejection fraction ($p = 0.58$). Ten additional swine were studied to determine the effect of insertion site (femoral versus jugular) and distance of thermistor from the pulmonary valve. These values were also compared with values obtained by ventriculography. Insertion by the femoral site resulted in a greater distance between the thermistor and the pulmonic valve. Ejection fractions obtained with femoral insertion were significantly less than those acquired from catheters placed via the jugular site ($p = 0.008$) and ventriculography ($p = 0.006$). Ejection fractions obtained by catheters placed via the jugular site were not different from those obtained by ventriculography ($p = 0.35$). This group of investigators concluded that
thermodilution offered a valid and reliable technique for measurement of right ventricular ejection fraction when appropriate catheter placement is obtained.

In a recent investigation of optimal thermodilution technique, Safcsak and Nelson (1994) compared RVEF values obtained using cold injectate with those obtained using room temperature injectate in 60 mechanically ventilated subjects. There was no significant difference in ejection fraction measured with cold injectate and room temperature injectate in 111 paired measurements ($p = .752$). Ejection fraction values obtained with room temperature and cold injectate were highly correlated ($r = .94$, $p < 0.001$). High correlations existed regardless of variations in body temperature, heart rate, CI, CVP, PVR, RVEDV or stroke work index (SWI). Reproducibility was demonstrated by mean coefficients of variation of 9.7% for room temperature injectate and 8% for cold injectate. These investigators suggested room temperature injectate may produce reliable measures of RVEF in critically ill, mechanically ventilated surgical patients. However, the current manufacturer of thermodilution RVEF technology continues to recommend cold injectate to maximize the signal to noise ratio and improve accuracy of these measures (Baxter Edwards Critical Care Division).

In summary, thermodilution RVEF has been found to be a valid and reliable technique for measurement of global right ventricular performance when compared to ventriculography (Morrison, et al., 1987; Spinale, et al., 1990; Voelker, et al., 1988), two dimensional echocardiography (Jardin, et al., 1985), bench flow ejection (Eaton, 1988; Ferris & Konno, 1992) and nuclear techniques (Dhainaut, Brunet, Monsallier, Villemant, Devaux, Konno, et al., 1987; Kay, et al., 1983; Morrison, et al., 1987; Vincent, et al., 1986). The ability
to obtain reliable, valid and frequent bedside measures of RVEF by thermodilution offers important information to the clinician about global right ventricular performance.

Puritan Bennett 7200 Ventilator

Control mode MV, CPAP and PS ventilation were delivered with a Puritan Bennett 7200ae series mechanical ventilator (Model 7200ae, Carlsbad, CA) via a standard, disposable ventilator circuit. This pneumatic system is microprocessor controlled. The 7200ae ventilator can deliver tidal volumes within the range of 0.10 to 2.5 liters, respiratory rates of 0.5 to 70 breaths/minute, peak inspiratory flow rates of 10 to 120 liters/minute and a fractional concentration of oxygen in inspired gas from .21 to 1.00.

Ventilator modes may be described by the factors that initiate delivery of a mechanical breath, factors that limit the duration/size of the breath and factors that cycle the ventilator or end the inspiratory phase and permit expiration (Shapiro, Kacmarek, Cane, Peruzzi, & Hauptman, 1991). Control mode ventilation provides full ventilatory support, so that the ventilator furnishes the necessary energy to maintain carbon dioxide homeostasis. It is time initiated, volume limited and volume cycled. A preset volume of gas is delivered at a predetermined frequency. Pressure support ventilation is a volume variable mode of ventilation. This mode is pressure initiated, pressure limited and flow cycled. Initiation of pressure support is triggered by a pressure drop in the circuit indicating inspiratory effort. A rapid flow of gas is delivered and maintains a set inspiratory airway pressure. When the flow rate reaches a level preset by the manufacturer, flow ceases and exhalation begins. CPAP is the application of positive airway pressure during the entire duty cycle of a spontaneous ventilation. CPAP delivered by the 7200ae
ventilator uses a demand flow system that provides rapid gas flow during spontaneous inspiration. Airway pressure at end-exhalation is maintained by a preset exhalation valve.

**Gould Graphic Recorder**

Statham pressure transducers calibrated against a column of mercury measured pressure variables (Paw, Pos, Pab, arterial and pulmonary artery pressures). The transducers were connected to a Gould graphic recorder for continuous data collection. After a thirty minute warmup period, this recorder has a reported gain stability of .05% for a 24 hour period. Reliability/reproducibility and validity/accuracy of these measures was assured by mercury calibration of each transducer before each experiment, evaluation of catheter placement via direct visualization and waveform analysis, respectively.

**Radiometer blood gas analyzer (Model ABL 30)**

ABG analysis was performed by a Radiometer blood gas analyzer (Model ABL 30). This equipment was automatically calibrated every 30 minutes using a one point calibration and every two hours using a two point calibration. Calibration efficacy was periodically tested by analysis of solutions with known values. The manufacturer has established that for PaO2 values between 77 and 140 mmHg, repeatability is ± 0.8 mmHg, for PaCO2 values between 28 and 57 mmHg, repeatability is ± 0.4 mmHg and when pH ranges between 7.15 and 7.64, repeatability is ± 0.0025.

**Procedure**

The canine subjects were weighed the afternoon before the experiment to permit calculation of drug doses, intravenous fluid requirements and initial tidal volume. Following an overnight fast, a heartworm free, non-
conditioned canine was premedicated with buprenorphine (0.05mg/kg IM). Intravenous access was obtained by percutaneous technique and ketamine (5mg/kg IV) and diazepam (0.2mg/kg IV) were then administered. Complete anesthesia was obtained with a bolus of chloralose (80mg/kg IV) and followed by hourly titrated doses (40 - 60 mg/kg/hr). Following loss of consciousness, the subject was intubated with an 8mm ID endotracheal tube and manually ventilated. Hair was removed from the anterior neck, abdomen and groin areas where surgical incisions were necessary. The subject was manually ventilated during transport to the laboratory on a wheeled cart. Upon arrival to the laboratory, the subject was transferred to the operating table and secured in a supine position with soft restraints. The proximal endotracheal tube was connected to the mechanical ventilator and controlled MV was initiated with a Vt of 12 ml/kg, room air FiO2 and a respiratory frequency of 10 breaths/minute. A circulating, heated water blanket was in place between the subject and the operating table surface to maintain body temperature within a physiologic range. The pulse oximetry probe of the Explorer computer was placed on the subject’s tongue to provide a continuous estimate of arterial oxygenation. Standard lead II electrocardiographic monitoring was initiated to capture continuous heart rate. Operative areas were cleansed with an iodophor based solution and surgical areas were draped to provide adequate exposure.

Degree of jaw tone was assessed to ensure adequate anesthesia prior to surgical cutdowns and during experimentation. The right femoral vein and artery were then cannulated. A 4 to 5 centimeter incision was made in the left groin using an electrocautery unit. A fluid primed cannula was threaded into the vein and the distal tie secured. Intravenous solution consisting of a
five percent dextrose in half normal saline solution was then administered by infusion pump at a rate calculated to deliver total fluids at 10ml/kg/hr.

A fluid primed arterial cannula was threaded into the femoral artery and a distal tie was tightened. The arterial cannula was connected to a mercury calibrated Statham transducer for continuous monitoring of arterial blood pressure. Cannula patency was maintained by heparinized flush solution (normal saline with sodium heparin 1500 U/500ml). Arterial blood gases were obtained immediately following placement of the arterial catheter.

ABGs were collected by attaching a 3 ml syringe to the arterial catheter via a stopcock, withdrawing a 2 ml discard volume, connecting a heparinized 3 ml syringe and withdrawing a 2 ml sample. The arterial cannula was flushed with heparanized solution to maintain patency. The sample syringe was then disconnected, capped, gently rotated and immediately analyzed (Radiometer analyzer, model ABL 30) to determine $P_aO_2$, $P_aCO_2$, pH, $HCO_3^-$. ABG analysis was performed prior to and following each of the ventilatory permutations and as indicated by subject condition. Values outside of a priori set parameters were addressed by ventilator changes and/or intravenous administration of sodium bicarbonate. These a priori parameters were a $P_aO_2$ between 80 - 120 mmHg, a $P_aCO_2$ between 35 - 45 mmHg, a pH value between 7.35 - 7.45 and arterial $HCO_3^-$ between 23 - 28 mEq/liter.

Complete airway control was ensured by the placement of a size 9 inner diameter endotracheal tube (Mallinckrodt, Inc., Glenn Falls, NY) via a tracheotomy. A 6 to 8 centimeter incision was made lengthwise over the midtracheal region. The trachea was exposed by blunt dissection and separation of the overlying muscle layer. An opening was created by
electrocautery between the third and fourth tracheal rings. The oral endotracheal tube was removed by an assistant as the operator placed the size 9 endotracheal tube via the tracheotomy. The endotracheal tube cuff was inflated and the ventilator connected to maintain adequate ventilation. The tracheotomy tube was securely tied with the umbilical tape. The endotracheal tube airway pressure (Paw) port was then connected to a mercury calibrated statham transducer to measure Paw.

Next, a balloon catheter was placed under the right hemidiaphragm to directly measure abdominal pressure changes and an esophageal balloon catheter was placed to indirectly measure ITP. A 12 to 15 centimeter midline laparotomy incision was made with an electrocautery unit. The peritoneum was visualized and carefully opened following separation of the abdominal muscle layer. The proximal balloon catheter was externalized through a stab wound. The balloon lumen of this catheter was securely connected to a mercury calibrated Statham transducer and eight milliliters of air were placed in the catheter's balloon. This was zeroed at the level of the diaphragm. The distal catheter with the inflated balloon was then placed under the right hemidiaphragm and an abdominal pressure waveform visualized to ensure adequate placement.

Prior to closure of the abdominal incision, the esophageal balloon catheter was placed. This catheter has two balloons, one placed in the stomach and the other in the distal esophagus. The esophagus was visualized using a laryngoscope, then dilated with a 1 1/2 to 2 centimeter inner diameter polyvinylchloride tube. The well lubricated balloon catheter was manually threaded into the esophagus until the tip of the catheter with the gastric balloon could be palpated through the gastric wall. The gastric balloon was
inflated with 30 ml. of air and withdrawn until resistance was felt. This placed the gastric balloon in the fundus of the stomach and ensured the esophageal balloon was placed in the distal third of the esophagus. The esophageal balloon was then inflated with air and connected to a mercury calibrated Statham transducer. This catheter was secured to the lower jaw of the subject with a soft tie. The $P_{aw}$, $P_{ab}$ and $P_{es}$ waveforms were then inspected for quality. Catheter manipulation and/or rezeroing were performed as necessary. The abdominal incision was closed in two layers.

A six lumen, balloon tipped, pulmonary artery catheter with a rapid response thermistor and intracardiac electrodes (Baxter Healthcare Corp, Model 93A-750H-7.5F, Santa Ana, CA) was placed in the pulmonary artery via the right jugular vein. The pulmonary artery catheter had been previously flushed with heparinized saline and connected to two mercury calibrated Statham transducers interfaced with a continuous monitoring system. One of these transducers was connected to the distal pulmonary artery lumen for pulmonary artery pressure and PAOP monitoring; while the second was connected to the proximal monitoring/infusion lumen for continuous monitoring of RAP. With continuous distal lumen pressure monitoring, the catheter was gently advanced until a right atrial waveform was visualized. At this point, 1 and 1/2 milliliters of air were placed in the balloon of the pulmonary artery catheter. The catheter was advanced through the right ventricle and into the pulmonary artery to a wedge position. The balloon was then deflated and the pulmonary artery waveform inspected. Catheter position was secured by the proximal tie when PAOP could be consistently obtained. The intracardiac electrodes in the catheter were connected to the Explorer computer. The catheter thermistor had been previously attached to
the Explorer, which then displayed pulmonary artery temperature continually once the catheter was placed. The proximal injectate port was connected to a flow-through temperature injectate probe (Model 93-522) and tubing set designed for repeated injections of solution for thermodilution CO measures (CO Set Closed Injectate Delivery System, Baxter Edwards). This temperature probe interfaced directly with the Explorer system.

