HIGH FREQUENCY INTERVENTION (HIFI) TRIAL

P R O T O C O L

September 18, 1985

TABLE OF CONTENTS

TABLE OF CONTENTS (continued)

TABLE OF CONTENTS (continued)

LIST OF EXHIBITS

HIGH FREQUENCY INTERVENTION (HIFI) TRIAL

I. Introduction

A. Background

Ventilation of the neonate, whether premature or full-term, is never a trivial matter. While conventional mechanical ventilation (CMV) for Respiratory Distress Syndrome (RDS) has greatly improved neonatal mortality and morbidity, serious problems with this and other pulmonary diseases causing respiratory failure in the newborn still exist. Babies still die of respiratory failure, both acute and chronic. Bronchopulmonary dysplasia (BPD) appears to be an increasing cause of late death, of greatly prolonged hospitalization, and of premature respiratory handicap. This increased morbidity is associated with and probably due to increasing survival of very low birthweight infants (Smythe, 1981). It appears that interruption of the normal process of cardiopulmonary maturation coupled with elements of oxygen toxicity and barotrauma predispose the neonate to the development of chronic lung disease or so-called bronchopulmonary dysplasia. It has been estimated that 15-30% of those infants who require mechanical ventilation will develop BPD (Edwards, 1977).

Positive pressure ventilators specially designed for the neonate have been commercially available for several years and, as with their adult counterparts, can be classified as primarily volume-priority or pressure-priority devices. In the former, a set volume is delivered per respiratory cycle, regardless of the pressure required (with appropriate limiting safety devices). In the latter, gas is delivered until a preset pressure is reached and held until expiration is initiated. The merits of each and the indications and contraindications for their use are well known, but defining the contribution of the various components of conventional mechanical ventilation in the development of BPD are hampered by technical factors unique to neonatal respiratory physiology.

Both of these conventional forms of ventilating devices rely on convection and diffusion for the exchange of gas in the lungs and bronchi much as in normal, spontaneous breathing (Slutsky, et al. 1980). The classic model of pulmonary gas exchange requires that tidal volume

exceeds dead space for effective exchange to occur. However, recent work which describes flow in rigid tubes, matched with the bronchial tree for Reynolds and Peclet numbers, suggests that complete ventilation can occur with tidal volumes that are substantially smaller than dead space (Haselton and Scherer, 1980).

Since the late 1950s, devices have been designed which appear to support ventilation at rates much higher than those which occur during spontaneous respiration or with conventional mechanical ventilators (e.g., Frantz, et al. 1983; Pokora, et al. 1983; Truog, et al. 1983; Slutsky, et al. 1980; Carlon, et al. 1981; Smith, et al. 1980). In 1957, John Emerson patented an "airway vibrator" (oscillator) capable of producing ventilation rates up to 2000 breaths per minute. About ten years later, relatively high-frequency (60-100 per minute) ventilation was applied to experimental animals to reduce the phasic effects of respiration on baroreceptor response during experiments investigating the carotid sinus reflex (Öberg and Sjöstrand, 1969). Shortly thereafter the same concepts were applied to adult humans, but specifically for the purpose of improved gas exchange (e.g., see Sjöstrand's Review, 1977).

As the term high frequency ventilation suggests, a principal facet of all forms of this mode of ventilatory support is the use of respiratory frequencies much greater than normal breathing rates. Although this aspect of the definition is universally accepted, agreement on other issues has not been reached. A major impediment to the establishment of standard definitions is the importance of a description of the unique device used in each trial as an integral part of the definition. As early published data appeared, this led to confusion and difficulty in efforts to compare results and understand mechanisms. Nonetheless, some standard definition is required because current theories regarding successful gas exchange during high frequency ventilation are quite different from traditional concepts.

Since those early reports, it is clear that at least three distinct forms of high-frequency ventilators have evolved: high frequency positive pressure ventilators; high frequency jet ventilators, and high frequency ventilators.

High frequency positive pressure ventilators (HFPPV) are merely conventional pressure-priority devices utilized at rapid rates approximating 60-150 per minute. In some respects, this is really an extension of conventional mechanical ventilation. Investigations with this form of ventilation utilizing rapid rates and short inspiratory times have been conducted by Bland et al. (1980) and Boros et al. (1980).

High frequency jet ventilation (HFJV) is produced by a specialized, relatively well-defined apparatus generating respiratory rates approximating 150-400 per minute. Jet ventilation involves rapid delivery of small pulses of oxygen enriched gas via a cannula in the upper airway. The accentuated flow through this small-bore tube develops an area of relative negative pressure which entrains the surrounding low flow of humidified gas into the patient's airway. In essence, a venturi-like mechanism draws additional gas to augment the tidal volume. Passive expiration results as gas returns to atmosphere either around or through a side arm on the endotracheal tube.

High frequency ventilation (HFV) is delivered by specialized, widely variable apparatuses (piston pump, ball valve interruptor, or accoustic speaker) generating respiratory rates of 400-2400 per minute. These devices are generally divided into two classes. As the piston-actuated or acoustic devices are characterized by active accentuation of gas movement both toward and away from the patient, they are generally called high frequency oscillators (HFO). The device which "chops" unidirectional flow with a ball valve is termed a high frequency flow interrupter (HFFI).

Regardless of the exact form of high frequency ventilation, the intent is to provide adequate oxygenation and ventilation while maintaining F_IO_2 and peak and/or mean airway pressures as low as is practical in the hope of minimizing pulmonary damage and BPD.

B. Literature Review

The definition of "high-frequency" has changed since Heijman, et al. (1977) suggested that artificial ventilation at 60 breaths/minute (bpm) which mimicked the rapid, shallow breathing of the RDS child might be more effective than the conventional slower, deeper breaths. The technique was initially applied to infants with normal pulmonary systems

who were undergoing and recovering from routine surgery with satisfactory results.

Bland, et al. (1980), used rates of 60-110 bpm to ventilate premature infants with severe RDS. While this work was neither comparative nor conclusive, it demonstrated that adequate gas exchange could be maintained in this population by rapid, shallow breathing with relatively few complications.

Boros and Campbell (1980) alternately using low-frequency high-tidal volumes and high-frequency (60-80 bpm) low-tidal volumes, ventilated neonates having severe lung disease (RDS, pulmonary hemorrhage, and respiratory failure). Controlled variables were inspiratory/expiratory (I/E) time ratio, frequency, and tidal volume; but as an index of oxygenation, the PaO_2/F_IO_2 ratio was generally most dependent on mean airway pressure ($\bar{P}aw$). The best oxygenation occurred at the highest $\bar{P}aw$.

Smith, et al. (1980), using a fluidic logic-controlled jet ventilator with normal dogs investigated gas exchange up to 600 bpm, with no remarkable adverse effects up to 400 bpm. Above this rate, heart rate decreased, cardiac output fell, and peripheral resistance increased. Adequate gas exchange was obtained with both low tidal volumes (approximately 50% of calculated dead space) and low intratracheal pressures (3-7 mm Hg, peak; 1.6-2.8 mm Hg, end expiratory; $\bar{P}aw$ not reported).

Considerably higher frequencies (up to 1800 bpm) were used by Frantz, et al. (1980) for brief ventilation of premature infants with a ball-valve flow interrupter. Adequate ventilation was achieved using the same gas mixture as with CMV, but with the development of a mean tracheal pressure only half that of the proximal airway pressure.

Butler, et al. (1980), ventilated both physician volunteers and a wide range of patients at a rate of 1800 bpm and with tidal volumes approximately one-half the dead space. The primary result was a decrease in right-to-left pulmonary shunt, going from CMV to a piston HFO, in adult patients with obstructive lung disease.

A piston pump was used by Marchak, et al. (1981) to ventilate neonates with severe RDS. In a comparison with CMV, reduced $PaCO_2$ and adequate PaO_2 at a lower F_IO_2 were achieved with the HFO.

Most of the work during this period suggests that in larger studies, a significant reduction in various barotraumas might be achieved with the reduced peak pressures and flow which are characteristic of HFV. Studies with both animals and humans began to look in more detail at the effects that HFV support has on a variety of artificial-ventilation-induced complications.

Truog, et al. (1983) compared CMV and HFO (10 Hz) in premature primates, using each animal as its own control. The methods were matched to the same $\bar{P}aw$. HFO produced both a decreased $PaCO_2$ and an increased PaO_2 at a lower peak airway pressure than did CMV. No differences in the mechanical properties or in the phospholipid content of the postmortem lungs of matched sets of animals were noted.

Pleural effusions were found in dogs ventilated with a piston HFO for 36 hours (Rehder, et al., 1983) while a comparison group maintained on CMV showed no exudate. Matching of ventilation was done by achieving a $PaCO_2$ of 35 mm Hg with both methods. No striking differences in either respiratory or cardiovascular function were found.

In a later study by Frantz, et al. (1983), adequate ventilation at lower peak inspiratory pressures was again demonstrated for the HFFI (12 Hz) in premature infants with RDS and pulmonary interstitial emphysema (PIE).

Premature lamb twins ventilated conventionally and with HFO (45 Hz) using similar $\bar{P}aw$ and $F_IO_2 = 1.0$ gave similar blood gases (Saramiento, et al. 1983), but all of the CMV lambs (4) showed lung damage (hyaline membranes or epithelial necrosis). Only 2 of the 6 animals ventilated with HFO had hyaline membranes. For both ventilation methods, increasing $\bar{P}aw$ resulted in increased protein leak between alveolar and vascular space, increased surface tension, and decreased surfactant pool size.

Neonates with respiratory failure, ventilated with HFJV (250 bpm) (Pokora, et al. 1983) showed decreased air leaks, improved PaO_2/F_IO_2, and decreased $PaCO_2$. Long-term (> 20 hours) ventilation, however, was associated with significant tracheal obstruction.

Jefferies, et al. (1983) addressed the question of pulmonary edema being a result of reduced modulation of lung lymph flow by HFV. Sheep and a goat were subjected to CMV and HFO (15 Hz) while lung lymph flow was determined. Even with increased flow provoked by air microemboliza-

tion of the lung, no significant difference between HFO and CMV was found. The methods were matched for a normal $PaCO_2$.

HFJV was compared with CMV in oxygenation of adult rabbits having saline lavage-induced pulmonary injury (Hamilton, et al. 1984). In addition, the CMV animals developed hyaline membranes, whereas the HFO ventilated animals did not. The difference in response is attributed to the smaller pressure excursions about a higher lung volume achieved with HFO.

HFJV was compared with CMV in RDS premature infants (Carlo, et al. 1984) and showed for similar PaO_2, that $\bar{P}aw$, peak inspiratory pressure, and $PaCO_2$ decreased with HFJV.

Boynton, et al. 1984 treated twelve neonates who had inadequate gas exchange on conventional ventilation with a combination of high frequency oscillatory ventilation and intermittent conventional ventilation. Within ten hours the mean arterial $PaCO_2$ fell significantly and the mean airway pressure was substantially reduced. They concluded that a combination of HFV and CMV can be successful in some neonates with respiratory failure.

The literature certainly shows that it is possible to provide adequate ventilation in both normal and diseased lungs using volumes excursions which are smaller than traditionally-calculated dead space. There are, however, no consistent guidelines for choosing a ventilation rate, $\bar{P}aw$, tidal volume, end expiratory pressure, F_IO_2, or other respirator settings.

As with CMV, complications are also associated with HFV, but without some uniformity in the reported studies, comparison of results and assignment of causative factors is difficult.

C. Justification

The pathogenesis of BPD clearly involves the use of CMV and high concentrations of inspired oxygen. High inspiratory and end-expiratory pressures (together giving high mean airway pressures) are considered to barotraumatize the lung, causing air leaks (pulmonary interstitial emphysema, pneumothorax, etc.) and parenchymal lung injury. Moreover, the occurrence of PIE is associated with a relatively high incidence of BPD. When irreversible, the spectrum of outcomes varies

between mild deficits in pulmonary function testing and a progressive course ending in cor pulmonale and death.

It is generally believed that use of lower mean and peak airway pressures for shorter periods of time will reduce the incidence of BPD. Experience in both animals and human neonates has demonstrated that when compared with CMV, similar gas exchange by the diseased lung can be achieved with lower mean and peak airway pressures by using HFV. High frequency ventilation may thus reduce barotrauma and lung injury, reduce the period of requirement of mechanical ventilation and of hospitalization, and lower long-term pulmonary morbidity and mortality from BPD and cor pulmonale.

However, the human experience with HFV has been gained only in the context of "rescue" operations of infants with terminal or near-terminal pulmonary failure, or in less ill infants for very brief periods of time. As some doubt exists about both the efficacy and safety of HFV and one may question the effect to broaden the indications for use of HFV beyond "rescues", a clear answer to questions about both efficacy and safety can come only from a clinical trial.

Because of a number of important methodological problems, it will be necessary to study a large number of patients. Firstly, the patient material is quite heterogeneous: wide variation exists in gestational age and in the presence and magnitude of pulmonary maladaptation to extrauterine life at each gestational age. Both the disorders of pulmonary adaptation (surfactant deficiency, delayed absorption of lung liquid, so-called "immature lung", pulmonary aspiration of amniotic fluid uncontaminated by meconium, persistent pulmonary hypertension, etc.) and pulmonary diseases do not always have specific diagnostic findings and are therefore difficult to delineate. The situation is further confounded by the rapid unpredictable resolution of a significant percentage of neonatal lung problems; these patients then represent a dilution of the patient material in any trial.