Once instrumentation was complete, the subject received a loading dose of sodium heparin 200 Units, followed by 100 Units each hour to maintain catheter patency. Oxygenation, acid base state and hemodynamic status were assessed for deviations (>15%) from initial baseline measures taken prior to instrumentation and an appropriate stabilization period was employed. Animals randomized to Group 2 received propranolol 2mg/kg IV bolus to induce biventricular failure. Propranolol 1 mg/kg was administered each hour to ensure continued β blockade.

All physiologic data was recorded on three systems. A conventional eight channel graphic recorder (Gould 2800, Cleveland, OH) was used to record ECG and pressure data. These data were simultaneously recorded on the hard drive of a 486 Compaq computer using the Data Acquisition and Analysis System (DASA, Gould, Cleveland, OH). This system has a 16 channel analog to digital converter with a sampling rate of 50kHz. The Explorer (Baxter Healthcare Corp, Santa Ana, CA) captured thermodilution CO and RVEDV. All data were analyzed off line. Additional calculation of derived variables was performed by a standard computer spreadsheet program (Clarisworks, Claris Corporation, Santa Clara, CA).
Protocol

Following instrumentation, each subject was randomly exposed to four ventilatory permutations, which included: 1) spontaneous ventilation (t-piece), 2) spontaneous ventilation through an in-line 3 millimeter resistor (Resistor), 3) PS 5 cm. and 4) CPAP 5 cm. Random exposure to the ventilatory permutations ensured that obtained results were not due to an order effect or secondary to changes over time. The spontaneous ventilation permutation (t-piece) consisted of ventilation via the tracheotomy tube with supplemental oxygen administered through a t-piece as required to maintain hemoglobin saturation ≥ 94%. The resistor permutation involved spontaneous ventilation via a 3 mmID endotracheal tube attached to the existing tracheotomy tube. Again, supplemental oxygen was administered as necessary. CPAP 5 cm was administered by the Bennett 7200ae and consisted of an airway pressure of 5 cm H₂O above atmospheric pressure throughout the spontaneous duty cycle. PS 5 cm, was also delivered by the Bennett 7200ae and consisted of the application of 5 cm H₂O inspiratory pressure support during spontaneous ventilation.

Data collection was identical for each of the four permutations (Figure 3.). Blood pressure, heart rate and core body temperature were continuously monitored to determine the condition of the subject. Baseline pressure and volume values were obtained on controlled MV prior to each permutation. Pressure data were collected continuously during the first 5 minute period of each permutation to describe the transition period from MV to each permutation. Following the 5 minute transition period, volumetric and pressure data were then obtained for comparison to baseline values. Arterial blood gases were analyzed prior to each permutation and ten minutes after
return to baseline MV to ensure adequate alveolar ventilation. A minimum stabilization period of 20 minutes between each permutation ensured the measured parameters return to baseline mechanical ventilation values prior to the next ventilatory permutation.
Figure 3. Data Collection Time Line For One Permutation

MV = mechanical ventilation
ABG = arterial blood gas
PAOP = pulmonary artery occlusion pressure
CO = cardiac output
Data Analysis

Data were analyzed off line using the Data Acquisition and Analysis program (Gould, Cleveland, OH). Derived variables were calculated from standard mathematical formulas (Appendix B) placed in a standard computer spreadsheet (Clarisworks, Santa Clara, CA). Statistical analyses were performed by standard statistical computer packages (BMDP, Minitab).

Unpaired t-tests, were used to compare Group 1 and Group 2 means. For analysis purposes, each ventilatory permutation was considered a separate experiment, since each included a new baseline value. This allowed each subject to be its' own control. Mean baseline values were compared with mean values obtained following the transition to the permutation by repeated measures analysis of variance (ANOVA-RM). ANOVA-RM was used to identify the presence of main effects and/or interactions between group and time. If main effects were detected, paired t-tests were used to determine which means were significantly different from baseline. Significance level for this study was set a priori at the $\alpha = .05$ level and a Bonferroni correction was employed when multiple t-tests were used.
CHAPTER IV
RESULTS

Introduction

The focus of this study was to describe the changes in right heart hemodynamics associated with the transition from MV to SpV. Figure 1. displays the relationships between the major dependent variables. To review, cardiac output is the product of the heart rate and stroke volume. Stroke volume is determined by the preload, afterload and degree of contractility of the ventricle. In this study, right ventricular end-diastolic volume was the measure of preload, pulmonary vascular resistance the measure of afterload and right ventricular stroke work the measure of contractility. These variables were measured during a baseline period of MV and again following a 5 minute transition period of each of four ventilatory permutations (T-piece, Resistor, PS, CPAP).

The results of this investigation will be presented as follows: (a) description of the sample; (b) changes in cardiac output; (c) changes in heart rate; (d) changes in stroke volume; (e) changes in preload; (f) changes in afterload; and (g) changes in contractility.

Description of Sample

The sample consisted of 20 unconditioned, male, heartworm free, anesthetized canines randomly place into two groups. Group 1 animals were studied with normal biventricular function; while Group 2 subjects received propranolol to induce biventricular heart failure. General characteristics of
the canines are presented in Table 1. When the mean weight, length and body surface area (BSA) of the two groups were compared, the groups were not significantly different as shown in Table 2.

Table 1.
General Characteristics of the Sample

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<tr>
<td>14</td>
<td>1</td>
<td>22.27 kg</td>
<td>39 in</td>
<td>0.80 M²</td>
</tr>
<tr>
<td>15</td>
<td>1</td>
<td>23.18 kg</td>
<td>39 in</td>
<td>0.82 M²</td>
</tr>
<tr>
<td>16</td>
<td>1</td>
<td>22.27 kg</td>
<td>38 in</td>
<td>0.80 M²</td>
</tr>
<tr>
<td>17</td>
<td>2</td>
<td>21.82 kg</td>
<td>39 in</td>
<td>0.79 M²</td>
</tr>
<tr>
<td>18</td>
<td>1</td>
<td>22.27 kg</td>
<td>41 in</td>
<td>0.80 M²</td>
</tr>
<tr>
<td>19</td>
<td>2</td>
<td>23.18 kg</td>
<td>40 in</td>
<td>0.82 M²</td>
</tr>
<tr>
<td>20</td>
<td>2</td>
<td>24.09 kg</td>
<td>40 in</td>
<td>0.85 M²</td>
</tr>
</tbody>
</table>

Group:
Group 1 = normal ventricular function
Group 2 = propranolol induced

Weight : kg = kilograms
Length : in = inches
BSA : M² = square meters

BSA = K x W²/3 x 10⁴ with K = to 10.1 for canines and W = body weight in grams
### Table 2.
Comparison of Group 1 and Group 2 Mean Weight, Mean Length and Mean Body Surface Area

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I</th>
<th>Group II</th>
<th>df</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>23.00 kg</td>
<td>23.23 kg</td>
<td>17</td>
<td>0.46</td>
<td>0.65</td>
</tr>
<tr>
<td>SD</td>
<td>± 1.22 kg</td>
<td>± 1.02 kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length</td>
<td>40.1 in</td>
<td>40.7 in</td>
<td>17</td>
<td>0.85</td>
<td>0.41</td>
</tr>
<tr>
<td>SD</td>
<td>± 1.60 in</td>
<td>± 1.57 in</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSA</td>
<td>0.82 M²</td>
<td>0.81 M²</td>
<td>15</td>
<td>-0.59</td>
<td>0.57</td>
</tr>
<tr>
<td>SD</td>
<td>± 0.03 M²</td>
<td>± 0.04 M²</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Group:**
- Group 1 = normal biventricular function
- Group 2 = propranolol induced biventricular failure

Weight in kg = kilograms
Length in in = inches
BSA in M² = body surface area in square meters

**Subject Ventilatory Parameters and Arterial Blood Gases**

All subjects received controlled mechanical ventilation via a size 9.0 mm. inner diameter endotracheal tube introduced through a tracheotomy. Controlled mechanical ventilation was administered by a Bennett 7200ae microprocessor controlled ventilator. During the experiments, ventilator settings were adjusted to maintain baseline arterial blood gases within preset limits. The ventilator settings required by the subjects to maintain physiologic arterial blood gases are listed in Table 3. When the mean $V_t$, $F_iO_2$ and respiratory rate ($f$) required to maintain stable arterial blood gases in the two groups were compared, the settings were similar as shown in Table 4.
### Table 3.

**Ventilator Setting for the Sample**

<table>
<thead>
<tr>
<th>Canine</th>
<th>Group</th>
<th>VT</th>
<th>FiO2</th>
<th>f</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>2</td>
<td>.53 L</td>
<td>0.30</td>
<td>11</td>
</tr>
<tr>
<td>02</td>
<td>1</td>
<td>.54 L</td>
<td>0.21</td>
<td>11</td>
</tr>
<tr>
<td>03</td>
<td>1</td>
<td>.54 L</td>
<td>0.21</td>
<td>11</td>
</tr>
<tr>
<td>04</td>
<td>2</td>
<td>.51 L</td>
<td>0.21</td>
<td>10</td>
</tr>
<tr>
<td>05</td>
<td>1</td>
<td>.50 L</td>
<td>0.28</td>
<td>11</td>
</tr>
<tr>
<td>06</td>
<td>2</td>
<td>.52 L</td>
<td>0.21</td>
<td>10</td>
</tr>
<tr>
<td>07</td>
<td>2</td>
<td>.53 L</td>
<td>0.25</td>
<td>10</td>
</tr>
<tr>
<td>08</td>
<td>1</td>
<td>.54 L</td>
<td>0.25</td>
<td>12</td>
</tr>
<tr>
<td>09</td>
<td>2</td>
<td>.53 L</td>
<td>0.25</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>.53 L</td>
<td>0.26</td>
<td>10</td>
</tr>
<tr>
<td>11</td>
<td>1</td>
<td>.53 L</td>
<td>0.25</td>
<td>10</td>
</tr>
<tr>
<td>12</td>
<td>1</td>
<td>.52 L</td>
<td>0.27</td>
<td>10</td>
</tr>
<tr>
<td>13</td>
<td>2</td>
<td>.52 L</td>
<td>0.25</td>
<td>10</td>
</tr>
<tr>
<td>14</td>
<td>1</td>
<td>.47 L</td>
<td>0.25</td>
<td>10</td>
</tr>
<tr>
<td>15</td>
<td>1</td>
<td>.50 L</td>
<td>0.30</td>
<td>11</td>
</tr>
<tr>
<td>16</td>
<td>1</td>
<td>.50 L</td>
<td>0.30</td>
<td>10</td>
</tr>
<tr>
<td>17</td>
<td>2</td>
<td>.50 L</td>
<td>0.25</td>
<td>10</td>
</tr>
<tr>
<td>18</td>
<td>1</td>
<td>.47 L</td>
<td>0.25</td>
<td>10</td>
</tr>
<tr>
<td>19</td>
<td>2</td>
<td>.50 L</td>
<td>0.25</td>
<td>10</td>
</tr>
<tr>
<td>20</td>
<td>2</td>
<td>.50 L</td>
<td>0.25</td>
<td>10</td>
</tr>
</tbody>
</table>

**Group:**
- Group 1 = normal biventricular function
- Group 2 = propranolol induced biventricular failure

**VT:** $L = \text{liters}$

**FiO2:** fraction of inspired oxygen

**f:** breaths/minute
Table 4.

Comparison of Group 1 and Group 2 Ventilator Settings

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1</th>
<th>Group 2</th>
<th>df</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vt</td>
<td>0.511 L</td>
<td>0.517 L</td>
<td>13</td>
<td>0.62</td>
<td>0.54</td>
</tr>
<tr>
<td></td>
<td>± 0.0273</td>
<td>± 0.0134</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FiO2</td>
<td>0.257</td>
<td>0.248</td>
<td>17</td>
<td>-0.70</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td>± 0.0316</td>
<td>± 0.0253</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>f</td>
<td>10.6 b/m</td>
<td>10.1 b/m</td>
<td>12</td>
<td>-2.06</td>
<td>0.062</td>
</tr>
<tr>
<td></td>
<td>± 0.699</td>
<td>± 0.316</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Group:
- Group 1 = normal biventricular function
- Group 2 = propranolol induced biventricular failure

Group values are mean ± standard deviation.