Because of the existence of a large number of variables, the evaluation of safety demands a large clinical trial. The frequency of severe intraventricular hemorrhage, periventricular leukomalacia, hydrocephalus, necrotizing enterocolitis, subglottic stenosis and necrotizing tracheobronchitis will need to be compared in the experi-

mental and conventional treatment groups. Whereas some complications occur relatively infrequently, others which are important causes of permanent handicap are relatively frequent. As some of this handicap becomes evident only after a latent period of more than a year, assessment of which is the better method of ventilation in a global sense will be possible only after a period of follow-up of about eighteen months.

Thus a clinical trial of HFV involves an important number of variables both at the point of entry to the trial and at the time of evaluating the outcome. The large number of patients required for this effort can be recruited in a multicenter trial. With an escalating incidence of chronic lung disease in ventilated preterm neonates, a treatment that reduces lung injury and long-term morbidity will have an important effect on the economic and emotional costs of this complication and requires systematic evaluation.

II. Objectives of the Study

The primary objective of the study is to assess the efficacy and safety of HFV by comparing HFV infants to CMV infants in regard to the following outcome variables:

1. Incidence of Chronic Lung Disease (CLD) sometimes referred to as BPD. This is defined on the basis of
   a) need of supplemental oxygen on the 28th postnatal day and for more than 21 days of the first 28 days after birth and
   b) abnormal chest radiography findings persisting until the 28th day.
2. Severity of pulmonary insufficiency at 14 and 28 days postnatal age;
3. Proximal airway pressures and F_IO_2 required to provide adequate oxygenation and ventilation during first 72 hours after birth;
4. Incidence among HFV infants that oxygenation and ventilation become severely inadequate to the extent that CMV is substituted for HFV.
5. Incidence among CMV infants that oxygenation and ventilation become severely inadequate to the extent that HFV is substituted for CMV.
6. Mortality rate up to 18 months (corrected) age;
7. Incidence of massive air-leak;
8. Incidence of major intraventricular hemorrhage.

The secondary objective of the study is to determine the effect of HFV on the incidence of other common complications of prematurity and ventilatory failure detectable up to 18 months corrected age. This objective will be met by assessing the following outcome variables:

1. Air-leak of any degree;
2. Intraventricular hemorrhage of any degree;
3. Symptomatic patent ductus arteriosus;
4. Necrotizing enterocolitis;
5. Retrolental fibroplasia;
6. Pulmonary infection;
7. Pulmonary hemorrhage;

8. Duration of mechanical ventilation;
9. Duration and dose of oxygen requirement;
10. Age when 90 or greater cal/kg/day attained by enteral route;
11. Age when birthweight regained;
12. Dose and duration of oxygen therapy at home;
13. Need for rehospitalization for respiratory or other illnesses during 18 months;
14. Pulmonary status at 18 months corrected age; and
15. Neurodevelopmental status at 18 months corrected age.

A. Hypotheses

1. High frequency ventilation is superior to conventional mechanical ventilation when used to support premature infants with ventilatory failure beginning at or shortly after birth. Compared to infants managed with CMV, infants managed with HFV have
   a. a lower incidence of CLD;
   b. less severe pulmonary insufficiency at 14 and 28 days post-natal age;
   c. adequate oxygenation and ventilation at reduced airway pressures/oxygen exposure during the first 72 hours after birth; and
   d. less pulmonary-related morbidity in the first 18 months of life.
2. High frequency ventilation is as safe as CMV when used to support premature infants with ventilatory failure beginning at or shortly after birth.
   a. Mortality rate up to 18 months (corrected) age is not influenced by the method of mechanical ventilation.
   b. The incidence of massive air-leak is not influenced by the method of mechanical ventilation.
   c. The incidence of major intraventricular hemorrhage is not influenced by the method of mechanical ventilation.

3. Complications such as air-leak (of any degree), symptomatic patent ductus arteriosus, necrotizing enterocolitis, pulmonary infection, retrolental fibroplasia, etc., often occur in premature infants with ventilatory failure. There are no differences in the incidences of these complications between HFV and CMV when used to support premature infants with ventilatory failure beginning at or shortly after birth.
4. There is no difference in neurodevelopmental status at 18 months (corrected) age between infants who were supported by CMV and infants who were supported by HFV.

III. Ventilators

A. Consideration of Jet Ventilators vs. Oscillators or Flow Interrupters

The Committee recognized that there is a fundamental difference between high frequency jet ventilators, which are typically operated at frequencies of 150-400 breaths/minute, and high frequency oscillatory ventilators or flow interrupters, which are typically operated at 400-2400 breaths/minute. Aside from the frequency at which the machines are operated, the mechanism of action is thought to be different. The jet ventilators use a compressed gas source at relatively high pressure with the gas being delivered through a small bore tube opening some distance down the endotracheal tube. Gas resident in the endotracheal tube may be entrained with the compressed gas flow. The pressure contour is complex. The oscillatory ventilators deliver a pressure pulse that much more resembles a sine wave, with an expiratory phase that involves active withdrawal of gas from the respiratory system and tidal volumes that may be a small fraction of the dead space. With the flow interrupters the tidal volume is also a small fraction of the dead space, while expiration is totally passive, relying largely on the recoil of the respiratory system. Both the oscillators and interrupters are typically used at higher frequencies than are the jet ventilators. While acknowledging some differences between the flow interrupters and oscillators, the Committee felt that these two types of machines were more similar to each other than to either jet ventilators or conventional mechanical ventilators.

The Committee considered the option of conducting a trial designed to compare all three modes of ventilation against each other or at least to compare the two high frequency modes independently against conventional ventilation. However, considerations of logistics and statistical power precluded either of these options, and the Committee was forced into choosing between jets or oscillators/interrupters as the high frequency mode to be evaluated.

While the collective experience of the Committee and its consultants was not uniform, there was much more concern expressed regarding the side effects (such as tracheal lesions) of prolonged high frequency jet ventilation than with the side effects of prolonged ventilation with

high frequency oscillation or flow interruption. On this basis, the Committee decided to consider only oscillators or interrupters for inclusion in the trial.

B. Bench Testing of Devices

The Biomechanics Institute in Boston compared the mechanical performance of eight neonatal high frequency ventilators under identical operating conditions. This study employed in vitro models which embodied the essential mechanical properties of the neonatal respiratory system in health and in varying severity of disease. The principal physiological characteristics examined were tidal volume delivered, frequency dependence of the volume delivered, load dependence of volume delivered, peak inspiratory flow rate, and waveform characteristics of volume delivered, flow, distal pressure and proximal pressure. Substantial differences were observed between devices with regard to these measures, but some common features emerged. Tidal volume increased with endotracheal tube size, but was insensitive to changes in respiratory system compliance; tidal volume diminished with increasing frequency in 7 of the 8 devices. Peak inspiratory flow rates for a given tidal volume and frequency were smallest in the group of oscillators as compared with jets and flow interrupters. The oscillator group is recommended for use in the High Frequency Intervention Trial because of substantial positive clinical experience, smaller peak inspiratory flow rates for any given frequency and tidal volume, and physiological equivalence of the devices within this group.

A detailed discussion of the bench testing is given in Appendix D.

C. Ventilator Choice

As a result of the extensive Bench testing and a detailed study of the Metran Oscillator on rabbits and infants by Dr. A. Charlie Bryan, the Mera BMO 20N Hummingbird was chosen as the high frequency ventilator to be used in this study.

D. Animal Experience and Training With the Ventilator

Once FDA approval in the form of an Investigational Device Exemption has been received, two investigators (including the principal investigator(s)) from each Center will participate in a two-day training session with the HFV device at a regional center experienced in its use. This session will involve familiarization with the various operational

modes of the machine and with the safety features and possible causes of breakdown. Following that will be a period of hands on experience in ventilating one or more anesthetized rabbits per investigator.

Following the regional meeting, each pair of investigators will repeat the exercise at his or her own institution so that the medical staff involved with patient care can learn the capabilities and limitations of the machine. Hands on experience in ventilating a laboratory animal shall be provided for all those expressing an interest. An abbreviated indoctrination shall be provided for all new staff who join the study after enrollment has begun. Use of the machine with both normal and injured lungs will be required of each participant.

E. Human Experience Before the Initiation of the Trial

In order that the HFV device be given the most objective evaluation, it is important that each center has reached at least a basic level of competence with the new machine and that the personnel be familiar with the protocol for its use. To this end, each center shall screen, obtain informed consent, and ventilate with HFV at least five infants but not more than ten who meet the entry criteria specified in "Patient Selection". The patients are to be managed according to the guidelines described in Sections X through XI, including those for failure on HFV. Since this period will be a learning experience, none of the data collected will be analyzed as true study data. It is expected that this experience will be gained in a period not to exceed 6 weeks. The length of this study is at the discretion of the principal investigator.

IV. Patient Selection

Infants will be considered candidates for this study if they have respiratory distress with respiratory failure, including HMD, pneumonia, persistent pulmonary hypertension, etc., and are in need of mechanical ventilation. The criteria for mechanical ventilation will vary by weight group and the underlying pulmonary disorder. Therefore the term "respiratory failure" is loosely defined to include hypercapnia, hypoxemia requiring supplemental O_2 and apnea or abnormally low respiratory frequency. Twins who meet the qualifications will be eligible for randomization to the same form of treatment but multiple births of more than two will be excluded.

A. Eligibility Criteria:

1. Birthweight 750-2000 grams (includes AGA, SGA, LGA);
2. Age - up to 24 hours;
3. Infants may be treated with CMV for as long as 12 hours prior to qualifying. The 12 hour limit on CMV permits the inclusion of infants wherein CMV has been initiated at an outside hospital, makes allowance for variability of mechanical ventilation criteria from center to center and allows for the inclusion of infants ventilated for apnea who will eventually (< 12 hours) meet the qualification criteria for randomization.
4. Infants weighing between 750-1250 grams need only require assisted ventilation to be eligible for randomization. Qualification for infants in the 1251-2000 gram range will be based on a $PaO_2/F_IO_2 < 100$ and receiving CMV at a $\bar{P}aw$ of $\geq$ 9 cm H_2O. Qualification for randomization is based on blood gas criteria which might reasonably predict the need for mechanical ventilation to continue beyond a few hours. These qualifying criteria must be confirmed by 2 consecutive blood gas determinations at least 30 minutes apart and not more than 90 minutes prior to randomization and treatment.

B. Exclusion Criteria

1. meconium aspiration,
2. neuromuscular conditions affecting respiration (e.g., major CNS malformation or pathology),
3. hydrops fetalis,
4. congenital heart disease except PDA, and asymptomatic atrial or ventricular septal defects,
5. major congenital malformations, e.g., chromosomal, diaphragmatic hernia, hypoplastic lung (Potter-like syndrome), gastrointestinal,
6. multiple births of three or more,
7. infant judged nonviable by the center PI or designate.

C. Informed Consent

In seeking informed consent, the following information shall be provided to the parent(s) of each subject.

(1) A statement that the study involves research, an explanation of the purposes of the research, the expected duration of the subject's participation, and a description of the procedures to be followed.

(2) A description of any reasonably foreseeable risks or discomforts to the subject.

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research.

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.

(6) An explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

(8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

The Consent Forms for the Pilot Study and for the Main Study are given in Appendix B.

V. Baseline Measurements

Baseline measurements refer to data which are collected on the mother and infant up until the time of randomization and treatment. These data will be collected via a Screening Form, a Maternal and Perinatal Data Form, and an Infant Entry and Hospital Form. The Screening Form will be completed on any infant meeting the minimum requirements of the study and will determine the eligibility of the infant for randomization. If the infant is not eligible for randomization, no further data beyond the Screening Form will be collected. Information collected during screening will include:

1. Date of birth, time of birth, birthweight, date of screening.
2. Preliminary diagnoses - apnea, pneumonia, RDS, etc.
3. Exclusion criteria - congenital diseases and malformations, multiple births $\geq$ 3.
4. Blood gases.
5. Participation, ventilator assignment.
6. Consent.

The Maternal and Perinatal Data Form and the Infant Entry and Hospital Form will be completed for all infants who are eligible for randomization. Data which are to be included on these data forms are as follows:

A. Maternal and Perinatal Data

1) Demographic - date of birth, education, marital status, occupation.
2) Pre-pregnancy history - diabetes, chronic hypertension.
3) Pregnancy History - gravida, full term, abortion, stillborn.
4) Smoking, alcohol, recreational drugs, illnesses, complications.
5) Labor and Delivery - gestational age, rupture of membranes, length of labor, complications, medications.

B. Infant Entry and Hospital Form

1) Birthdate, sex, ventilator assignment.
2) Fetal and Perinatal Data - cord prolapse, placenta previa/abruptio, fetal lung maturity, fetal distress, scalp pH.

3) Delivery - vaginal, caesarean, Apgar scores.

4) Resuscitation - intubation, cardiac massage, bag and mask.

5) Weight, length, head circumference.

6) Diagnoses - RDS, pneumonia, BPD, PDA, IVH, infections.

7) Medications, antibiotics, steroids, diuretics, sedation, methylxanthenes, etc.

8) Study outcome - crossover, extubation, weaned to CPAP.

9) Patient Disposition - discharged to home, to other hospital, died.

VI. Randomization Procedures

The design for this trial is a two-armed treatment design (e.g., conventional mechanical ventilation and high frequency ventilation) in which treatment assignment is randomized within hospital and within infant birthweight groups defined by 250 gm increments from 750 gm to 1500 gm and a single stratum for infants between 1501 and 2000 gm. Since this study will enroll patients at all hours at the clinics and the time interval between identification of an eligible patient for randomization and treatment is critically short, a distributed randomization scheme will be implemented.