Vt in L = tidal volume in liters/minute
FiO2 = fraction of inspired oxygen
f in b/m = frequency in breaths/minute

A minimum of five arterial blood gases were obtained from each subject. Arterial blood gases were collected and measured immediately following placement of the femoral arterial catheter and prior to baseline data collection in each of the four permutations. The two groups did not exhibit significant differences in mean baseline values of pH, PaO2, PaCO2 or HCO3 as shown in Table 5.
Table 5.
Comparison of Group 1 and Group 2 Mean Baseline Arterial Blood Gas

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1</th>
<th>Group 2</th>
<th>df</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.307 ± 0.037</td>
<td>7.313 ± 0.0496</td>
<td>90</td>
<td>0.73</td>
<td>0.47</td>
</tr>
<tr>
<td>PaO2</td>
<td>110.42 ± 18.0</td>
<td>107.2 ± 18.3</td>
<td>97</td>
<td>-0.89</td>
<td>0.38</td>
</tr>
<tr>
<td>PaCO2</td>
<td>38.47 ± 4.37</td>
<td>37.11 ± 5.09</td>
<td>95</td>
<td>-1.4</td>
<td>0.15</td>
</tr>
<tr>
<td>HCO3</td>
<td>18.73 ± 1.31</td>
<td>18.44 ± 2.39</td>
<td>75</td>
<td>-0.75</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Group:
- Group 1 = normal biventricular function
- Group 2 = propranolol induced biventricular failure

PaO2 = partial pressure of oxygen in millimeters of mercury
PaCO2 = partial pressure of carbon dioxide in millimeters of mercury
HCO3 = milliequivalents per liter

Efficacy of Propranolol Model of Biventricular Heart Failure

Administration of an intravenous bolus of the β adrenergic antagonist, propranolol, 2mg/kg., followed by 1mg/kg. hourly doses achieved a clinically significant degree of biventricular failure in Group 2 subjects. Table 6 illustrates that Group 2 subjects' mean CO, SV, RVEF and MAP were reduced; while mean MPAP, PAOP, PVR and SVR were increased when compared to Group 1 subjects. Mean HR and RVSW values were not different between the groups. These hemodynamic changes are commonly detected in humans with heart failure and are consistent with hemodynamic changes developed in a rapid pacing model of biventricular heart failure (O'Brien, Ianuzzo, Moe, Stopps, & Armstrong, 1990). Statistical significance was not reached due to small sample size and the degree of variability.
### Table 6.

Comparison of Group 1 and Group 2 Mean Cardiac Output, Mean Stroke Volume, Mean Heart Rate, Mean Right Ventricular Ejection Fraction, Mean Mean Arterial Pressure, Mean Pulmonary Artery Pressure, Mean Pulmonary Artery Occlusion Pressure, Mean Pulmonary Vascular Resistance, Mean Systemic Vascular Resistance and Mean Right Ventricular Stroke Work

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I</th>
<th>Group II</th>
<th>df</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO</td>
<td>2.84 L.</td>
<td>2.2 L.</td>
<td>18</td>
<td>1.68</td>
<td>0.111</td>
</tr>
<tr>
<td>SD</td>
<td>± 1.03</td>
<td>± 0.645</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SV</td>
<td>28.9 ml.</td>
<td>20.9 ml.</td>
<td>18</td>
<td>1.6</td>
<td>0.126</td>
</tr>
<tr>
<td>SD</td>
<td>± 13.15</td>
<td>± 8.71</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>104.3 BPM</td>
<td>110.5 BPM</td>
<td>18</td>
<td>-0.58</td>
<td>0.57</td>
</tr>
<tr>
<td>SD</td>
<td>± 20.47</td>
<td>± 27.02</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVEF</td>
<td>0.355</td>
<td>0.292</td>
<td>18</td>
<td>1.26</td>
<td>0.57</td>
</tr>
<tr>
<td>SD</td>
<td>± 0.113</td>
<td>± 0.103</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP</td>
<td>132.8 mm.</td>
<td>120.6 mm.</td>
<td>18</td>
<td>1.6</td>
<td>0.127</td>
</tr>
<tr>
<td>SD</td>
<td>± 14.34</td>
<td>± 19.34</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPAP</td>
<td>22.6 mm.</td>
<td>26.1 mm.</td>
<td>18</td>
<td>-1.13</td>
<td>0.275</td>
</tr>
<tr>
<td>SD</td>
<td>± 6.81</td>
<td>± 7.15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAOP</td>
<td>10.9 mm.</td>
<td>13.7 mm.</td>
<td>18</td>
<td>-0.77</td>
<td>0.453</td>
</tr>
<tr>
<td>SD</td>
<td>± 8.11</td>
<td>± 8.28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVR</td>
<td>375 dynes</td>
<td>448.5 dynes</td>
<td>18</td>
<td>-0.76</td>
<td>0.453</td>
</tr>
<tr>
<td>SD</td>
<td>± 227.7</td>
<td>± 201.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVR</td>
<td>4191 dynes</td>
<td>4755 dynes</td>
<td>18</td>
<td>-0.71</td>
<td>0.487</td>
</tr>
<tr>
<td>SD</td>
<td>± 1630</td>
<td>± 1920</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVSW</td>
<td>7.75 gm.</td>
<td>7.05 gm.</td>
<td>18</td>
<td>0.50</td>
<td>0.621</td>
</tr>
<tr>
<td>SD</td>
<td>± 2.23</td>
<td>± 3.79</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

L. = Liters/minute  
m. = mmHg  
ml. = milliliters/minute  
dynes = dynes/sec/cm^5  
gm. = gram meters/beat  
BPM = beats/minute  
Group 1 = normal biventricular function  
Group 2 = propranolol induced biventricular failure
Changes in Cardiac Output

Baseline values of mean CO for the four ventilatory conditions were similar in Group 1. Group 1 subjects experienced a significant increase in mean CO with T-piece, Resistor and CPAP as shown in Figure 4. Transition to T-piece increased mean CO by 0.777 L/min.; while Resistor produced an average increase of 1.009 L/min. and CPAP a mean increase of 0.663 L/min. Group 2 subjects also demonstrated similar values of mean CO at baseline for the four ventilatory conditions. Group 2 subjects demonstrated similar statistically significant changes in mean CO with T-piece, Resistor and CPAP as shown in Figure 5. Following transition to T-piece, the mean CO increased by 0.415 L/min.; while Resistor produced a 0.426 L/min. increase and CPAP resulted in a mean increase of 0.223 L/min. Mean CO with PS was not significantly altered in either group. Significant interactions were identified between group and time for the variable mean CO during Resistor (p = 0.05) and CPAP (p = 0.003). Table 7. presents mean CO values ± standard deviation for both groups at baseline and following transition to each of the four permutations.

CI is the CO per square meter of BSA. This value standardizes the CO for body size which allows hemodynamic variables from subjects of different body size to be compared. CI in Group 1 subjects again differed significantly from baseline with T-piece, Resistor and CPAP as shown in Figure 6. Transition to T-piece increased mean CI by 0.981 L/min.; while Resistor produced a mean increase of 1.245 L/min. and CPAP a mean increase of 0.815 L/min. Group 2 subjects also differed significantly from baseline with T-piece, Resistor and CPAP as shown in Figure 7. With transition to T-piece, mean CI increased by 0.515 L/min.; while Resistor produced a 0.529 L/min.
increase and CPAP resulted in an increase of 0.276 L/min. Again, mean CI with PS was not significantly altered in either group. Significant interactions were identified between group and time for the variable mean Cl during Resistor ($p = 0.05$) and CPAP ($p = 0.004$). Group means ± standard deviations of Cl are presented in Table 8. An increase in CO/Cl may be the result of either an increase in heart rate and/or an increase in stroke volume.
Figure 4. Group 1 Cardiac Output Changes

* $p < 0.0001$ compared with baseline value

** $p = 0.0006$ compared with baseline value

*** $p = 0.0001$ compared with baseline value

$n = 10$
Figure 5. Group 2 Cardiac Output Changes

- * p = 0.03 compared with baseline value
- ** p = 0.05 compared with baseline value
- *** p = 0.02 compared with baseline value

n = 10
## Table 7.

### Group 1 and Group 2 Mean Cardiac Output at Baseline and After Transition to Spontaneous Ventilation, Spontaneous Ventilation with a Resistor, Pressure Support and Continuous Positive Airway Pressure

<table>
<thead>
<tr>
<th>Group 1</th>
<th>T-piece</th>
<th>Resistor</th>
<th>PS</th>
<th>CPAP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>2.836 L</td>
<td>2.926 L</td>
<td>2.691 L</td>
<td>2.889 L</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>± 1.026</td>
<td>± 0.785</td>
<td>± 0.805</td>
<td>± 1.023</td>
</tr>
<tr>
<td><strong>Permutation</strong></td>
<td>3.64 L *</td>
<td>3.935 L **</td>
<td>2.806 L</td>
<td>3.552 L ***</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>± 1.172</td>
<td>± 0.676</td>
<td>± 0.848</td>
<td>± 1.197</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 2</th>
<th>T-piece</th>
<th>Resistor</th>
<th>PS</th>
<th>CPAP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>2.194 L</td>
<td>2.325 L</td>
<td>2.301 L</td>
<td>2.206 L</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>± 0.645</td>
<td>± 0.723</td>
<td>± 0.458</td>
<td>± 0.692</td>
</tr>
<tr>
<td><strong>Permutation</strong></td>
<td>2.609 L †</td>
<td>2.751 L ††</td>
<td>2.252 L</td>
<td>2.429 L †††</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>± 0.946</td>
<td>± 1.241</td>
<td>± 0.466</td>
<td>± 0.853</td>
</tr>
</tbody>
</table>

*  p < 0.0001 compared with baseline value
** p = 0.0006 compared with baseline value
*** p = 0.0001 compared with baseline value
†  p = 0.03  compared with baseline value
†† p = 0.05  compared with baseline value
††† p = 0.02  compared with baseline value

Group values are mean ± standard deviation.