Under this system, RTI will furnish each of the clinical units the following:

1. a set of computer-generated ID labels to be used for patients who are candidates for the study. A screening form will be initiated on all such infants, the computer-generated ID label will be affixed to the form, the form will be filled out as completely as possible, and will be forwarded to RTI.
2. A set of sealed envelopes for each birthweight stratum. These envelopes will be used for the infants who are eligible and whose parents have given consent for participation in the study. This set of envelopes will have sequentially assigned numbers on the outside to permit them to be taken in order, and to permit them to be properly reordered in case accidental shuffling occurred. These envelopes will be sequentially assigned to participating infants who are not eliminated by the initial exclusion criteria and will contain the treatment assignment and all computer-generated labels necessary for the patients' data forms and other study materials. The Coordinating Center will monitor the adherence to the assignment system by using the sequence number, date, and time of screening.

The major advantage of this system is its operational ease at the centers. Once an infant is determined to be a candidate for the study, the appropriate treatment can readily be assigned with little difficulty.

For this system to function satisfactorily, the principal investigator should assume the responsibility for the integrity of the screen-

ing and randomization system. Any cases of violation of the system (for example, not enrolling the patient after finding out what the patient would be assigned to) should be closely monitored by the principal investigator, must be made known to the Coordinating Center, and all treatment assignment envelopes for such cases should be returned to Coordinating Center with relevant information.

In addition to the strata which have been introduced into the design by the birthweight groups, the random assignment of the treatment to the infants within these strata will be done with a random size blocking scheme which will ensure balance within each of the strata.

Since the HFVs are in limited supply, the possibility arises that a clinic has no HFV available at various times. At such times, candidate infants cannot be randomized. Because it is deemed desirable to assign twins to the same type of ventilator, twin infants obviously cannot be considered for randomization unless at the time of their availability there are at least two HFVs available. Multiple births of more than two infants will not be eligible for randomization. There will be at least one backup HFV in each clinic center. When a HFV breaks down, it will be replaced by the backup, and the manufacturer, upon notification, will deliver a replacement backup within three days. When an infant terminates use of a HFV, the machine will be reserved from assignment to another infant for three days to provide for the possibility that the infant who terminated will re-initiate use.

When investigators make decisions regarding the assignment of HFV machines, priority should be given to ensuring that infants already enrolled in the trial have access to a machine should they need one, since if the protocol is violated by the use of CMV, the infant cannot be discounted from analysis. At any center, there are potentially three pools of HFV machines: "regular", "backup", and "3-day reserve". If a new machine is needed by an infant already enrolled in the study, the pools should be tapped in that order. That is, if there is a breakdown of an HFV machine or a switch from CMV, a "regular" machine is to be used, if available, even if this should result in enrollment being interrupted. If a "regular" machine is not available, a "backup" machine is to be used. If neither a "regular" nor a "backup" is available, a machine being held on "3-day reserve" for a different infant is

to be used. Finally, of course, CMV should be used until an HFV machine becomes available if all three pools are depleted. The same scheme applies to a baby who has been weaned from HFV but who requires ventilation some time later (unless, of course, that baby's "3-day reserve" machine is still available). The suggested strategy for utilization is summarized in tabular form in Appendix C.

VII. Sample Size and Power

The target sample size planned for this trial is 1500 which is expected to be reached after a year of recruitment. The recently completed NHLBI study to evaluate the Efficacy of Antenatal Steroid Therapy in the Prevention of Respiratory Distress Syndrome provides data on 160 infants of less than 2000 grams weight who were treated with mechanical ventilation. Preliminary analysis indicates that 18% of this group suffered from chronic lung disease. If this is assumed to be a reasonable level for the mechanical ventilator groups of the current study, then the proposed sample size divided evenly between two treatment groups will be sufficient to detect a 36% reduction (i.e., from about 18% to 11.5%) in the BPD rate at a 5% level of significance and a 90% power (two-tailed test). This sample size will also permit at this same power and significance level a detection of a 25% reduction in the mean value of any outcome variable with a coefficient of variation (i.e., standard deviation divided by the mean) of not more than 150%.

VIII. Data Analysis

A. Introduction

RTI and NIH statisticians will analyze the data and prepare reports for the periodic meetings of the Steering Committee and the Policy Advisory Board. The staff will also provide the necessary statistical expertise and data processing support for the publication of scientific manuscripts based on the study data. Several manuscripts based on the study data will be prepared for publication and such manuscripts will require methodology and analysis spanning the spectrum of statistics. The techniques which may be required in support of all the possible manuscripts generated by this study cannot be completely anticipated; therefore, attention will be focused on the types of analyses pertinent to the primary and secondary objectives of the study.

The analysis procedures for the study are basically of two types.

- Descriptive Statistics: Distributions and tabulations indicating the general description of the study population, the progress of the study and crosstabulations involving outcomes and factors known to or suspected to be associated with these outcomes.
- Detailed statistical analyses to assess the efficacy of high-frequency ventilation and to address other substantive issues.

B. Descriptive Analysis

Descriptive statistical analysis and related data presentations will be divided into four types.

(1) Those which depict the progress and status of the study with respect to screening, enrollment, refusals, terminations (death, dropouts, and lost to follow-up), follow-ups, and completetion of various forms. This set of tabulations is meant to provide necessary information for monitoring the enrollment and data acquisition aspects of this study. Also included in this type are tabulations depicting the status of the computer data base (number of forms received, keyed, rejected at the time of edit, passed edit, and in the final data base) for each study form and summary statistics based on

these data. This set of tabulations will be useful for monitoring the data processing aspects of this study.

(2) Those which compare the enrolled infants (randomized and enrolled) and those who were eligible but not entered (i.e., refusals, patients in conflicting protocols, etc.) on baseline variables such as Apgar scores, birthweight, gestational age, race, sex, inborn or not, etc. The purpose of this set is to assess the limitations of the study with respect to its generalizability to the population of eligibles.

(3) Those which compare the two treatment groups (conventional mechanical ventilation/high-frequency ventilation) on summary statistics (mean/median) of performance measures such as number of days the infant is in need of treatment, mean airway pressure required to maintain adequate blood gases, etc.

(4) Two way cross tabulations depicting associations between treatment and outcomes (death, neonatal chronic lung disease, patent ductus arteriosus, intracranial hemorrhage, developmental abnormalities at 18 months, etc.), between outcomes and baseline variables, and among outcomes.

The purpose of these descriptive analyses and tabulations is to provide an overall picture of the study including a feel for the internal validity and generalizability of the study results. These tabulations will also give an overall idea of the progress of the study and a frame of reference with which to compare the results of this study to other studies. The tabulations describing the distribution of baseline variables and outcomes and their interrelationships will be particularly helpful in understanding the reasons for differences, if any, between the results of this study and other studies. Such analyses are common in multicenter clinical studies and detailed discussion of such graphs, tables, and histograms as may be appropriate will not be made here. Suffice it to say that these analyses will be carried out using a standard statistical package, preferably SAS (Statistical Analysis System, SAS Institute, 1982), and will be disseminated to the appropriate groups (Steering Committee, Policy Advisory Board) at each of its periodic meetings. As table formats become finalized during the earlier phase of the study, they will be computer generated, thus reducing the

chance of transcription errors and negating the need for typing of the tables.

C. Statistical Analysis for Assessing the Effect of High-Frequency Ventilation and Other Substantive Issues

The general strategy for the analysis of the effects on outcomes will be to use a general linear model (e.g., analysis of covariance) for those endpoints which are continuous in nature (e.g., the number of days the infant is in need of mechanical ventilation), to use a logistic regression model for those endpoints which are dichotomous in nature (e.g., chronic lung disease) and to use multiple contingency table analysis or the general methodology for analysis of categorical data based on minimum chi-square methods (Grizzle, Starmer, and Koch, 1969) for those endpoints which are polytomous (e.g., a classification of Bayley mental development index into 3 categories corresponding to normal, suspected, abnormal).

1. Statistical Adjustment to the Treatment Comparisons

The proposed trial is a randomized experiment and in general should uniformly distribute factors which are known or are already determined at the time of entry into the study, across the treatment groups. It may very well happen, however, that in the process of performing the analysis one finds a preponderance of infants with a certain factor in one of the treatment groups. (This could happen by chance or by certain actions taken following screening/treatment assignment. For example, if some of the clinicians permit only "severe" cases to be treated with high-frequency ventilation, certain patients assigned to this mode of therapy may be shown as refusals and consequently there may be a preponderance of "severe" patients in the high-frequency ventilation group). If baseline (i.e., measurements taken before treatment) variables are available to index the risk factor which does not appear to be evenly distributed among the treatments, then these variables may be used to compensate for the imbalance in the treatment groups through covariance adjustments. It may also be that certain baseline measurements correlate well with the endpoints of interest and hence may be used to enhance the power of the statistical analyses. Thus, there will be a set of baseline variables which will be used in statistically adjusting the treatment comparisons for the outcomes of

interest. For this study the variables that may be used in statistical adjustments for treatment comparisons will include: sex, race, variables which reflect the severity of the need for ventilatory support, Apgar scores, Dubowitz score, birthweight, clinical diagnosis (the diagnostic category of respiratory distress), etc. Since clinical center will be a stratification variable, it will also be included in the models for the analysis of outcomes.

The actual list of baseline variables to be used for covariance adjustment will be developed from a larger list than that given above by stepwise procedures and by discussions with the study physicians. This is an iterative process which will develop over the course of the trial and will result in a final set of covariables for which outcomes analyses will be adjusted. Care must be taken in choosing the number of covariables to use in adjustment of analyses involving discrete events (e.g., death) for the analysis techniques available are notoriously unstable when a large number of covariates are involved and the number of events is small.

For the analysis of outcomes data related to infant development at 12 months, the choice of variables for adjustment includes those measured or determined at the time the infant was entered into the study and variables measured or determined subsequently. The latter group may include medical complications and conditions which may be directly affected by the treatment and are also known (or suspected) to be causally related to the outcomes which manifest subsequently. Inclusion of such variables as independent variables in a model for the analyses of later outcomes sometimes appears to lead to conflicting results (The Coronary Drug Project Research Group, 1980). Therefore, careful consideration will be given to the substantive and statistical implications of incorporating/not incorporating these variables in models used for statistical analysis.

2. Analysis of Continuous Type Outcomes

For the purpose of illustrating the analysis of outcome variables which are of the continuous type, consider the MDI from the Bayley at the 18-month evaluation. The independent variables for this illustration will include the following:

- clinical center (C)
- treatment (T)
- birth weight (W)
- clinical diagnosis at entry (D)

The general form of the model which would be appropriate for analyzing the treatment difference in the MDI would be given by:

$$Y_{ijk\ell} = \mu + T_i + C_j + D_k + \beta w_{ijk\ell} + (TC)_{ij} + (TD)_{ik} + \varepsilon_{ijk\ell} \qquad (1)$$

where

$Y_{ijk\ell}$ = the MDI of the infant (infant ℓ given treatment i in clinic j and diagnosis category k)

μ = the overall mean

T_i = effect associated with treatment i (i = 1 if conventional mechanical ventilation and = 2 if high-frequency ventilation)

C_j = effect associated with clinic j (j = 1, 2, ..., 10)

D_k = effect associated with diagnostic category k (k = 1, 2, ..., K)

$(TC)_{ij}$ = the joint effect (interaction) of j^{th} clinical center and treatment i

$(TD)_{ik}$ = the joint effect (interaction) of k^{th} therapeutic category and treatment i

$w_{ijk\ell}$ = birthweight of the infant - a covariable to be used to adjust treatment comparisons

β = regression coefficient

$\varepsilon_{ijk\ell}$ = a random error term assumed to be distributed as a normal distribution with mean 0 and constant variance.

Various hypotheses related to parameters of this model can be tested using standard procedures used in general linear model analysis (see for example GLM procedures in SAS).

The major hypothesis of interest is whether there is a difference in the MDI between those treated with conventional mechanical ventilation and those treated with high-frequency ventilation.

If the hypothesis is $T_1 = T_2 = 0$ and

$(TC)_{11} = (TC)_{21} = (TC)_{12} = (TC)_{22} = \ldots = (TC)_{1,10} = (TC)_{2,10} = 0$ and

$(TD)_{11} = (TD)_{21} = (TD)_{21} = (TD)_{22} = \ldots = (TD)_{1K} = (TD)_{2K} = 0$ (i.e., main effect of treatment, the treatment x center interaction and treatment x diagnosis interaction are simultaneously zero) is not rejected, one can (within the context of the variables included in the analysis) conclude that there is no difference between the conventional mechanical ventilation group and the high-frequency ventilation group in the MDI scores. If the hypothesis is rejected, one would proceed further through tests of subhypotheses involving the main effect of treatment alone (i.e., whether the overall differences in MDI between the two modes of therapy is significant), and/or interactions alone (e.g., magnitude of the effect is different in certain centers/certain diagnostic categories) and/or subsets of main effect and interactions to identify subgroups (centers, diagnostic categories) in which the effect of the treatment appears to be different.

Summary statistics (mean, standard errors, and sample size) related to the effects which are found to be statistically significant will be presented when it is appropriate. For example, if the interaction between center and treatment is statistically significant, a table comparing the mean for the conventional mechanical ventilation group to the mean for the high-frequency ventilation group for each of the clinical centers may be presented. If the interaction between diagnostic category and treatment is statistically significant then a table comparing the means of infants in the two treatment groups within each diagnostic category may be presented. Tables showing estimates based on the model (least square means provided by SAS or means based on other appropriate weights) may also be presented where appropriate. Such tabular presentations are easily understood and clinical researchers may, in some cases, be able to compare these data with those in the literature.

It is worth noting here that the analysis of the type discussed above can be done at varying levels of complexity and can be used to assess (test) a wide range of hypotheses related to the effect of high-frequency ventilation as well as the effect of explanatory/independent variables such as birthweight and diagnostic category or the duration of ventilation. A significant difference among the centers (i.e., if the hypotheses $C_1 = C_2 = \ldots = C_{10} = 0$ is rejected) may indi-

cate that the attempts to standardize the methods of operating high-frequency ventilators (or conventional ventilators) were not successful. Thus the analysis of the type described above can be used for both assessing the performance of high-frequency ventilation relative to conventional mechanical ventilation and for monitoring the clinics on some aspects of the protocol.

3. Analysis of Categorical Type Outcomes

Most of the outcomes which will be used to evaluate the major hypotheses of the study (see section II.A) are dichotomous (e.g., death, bronchopulmonary displasia) or polytomous (e.g., grouping pulmonary insufficient frequency into three categories -- mild, moderate, severe -- or cause specific mortality rates) rather than continuous variables. Appropriate statistical analysis strategies for such variables will range from simple chi-square type analysis, comparison of two proportions, and stratified analysis using Mantel-Haenzel type procedures to more complex analytical strategies based on logistic regression models and multiple contingency table analysis methods.

To illustrate these models consider the analysis of a classification of pulmonary insufficiency into three categories. Other variables in this analysis will include an SES index (3 levels) , initial diagnostic category (say 3 levels) and treatment (2 levels). These data can be organized as a four-way contingency table with SES as the first dimension (S with 3 levels), diagnostic category (D with 3 levels) as the second dimension, treatment (2 levels) as the third dimension and infant status (pulmonary insufficiency with 3 levels) as the last dimension. This data can be further summarized as a 3 x 3 x 2 x 3 matrix of rates where the entry in the i, j, k^{th} row, $P_{ijk} = (p_{ijk1}, P_{ijk2}, P_{ijk3})$ is a vector of proportion of infants in each category of insufficiency outcomes among infants in the i^{th} SES level, j^{th} diagnostic category and k^{th} treatment. This data can be analyzed using the minimum chi-square categorical data analysis methods developed by Grizzle, Starmer, and Koch [GSK] (1969). A model for this analysis is

$$f(P_{ijk}) = \mu + S_i + D_j + T_k + (DT)_{jk}$$

where $f(P_{ijk})$ = a function of P_{ijk}

(for example $f(P_{ijk}) = \log p_{ijk3}$, i.e., the proportion of severe patients or $\log(p_{ijk3}/1-p_{ijk3})$)

μ = overall mean

S_i = effect associated with the i^{th} SES classification

D_j = effect associated with j^{th} diagnostic category

T_k = effect associated with k^{th} treatment

$(DT)_{jk}$ = the joint effect (interaction of the j^{th} diagnostic category and k^{th} treatment.

Various hypotheses related to parameters S_i, D_j, T_k and $(DT)_{jk}$ can be tested using the minimum chi-square method. (The FUNCAT procedures in SAS will be a help in the required statistical computations.) This analysis is somewhat similar to the general linear model analysis for outcomes which are continuous. The major hypothesis of interest is whether the effect of treatment (as indicated by the differences between the two treatment groups in $f(P_{ijk})$) is statistically significant. These differences are adjusted for the possible effect of SES and the differential effect of the diagnostic categories. If the hypothesis $T_1 = T_2 = 0$ and $(DT)_{11} = (DT)_{12} = (DT)_{21} = (DT)_{22} = \ldots = (DT)_{32} = 0$ (i.e., the main effect of treatment and diagnostic category x treatment interaction are simultaneously zero) is not rejected, one can conclude that there is no difference between the two treatments or that there is no treatment effect on this outcome (in the context of the variable included in the model). If the hypothesis is rejected one would proceed further with tests of subhypotheses involving main effects alone and/or interactions alone and/or subsets of main effects and interactions to identify subgroups (diagnostic categories, SES categories, etc.) in which the effect of treatment appears to be different.

The logistic regression model analysis will be similar to the analyses discussed above but can deal only with dichotomous outcomes such as bronchopulmonary displasia. The dependent variable will always be a rate or a probability and the estimation and test of hypothesis will be based on the maximum likelihood method (as opposed to minimum square based methods). Both the logistic regression analysis and the GSK method can include continuous covariates for adjustment of treatment

differences. The loglinear model based multiple contingency table analysis, on the other hand, cannot deal with continuous covariates but can be used to analyze polytomous outcomes. The method of estimation and test of hypotheses is based on maximum likelihood and the approach is capable of dealing with a much broader class of hypothesis than the logistic regression analysis. The nature of independent and dependent variables which ultimately are used to test the hypotheses will decide the choice of the method of analysis.

In the above discussions, treatment differences were adjusted for several variables simultaneously. A stratified analysis using the Mantel-Haenzel type procedures will be pursued during earlier stages of analyses when it is more appropriate to do several stratified analyses, stratifying for one variable at a time. Pursuing this strategy may lead to a better understanding of the data especially in situations where the stratification variable is one which could be affected by the treatment. Consistency of the ordering of the magnitude of the outcomes between the two treatment groups in all the strata (except perhaps a few), which is demonstrated using the Mantel-Haenzel procedure and the associated tabular displays is sometimes much more easily understood than model-based analysis. Therefore this type of analysis will be done and the results displayed as part of the background data for the conclusions based on model-based analysis discussed earlier.

The tabular presentations related to the findings of these analyses will be similar to those used in the analysis based on general linear model analysis. Instead of the means, the rates or odds will be displayed for categorical endpoints.

4. Incorporating Outcomes Detected Posterior to Treatment in the Analysis of Subsequent Outcomes

The design of the study calls for measurement and diagnosis of a number of conditions following the treatment. Some of the outcomes identified earlier in time may be causally related to outcomes measured later in time.

Since the patients are allocated at random to the mode of ventilation in this study, a variety of analyses excluding these variables will provide unbiased estimates of the effects of the treatment. However, in such analyses the explanation of the effectiveness of the therapy will

be only in terms of baseline variables. These analyses are unsatisfactory in situations where there are hypotheses related to the causal chains involving baseline variables, intermediate outcomes and final outcomes. They may also be unsatisfactory for analysis of follow-up outcomes in situations where there is non-random attrition in the study population (due to death, withdrawal from study or loss to follow-up).

One approach to incorporating such variables is to include them as stratification variables or covariates. In such an analysis the estimate of the effect of the treatment will differ from the estimated "effect of the treatment" based on the model excluding the variable. The covariates remove not only the effect of the covariate but may also remove part of the treatment effect.

Another approach is to analyze the data using a system of recursive models (a special type of simultaneous equations) instead of the single equation model. This approach is well developed and is included in textbooks of quantitative methods in sociology and economics (Intriligator, 1978; Namboodiri et al., 1975). Applications of these methods in clinical studies are few (Susser, 1982). In this approach one can separate the direct and indirect effects of variables on the effectiveness of the treatment. These techniques are appropriate where the outcome variables involved are continuous variables. When the data are organized as multiple contingency tables the modified path analysis approach proposed by Goodman (1973) is more appropriate than the recursive equation formulation used in econometrics.

These methods can be applied if intermediate outcome variables are to be included in the analysis. It should be pointed out, however, that experience with these methods in the analysis of data from clinical trials is limited and therefore may require some development before they can be applied.

D. Periodic Monitoring of the Trial

One very important factor in the monitoring of a clinical trial is that all the analyses are performed periodically (e.g., every six months) and the results are viewed by the Policy Advisory Board in order to decide if the protocol should continue as is, the protocol should be altered and the study continued, or the study should be halted (Friedman, et al. 1981). This "multiple looking" at the data introduces

a statistical complication in the interpretation of results if one is simply to consider nominal significance levels of say 5 percent at each of the looks. To provide some adjustment for this multiple examination of the data, particularly the endpoint data, sequential graphs of the analysis of the key endpoints along with significance bounds which adjust the significance level at each look to attain a nominal significance level of say 5 percent at the end of the study will be prepared. Such graphs will be included along with the other information in the report to the Policy Advisory Board. In the past, RTI has used the O'Brien-Fleming bounds (O'Brien and Fleming, 1979) in the preparation of these graphs. Recent work by Lan et al. (1984), however, proposes bounds which may offer some advantages over those of O'Brien and Fleming.

A second important analysis activity which is helpful to the PAB in making decisions on the continuation of the study is conditional power calculations (Lan, et al., 1982). It is of interest, for example, to know what the chances are of obtaining a significant result at the end of the study given the results at some point in time during the study. These calculations may be made under various assumptions about the future trends of the trial (e.g., same trend as seen to date, treatment effect is 20% greater in the future than to date, etc.) and they give the Board members an estimate of the odds that the study would have turned out positive should they decide to stop it at that point in time. Sequential bounds are available for one-tailed or two-tailed monitoring.

Outcome variables for periodic monitoring of this study will include: (1) incidence of bronchopulmonary dysplasia, (2) death rates, (3) morbidity rates, (4) incidence of air leaks, and (5) incidence of intraventricular hemorrhage.

E. Analysis Problems

The endpoint data generated from this study will suffer from the same basic problem that is present to some degree in data collected from any trial: specific endpoint determination will not be available on all randomized patients. Problems in interpretation of the analysis occur if missing endpoint data are not randomly distributed between the two treatment groups. For example, the primary endpoint of the study, chronic lung disease, competes with death and treatment failure as an endpoint. It if happens that one treatment group has a higher treatment

failure rate and a lower CLD rate, then the results become difficult to interpret.

One solution to this quandary is to analyze a composite outcome variable which is formed as a function of the competing outcomes. In the above situation, one may look at the incidence of death or treatment failure or CLD and this index should be available on virtually everyone. Methods discussed in section VIII.C.3 are appropriate for analyzing this rate. Refinements in this strategy may be made by differentially weighting the components of the index to reflect the relative "importance" of each.

If a weighted index is used, then the methods of section VIII.C.2 will be appropriate.

IX. Guidelines for Use of Conventional Mechanical Ventilation and High-Frequency Ventilation

After an infant has been randomized to either group, ventilatory management will be standardized as much as possible. The infant should remain on the assigned ventilator throughout the entire course of treatment unless the criteria for switchover are met. However, an infant originally randomized to HFV may be switched to CMV after 30 days if continued HFV therapy is deemed unadvisable by the medical staff. For both HFV and CV groups, minimal ventilatory parameters to be monitored comprise: F_IO_2, $\bar{P}aw$, peak-to-peak proximal airway pressure, gas flow, frequency (including I:E ratio) and gas temperature. Changes in oxygenation can be accomplished via F_IO_2 and/or $\bar{P}aw$ such as to maintain a PaO_2 of 50 to 80 torr. Ventilation can be altered via rate and/or tidal volume changes during CMV, and only tidal volume changes during HFV (see later) in order to keep a pH of 7.25 to 7.45, usually accomplished at a $PaCO_2$ of 35 to 60 torr during the acute phase of respiratory distress.

A. Criteria for Treatment Failure

For either group, failure of treatment (a mandatory switch of ventilators) will occur when an infant has either one of the following:

1. Both a $PaCO_2 > 65$ torr and a $PaO_2 < 45$ torr in an F_IO_2 of 1.0 and a $\bar{P}aw$ of at least 15 cm H_2O, or
2. A PaO_2 of < 35 torr alone with a $\bar{P}aw$ of at least 15 cm H_2O.

The poor arterial blood gas values ($PaCO_2$, PaO_2) must persist in spite of two ventilator changes with accompanying blood gases within one hour. An attempt will be made to obtain two successive blood gases or ventilator setting changes within one hour after encountering an unacceptable blood gas. An acute event with temporary deterioration in condition, such as pneumothorax, is not criteria for switchover.

B. Criteria for Possible Return to Previous Therapy After Switchover

If a baby reaches criteria and is switched to the other ventilator, the initial $\bar{P}aw$ on the new ventilator should be the same as that from which the infant is switched. Arterial blood gases should be

done to document the change. Three things may happen on the new form of treatment.

1. Condition gets worse:

It is assumed that the infant was switched to the new ventilator because either the PaO_2 was < than 45 mm Hg and the $PaCO_2$ was > 65 mm Hg or PaO_2 was < than 35 mm Hg with increased $\bar{P}aw$. Therefore:

   a. If the arterial blood gas values worsen greater than 10 mm Hg for either PaO_2 or $PaCO_2$, the infant will be switched back to the original ventilator.
   b. Observation of the infant for as short a period as 15 minutes with at least one arterial blood gas will be performed before deciding that the baby is worse and needs to have the ventilator changed.

2. Condition remains the same: may stay up to six hours but then must go back to previous therapy.
3. Condition improves: must leave infant on the present form of ventilator.

It is possible to have more than one switchover in type of ventilator therapy during treatment.

A flow diagram depicting the course of an infant into the study, through randomization, and into the hospital phase is given in Figure 1.

After randomization of an infant, the protocol for initial ventilatory management will depend upon whether the infant is or is not already receiving conventional ventilation (CMV). In infants randomized to HFV and already stabilized on CMV, mean airway pressure ($\bar{P}aw$) and inspired oxygen (F_IO_2) will be maintained at the previous CMV values. In infants not yet receiving CMV, HFV will begin at a $\bar{P}aw$ of around 8-10 cm H_2O in the F_IO_2 that preceded assisted ventilation. In all instances of HFV, frequency will be set at 15 Hz and maintained at that level, even during weaning which will be accomplished by lowering the pressure swings and $\bar{P}aw$ once F_IO_2 is between .4 and .7 depending on the level of $\bar{P}aw$. Infants on HFV will be mechanically sighed and suctioned when clinically indicated. Peak pressure of the sigh will be monitored and delivered at up to 15 cm H_2O in excess of the current $\bar{P}aw$ and maintained for up to 1 second.