**Group:**
- Group 1 = normal biventricular function
- Group 2 = propranolol induced biventricular failure

**L = liters/minute**

**T-piece = spontaneous ventilation**

**Resistor = spontaneous ventilation with resistor**

**PS = pressure support 5cm.**

**CPAP = continuous positive airway pressure 5 cm.**
Baseline a Permutation C i

Resistor T-piece Ventilatory Status

p = < 0.001 compared with baseline value
p = 0.0007 compared with baseline value
p = 0.0001 compared with baseline value

Figure 6. Group 1 Cardiac Index Changes
**Figure 7.** Group 2 Cardiac Index Changes

- **Baseline Cl**: T-piece
- **Permutation Cl**: Resistor, PS, CPAP

- **T-piece**: Cardiac Index = 2.7
- **Resistor**: Cardiac Index = 3.2
- **PS**: Cardiac Index = 2.8
- **CPAP**: Cardiac Index = 2.7

- * p = 0.03 compared with baseline value
- ** * p = 0.05 compared with baseline value

*n = 10*
Table 8.

Group 1 and Group 2 Mean Cardiac Index at Baseline and After Transition to Spontaneous Ventilation, Spontaneous Ventilation with a Resistor, Pressure Support and Continuous Positive Airway Pressure

<table>
<thead>
<tr>
<th>Group 1</th>
<th>T-piece</th>
<th>Resistor</th>
<th>PS</th>
<th>CPAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>3.469 L</td>
<td>3.565 L</td>
<td>3.28 L</td>
<td>3.521 L</td>
</tr>
<tr>
<td>SD</td>
<td>± 1.249</td>
<td>± 0.912</td>
<td>± 0.934</td>
<td>± 1.214</td>
</tr>
<tr>
<td>Permutation</td>
<td>4.452 L *</td>
<td>4.81 L **</td>
<td>3.419 L</td>
<td>4.338 L ***</td>
</tr>
<tr>
<td>SD</td>
<td>± 1.4314</td>
<td>± 0.795</td>
<td>± 0.986</td>
<td>± 1.445</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 2</th>
<th>T-piece</th>
<th>Resistor</th>
<th>PS</th>
<th>CPAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>2.666 L</td>
<td>2.828 L</td>
<td>2.799 L</td>
<td>2.681 L</td>
</tr>
<tr>
<td>SD</td>
<td>± 0.805</td>
<td>± 0.919</td>
<td>± 0.612</td>
<td>± 0.867</td>
</tr>
<tr>
<td>Permutation</td>
<td>3.182 L †</td>
<td>3.358 L ††</td>
<td>2.737 L</td>
<td>2.957 L †</td>
</tr>
<tr>
<td>SD</td>
<td>± 1.213</td>
<td>± 1.582</td>
<td>± 0.607</td>
<td>± 1.074</td>
</tr>
</tbody>
</table>

* p < 0.0001 compared with baseline value
** p = 0.0007 compared with baseline value
*** p = 0.0001 compared with baseline value
† p = 0.03 compared with baseline value
†† p = 0.05 compared with baseline value

Group values are mean ± standard deviation.

Group:
Group 1 = normal biventricular function
Group 2 = propranolol induced biventricular failure
L = liters/minute/M²
T-piece = spontaneous ventilation
Resistor = spontaneous ventilation with resistor
PS = pressure support 5 cm.
CPAP = continuous positive airway pressure 5 cm.
Changes in Heart Rate

Baseline mean HR was similar in both groups. There were no statistically significant changes in heart rate in either Group 1 or Group 2 with any of the four permutations as shown in Figure 8 and Figure 9 respectively. Group 1 subjects increased mean HR by 7.2 beats/min with T-piece, by 15.8 beats/min with Resistor, by 3.3 beats/min with PS and decreased mean HR by 0.5 beats/min. with CPAP. Group 2 subjects increased mean HR by 5.2 beats/min with Resistor and 1 beat/min with CPAP, but decreased mean HR by 2.6 beats/min. with T-piece and 1.1 beats/min. with PS. Group means ± standard deviations of heart rate are presented in Table 9. These findings indicated the increases in CO were not primarily the consequence of changes in heart rate.
Figure 8. Group 1 Heart Rate Changes
Figure 9. Group 2 Heart Rate Changes
Table 9.

Group 1 and Group 2 Mean Heart Rate at Baseline and After Transition to Spontaneous Ventilation, Spontaneous Ventilation with a Resistor, Pressure Support and Continuous Positive Airway Pressure

<table>
<thead>
<tr>
<th></th>
<th>T-piece</th>
<th>Resistor</th>
<th>PS</th>
<th>CPAP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>104.3 bpm</td>
<td>94.1 bpm</td>
<td>102.8 bpm</td>
<td>115.3 bpm</td>
</tr>
<tr>
<td>SD</td>
<td>± 20.47</td>
<td>± 21.12</td>
<td>± 24.1</td>
<td>± 37.9</td>
</tr>
<tr>
<td>Permutation</td>
<td>111.5 bpm</td>
<td>109.9 bpm</td>
<td>106.1 bpm</td>
<td>114.8 bpm</td>
</tr>
<tr>
<td>SD</td>
<td>± 30.96</td>
<td>± 20.9</td>
<td>± 18.41</td>
<td>± 34.6</td>
</tr>
<tr>
<td><strong>Group 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>110.5 bpm</td>
<td>106.6 bpm</td>
<td>108.8 bpm</td>
<td>107.0 bpm</td>
</tr>
<tr>
<td>SD</td>
<td>± 27.02</td>
<td>± 21.2</td>
<td>± 21.63</td>
<td>± 19.49</td>
</tr>
<tr>
<td>Permutation</td>
<td>107.9 bpm</td>
<td>111.8 bpm</td>
<td>107.7 bpm</td>
<td>108.0 bpm</td>
</tr>
<tr>
<td>SD</td>
<td>± 22.4</td>
<td>± 17.66</td>
<td>± 19.69</td>
<td>± 19.8</td>
</tr>
</tbody>
</table>

Group values are mean ± standard deviation.

Group:
Group 1 = normal biventricular function
Group 2 = propranolol induced biventricular failure

bpm = beats/minute

T-piece = spontaneous ventilation
Resistor = spontaneous ventilation with resistor
PS = pressure support 5cm.
CPAP = continuous positive airway pressure 5 cm.
changes in stroke volume

Baseline values of mean SV for the four ventilatory conditions were similar in Group 1. Group 1 subjects significantly increased mean SV with T-piece and CPAP as shown in Figure 10. Mean SV increased by 6.2 ml. with T-piece and 5.8 ml. with CPAP. Although Resistor increased mean SV by 4.4 ml, this increase was not statistically significant (p = 0.08). PS produced an insignificant mean increase in mean SV. Baseline values of mean SV for the four ventilatory conditions were similar for Group 2. Group 2 significantly increased mean SV only during T-piece as shown in Figure 11. T-piece produced a mean SV increase of 4.7 ml; while Resistor resulted in a 2.9 ml increase, PS a 0.3 ml decrease and CPAP a 2.1 ml increase in mean SV. Group means ± standard deviations of stroke volume are presented in Table 10.

Mean stroke volume index was significantly increased in Group 1 subjects with T-piece and CPAP as shown in Figure 12. Mean SVI increased by 7.49 ml. with T-piece and 6.99 ml. with CPAP; while Resistor increased mean SVI by 5.3 ml and PS produced an insignificant decrease. Group 2 subjects significantly increased mean SVI only with T-piece as shown in Figure 13. Mean SVI increased on average by 5.81 ml. with T-piece, 3.62 ml. with Resistor, 2.55 ml. with CPAP and decreased mean SVI by an average of 0.38 ml. with PS. Group means ± standard deviations of mean stroke volume index are presented in Table 11. There were no group by time interactions for the variables SV and SVI. These findings indicate the increases seen in CO were primarily due to the augmentation of stroke volume. Stroke volume is determined by preload, afterload and contractility.
Figure 10. Group 1 Stroke Volume Changes

- Baseline SV
- Permutation SV

T-piece Resistor PS CPAP

ml/beat

50
40
30
20
10
0

Stroke Volume

Ventilatory Status

n = 10

*p = 0.009 compared with baseline value

**p = 0.03 compared with baseline value
Figure 11. Group 2 Stroke Volume Changes

* $p = 0.006$ compared with baseline value  

$n = 10$
Table 10.

**Group 1 and Group 2 Mean Stroke Volume at Baseline and After Transition to Spontaneous Ventilation, Spontaneous Ventilation with a Resistor.**

Pressure Support and Continuous Positive Airway Pressure

<table>
<thead>
<tr>
<th></th>
<th>T-piece</th>
<th>Resistor</th>
<th>PS</th>
<th>CPAP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>28.9 ml</td>
<td>32.7 ml</td>
<td>28.1 ml</td>
<td>27.9 ml</td>
</tr>
<tr>
<td>SD</td>
<td>± 13.15</td>
<td>± 11.97</td>
<td>± 10.77</td>
<td>± 13.41</td>
</tr>
<tr>
<td>Permutation</td>
<td>35.1 ml *</td>
<td>37.1 ml</td>
<td>28.2 ml</td>
<td>33.7 ml **</td>
</tr>
<tr>
<td>SD</td>
<td>± 14.49</td>
<td>± 9.59</td>
<td>± 12.15</td>
<td>± 16.02</td>
</tr>
<tr>
<td><strong>Group 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>20.9 ml</td>
<td>23.00 ml</td>
<td>21.7 ml</td>
<td>21.2 ml</td>
</tr>
<tr>
<td>SD</td>
<td>± 8.71</td>
<td>± 8.83</td>
<td>± 5.64</td>
<td>± 8.07</td>
</tr>
<tr>
<td>Permutation</td>
<td>25.6 ml †</td>
<td>25.9 ml</td>
<td>21.4 ml</td>
<td>23.3 ml</td>
</tr>
<tr>
<td>SD</td>
<td>±10.89</td>
<td>±12.42</td>
<td>± 4.84</td>
<td>± 9.17</td>
</tr>
</tbody>
</table>

* p = 0.009 compared with baseline value
** p = 0.03 compared with baseline value
† p = 0.006 compared with baseline value

Group values are mean ± standard deviation.

**Group:**
- Group 1 = normal biventricular function
- Group 2 = propranolol induced biventricular failure

ml = milliliters/minute

T-piece = spontaneous ventilation
Resistor = spontaneous ventilation with resistor
PS = pressure support 5 cm.
CPAP = continuous positive airway pressure 5 cm.
Figure 12. Group 1 Stroke Volume Index Changes
Figure 13. Group 2 Stroke Volume Index Changes

* $p = 0.006$ compared with baseline value  

$n = 10$
Table 11.

Group 1 and Group 2 Mean Stroke Volume Index at Baseline and After Transition to Spontaneous Ventilation, Spontaneous Ventilation with a Resistor, Pressure Support and Continuous Positive Airway Pressure

<table>
<thead>
<tr>
<th></th>
<th>T-piece</th>
<th>Resistor</th>
<th>PS</th>
<th>CPAP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td>35.4 ml</td>
<td>39.92 ml</td>
<td>34.26 ml</td>
<td>34.01 ml</td>
</tr>
<tr>
<td>SD</td>
<td>± 16.09</td>
<td>± 14.47</td>
<td>± 12.92</td>
<td>± 16.18</td>
</tr>
<tr>
<td><strong>Permutation</strong></td>
<td>42.89 ml*</td>
<td>45.22 ml</td>
<td>34.39 ml</td>
<td>41.00 ml **</td>
</tr>
<tr>
<td>SD</td>
<td>± 17.67</td>
<td>± 10.98</td>
<td>± 14.64</td>
<td>± 18.99</td>
</tr>
<tr>
<td><strong>Group 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td>25.35 ml</td>
<td>27.92 ml</td>
<td>26.36 ml</td>
<td>25.74 ml</td>
</tr>
<tr>
<td>SD</td>
<td>±10.57</td>
<td>± 10.95</td>
<td>± 7.27</td>
<td>± 9.98</td>
</tr>
<tr>
<td><strong>Permutation</strong></td>
<td>31.16 ml †</td>
<td>31.54 ml</td>
<td>25.98 ml</td>
<td>28.29 ml</td>
</tr>
<tr>
<td>SD</td>
<td>±13.55</td>
<td>± 15.65</td>
<td>± 6.18</td>
<td>± 11.22</td>
</tr>
</tbody>
</table>

* p = 0.009 compared with baseline value
** p = 0.03 compared with baseline value
† p = 0.006 compared with baseline value

Group values are mean ± standard deviation.

Group:
- Group 1 = normal biventricular function
- Group 2 = propranolol induced biventricular failure

ml = milliliters/minute/M²

T-piece = spontaneous ventilation
Resistor = spontaneous ventilation with resistor
PS = pressure support 5cm.
CPAP = continuous positive airway pressure 5 cm.
Changes in Preload

The computer algorithm which calculates right ventricular ejection fraction and right ventricular volumes does not function when heart rate exceeds 140 beats per minute. Four of the twenty subjects experienced significant tachycardia during data collection which resulted in missing volumetric data for these subjects. The remaining 16 subjects (8 subjects in each group) were included in the analysis of volumetric data.

Group 1 baseline values of mean RVEDV were similar for the four ventilatory conditions. Group 1 subjects significantly increased mean RVEDV with T-piece and Resistor as shown in Figure 14. Mean RVEDV increased by 17 ml. with T-piece and 24.1 ml. with Resistor. PS produced a 0.7 ml mean increase in RVEDV; while CPAP increased RVEDV on average by 2.26 ml. Group 2 baseline values of mean RVEDV were similar for the four ventilatory conditions. Group 2 significantly increased mean RVEDV only during Resistor as shown in Figure 15. T-piece produced a mean RVEDV increase of 4.99 ml; while Resistor resulted in a 12.87 ml increase and CPAP a 15 ml increase in mean RVEDV. PS produced a small 3.38 ml. mean decrease in RVEDV. Although CPAP produced the largest volume change in Group 2, this increase was not statistically significant ($p = 0.10$). Group means ± standard deviations of RVEDV are presented in Table 12.

Mean RVEDVI was significantly increased in Group 1 subjects with T-piece and Resistor as shown in Figure 16. Mean RVEDVI increased by 20.9 ml. with T-piece and 29.3 ml. with Resistor; while PS increased mean RVEDVI by 1.2 ml and CPAP produced a 2.23 ml. mean increase. Group 2 subjects significantly increased mean RVEDVI only with Resistor as shown in Figure 17. Mean RVEDVI increased on average by 6.04 ml. with T-piece, 15.68
ml. with Resistor and 17.81 ml. with CPAP, but decreased by an average of 4.28 ml with PS. Group means ± standard deviations of mean RVEDVI are presented in Table 13. There were no significant group by time interactions for the variables mean RVEDV and mean RVEDVI.
Figure 14. Group 1 Right Ventricular End-Diastolic Volume Changes

* $p = 0.014$ compared with baseline value

** $p = 0.031$ compared with baseline value

$n = 8$
Figure 15. Group 2 Right Ventricular End-Diastolic Volume Changes
Table 12.

Group 1 and Group 2 Mean Right Ventricular End-Diastolic Volume at Baseline and After Transition to Spontaneous Ventilation, Spontaneous Ventilation with a Resistor, Pressure Support and Continuous Positive Airway Pressure

<table>
<thead>
<tr>
<th></th>
<th>T-piece</th>
<th>Resistor</th>
<th>PS</th>
<th>CPAP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td>80.3 ml</td>
<td>89.9 ml</td>
<td>78.3 ml</td>
<td>91.62 ml</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>±28.7</td>
<td>±33.7</td>
<td>± 29.2</td>
<td>± 17.57</td>
</tr>
<tr>
<td><strong>Permutation</strong></td>
<td>97 ml *</td>
<td>114 ml **</td>
<td>79 ml</td>
<td>93.88 ml</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>± 31.2</td>
<td>± 42.3</td>
<td>± 25.28</td>
<td>± 20.73</td>
</tr>
<tr>
<td><strong>Group 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td>80.63 ml</td>
<td>85.75 ml</td>
<td>79.62 ml</td>
<td>84.38 ml</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>±13.76</td>
<td>± 13.31</td>
<td>± 17.49</td>
<td>± 12.42</td>
</tr>
<tr>
<td><strong>Permutation</strong></td>
<td>85.62 ml</td>
<td>98.62 ml †</td>
<td>76.25 ml</td>
<td>99.38 ml</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>±15.24</td>
<td>± 15.09</td>
<td>± 13.83</td>
<td>± 19.35</td>
</tr>
</tbody>
</table>

* p = 0.014 compared with baseline value
** p = 0.031 compared with baseline value
† p = 0.025 compared with baseline value

Group values are mean ± standard deviation.
Group:
Group 1 = normal biventricular function
Group 2 = propranolol induced biventricular failure
ml = milliliters
T-piece = spontaneous ventilation
Resistor = spontaneous ventilation with resistor
PS = pressure support 5 cm.
CPAP = continuous positive airway pressure 5 cm.
Figure 16. Group 1 Right Ventricular End-Diastolic Volume Index Changes

**Baseline RV EDVI**  
**Permutation RV EDVI**

<table>
<thead>
<tr>
<th>Ventilatory Status</th>
<th>RV EDVI (ml/M²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-piece</td>
<td>98</td>
</tr>
<tr>
<td>Resistor</td>
<td>109</td>
</tr>
<tr>
<td>PS</td>
<td>95</td>
</tr>
<tr>
<td>CPAP</td>
<td>112</td>
</tr>
</tbody>
</table>

- * p = 0.01 compared with baseline value
- ** p = 0.03 compared with baseline value

n = 8
Figure 17. Group 2 Right Ventricular End-Diastolic Volume Index Changes

*p = 0.025 compared with baseline value  n = 8
Table 13.

Group 1 and Group 2 Mean Right Ventricular End-Diastolic Volume Index at Baseline and After Transition to Spontaneous Ventilation. Spontaneous Ventilation with a Resistor. Pressure Support and Continuous Positive Airway Pressure

<table>
<thead>
<tr>
<th>Airway Pressure</th>
<th>T-piece</th>
<th>Resistor</th>
<th>PS</th>
<th>CPAP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td>97.6 ml</td>
<td>109 ml</td>
<td>95 ml</td>
<td>111.8 ml</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>±34.7</td>
<td>±40.2</td>
<td>±35.1</td>
<td>±23.53</td>
</tr>
<tr>
<td><strong>Permutation</strong></td>
<td>118.5 ml*</td>
<td>138.3 ml **</td>
<td>96.2 ml</td>
<td>114.03 ml</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>±38.7</td>
<td>±50.8</td>
<td>±31.3</td>
<td>±24.12</td>
</tr>
<tr>
<td><strong>Group 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td>97.74 ml</td>
<td>104.1 ml</td>
<td>96.84 ml</td>
<td>102.53 ml</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>±16.12</td>
<td>±16.88</td>
<td>±25.25</td>
<td>±16.25</td>
</tr>
<tr>
<td><strong>Permutation</strong></td>
<td>103.78 ml</td>
<td>119.78 ml †</td>
<td>92.56 ml</td>
<td>120.34 ml</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>±18.12</td>
<td>±19.5</td>
<td>±17.24</td>
<td>±22.13</td>
</tr>
</tbody>
</table>

*  p = 0.01 compared with baseline value
**  p = 0.03 compared with baseline value
†  p = 0.025 compared with baseline value

Group values are mean ± standard deviation.

Group:
- Group 1 = normal biventricular function
- Group 2 = propranolol induced biventricular failure

ml = milliliters/M²

T-piece = spontaneous ventilation
Resistor = spontaneous ventilation with resistor
PS = pressure support 5cm.
CPAP = continuous positive airway pressure 5 cm.
Changes in Intrathoracic Pressure

The amount of blood returned to the right ventricle is influenced by the magnitude of the pressure gradient between the abdominal vena cava and the right ventricle. Since IT P is directly reflected on the heart, a reduction in IT P should lower right atrial pressure and augment this gradient. Esophageal pressure (Pes) measured by a balloon catheter placed in the distal third of the esophagus was the indirect measure of intrathoracic pressure for this study. Baseline mean Pes was similar for both groups. Group 1 subjects significantly reduced mean Pes during T-piece and Resistor as shown in Figure 18. Mean Pes decreased by 1.293 inches of water pressure with T-piece, by 1.868 inches with Resistor and by 0.605 inches with CPAP, but essentially did not change with PS. Group 2 subjects significantly reduced mean Pes with T-piece, Resistor and CPAP as shown in Figure 19. Mean Pes decreased by 1.33 inches of water pressure with T-piece, by 1.126 inches with Resistor and by 0.418 inches with CPAP, but again did not change with PS. Group means ± standard deviations of mean Pes are presented in Table 14. There were no significant group by time interactions for the variable mean Pes.
Baseline Pes

Permutation Pes

Ventilatory Status

CPAP

PS

Resistor

T-piece

Figure 18. Group 1 Mean Esophageal Pressure Changes

* p = 0.002 compared with baseline value

** p = 0.001 compared with baseline value

n = 10
Figure 19. Group 2 Mean Esophageal Pressure Changes

*  p = 0.001 compared with baseline value
** p = 0.003 compared with baseline value
*** p = 0.04 compared with baseline value

n = 10
Table 14.

Group 1 and Group 2 Mean Esophageal Pressure at Baseline and After Transition to Spontaneous Ventilation, Spontaneous Ventilation with a Resistor, Pressure Support and Continuous Positive Airway Pressure

<table>
<thead>
<tr>
<th></th>
<th>T-piece</th>
<th>Resistor</th>
<th>PS</th>
<th>CPAP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td>2.93 in</td>
<td>2.78 in</td>
<td>2.81 in</td>
<td>2.56 in</td>
</tr>
<tr>
<td>SD</td>
<td>±3.82</td>
<td>±3.61</td>
<td>±3.7</td>
<td>±3.57</td>
</tr>
<tr>
<td><strong>Permutation</strong></td>
<td>1.64 in *</td>
<td>0.92 in **</td>
<td>2.80</td>
<td>1.95 in</td>
</tr>
<tr>
<td>SD</td>
<td>±3.7</td>
<td>±3.59</td>
<td>±3.76</td>
<td>±3.75</td>
</tr>
<tr>
<td><strong>Group 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td>3.00 in</td>
<td>2.42 in</td>
<td>2.68 in</td>
<td>2.59 in</td>
</tr>
<tr>
<td>SD</td>
<td>±4.1</td>
<td>±3.36</td>
<td>±3.38</td>
<td>±3.45</td>
</tr>
<tr>
<td><strong>Permutation</strong></td>
<td>1.67 in *</td>
<td>1.30 in †</td>
<td>2.67 in</td>
<td>2.17 in ††</td>
</tr>
<tr>
<td>SD</td>
<td>±3.92</td>
<td>±3.63</td>
<td>±3.84</td>
<td>±3.56</td>
</tr>
</tbody>
</table>

* p = 0.002 compared with baseline value
** p = 0.001 compared with baseline value
† p = 0.003 compared with baseline value
†† p = 0.04 compared with baseline value

Group values are mean ± standard deviation.