FLOW DIAGRAM

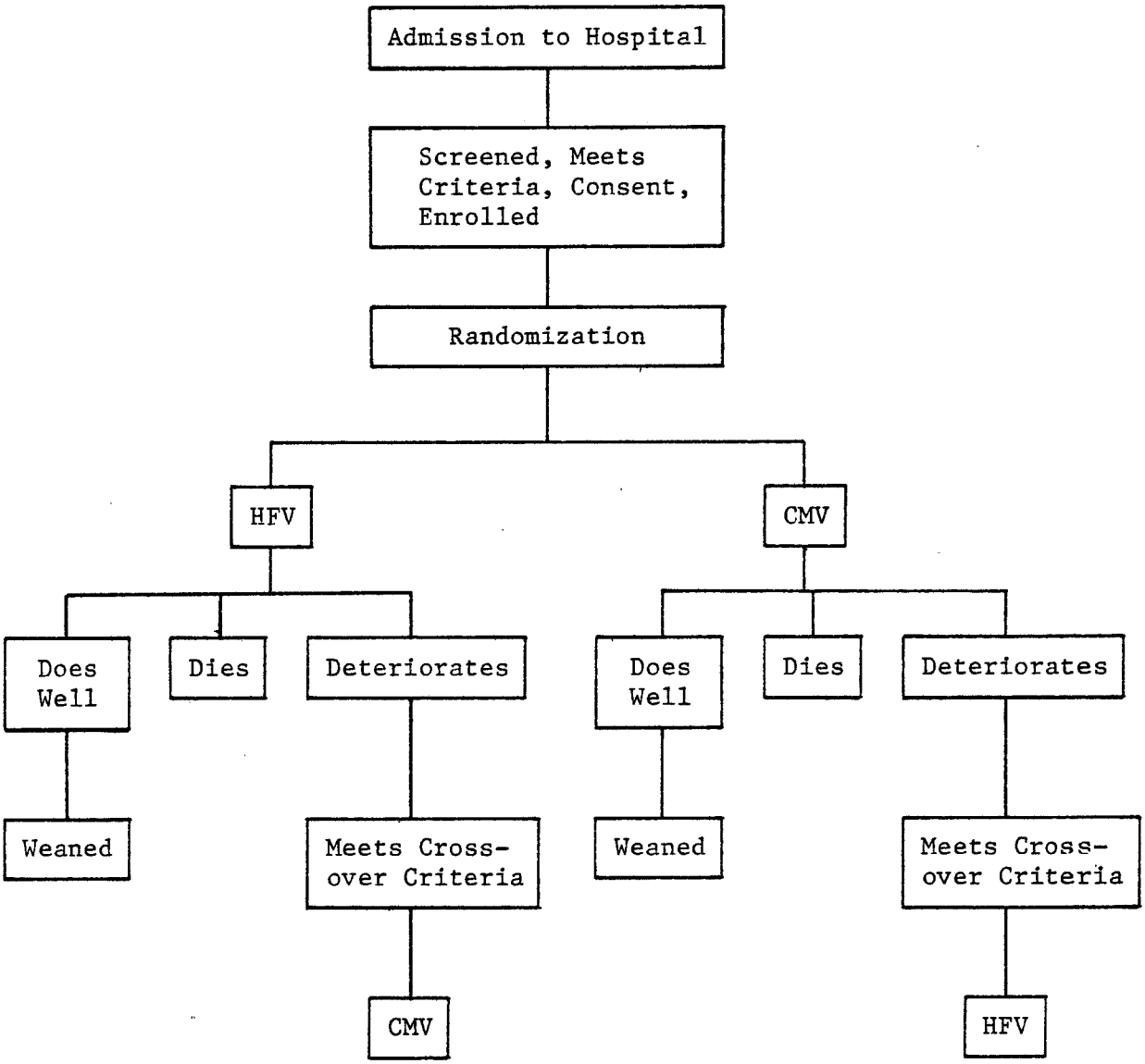


Figure 1.

In infants randomized to CMV, time cycled pressure limited ventilators will be used and guidelines for ventilatory management will also be set in order to maintain satisfactory blood gases. For the infant in whom CMV is being commenced, suggested initial settings are a frequency of 20 to 40/min, peak inspiratory pressure (PIP) of 20 to 25 cm H_2O, positive end expiratory pressure (PEEP) of 2 to 5 cm H_2O, and inspiratory duration of 0.3 to 1.0 sec, all depending on the severity of lung disease. Weaning for hyperoxemia is accomplished by initially decreasing F_IO_2 until it reaches between .4 and .7, then decreasing $\bar{P}aw$ (via PIP, PEEP and/or I:E ratio). This will need to be modified depending on the infants $PaCO_2$. Suctioning and sighing during CMV will be done according to each units clinical practice while monitoring airway pressure not to exceed 10 cm H_2O above the infants current peak inspiratory pressure.

C. Temperature and Humidification of Inspired Gas

During either HFV or CMV inspired gas will be warmed to 34 - 37°C, measured at the airway. Humidification will be provided during CMV by the method currently in use at each institution. During HFV, the system recommended by the manufacturer will be used.

D. Protocol Interruption

The mode of ventilation (CMV or HMV) may be interrupted for procedures such as surgery, special diagnostic procedures, unavailability of respirator or other changes. A "Protocol Interruption Form" should be filled out if the interruption is longer than one hour.

X. Suggested Guidelines for Standard Clinical Care

A. Thermoregulation

Infants will be nursed either in radiant warmers or isolettes with the skin servo controlled at approximately 36.5°C to maintain rectal or axillary temperature at 36.5 - 37.0°C. Doubled walled isolettes and/or single walled units with plexiglas shields are recommended in order to improve thermoregulation and decrease insensible water loss. Efforts should be made to move infants from radiant warmers to isolettes as soon as possible after stabilization. Humidification (>60%) may also be desirable for infants < 1000 gms.

B. Monitoring

All infants should have continuous monitoring of heart rate, respiration, blood pressure, and when indicated (i.e., unstable cardiovascular condition and questionable hypotension) central venous pressure. These parameters should be recorded at least q 2 hours. Arterial blood pressure transducers should be kept at the mid-thoracic level. A central venous line is especially valuable when volume expansion is considered. Arterial blood pressure and intermittent arterial blood gases will be monitored with umbilical or radial arterial lines when possible. If arterial access is not possible then blood pressure should be monitored non-invasively. Transcutaneous monitoring of PaO_2 and $PaCO_2$ (when available) should be used continuously during the patient's acute course.

C. Blood Pressure Support

Normal values will be defined based on data from Versmold, et al. (1981) for the first 12 hours of age, subject to clinical assessment and judgement, perinatal history, heart rate, color, capillary filling, urine output, central venous pressure and acid-base status.

Volume expansion should, as much as possible, be restricted to infants with histories of blood loss or low central venous pressure. Ventilation, correction of acid-base status, and adequate assessment of blood pressure and CVP values (i.e., attention to transducer position and characteristics of the arterial wave form) should precede volume expansion.

Treatment of hypotension secondary to volume depletion should consist of 10 cc/kg over 30 minutes of preferably whole blood. If not

available, fresh frozen plasma or 5% albumin is adequate. Rarely, unless there has been evidence of gross hemorrhage, should hypotension of undefined etiology be treated with more than 10 cc/kg. Pressor agents (Dopamine, Dobutamine and Isuprel) should be used if there is no response to volume. Volume expansion in the absence of a history of hemorrhage should be approached cautiously. Central venous pressure monitoring should be used if possible to assist in decision making.

D. Suggested Guidelines For Fluid Management

Fluid management will consist of administration of 60 to 80 cc/kg/day in the first 24 hours with increments of 10-20 ml/kg/day, thereafter, to a maximum of 150 cc/kg/day unless otherwise clinically indicated. Individual adjustments in fluids will be made by considering urine output, urine osmolality, "appropriate" variations in weight gain, use of radiant warmers, and need for phototherapy. Weights should be measured at least q 24 hours.

Fluids should initially consist of 5-10% glucose to which electrolytes are added to maintain serum electrolytes within normal limits.

E. Suggested Guidelines For Parenteral Nutrition

Parenteral nutrition should begin by day 4 of life if enteral feedings are not established. The composition of parenteral alimentation should include:

1. crystalline amino acids providing up to 2.5 gm/kg/day;
2. glucose to begin at 6 to 8 mg/kg/min (8-12 gm/kg/day) given as a 10 or 12.5% solution if given peripherally;
3. fat at 1 to 2.5 gm/kg/day to begin at 5 - 7 days of life. Infusion should be given over 12-18 hours with assessment of turbidity or triglyceride levels as necessary after initiation of the infusion;
4. intravenous multivitamins and minerals as per unit protocol.

Enteral feeding by intermittent or continuous intragastric or transpyloric feedings should be started as per unit protocol.

F. Patent Ductus Arteriosus

Symptomatic or hemodynamically significant PDA is diagnosed when cardiac or pulmonary function is compromised by left to right shunting through the ductus. This may be manifested by cardiomegaly, increased pulmonary vascularity or edema, deterioration in lung function

and physical findings including murmur, bounding pulses and a hyperactive precordium. In addition, its presence may be documented by echocardiogram and Doppler flow studies. Acceptable management of this condition includes anti-congestive measures, use of oral or IV indomethacin or surgical ligation. Unless contrary indicated by co-existing medical conditions, closure of the ductus will be sought in any infant with symptomatic PDA and ventilatory failure.

G. Diuretic Therapy

Diuretic therapy will be given at the discretion of the attending physician. Diuretics are indicated for the following conditions:

1. medical therapy for a PDA and/or congestive heart failure;
2. for patients with evidence of chronic lung disease; or
3. infants who develop a pattern of pulmonary edema with or without a clinically evident PDA or have had excessive weight gain over a 24-hour period.

H. Methylxanthines

Methylxanthines may be used for weaning infants from the ventilator when the infant is on low respiratory settings and F_IO_2, and is unable to be weaned due to poor respiratory effort.

I. Transfusions

The hematocrit should be maintained at greater than or equal to 30-40% while the infant is on oxygen or mechanical ventilation. In addition, transfusion should be considered when the infant has approximately 10% of his blood volume withdrawn secondary to either acute or chronic blood drawing.

J. Apnea

Nasal or nasopharyngeal CPAP as well as aminophylline may be used to treat recurrent apnea.

K. Antibiotics

No routine or prophylactic antibiotics should be given for arterial lines or because the infant is on mechanical ventilation.

L. Muscle Relaxants and Sedation

Routine use of muscle relaxants and sedation is not encouraged and should be used at the discretion of the attending physician. They

may be used only in infants who show acute deterioration in PaO_2 in association with excessive spontaneous activity or when a peak inspiratory pressure > 30 cm H_2O and F_IO_2 > .75 are necessary to keep a PaO_2 > 50 mm Hg.

XI. Monitoring During Hospitalization

Infant data collected during the course of the hospital stay will be collected on a Hospital Form which will be completed at the time of discharge from the hospital. It will contain nursery data (initial measurements and observations including vital signs), use of ventilatory support (type, duration, performance characteristics), data characterizing the care received in the hospital and data on complications of various systems (pulmonary, cardiovascular, neurological, etc.). This form will also include a final evaluation of the various systems at discharge from the hospital. Specific data to be collected will include:

Flow Data Form

- Date of birth, sex, make and model of ventilator. Date ventilator therapy began and ended. Dates of subsequent crossovers. Make of model of crossover ventilator.
- Blood Gas Data - PaO_2, $PaCO_2$, pH.
- Ventilator Variables - % O_2. Ventilator rate. Inspiratory/Expiratory Time. PIP. PEEP. $\bar{P}aw$. Flow Rate. Muscle Relaxants.
  (These data will be recorded twice before entry, at entry, and every two hours up to six hours, every six hours up to 36 hours, every twelve hours up to 96 hours, at 5, 7, 10 days, and then weekly.)
- Cardiac/Respiratory Variables - Heart rate. Respiratory rate. Blood pressure.
  (These data will be monitored as above up to 48 hours.)
- Nutrition/Environment - Fluid intake. Calorie intake. Bed type. Weight.
  (These data will be monitored daily for 5 days, on the 7th day, and then weekly.)

XII. Monitoring During Follow-up

The main objectives of the follow-up portion of the study are:

Objective 1): To evaluate the neurodevelopmental status of the survivors of each stream. This objective must be designed to prove hypothesis 2, namely HFV is as safe as CMV when used to support premature infants. That is, there will be no difference between the streams in the proportion of infants with cerebral palsy, hydrocephalus, profound hypotonia, delayed motor development (Bayley PDI) or delayed mental development (Bayley MDI). With the exceptions of profound hypotonia and mild spastic diplegia, all the major neurologic defects should be identified in each stream by 12 months post-term. However, the evaluation of motor and mental development is severely hampered in the presence of chronic somatic disease such as BPD and by the presence of visual and/or hearing deficits. Children with BPD typically have prolonged hypotonia and poor motor development until their respiratory function has improved. At 12 months (post-term) they still show considerable motor and speech delay. However, during the ensuing months, as their health improves, they have an accelerated development so that, as a group, they do not differ from matched ventilator non-BPD survivors in Bayley testing by 18 months post-term.