Group:
- Group 1 = normal biventricular function
- Group 2 = propranolol induced biventricular failure

in = inches of water pressure
T-piece = spontaneous ventilation
Resistor = spontaneous ventilation with resistor
PS = pressure support 5 cm.
CPAP = continuous positive airway pressure 5 cm.
Changes in Abdominal Pressure

In addition to ITP changes, abdominal pressure (Pab) changes may also influence the pressure gradient for venous return. Diaphragm descent not only reduces ITP, it also potentially increases abdominal pressure as the diaphragm moves downward. For this study, abdominal pressure was measured by a balloon catheter placed superior and posterior to the liver via an abdominal incision. A two layer suture closure was employed to ensure the abdominal cavity was tightly closed and abdominal pressure values would accurately represent pressure changes during the different ventilatory permutations. Abdominal pressure measures were not obtained in two subjects. One canine experienced abdominal bleeding from adhesions due to prior abdominal trauma; while a second was found to have a tightly distended gallbladder. It was thought that movement of the organ during placement of the abdominal catheter could result in subsequent organ rupture with bile peritonitis. Two other subjects had significant periods of missing data and were excluded from the analysis. Data from the remaining sixteen subjects were analyzed.

The abdominal pressure values measured in the study varied widely between subjects, even though the balloon catheter was zeroed and tested prior to each experiment. Examination of the mean Pab values obtained in the experiments placed their validity in question. For this reason the measured values were not considered valid representations of actual intra-abdominal pressure and transdiaphragmatic pressure was not calculated as previously planned. The data did validly represent the degree of change in Pab with the four ventilatory permutations and were used to calculate the mean difference between maximum and minimum Pab and the percent
change in $P_{ab}$. Group 1 and Group 2 mean $P_{ab}$ change values were not significantly different for the four ventilatory permutations, so the groups were combined for this portion of the analysis. The mean difference in $P_{ab}$ was significantly increased with Resistor and CPAP ($p = 0.01$). $P_{ab}$ increased on average by 0.512 inches of water pressure with T-piece, by 0.929 inches with Resistor, by 0.062 inches with PS and by 1.059 inches with CPAP. When calculated as percent change, T-piece produced an average 11.6% increase in $P_{ab}$, Resistor a 19.3% mean increase, PS a 6.41% mean increase and CPAP a 39.8% mean increase in $P_{ab}$. Means ± standard deviations of $P_{ab}$ change and the mean percent increase in $P_{ab}$ with the four permutations are presented in Table 15.

### Table 15.

<table>
<thead>
<tr>
<th>Spontaneous Ventilation</th>
<th>Spontaneous Ventilation with a Resistor</th>
<th>Pressure Support</th>
<th>Continuous Positive Airway Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>SV</td>
<td>Resistor</td>
<td>PS</td>
<td>CPAP</td>
</tr>
<tr>
<td><strong>Mean $P_{ab}$ difference</strong></td>
<td>0.512 in ± 0.931</td>
<td>0.929 in * ± 0.659</td>
<td>0.062 in ± 0.272</td>
</tr>
<tr>
<td><strong>Mean % Change</strong></td>
<td>11.6% ± 55.2</td>
<td>19.3% ± 65.1</td>
<td>6.41% ± 30.63</td>
</tr>
</tbody>
</table>

* $p = 0.01$

Group values are mean ± standard deviation.

Group:
- Group 1 = normal biventricular function
- Group 2 = propranolol induced biventricular failure

in = inches of water pressure

T-piece = spontaneous ventilation
Resistor = spontaneous ventilation with resistor
PS = pressure support 5 cm.
CPAP = continuous positive airway pressure 5 cm.
Changes in Afterload

Baseline values of mean pulmonary vascular resistance were statistically similar in both groups. Group 1 subjects significantly decreased mean PVR with Resistor as shown in Figure 20. Mean PVR decreased by 112.2 dynes with Resistor. T-piece reduced PVR by an average of 108.8 dynes which approached statistical significance ($p = 0.06$). PS produced a 28.8 dyne mean reduction in PVR; while CPAP reduced PVR on average by 26.7 dynes. Group 2 significantly decreased mean PVR with T-piece and Resistor as shown in Figure 21. T-piece produced a mean PVR decrease of 134.4 dynes; while Resistor resulted in a 163 dyne reduction. Mean PVR was essentially unchanged with PS in Group 2, but CPAP produced a 23.7 dyne increase in mean PVR. Group means ± standard deviations of PVR are presented in Table 16. There was no significant group by time interactions for the variable mean PVR.
Group 1 Pulmonary Vascular Resistance Changes

- Baseline PVR
- Permutation PVR

**Figure 20.** Group 1 Pulmonary Vascular Resistance Changes
Figure 21. Group 2 Pulmonary Vascular Resistance Changes
Table 16.

Group 1 and Group 2 Mean Pulmonary Vascular Resistance at Baseline and After Transition to Spontaneous Ventilation, Spontaneous Ventilation with a Resistor, Pressure Support and Continuous Positive Airway Pressure

<table>
<thead>
<tr>
<th></th>
<th>SV</th>
<th>Resistor</th>
<th>PS</th>
<th>CPAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>375 dynes</td>
<td>297.9 dynes</td>
<td>379.7 dynes</td>
<td>360.9 dynes</td>
</tr>
<tr>
<td>SD</td>
<td>±227.5</td>
<td>±99.6</td>
<td>± 84.8</td>
<td>± 142.6</td>
</tr>
<tr>
<td>Permutation</td>
<td>266.2 dynes</td>
<td>185.7 dynes</td>
<td>350.9 dynes</td>
<td>334.2 dynes</td>
</tr>
<tr>
<td>SD</td>
<td>± 106.1</td>
<td>± 74.1</td>
<td>± 98.7</td>
<td>± 199.7</td>
</tr>
<tr>
<td>Group 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>448.5 dynes</td>
<td>412.5 dynes</td>
<td>418.9 dynes</td>
<td>423.4 dynes</td>
</tr>
<tr>
<td>SD</td>
<td>±201.5</td>
<td>±222.1</td>
<td>± 131.6</td>
<td>± 212</td>
</tr>
<tr>
<td>Permutation</td>
<td>314.1 dynes</td>
<td>249.5 dynes</td>
<td>418 dynes</td>
<td>447.1 dynes</td>
</tr>
<tr>
<td>SD</td>
<td>±164</td>
<td>±136.6</td>
<td>± 172.1</td>
<td>±160</td>
</tr>
</tbody>
</table>

*  p = 0.001 compared with baseline value
†  p = 0.009 compared with baseline value
‡ ‡ p = 0.004 compared with baseline value

Group values are mean ± standard deviation.

Group:
Group 1 = normal biventricular function
Group 2 = propranolol induced biventricular failure
dynes = dynes/second/cm⁻⁵
T-piece = spontaneous ventilation
Resistor = spontaneous ventilation with resistor
PS = pressure support 5cm.
CPAP = continuous positive airway pressure 5 cm.
Changes in Contractility

Baseline values of mean RVSW were statistically similar in Group 1. Group 1 subjects significantly increased mean RVSW with T-piece and CPAP as shown in Figure 22. On average, RVSW increase by 2.029 gram meters/beat with T-piece and 3.27 gram meters/beat with CPAP. Resistor resulted in a 0.724 gram meter mean increase, but PS essentially did not change mean RVSW. Baseline values of mean RVSW were similar in Group 2. Group 2 subjects also significantly increased mean RVSW during T-piece and CPAP as shown in Figure 23. T-piece produced a mean RVSW increase of 1.78 gram meters/beat; while CPAP resulted in a mean 1.69 gram meter/beat increase. Resistor produced a mean 0.66 gram meter/beat increase, but PS reduced RVSW 0.26 gram meters/beat on average. Group means ± standard deviations of RVSW are presented in Table 17.

Mean RVSWI was also significantly increased in Group 1 subjects with T-piece and CPAP as shown in Figure 24. RVSWI increased on average by 2.45 gram meters/beat with T-piece and 3.94 gram meters/beat with CPAP. Resistor increased mean RVSWI by 0.88 gram meters/beat; while PS essentially did not change mean RVSWI. Again, Group 2 subjects significantly increased mean RVSWI with T-piece and CPAP as shown in Figure 25. RVSWI increased on average by 2.22 gram meters/beat with T-piece and 2.05 gram meters/beat with CPAP. Resistor increased mean RVSWI by a mean of 0.84 gram meters/beat; while PS produced a mean 0.32 gram meter/beat reduction in RVSWI. Group means ± standard deviations of mean RVSWI are presented in Table 18. There were no significant group by time interactions for the variables mean RVSW and mean RVSWI.
Figure 22. Group 1 Right Ventricular Stroke Work Changes
Figure 23. Group 2 Right Ventricular Stroke Work Changes
Table 17.

Group 1 and Group 2 Mean Right Ventricular Stroke Work at Baseline and After Transition to Spontaneous Ventilation, Spontaneous Ventilation with a Resistor, Pressure Support and Continuous Positive Airway Pressure

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Resistor</th>
<th>PS</th>
<th>CPAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>SV</td>
<td>7.751 gm-m</td>
<td>8.636 gm-m</td>
<td>7.774 gm-m</td>
<td>7.4 gm-m</td>
</tr>
<tr>
<td>SD</td>
<td>±2.233</td>
<td>± 2.969</td>
<td>± 2.536</td>
<td>± 4.05</td>
</tr>
<tr>
<td>Permutation</td>
<td>9.78 gm-m *</td>
<td>9.36 gm-m</td>
<td>7.775 gm-m</td>
<td>10.67 gm-m *</td>
</tr>
<tr>
<td>SD</td>
<td>± 3.91</td>
<td>± 3.43</td>
<td>± 2.69</td>
<td>± 5.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 2</th>
<th>Baseline</th>
<th>Resistor</th>
<th>PS</th>
<th>CPAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>SV</td>
<td>7.05 gm-m</td>
<td>8.23 gm-m</td>
<td>7.66 gm-m</td>
<td>7.6 gm-m</td>
</tr>
<tr>
<td>SD</td>
<td>±3.79</td>
<td>± 4.01</td>
<td>± 3.8</td>
<td>± 3.41</td>
</tr>
<tr>
<td>Permutation</td>
<td>8.83 gm-m †</td>
<td>8.89 gm-m</td>
<td>7.4 gm-m</td>
<td>9.29 gm-m ††</td>
</tr>
<tr>
<td>SD</td>
<td>±4.8</td>
<td>± 4.76</td>
<td>± 3.5</td>
<td>±4.77</td>
</tr>
</tbody>
</table>

* p = 0.03 compared with baseline value
† p = 0.04 compared with baseline value
†† p = 0.05 compared with baseline value

Group values are mean ± standard deviation.

Group:
Group 1 = normal biventricular function
Group 2 = propranolol induced biventricular failure

gm-m = gram meters/beat
T-piece = spontaneous ventilation
Resistor = spontaneous ventilation with resistor
PS = pressure support 5cm.
CPAP = continuous positive airway pressure 5 cm.
Figure 24. Group 1 Right Ventricular Stroke Work Index Changes

* p = 0.03 compared with baseline value
n = 10
Figure 25. Group 2 Right Ventricular Stroke Work Index Changes
Table 18.