It is expected that 20 to 30% of the infants in the CMV stream will develop BPD. It is highly probable that a significantly smaller proportion of the HFV will be so affected. Bayley testing at 12 months post-term would favor the HFV stream because of the spurious low scores for the more numerous BPD survivors in the CMV stream. This bias could obscure adverse cognitive sequelae to HFV unless testing is delayed to a point when BPD per se no longer influences the scores. Therefore, Bayley testing should be delayed until at least 18 months post-term.

Interpretation of low Bayley scores requires a knowledge of visual and auditory acuity. Both visual and auditory deficits are common sequelae to ventilation in premature infants. The effect of prolonged oscillation on the integrity of the eye and hearing apparatus is not known. Ophthalmologic and audiometric examinations are strongly recommended during the period from 6 to 18 months of age.

Objective 2): To evaluate pulmonary status of the survivors in each stream at 12 months. This objective must be designed to prove hypothesis 1, namely that HFV is superior to CMV in preventing chronic lung pathology. Specific pulmonary function tests are impractical for the whole study population. The pulmonary status will be inferred by a review of the hospitalizations and respiratory infections and by growth velocity. The latter has shown to be a valid, although not specific, indirect indicator of pulmonary function. Clinical evaluation will be limited to a routine chest examination, chest x-ray and oxygen saturation (determined by pulse oximeter). Mild and moderate cases of BPD show a marked decrease in symptomatology at approximately 6 months post-term. Severe cases do not improve until about 9 to 12 months post-term. The second visit should be scheduled at 8 to 9 months post-term in order to identify the most severe cases of BPD.

The minimum recommendations for the follow-up is as follows:

first visit	term ± 3 weeks
	baseline data for growth parameters.
second visit	9 months post-term ± 1 month
	Pulmonary status - include chest x-ray for abnormal x-ray on discharge, O_2 saturation - audiometry - evaluate growth velocity during interval from term date.
third visit	18 months post-term ± 1 month
	neurodevelopmental status - Bayley test - environmental questionnaire - ophthalmologic examination.

The extension to 18 months post-term is considered essential. The ear and eye examinations are important additions for this study to reach full potential. The 9 month visit is essential for accurate evaluation of clinical pulmonary status and will also be helpful in reducing attrition to the study.

In addition to the above evaluations which should be performed at all centers, pulmonary function tests are to be performed by a limited number of centers with that capability at 3 months and at 12 months of age. The tests to be performed include the measurement of pulmonary resistance, pulmonary compliance and transcutaneous oxygen saturation.

So far as it is possible, follow-up personnel will be blinded to the treatment method an infant received.

A. Information on Terminations/Deaths

Information on cases which are terminated from the study for any reason (including death) will be collected on a Termination Form. The form will contain the date and time of termination, reason for termination, and autopsy results if a post-mortem examination was performed on a deceased infant. A Mortality Classification Committee will be established to assure uniformity in determining cause of death.

B. Autopsy Form

A routine autopsy should be performed on expired infants at all centers, if possible. The report should contain the following:

1. Primary and secondary causes of death.
2. Routine gross and microscopic examination of all major organs.
3. Visual evaluation of the trachea with attention paid to the trachea opposite the tip of the endotracheal tube and the carina. This evaluation should include indication of degree of edema and inflammation and the degree of necrosis at these two sites.

There should be a more detailed morphologic and morphometric examination of the respiratory system at the centers with the capacity to perform these detailed studies. These centers should agree on the specifics of mode of tissue fixation, staining techniques, and other analyses. This work is a higher priority for the overall trial.

XIII. Quality Control

The data for this study will be collected and recorded on standardized data forms by the personnel at the participating centers and forwarded without delay to the Coordinating Center for data processing. At the Coordinating Center the forms will be edited and converted to machine-readable form by Coordinating Center staff and will be incorporated into a data management system designed to provide an up-to-date inventory of the data base and to allow easy access to the data for analysis purposes. General procedures for assuring the quality of the data will be provided by the Steering Committee who will review the study protocol for quality control in the following areas:

a. clarity of procedure manual including definition of terminology,

b. practical degree of allowable flexibility in patient management,

c. inclusion of quality control procedures in the protocol design.

In addition to the overall attention to quality control by the Steering Committee, specific procedures will be implemented at the participating centers and at the Coordinating Center to ensure that the final data resulting from the study is accurate. These procedures are discussed in the following sections.

A. Clinical Center Procedures

The proficiency of center staff in high frequency ventilation will be assessed by documentation of the initial orientation, review of experience with pre-trial patients, and on-going in-service training for neonatal health care personnel (nursing, respiratory therapist/technology, house staff). The compliance with the study protocol will be determined by an on-site random review of patient charts, logbook, etc. to validate accuracy of reported data. At the Coordinating Center, a review of a random sample of submitted data forms for completeness and adherence to guidelines will be periodically conducted. The areas of concern in this random review will include:

a. Enrollment and randomization procedures,

b. Adherence to the study protocol for conventional and high frequency ventilation,

c. Adherence to the performance of all the required diagnostic studies on protocol infants,

d. Completeness of data forms,

e. Adherence to minor study details,

f. Quality control of equipment and laboratory procedures.

Procedures which will receive attention are:

1. ventilators (both HFV and conventional) - specify type of conventional ventilation
   - preventive maintenance, recalibration procedures
   - accurate measurement of airway pressure, inspired oxygen, cycle times
   - humidification system
2. blood gas analysis
   - blood gas machine: location, proficiency of operations, quality control measures
   - sampling technique: site, method (e.g., use of dry rather than liquid heparin), lag time to analysis
3. indirect blood gas monitoring (skin PO_2 etc.)
   - quality control for calibration and methodology
4. blood pressure measurement
   - method (indirect, intravascular)
   - calibration of transducers, mechanical manometers, etc.
5. ultrasound technique - cardiac and head
6. radiology
7. other tests as indicated by protocol (e.g., L/S ratio).

B. Coordinating Center Procedures

Quality control at the Coordinating Center will be aimed at ensuring that data used in analysis and reporting are as free as possible from errors and inconsistencies. Areas of concern include:

a. confidentiality of patient identification

b. loss of data in transit (a log of received data will be compared with records kept at the participating centers)

c. scan editing of the data forms received

d. data entry

e. machine editing

f. report of errors/omissions to clinical centers, quality control subcommittee chairman, and NIH

g. incorporating correction of errors into the data base.

In order to assess the degree to which the Coordinating Center and the clinical centers adhere to quality control procedures, site visits will be conducted once early in the trial at each participating center and at the Coordinating Center. Site visits should be conducted at least annually thereafter. The site visit team will be composed of a program office representative, a Coordinating Center representative, and one member from one of the clinical centers. Consultants may be added to the site visit team as needed.

XIV. Organizational Structure

A. Introduction

The different groups in the organizational structure of this study include the following participating units: individual clinical centers, a coordinating center, and the National Heart, Lung and Blood Institute. The participating units in the study are tied together through a study administration, which is designed to maintain operations in the study and to insure effective communication and cooperation among the various study units. The administrative units include a Policy Advisory Board, a Steering Committee, and several working subcommittees established by the Steering Committee.

B. Participating Units

The functions of the participating units of this study are described below.

1. Clinical Centers

Clinical centers are responsible for recruiting the required number of patients, administrating assigned therapy, coordinating patient care, and collecting the information required by the study protocol. The professional and clerical organization of each clinical center will differ, but each clinical center will have one person specifically identified as the data coordinator. This person will be responsible for such critical matters as appointment scheduling for follow-up procedures, checking the completeness of forms and forwarding them to the coordinating center.

2. Coordinating Center

The Coordinating Center has a major role in design, implementation, and execution of the study. This staff has the responsibility for collecting, editing, storing, and analyzing all data received from the clinical centers. Some specific functions of the Coordinating Center are: to work with the investigators in the development and pretesting of forms and procedures and in the preparation of the Manual of Operations; to make a random assignment to a treatment group for each participant; to assume responsibility for review of all data transmitted on the forms; to check the completeness of records and periodically prepare performance reports to participating clinical centers; to analyze periodically the frequency of new events and side reactions by

treatment group and to report these data to the Policy Advisory Board; to prepare interim, technical, and statistical reports for the periodic meetings of the study participants; to prepare recruitment charts for each clinical center; and to assist in the preparation of reports of the study for publications.

3. National Heart, Lung and Blood Institute Project Office

The Structure and Function Branch of the Division of Lung Diseases (DLD) and the Biometrics Research Branch of the Division of Epidemiology and Clinical Applications (DECA), National Heart, Lung and Blood Institute are responsible for providing organizational, scientific, and statistical direction to the study. The Scientific Project Officer is a voting member of the Steering Committee and a non-voting member of the Policy Advisory Board.

The Contract Officer is responsible for all administrative matters related to the award and conduct of contracts.

C. Study Administration

The participating units of the study are coordinated by the Division of Lung Diseases, the Policy Advisory Board, and the Steering Committee. The Steering Committee with working subcommittees and consultants is the administrative body of the study during the Planning Phase.

1. Policy Advisory Board

The Policy Advisory Board acts in a senior advisory capacity to the Division of Lung Diseases on policy matters throughout the duration of the study. In addition, it periodically reviews study results and evaluates the study treatment for beneficial and adverse effects.

The Board is composed of a Chairman, plus additional voting members who are appointed by the DLD for the duration of the study, and the scientific Project Officer as an ex officio, non-voting member. Board meetings are attended, when appropriate, by senior representatives from the Coordinating Center, as well as the Chairman of the Steering Committee. Additional board members or consultants may be appointed if deemed necessary by the DLD in response to recommendations from the Board. No voting member of the Policy Advisory Board may participate in the study as an investigator. Others in his/her institution, however, will not be

excluded from participation because of his/her Board membership. Meetings of the Board will be called by the Chairman no less than twice a year.

Specific functions of the Policy Advisory Board are:

a. To review and approve the Protocol and Manual of Operations.

b. To review the progress of the study, approve ancillary studies (with the possible effect on the main study being the major criterion); approve major changes in the Protocol and Manual of Operations, and make recommendations to the DLD.

c. To make recommendations to the DLD on any proposed early termination of the study because of adverse or beneficial treatment effects. To this end, study data will be periodically reviewed and evaluated by the Panel.

d. To assist the DLD in resolving problems referred by the Steering Committee.

e. To make recommendations to the DLD on the discontinuation of individual Clinical Centers which perform unsatisfactorily.

2. Steering Committee

The Steering Committee provides scientific direction for the study at the operational level. The permanent members of the Steering Committee are one member from each clinical center and Coordinating Center, and the DLD Project Officer.

Specific functions of the Steering Committee are:

a. To make recommendations to the Policy Advisory Board concerning changes in the Protocol and Manual of Operations.

b. To review all proposed ancillary studies and to report all recommendations to the Policy Advisory Board.

c. To advise and assist the Coordinating Center on operational matters.

d. To monitor the performance of the individual clinical centers with regard to patient recruitment and patient follow-up studies.

The Steering Committee will meet semiannually after recruitment begins. Additional meetings of the Steering Committee will be called by its Chairman as necessary.

3. Subcommittees

The Chairman of the Steering Committee shall appoint subcommittees as needed throughout the course of the study. Permanent subcommittees of the trial are:

a. Ventilator Subcommittee

b. Quality Control Subcommittee

c. Design and Analysis Subcommittee

d. Publications and Ancillary Studies Subcommittee.

The respective roles of these subcommittees are outlined in the study Constitution.

4. Hospitals and Clinical Investigators of the HIFI Study

The institutions participating in this study as clinical centers and the investigators are listed below:

a. St. Margaret's Hospital
Respiratory Therapy
90 Cushing Avenue
Boston, Massachusetts

New England Medical Center
25 Harvard Street
Boston, Massachusetts

Brigham & Women's Hospital
89 Fenwood at Brookline Avenue
Boston, Massachusetts

Ivan Frantz, M.D.
Renee Fox, M.D.

b. University of California, San Diego
UCSD Medical Center H638A
225 Dickinson Street
San Diego, California

Frank Mannino, M.D.

c. Case Western Reserve University
Department of Pediatrics
2101 Adelbert Road
Cleveland, Ohio

Richard J. Martin, M.D.
Waldemar Carlo, M.D.

d. WS108, Women's Hospital
735 Dame Avenue
Winnipeg, Manitoba
Canada

St. Boniface Hospital
409 Tache Street
Winnipeg, Manitoba
Canada

Henrique Rigatto, M.D.
Maria Davi, M.D.

e. University of Miami
Post Office Box 016960
Miami, Florida 33136

Eduardo Bancalari, M.D.
Ronald Goldberg, M.D.

f. Children's Hospital of Philadelphia
34th Street & Civic Center Boulevard
Philadelphia, Pennsylvania

Pennsylvania Hospital
8th and Spruce Street
Philadelphia, Pennsylvania

William Fox, M.D.
Alan Spitzer, M.D.

g. Hospital for Sick Children
555 University Avenue
Toronto, Ontario
Canada

Mt. Sinai Hospital
600 University Avenue
Toronto, Ontario
Canada

Paul Swyer, M.D.
Pamela Fitzhardinge, M.D.

h. Vanderbilt University
Nashville, Tennessee

Robert Cotton, M.D.
Thomas Hazinski, M.D.

i. University of Washington
Seattle, Washington

W. Alan Hodson, M.D.
William Truog, M.D.

j. University of Wisconsin
Madison General Hospital
202 South Park Street
Madison, Wisconsin

Gary Gutcher, M.D.
Robert Perelman, M.D.

The Research Triangle Institute, Research Triangle Park, North Carolina 27707 is the Coordinating Center for the study. Dr. W. Kenneth Poole will be the Director of the Coordinating Center.

XV. Study Constitution

Article 1. Name

The name of this group shall be High Frequency Intervention (HIFI) Trial Steering Committee, hereinafter referred to as the Committee.

Article 2. Objective

The objective of this group shall be to provide scientific and operational guidance in carrying out cooperative clinical studies.

Article 3. Members and Representatives

Section 1. Membership is composed of collaborating institutions. The membership shall consist of the National Heart, Lung, and Blood Institute, the Coordinating Center, and hospitals or other clinical or research facilities, or of organized groups of such facilities that have been contracted by the NHLBI in response to their RFPs 84-4 and 84-6.

Section 2. Responsibilities of member institutions include close adherence to the protocol of the study including maintenance and prompt submission of complete and accurate data as required by the study protocol.

Section 3. Each member institution shall be represented by one person or his/her designee. Each representative must have a major clinical or research responsibility with respect to studies of interest to the Committee. The scientific project officer in charge of the project shall be a representative of the NHLBI. The Director of the Coordinating Center shall be a representative of the Coordinating Center.

Section 4. A member institution may resign from the Committee at any time provided the resignation is signed by the appropriate official of that institution and it has been accepted by the NHLBI.

Article 4. Officers

Section 1. The officers of the Committee shall be a Chairman, a Co-Chairman, and a Secretary. The Chairman and Co-Chairman shall be from different collaborating clinical centers. Each officer shall perform the duties specified by this constitution or by the Committee.

Section 2. The Chairman and the Co-Chairman shall be appointed by the NHLBI. The Coordinating Center shall serve as the Secretary.

Section 3. The Chairman shall determine the agenda for meetings, and preside over the Committee meetings. He shall appoint members to standing and ad hoc subcommittees with the approval of the Committee. The Co-Chairman shall serve in the absence of the Chairman. The Secretary shall record and distribute minutes of Committee meetings, notify members of meetings, keep and distribute protocols and other Committee documents, and maintain files of all Committee activities including files of scientific data.

Article 5. Executive Committee

Section 1. The Executive Committee shall be constituted of the Chairman, Co-Chairman, the Director of the Coordinating Center, and the NHLBI Scientific Project Officer in charge of the project.

Section 2. The Executive Committee shall be the governing body of the Committee. It shall have general supervision of the affairs of the Committee between Committee meetings.

Section 3. The Executive Committee may act in meetings, or by mail, or by telephone with written confirmation to the Chairman of each telephone vote.

Section 4. The Executive Committee shall be subject to the order of the Steering Committee and none of its actions shall conflict with the actions taken by the Steering Committee.

Article 6. Meeting

Section 1. There shall be a regular meeting of the Committee not less than twice a year.

Section 2. One representative each from seven member institutions shall constitute a quorum.

Section 3. The deliberations of the Committee shall be conducted in a parliamentary manner. Unless otherwise specified, all decisions shall be taken based on a simple majority of those present and voting, provided a quorum is established.

Section 4. The Committee may act in meetings, by mail or by telephone, with written confirmation to the Chairman of each telephone vote.

Section 5. Special meetings of the Committee shall be called by the Chairman, at the request of NHLBI, or at the written request of a majority of the members of the Committee.

Article 7. Consultants

The Committee with the concurrence of NHLBI may invite, as consultants, individuals whom it feels would contribute useful information to the Committee deliberations.

Article 8. Voting

Section 1. Each member institution shall have one vote concerning amendments to this Constitution, amendments to the protocols, and in all other matters.

Section 2. Each person appointed to a subcommittee (excluding consultants) shall have one vote.

Article 9. Subcommittees

Section 1. The Committee may establish or abolish any subcommittee it determines to be in its best interest.

Section 2. The membership and the chairmanship of any subcommittee shall be determined by the Chairman with the approval of the Committee.

Section 3. No subcommittee shall present a report outside the Committee unless it has been specifically authorized to do so by the Committee.

Article 10. Design and Analysis Subcommittee

This subcommittee shall consider and make recommendations on the experimental design for the study. These considerations shall include sample size, randomization procedures, and stratification variables, as well as other design issues. It shall monitor the number of recruitments and make suggestions regarding methods for recruitment, follow-up and other matters which will help meet the objective of the study in

more efficient ways. It shall develop plans for data analysis in collaboration with the Coordinating Center.

This subcommittee shall also deal with interpretations of diagnostic and endpoint criteria. It shall periodically review these criteria and recommend changes, if required, to the Committee.

Article 11. Ventilator Subcommittee

This subcommittee shall investigate and make recommendations to the Steering Committee regarding the appropriate high frequency ventilator(s) for the trial. It shall also work with the Quality Control subcommittee on matters regarding standardization of usage and quality control of the instrumentation.

Article 12. Clinical and Coordinating Center Quality Control Subcommittee

This subcommittee shall monitor the performance of the Clinical Centers and the Coordinating Center and report findings to the Committee. Information which would lend to the unblinding of the overall results of the Trial shall not be reviewed by this subcommittee.

Article 13. Publication and Ancillary Studies Subcommittee

This subcommittee shall review all written and oral presentations on the design, progress, and results of the study including any ancillary studies. The subcommittee shall at a minimum follow DLD guidelines on presentations and publications. It shall also review proposals for ancillary studies and make recommendations to the committee regarding these proposals.

Article 14. Publications

Section 1. The group shall present or publish from time to time the results of studies. Members and consultants are encouraged and urged to analyze and publish data based on the study, provided that they adhere to the DLD guidelines in Appendix A.

Section 2. The Chairman, with the approval of the Committee, may designate and appoint members to a Writing Subcommittee for any study

report. A Writing Subcommittee shall be automatically discharged when it submits its final report.

Section 3. There is likely to be a great variety of publication situations and degrees of appropriate acknowledgments for members and consultants, including the special requirements of some journals. Also, the interdisciplinary nature of the study requires that material intended for publication be reviewed by both representatives as well as appropriate advisors in other fields. Therefore, all papers for publication, abstracts, presentations at meetings, or other public distribution of results based on data for patients entered in the study must be sent to all members of the Publication and Presentation Subcommittee not less than two weeks prior to initial submission of the report. The Subcommittee shall decide (1) whether the scientific content of the paper and interpretation of the data are acceptable; (2) whether the contributions of members, representatives, and consultants are properly acknowledged; and (3) whether publication of the paper is in the best interest of the study. Each member of the Subcommittee shall notify the Chairman of the Subcommittee regarding his approval or disapproval of the report as submitted, with reasons for any disapproval and recommendations for changes. The Subcommittee Chairman shall then notify the principal author of the majority decision of the Subcommittee which may include approval, approval contingent upon specific revisions, approval with suggestions for revision and resubmission, or disapproval. In case the Subcommittee does not reach a majority decision, the matter will be deferred for decision by the Committee at its next meeting.

Section 4. Membership in the Committee implies agreement to abide by these procedures for all publication based on study data. The provisions of this Article apply to reports of Writing Subcommittees as well as other reports based on study data.

Section 5. The decision of the Committee may be appealed to the appropriate authority within the NHLBI. The authors shall abide by the final decision of the NHLBI.

Article 15. Amendment

This Constitution shall be amended at any Committee meeting by two-thirds vote of all regular members whether present or not, provided

that the amendment has been submitted in writing to all representatives not less than two weeks prior to voting on such amendment.

Article 16. Veto

The Director, Division of Lung Diseases, NHLBI, is empowered to exercise a veto on any decisions of the Committee including amendments to the Constitution which he/she considers not in the interest of the study. The veto, if exercised, should be communicated in writing to the Chairman within 30 days of the Committee decision.

Article 17. Human Use Review

Certifications of Human Use Review Committees of participating clinical centers are essential for the study. The participating clinical centers should arrange for the certification before the study begins. This will be the responsibility of principal investigators from clinical centers.

XVI. References

1. Bland, Richard D.; Kim, Marjorie H.; Light, Michael J.; and Woodson, Jane L. "High-Frequency Mechanical Ventilation in Severe Hyaline Membrane Disease," Crit. Care Med. 8:275-280, May 1980.
2. Boros, Stephen J.; and Campbell, Kathy. "A Comparison of the Effects of High Frequency-Low Tidal Volume and Low Frequency-High Tidal Volume Mechanical Ventilation," J. Ped., 97:108-112, July 1980.
3. Boynton, Bruce R.; Mannino, Frank; Davis, Ray F.; Kopotic, Robert J.; and Friederichsen, Guillermo. "Combined High-Frequency Oscillatory Ventilation and Intermittent Mandatory Ventilation in Critically Ill Neonates," Pediatrics, Vol. 105, No. 2, 297-302, August 1984.
4. Butler, W.J.; Bohn, D.J.; Bryan, A.C.; Froese, A.B. "Ventilation by High-Frequency Oscillation in Humans," Anesth. Analo. 59:577-584, August 1980.
5. Carlo, Waldemar; Chatburn, Robert L.; Martin, Richard J.; Lough, Marvin D.; Shivpuri, Chandra R.; Anderson, John V.; and Fanaroff, Avroy A. "Decrease in Airway Pressure During High-Frequency Jet Ventilation in Infants With Respiratory Distress Syndrome," J. Pediat. 104:101-107, January 1984.
6. Carlon, Graziano C.; Miodownik, Saul; Ray, Cole; Kahn, Roberta C. "Technical Aspects and Clinical Implications of High-Frequency Jet Ventilation With a Solenoid Value," Crit. Care Med., 9:47-50, January 1981.
7. Edwards, D.K.; Dyer, W.M.; Northway, W.H. "Twelve Years Experience With Bronchopulmonary Dysplasia." Pediatrics 59:839, 1977.
8. Frantz, I.D.; Stark, A.R.; and Dorkin, H.L. "Ventilation of Infants at Frequencies up to 1800/min," (Abst.) Ped. Res. 14:642, 1980.
9. Frantz, Ivan D. III; Werthammer, Joseph; and Stark, Ann R. "High-Frequency Ventilation in Premature Infants With Lung Disease: Adequate Gas Exchange at Low Tracheal Pressure," Pediatrics, 71:483-488, April 1983.

10. Friedman, L.M.; Furberg, C.D.; and Demets, D.L. "Fundamentals of Clinical Trials," John Wright Publishing Inc., London, 1981.
11. Goodman, L.A. "The Analysis of Multidimensional Contingency Tables When Some Variables Are Posterior to Others: A Modified Path Analysis Approach," Biometrika 60, 179-92, 1973.
12. Grizzle, J.E.; Starmer, C.F.; Koch, G.G. "Analysis of Categorical Data by Linear Models," Biometrics 25:489-504, 1969.
13. Hamilton, Philip P.; Onayemi, Adebusola; Smyth, John A.; Gillan, John E.; Cutz, Ernest; Froese, Alison B.; and Bryan, Charles A. "Comparison of Conventional and High-Frequency Ventilation: Oxygenation and Lung Pathology," J. App. Physiol. 55:131-138, 1984.
14. Haselton, F.R. and Scherer, P.W. "Bronchial Bifurcations and Respiratory Mass Transport," Science 208:69-71, 4 April 1980.
15. Heijman, Lilian; Nilsson, Lars-Göran; and Sjöstrand, Ulf. "High-Frequency Positive-Pressure Ventilation (HFPPV) in Neonates and Infants During Neuroleptal Analgesia and Routine Plastic Surgery, and in Postoperative Management," Acta Anesth. Scand. Suppl., 64:111-121, 1977.
16. Intriligator, M.D. Econometric Models, techniques and Applications, Prentice-Hall, New Jersey, 1978.
17. Jefferies, Ann L.; Hamilton, Philip; and O'Brodovich, Hugh M. "Effect of High-Frequency Oscillation on Lung Lymph Flow," J. Appl. Physiol. Resp. Environ. 5:1373-1378, 1983.
18. Lan, K.K.G; DeMets, David L; Halperin, Max. "More Flexible Sequential and Non-Sequential Designs in Long-Term Clinical Trials," Communications in Statistics, A. Vol. 13, 2339-2353, 1984.
19. Lan, K.K.G.; Simon, R.; and Helperin, M. "Stochastically Curtailed Tests in Long-Term Clinical Trials," Communications in Statistics, C1, 207-219, 1982.
20. Marchak, B.E.; Thompson, W.K.; Duffty, M.B.; Miyari, T.; Bryan, M.H.; Bryan, A.C.; and Froese, A.B. "Treatment of RDS by High-Frequency Oscillatory Ventillation: A Preliminary Report," J. Pediat. 99:287-292, August 1981.
21. Namboodiri, N.K.; Carter, L.W.; and Blalock, H.M., Jr. Applied Multivariate Analysis and Experimental Designs. McGraw-Hill Book Company, New York, 1975.