Group 1 and Group 2 Mean Right Ventricular Stroke Work Index at Baseline and After Transition to Spontaneous Ventilation, Spontaneous Ventilation with a Resistor, Pressure Support and Continuous Positive Airway Pressure

<table>
<thead>
<tr>
<th>Group 1 Values</th>
<th>Mean ± SD</th>
<th>Mean ± SD</th>
<th>Mean ± SD</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>9.5 ± 2.79</td>
<td>10.5 ± 3.43</td>
<td>9.44 ± 2.83</td>
<td>9.0 ± 4.83</td>
</tr>
<tr>
<td>Permutation</td>
<td>11.95 ± 4.85</td>
<td>11.38 ± 3.98</td>
<td>9.44 ± 3.03</td>
<td>12.94 ± 6.73</td>
</tr>
<tr>
<td>Group 2 Values</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Baseline</td>
<td>8.56 ± 4.56</td>
<td>10.02 ± 4.98</td>
<td>9.34 ± 4.84</td>
<td>9.26 ± 4.2</td>
</tr>
<tr>
<td>Permutation</td>
<td>10.78 ± 5.97</td>
<td>10.86 ± 6.0</td>
<td>9.02 ± 4.44</td>
<td>11.3 ± 5.87</td>
</tr>
</tbody>
</table>

* p = 0.03 compared with baseline value
† p = 0.05 compared with baseline value
‡‡ p = 0.02 compared with baseline value

Group values are mean ± standard deviation.

Group:
- Group 1 = normal biventricular function
- Group 2 = propranolol induced biventricular failure

gm-m = gram meters/m²/beat
T-piece = spontaneous ventilation
Resistor = spontaneous ventilation with resistor
PS = pressure support 5cm.
CPAP = continuous positive airway pressure 5 cm.
CHAPTER V
DISCUSSION

Discussion of Results

This study demonstrates that right heart hemodynamics are significantly altered during weaning from MV. When subjects in both groups were removed from controlled MV and exposed to T-piece, Resistor and CPAP, CO increased. There were no meaningful changes in CO with PS. The increase in CO with weaning in these subjects is similar to that found in other investigations reporting hemodynamic alterations during weaning from MV. Beydon, Cinotti, Rekik, Radermacher, Adnot, Meignan, Harf & Lemaire (1991) found a 36% increase in CO with spontaneous ventilation (MV 4.27 ±0.7 L/min to 5.81 ± 0.9 L/min). Genovese, Moscowitz, Tarasiuk, Graver & Scharf (1994) found no change in CI with CPAP 5 cm in normovolemic pigs; however, with hypervolemia, CPAP 5 cm increased CI by 13%. Teboul, et al (1988) found that SpV increased mean CI from 3.5 ± 1.1 L/min. to 4.3 ± 1.0 L/min. in their small sample of COPD patients (n = 7). In the current study, subjects with normal ventricular function increased CO by 0.8 L/min. with T-piece, by 1.1 L/min. with Resistor and by 0.7 L/min. with CPAP; while Group 2 subjects increased CO by 0.4 L/min. with T-piece, 0.4 L/min. with Resistor and 0.2 L/min. with CPAP. Changes in CO may be produced by alterations in HR and/or SV.

Neither group experienced significant changes in HR with the four ventilatory conditions. Similarly, Genovese, et al (1994) found no significant
change in HR with CPAP; however, Teboul, et al (1988) identified a significant increase in mean HR with T-piece. These investigators interpreted this HR increase as a response to catecholamine discharge stimulated by removal of MV. In the current study, neither group of subjects exhibited significant increases in mean HR during any of the four ventilatory conditions. Group 2 subjects received the β receptor antagonist, propranolol, which blocked the effects of catecholamine discharge in this group; but Group 1 subjects did not experience HR increases either. This suggests the CO increases were not associated with catecholamine discharge, but were due to changes in SV.

SV increased with T-piece, Resistor and CPAP in both groups. SV is determined by the degree of preload, afterload and ventricular contractility. In the current study, preload/RVEDV increased in both groups with T-piece, Resistor and CPAP. Since RVEDV is determined by the magnitude of the pressure gradient between the abdominal vena cava and the right atrium, factors that influence the size of this gradient must be considered. The primary mechanical alteration during weaning is the shift in ITP from positive to less than atmospheric pressure. This change should augment the gradient and increase the volume of venous return. Both groups of subjects exhibited reductions in meanPes/ITP with those ventilatory conditions that produced an increase in RVEDV (T-piece, Resistor and CPAP). In general, RVEDV increases were slightly larger in Group 1; however, in both groups of subjects, the pressure gradient increased and the volume of venous return was enhanced. This is contrary to the findings of Teboul, et al (1988). This group of investigators did not find an increase in RVEDV with SpV in their human subjects; however, Bastien, et al (1988) described significant increases in RVEDV with SpV in their post cardiac surgery human subjects. In the
current study, subjects produced increases in RVEDV as large as 27% of baseline value (Group 1 Resistor 24 ml increase) which indicates this pressure gradient was altered; consequently, the volume of venous return increased. Group 2 subjects increased RVEDV to a lesser degree. This was likely due to generalized \( \beta \) receptor blockade with modification of peripheral vascular resistance and blood pressure which influenced the gradient for venous return.

A second mechanical alteration found with weaning is a change in the activity of the diaphragm. Diaphragm contraction increases the size of the thoracic cavity which reduces the size of the abdominal cavity and increases \( P_{ab} \). \( P_{ab} \) is the second component of the pressure gradient for venous return. The diaphragm does not actively contract with controlled MV; however, active diaphragm contraction is necessary with weaning. In the current study, the ventilatory conditions, T-piece, Resistor and CPAP, produced increases in mean \( P_{ab} \). This finding is compatible with those in recent investigations of diaphragm work during weaning. Torres, Kacmarek, Kimball, Qvist, Stanek, Whyte & Zapol (1993) found that CPAP decreased the resting length of both costal and crural portions of the diaphragm by increasing end-expiratory lung volume (EELV). This muscle shortening produced a less than optimal muscle length for force generation. During expiration, the increased EELV necessitated recruitment of abdominal muscles in an attempt to return the diaphragm to its' optimal resting length and abdominal muscle contraction increased \( P_{ab} \). Sassoon, Lodia, Rheeman, Kuei, Light and Mahutte (1992) determined that demand flow CPAP, as was used in the current study, increased inspiratory work of breathing, since it necessitated a greater decrease in airway pressure to produce gas flow into the lungs.
PS did not alter the volume of preload, significantly reduce $P_{es}/ITP$ or increase $P_{ab}$ in the current study. PS provides a positive flow of gas in response to the initiation of a spontaneous breath, thereby minimizing changes in $P_{es}/ITP$ and $P_{ab}$. In addition, PS has been found to compensate for additional work of breathing imposed by the artificial airway and ventilator circuit, and when combined with CPAP, to significantly reduce work imposed by the demand flow CPAP system (Brochard, Rua, Lorino, Lemaire, & Harf, 1991; Torres, et al., 1993). The findings from the current study support the hypothesis that weaning from MV using T-piece, Resistor or CPAP results in a reduction in mean ITP and generates active diaphragm contraction which increases $P_{ab}$. These changes augment the pressure gradient for venous return to the right atrium and increase right ventricular preload/RVEDV.

RV afterload/PVR values were greater than normal human values at baseline in all animals (human normal $< 250$ dynes). Positive ITP with MV compressed both alveolar and extra-alveolar pulmonary vessels which reduced their compliance and increased resistance to forward blood flow. SpV with T-piece and Resistor removed the positive ITP generated by MV which increased vessel compliance and reduced PVR. Grant, Fitzpatrick and Leiber (1991) postulated a time varying pulmonary arterial compliance with SpV. Normally, inspiration produces an increase in pulmonary vessel compliance, since a traction effect increases vessel caliber. Blood volume is shifted from alveolar to extra-alveolar vessels during inspiration. With expiration, the traction effect is removed by lung tissue, chest wall and vessel recoil. Blood then moves into alveolar vessels for gas exchange. PS and CPAP produced little change in PVR. Ventilatory conditions that produce or maintain positive pressure within the thorax during any portion of the ventilatory
cycle may necessitate an increase in cardiac work to maintain forward movement of blood.

In the current study, RVSW or the pressure-volume work of the RV was increased by T-piece, Resistor and CPAP. Both groups of subjects exhibited increased stroke work in response to increased end diastolic volume which is an illustration of the Frank-Starling law of the heart. The Frank-Starling mechanism represents the intrinsic capacity of myocardial muscle to respond to an increase in stretch/EDV with an increase in SV. Several subjects increased RVSW well above maximum normal values (5-10 gm-m/beat), especially Group 2 with CPAP. The combination of increased preload and increased afterload with CPAP, particularly in Group 2 subjects, necessitated substantial increases in work to eject blood from the right ventricle. Potentially, subjects unable to augment stroke work in response to a greater volume would increase RVEDV and dilate the RV within the pericardium. With sufficient dilatation, the interventricular septum may impinge on the left ventricle and reduces its' compliance, filling and subsequently decrease global CO. RV dilatation would increase RV radius of curvature, RV wall stress and reduce RV nutritive myocardial blood flow, particularly during diastole, which could generate myocardial ischemia and RV dysfunction.

These data clearly demonstrate that weaning from MV can significantly alter RV hemodynamics. Both proposed hypotheses were supported by the findings of this investigation. These data indicate that changes in right heart hemodynamics were associated with reductions in ITP. RV preload, afterload and contractility were altered in both groups with the varied levels of ITP produced by MV, T-piece and Resistor. Also, the extent of right heart
hemodynamic change was different based on the degree of negative ITP produced by the two support mechanisms, PS and CPAP. CPAP produced significant changes in ITP, Pab and right heart hemodynamics; while PS induced minimal change. Dramatic changes in RV hemodynamics during weaning may induce cardiovascular instability, particularly in those individuals unable to evoke adequate compensatory mechanisms. The result may be reductions in oxygen delivery, weaning failure, and increased potential for morbidity and mortality. PS produced minimal hemodynamic change and may be a more suitable means of weaning individuals, particularly those with cardiac dysfunction. This study offers insight into right heart hemodynamic responses during weaning. This study will assist the critical care team to optimize cardiopulmonary function and deter cardiopulmonary complication during weaning from MV, while improving the likelihood of successful weaning from MV.

Limitations of the Study

The generalizability of this study is limited due to a number of factors. First, this study used a canine model to investigate right heart hemodynamic changes during weaning from MV. Although numerous cardiovascular investigations have used a canine model, the responses of human subjects to weaning may be different. However, this investigation was intended as a pilot study, and as such, provided fundamental knowledge as a basis for further investigation.

A second factor limiting generalizability of these findings is pathophysiological differences between the animal model and the human population they were intended to represent. These canine subjects had normal lungs and normal pulmonary function at the time of
experimentation; whereas, the population of COPD subjects with right heart
dysfunction exhibits significant pulmonary parenchymal and vascular
alterations that would potentially influence responses to weaning. In
addition, these canines received short term MV rather than prolonged MV.
In general, individuals who demonstrate difficulty weaning have received
MV for at least 1-3 days. A longer term exposure to MV may have induced
significant physiological change in these canines and altered study findings;
however, long term MV was not feasible in this pilot study.

A third factor influencing study generalizability is the administration of
general anesthesia using α chloralose. Although this form of anesthesia
produces minimal cardiovascular alterations while permitting the subject to
ventilate independently, this situation is not comparable with human
subjects experiencing weaning. In general, humans are not weaned from MV
until they are able to respond in some fashion to their environment. This
was neither an ethical, nor a feasible choice in this study.

Fourth, the propranolol model of heart failure did not produce structural
and biochemical myocardial modifications found with heart failure. These
changes might have modified the responses of the subjects in Group 2.
However, this model did produce hemodynamic alterations that are similar
to those found in humans with heart failure and changes in global CO were
congruent with other investigations.

Fifth, the measurement techniques for right ventricular volumes and
abdominal pressure resulted in a loss of usable data. Four subjects exhibited
tachycardia during experimentation which eliminated volumetric data for
these subjects. This is a limitation of the current technology and the
algorithm used in the computer calculation of right ventricular volumes.
Thermodilution technique did produce useful data in the remaining subjects. Although the abdominal catheter was consistently placed and zeroed, data varied widely and could not be considered a valid representation of actual abdominal pressure. This may have been secondary to changes in $P_{ab}$ related to operation or consistent operator error. Transdiaphragmatic pressure was not calculated for this reason. However, these data did represent the change from baseline in abdominal pressure during the different ventilatory conditions, so were analyzed in that manner.

The fifth and final factor reducing generalizability of these findings is the length of the experimental preparation. Each subject experienced four separate experiments during the course of the day. These experiments were conducted consecutively with stabilization periods between each. Subjects may have responded differently to the final ventilatory condition if it had been experienced earlier in the day. The four ventilatory conditions were randomized to minimize the occurrence of this bias.

**Implications for Nursing Practice**

This study offers critical care nurses fundamental knowledge of right heart hemodynamic changes with weaning from MV. Dramatic hemodynamic changes may produce hemodynamic instability which reduces oxygen delivery and may result in weaning failure. The shift in ITP from positive with MV to less than atmospheric with $SpV$ alters right heart preload, afterload and contractility. Compensatory mechanisms are invoked which intend to normalized hemodynamics and maintain the delivery of oxygen to metabolically active tissues. Individuals who are unable to compensate for these alterations, like those with right ventricular dysfunction, may experience significant morbidity and mortality.
The major implication of this study concerns the parameters critical care nurses employ to monitor patients during weaning from MV. Alterations in right heart hemodynamics during weaning may not be easily detected by standard monitoring parameters which include direct or indirect blood pressure, heart rate, heart rhythm, respiratory rate and oxygenation by pulse oximetry or arterial blood gas. Measures of ITP, right heart preload, afterload and contractility are not commonly monitored during weaning. Volumetric changes must be inferred from measures of pressure; however, the relationship between volume and pressure in the right ventricle is not a linear one. When available, a pulmonary artery catheter with right ventricular volumetric capabilities offers the critical care nurse a wealth of information about right heart performance. These measures would assist the critical care nurse to determine the degree of change in RV hemodynamics in the individual patient, as well as, to assess the efficacy of compensatory mechanisms invoked by these changes. With this type of information, right ventricular function may be optimized prior to removal from MV with subsequent reduction of complication due to hemodynamic instability. This could substantially reduce morbidity/mortality related to hemodynamic instability with weaning and increase the likelihood of weaning success. In the absence of a pulmonary artery catheter with volumetric capability, other valid and reliable parameters must be identified which indicate significant hemodynamic alterations prior to the development of significant complication.

Recommendations for Further Research

Further investigation of right heart hemodynamics during weaning from MV are necessary. This investigation was a pilot study, and as such, offers
fundamental information about hemodynamic responses to weaning. However, substantive research is necessary to clearly elucidate the relationship between changes in ITP, Pab and right heart hemodynamics in humans during weaning from MV. Investigation into the compensatory cardiovascular mechanisms invoked during weaning from MV would offer valuable insight and disclose potential avenues for intervention. However, before interventions can be employed effectively, hemodynamic instability must be recognized in the clinical setting.

A second focus for research involves the determination of appropriate monitoring parameters during weaning. Traditional clinical monitoring of blood pressure, heart rate, respiratory rate and arterial blood gases offer little information about right heart function and may not be effective indicators of significant hemodynamic change. Reliable, valid indicators of right heart function would provide invaluable information to the clinician during weaning from MV and permit early intervention. Intervention aimed at improving cardiovascular function would increase the likelihood of weaning success and reduce the potential for morbidity and mortality.
CHAPTER VI
SUMMARY

The purpose of this experimental study was to describe right heart hemodynamic changes during weaning from mechanical ventilation. This investigation examined right heart hemodynamics during baseline mechanical ventilation and following a 5 minute transition period to each of 4 ventilatory conditions: T-piece, Resistor, PS 5 cm. and CPAP 5 cm. The subjects were 20 male, mongrel canines randomized to 2 groups: Group 1 normal ventricular function and Group 2 propranolol induced biventricular failure. The subjects were premedicated with ketamine, buprenorphine and diazepam, then anesthetized with a chloralose. Mechanical ventilation was delivered with room air, a tidal volume of 10-12 ml/kg and a rate of 10 breaths/minute. Oxygen was administered as necessary to maintain PaO2 > 80 mmHg. Femoral arterial and venous cannulas were inserted via cutdown and a six lumen pulmonary artery catheter was placed via the right jugular vein also by cutdown. Balloon catheters were placed in the distal esophagus and under the right hemidiaphragm to measure esophageal and abdominal pressure changes, respectively. Lead II electrocardiogram and pressure data were collected by a Gould recorder and placed on the hard drive of a 486 Compaq computer. Thermodilution values of cardiac output and right ventricular volumes were determined by the Explorer computer. Arterial blood gases were monitored prior to each experiment and ventilator setting were adjusted to maintain values within preset ranges.
Following stabilization, subjects randomized to Group 2 received propranolol, a β receptor antagonist. Each subject was randomly subjected to four ventilatory conditions. Baseline values of the dependent variables were measured on controlled mechanical ventilation. The ventilatory condition was initiated and the subject permitted to stabilized for 5 minutes. A second set of dependent variable measures was then obtained. Each ventilatory condition had a new baseline condition, therefore, each was analyzed as a separate experiment. Unpaired t tests compared mean values of Group 1 and Group 2. Repeated measures analysis of variance was used to compare mean baseline values with mean values obtained with the ventilatory permutation. If main effects were identified, pairwise comparisons were used to determine which means were significantly different from baseline values.

Administration of propranolol to Group 2 subjects produced hemodynamic changes consistent with biventricular failure. Exposure to five minutes of T-piece, Resistor and CPAP induced significant increases in cardiac output in both groups of subjects. There were no meaningful cardiac output changes with PS. Cardiac output is the product of heart rate and stroke volume. Heart rate did not change in either group with any of the four ventilatory permutations. Stroke volume increased in both groups with T-piece, Resistor and CPAP; but again, there were no meaningful changes with PS. Stroke volume is determined by the degree of preload, afterload and contractility. Preload was increased with T-piece, Resistor and CPAP in both groups. Preload/venous return is influenced by the magnitude of the pressure gradient between the abdominal vena cava and the right atrium. Intrathoracic pressure was reduced with T-piece, Resistor and CPAP as indicated by esophageal pressure. Abdominal pressure increased with these
same ventilatory conditions. The reduction in intrathoracic pressure combined with the increase in abdominal pressure suggests the pressure gradient for venous return was augmented, consequently, preload increased in both groups of subjects. Afterload in both groups was reduced with T-piece and Resistor. In general, PS and CPAP maintained afterload at the baseline level, but in Group 2, CPAP produced an increase in afterload. Contractility as indicated by right ventricular stroke work was increased during T-piece, Resistor and CPAP in both groups of subjects.

The findings of this investigation suggest that weaning from mechanical ventilation may produce significant right heart hemodynamic changes. Hemodynamic changes observed with T-piece, Resistor and CPAP were associated with alterations in intrathoracic pressure and abdominal pressure induced by the return to spontaneous ventilation. PS generated minimal change in intrathoracic pressure, abdominal pressure and right heart hemodynamics.
APPENDIX A

APPROVAL FORM

INSTITUTIONAL LABORATORY ANIMAL CARE AND USE COMMITTEE
Appendix A
Approval Form
Institutional Laboratory Animal Care and Use Committee

THE OHIO STATE UNIVERSITY
INSTITUTIONAL LABORATORY ANIMAL CARE AND USE COMMITTEE

ACTION OF THE COMMITTEE

X Original Review

Periodic Review

ANIMAL USE PROTOCOL:
94A0070 Cardiovascular-Pulmonary Hemodynamics with Weaning from Mechanical Ventilation, Kathleen S. Stone and B.R. Schertel, Adult Health and illness Nursing

The Institutional Laboratory Animal Care and Use Committee took the following action on the protocol cited above:

X Approved

Disapproved

Approved with Modifications*

* Modifications requested by the Committee have been accepted by the Investigator(s) and, therefore, the protocol is APPROVED.

Approval of the protocol is for the period 06/01/94 through 09/01/95. The Committee will periodically contact investigators to seek information about approved protocols. Periodic contact for this protocol is next scheduled for 09/95.

The Investigator(s) shall immediately bring to the attention of the Institutional Laboratory Animal Care and Use Committee any changes proposed for the approved protocol as they relate to the care or use of laboratory animals. The Committee will decide whether the extent or type of changes proposed warrant formal Committee review. If such a review is deemed necessary, the chairperson shall schedule the review for the earliest feasible time.

Prior to the initiation of any projects you should contact the attending veterinarian or person in charge of animal care within the college in which your animals are to be housed. Additional information is generally required to comply with the specific college needs before the initiation of any projects. Failure to make such contact may delay the initiating of this project.

Certification of review and approval will be transmitted to external sponsors, as required, by the Research Foundation. INVESTIGATORS ARE RESPONSIBLE FOR CONVEYING A COPY OF THIS DOCUMENT TO THEIR SPONSORED PROGRAM DEVELOPMENT OFFICERS.

Date May 20, 1994
Signed (Chairperson)
APPENDIX B

FORMULAS FOR DERIVED VARIABLES
## Formulas for Derived Hemodynamic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit of Measure</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>SV</td>
<td>ml/beat</td>
<td>= (CO/HR) x 1000</td>
</tr>
<tr>
<td>SVI</td>
<td>ml/m²/beat</td>
<td>= (CI/HR) x 1000</td>
</tr>
<tr>
<td>EDV</td>
<td>ml</td>
<td>= SV/EF</td>
</tr>
<tr>
<td>EDVI</td>
<td>ml/m²</td>
<td>= EDV/BSA</td>
</tr>
<tr>
<td>ESV</td>
<td>ml</td>
<td>= EDV - SV</td>
</tr>
<tr>
<td>ESVI</td>
<td>ml/m²</td>
<td>= ESV/BSA</td>
</tr>
<tr>
<td>RVSW</td>
<td>gm-‐m/beat</td>
<td>= SV x (MPAP - RAP) x 0.0136</td>
</tr>
<tr>
<td>RVSWI</td>
<td>gm-‐m/m²/beat</td>
<td>= SVI x (MPAP - RAP) x 0.0136</td>
</tr>
<tr>
<td>SVR</td>
<td>dynes-‐sec/cm⁵</td>
<td>= 80 x (MAP - RAP)/CO</td>
</tr>
<tr>
<td>PVR</td>
<td>dynes-‐sec/cm⁵</td>
<td>= 80 x (MPAP - PAOP)/CO</td>
</tr>
</tbody>
</table>

**Variables:**
- CO = cardiac output
- HR = heart rate
- CI = cardiac index
- EF = ejection fraction
- BSA = body surface area
- MPAP = mean pulmonary artery pressure
- RAP = right atrial pressure
- MAP = mean arterial pressure
- PAOP = pulmonary artery occlusion pressure

**Units:**
- ml = milliliters
- m² = square meters
- gm-m = gram meters
- dynes-sec = dynes/second
- cm = centimeter
LIST OF REFERENCES