22. Oberg, P.A. and Sjöstrand, U. "Studies of Blood Pressure Regulation. I. Common Carotid Artery Clamping in Studies of the Carotid Sinus Baroceptor Control of the Systemic Blood Pressure," Acta. Paediatr. Scand., 75:276, 1969.
23. O'Brien, P.C.; and Fleming, T.R. "A Multiple Testing Procedure for Clinical Trials," Biometrics 35:549-556, 1979.
24. Pokora, Thomas; Bing, Dennis; Mammel, Mark; and Boros, Stephen. "Neonatal High-Frequency Jet Ventilation," Pediatrics, 72:27-32, July 1983.
25. Rehder, Kai; Schmid, Edith R.; and Knopp, Thomas J. "Long-Term High-Frequency Ventilation in Dogs," Am. Rev. Respir. Dis. 128:476-480, 1983.
26. Saramiento, Alfonso; Bryan, Charles; Jobe, Alan H.; Ikegami, Machiko; Jacobs, Harris C. "High-Frequency Oscillation (HFO) vs. Conventional Ventilation (CV) of Premature Lambs," (abstr.) Ped. Res. 17:333A, 1983.
27. SAS Users Guide: Statistics. SAS Institute, North Carolina 1982.
28. Sjöstrand, Ulf. "Review of the Physiological Rationale for and Development of High-Frequency Positive-Pressure Ventilation - HFPPV," Acta Anaesth. Scand. (supp. 64):7-27, 1977.
29. Slutsky, Arthur S.; Drazen, Jeffrey M.; Ingram, Roland H., Jr.; Kamm, Roger D.; Shapiro, Ascher H.; Fredberg, Jeffrey J.; Loring, Stephen H.; and Lehr, John. "Effective Pulmonary Ventilation With Small-Volume Oscillations at High Frequency," Science, 209:609-611, 1 August 1980.
30. Smith, R. Brian; Klain, Miroslav; and Babinski, Maciej. "Limits of High-Frequency Percutaneous Trans-tracheal Jet Ventilation Using a Fluidic Logic Controlled Ventilator," Canad. Anaesth. Soc. J. 24:351-356, July 1980.
31. Smyth, J.A.; et al. "Pulmonary Function and Bronchial Hyperreactivity in Long-Term Survivors of Bronchopulmonary Dysplasia." Pediatrics 68:336, 1981.
32. Susser, M.; and Stien, Z. "Third Variable Analysis: Application to Causal Sequences Among Nutrient Intake, Maternal Weight, Birth Weight, Placental Weight and Gestation," Stat. in Med. 1:105-120, 1982.

33. The Coronary Drug Project Research Group. "Influence of Adherence to Treatment and Response of Cholesterol on Mortality in the Coronary Drug Project," New England Journal of Medicine 303, No. 18, 1038-1041, 1980.

34. Truog, W.E.; Standaert, T.A.; Murphy, J.; Palmer, S.; Woodrum, D.E.; and Hodson, W.P. "Effect of High-Frequency Oscillation on Gas Exchange and Pulmonary Phospholipids in Experimental Hyaline Membrane Disease," Am. Rev. Respir. Dis., 127:585-569, 1983.

35. Versmold, Hans T.; Kitterman, Joseph A.; Fhibbs, Roderic H.; Gregory, George A.; and Tooley, William H. "Aortic Blood Pressure During the First Twelve Hours of Life in Infants With Birthweight of 610-4220 gms". Pediatrics 67:607, 1981.

APPENDIX A

APPENDIX A

I. GUIDELINES ON PUBLICATIONS AND ANCILLARY STUDIES

The principles under which the Publication Subcommittee will operate are stated in the following goals:

1. dissemination by publication of the maximum amount of information pertinent to the outcome of the collaborative study;
2. maximal sharing of results pertaining to ancillary studies;
3. the first priority of publication should be to those related to major results;
4. encouragement of the highest quality publication;
5. responsibility should reside within each center to be cognizant of all other studies involving the collaborative trial patients and potential publications on studies involving these patients;
6. studies should be brought to publication in a timely fashion through participation and critique of all of the investigators; and
7. all efforts should be made to facilitate the publication and presentation of ancillary studies in a fashion that will not intrude upon nor have a deliterious effect on the presentation or publication of data from the overall study.

The Publications Committee will use the following definitions and procedures in monitoring study publications and presentations.

A. Ancillary Studies

1. any study, procedure, or measurement required by the protocol will not be considered ancillary;
2. any study bearing on the end point will not be considered ancillary;
3. data collected by less than the total group (1-9 centers) will be considered ancillary;
4. data collected from any other study involving enrolled patients will be considered ancillary.

Studies peripheral to either outcome or treatment and not utilizing the randomization scheme for design or presentation or results will be considered [ancillary] "peripheral studies".

B. Press release: a press release is defined as a document given to radio, television, newspapers, scientific journals not indexed in the Index Medicus, and popular periodicals without national circulations.

Local press releases will not be reviewed by the Publications and Ancillary Studies Committee. Nevertheless, all these press releases must limit their substantive content to information items that have been described in the most recent request for proposals. A copy of each prepared release must be sent to the DLD Project Officer to maintain current knowledge of content for response to national queries. Also, copies of all press releases should be retained and sent to the Project Officer with Quarterly Reports. A central file of all press releases will be maintained by the Project Officer.

Project-wide press releases will be initiated by the Program Office and reviewed by the Publications and Ancillary Studies Committee.

C. Interview: an interview is any discussion with a member of the press, a science writer, or a radio or television commentator, which provides information for public dissemination.

Interviews are subject to the same editorial rules as press releases. Local information concerning participation by local organizations can be provided to encourage cooperation and acceptance of the program. The ethics and legalities of medical confidentiality apply to the names and risk statuses of individual participants.

D. Presentation: a presentation is the delivery of information that may be disseminated as a press release. This definition is independent of the forum. Under these guidelines a seminar within a closed academic setting would not be classified as a presentation.

Material for all presentations given outside closed academic communities must be reviewed by the Publications and Ancillary Studies Committee. These include presentations given to scien-

tific, professional, or public groups. Particular attention is drawn to presentation of material when proceedings of the meeting or workshop are likely to be published or publicized.

Presentations are subject to the same rules as press releases. If a presentation is limited to substantive information in the RFP and has no added interpretation or inferences, it can be given without prior review by the Publications and Ancillary Studies Committee. Any discussion of the true or ancillary projects that goes beyond those items of information must be submitted for review at least two weeks prior to the date of presentation. The Publication and Ancillary Studies Committee will identify scientific and professional forums where presentations about the Trial should be made on behalf of the group. It will bring these proposed forums for presentation to the Group for approval. From a list of volunteer investigators it will identify one or more persons to prepare and present the material. The written presentation must be reviewed by the Committee before it is presented.

E. Publication: a publication is any document submitted to a professional journal listed in the Index Medicus or any popular periodical with national circulation.

All publications and ancillary studies of results of the Trial will be prepared under the direction of the Publications and Ancillary Studies Committee. All official publications of the Trial will be written by committee and credit for authorship will be to the "High Frequency Intervention (HIFI) Trial Group". Publication of results of ancillary studies performed on participants admitted to the Trial will be allowed by individual investigators. Approval by the Publications and Ancillary Studies Committee is required if the ancillary study makes use of data collected according to the Trial Protocol. After the final results of the Trial are compiled and submitted for publication, individual investigators involved in the Trial may request access and publisher rights to data accumulated during the Trial.

Two categories of publications are discussed.

(1) Publications prepared on behalf of a limited number of investigators or centers. All manuscripts which describe:

(a) primary screening and recruitment procedures;

(b) any process of the Trial or information collected using defined procedures and protocols;

(c) any approved or informal ancillary study carried out in a Trial population; or

(d) any work supported partially or wholly by this Trial must be submitted to the Publications and Ancillary Studies Committee for review prior to submission to publication.

The Committee will review draft publications with the following objectives in mind:

(a) to make sure that no publication will have a deleterious effect on the Trial process, acceptance, or on the interpretation of its results;

(b) to correct factual and conceptual inaccuracies;

(c) to safeguard the rights of volunteer participants;

(d) to prepare comments to assist collaborating scientists to publish papers of the highest quality (the latter is accepted as a responsibility because all publications related to this Trial will affect public perception of its scientific rigor and operational activities); and

(e) to inform the Steering Committee and Policy Advisory Board of all public dissemination of information.

(2) Publications prepared as study-wide documents.

Basic papers of the Trial which must draw on data collected by all Centers will be identified by the Publications and Ancillary Studies Committee. The proposed series of publications will be submitted to the Committee for approval. An ad hoc committee of volunteers from the professional staffs of all collaborating Centers may be appointed to draft each paper. Each ad hoc committee will be charged with responsibility for writing the paper in a prescribed format within a stated time limit. The senior author of the paper will be clearly denoted as "The High Frequency Intervention Trial Group" with an asterisk to refer to the name of the Centers

and their principal investigators. Under this title and the appropriate reference to the Trial's investigators as the main author of the paper, the names of the members of the ad hoc committee who prepared the paper will be printed in sequence. The senior author will be either the Chairman of the ad hoc committee or the person who undertook most of the work in preparation of the paper. Other members of the ad hoc committee will be co-authors. This policy permits:

(a) the investigators of all Centers to be recognized and list the paper in their bibliographies;

(b) the preparation of a paper by a small group of investigators; and

(c) all investigators in all Centers to have an opportunity to participate in the preparation of basic papers and gain academic recognition for their contribution to the program.

The objective of the proposed Editorial Policy is:

(a) to have the highest quality presentations and papers from the Trial and its collaborating investigators;

(b) to make sure that all investigators have the opportunity to participate in study-wide presentations and the preparation of papers; and

(c) to make sure that no press release, interview, presentation or publication will have a deleterious effect on the collaborative trial and the acceptance of its results.

II. REVIEW PROCESS

Review of these documents will fulfill two additional objectives: (1) protect academic prerogatives, and (2) avoid time restrictions on authors.

All press releases, interviews, presentations, and publications that require review by the Publications and Ancillary Studies Committee should be sent directly to the Project Officer who will immediately communicate with the Committee. At least three reviewers will be identified from a pre-prepared study-wide list of volunteers. Reviewers will be chosen for their expertise in the subject matter of the particular document and for their understanding of the study as a whole. Each reviewer will be asked to judge whether or not the publication as written will affect the Trial's process, its acceptance or the interpretation of its results. If the Committee agrees that the document can have a deleterious effect, the manuscript will be returned to the author with suggestions for appropriate changes. If the Committee agrees that the manuscript can have no deleterious effects, a letter so stating will be returned to the author with the manuscript. He/she will be free to follow through with presentation, press release, or submission of the manuscript for publication.

Each manuscript prepared for publication will be reviewed by a minimum of three reviewers. At least one will be a member of the Publications and Ancillary Studies Committee. When there is a particular technical question that cannot be confidently answered by the reviewers, the Publications and Ancillary Studies Committee will use outside consultants to obtain technical advice.

Investigators who challenge a Publications and Ancillary Studies Committee decision will be able to appeal to the Chairman of the Committee. The Policy Advisory Board of the NHLBI will be the final arbiter.

APPENDIX B

APPENDIX B

HIFI CONSENT FORM (Pilot Study)

Title: A study to compare high frequency mechanical ventilation and standard mechanical ventilation in newborn babies.

We are studying a new breathing machine or ventilator for newborn babies. This new method is called high frequency ventilation and we think it may work better than the standard machines in use now. This study is being done with other hospitals for newborns in the United States and Canada and is being paid for by the National Institutes of Health. Your newborn baby has been chosen because he/she has a breathing problem and needs one of the machines to help him/her breathe.

In this study we want to see if high frequency ventilation does a good job in helping your baby breathe. Your baby may be on the high frequency ventilator for part or all of the time that he/she needs help breathing. However, if your baby is not doing well, the other machine will be tried. Except for the breathing machine, your baby will receive the same standard care and other tests as other babies treated in this center. There will be no additional medicines, blood tests or costs. While your baby may not benefit directly from being in this study, the final results of this research will benefit other babies by showing whether or not the high frequency ventilators are better than standard breathing machines.

The standard breathing machines push air into the lungs at a normal breathing rate, about 30 to 60 times a minute for babies. The high frequency ventilators push a much smaller breath into the lungs at a very high rate, around 900 times a minute (15 times a second). High frequency ventilation has been used in a number of babies and the initial short term results have been encouraging. The direct risks with the high frequency machine are thought to be the same as the risks with the standard breathing machines. These risks include possible damage to the lungs, such as leaks of air (pneumothorax) and long term breathing problems (bronchopulmonary dysplasia or BPD). The smaller breath used in high frequency ventilation may decrease these risks. Since high

frequency ventilation is a relatively new form of treatment, there may be other risks that are not known at this time.

Records on your baby will be kept completely confidential although they may be shared with the U.S. Food and Drug Administration.

Taking part in this study is entirely voluntary. You may refuse to take part in the study or take away your consent at any time during the study and we will continue to give your baby the best medical and nursing care that we can. The _____ will not repay you for injuries that happen because of your baby being in this study. You may call _____ for more information about this or to report problems that come up because of this study.

SUBJECTS STATEMENT

Dr. _____ and/or his coworkers have explained this study to me and answered my questions. I understand the above information and agree to have my baby in the study. If I have any more questions or if I have problems that come up because of this study, I can contact Dr. _____ of his coworker at _____.

Parent/Guardian _____ Date _____

Witness _____

HIFI CONSENT FORM (Full Study)

Title: A study to compare high frequency mechanical ventilation and standard mechanical ventilation in newborn babies.

We are studying a new breathing machine or ventilator for newborn babies. This new method is called high frequency ventilation and we think it may work better than the standard machines in use now. This study is being done with other hospitals for newborns in the United States and Canada and is being paid for by the National Institutes of Health. Your newborn baby has been chosen because he/she has a breathing problem and needs one of the machines to help him/her breathe.

This study will compare the high frequency ventilators to the standard breathing machines. The type of machine your baby receives will be decided randomly (by chance). Your baby will be treated with that machine for as long as necessary. However, if your baby is not doing well, the other machine will be tried. Except for the breathing machine, your baby will receive the same standard care and other tests as other babies treated in this center. There will be no additional medicines, blood tests or costs. All babies in this study will be examined at nine and eighteen months of age to look for lung problems and to see how well they are growing. These exams are similar to the type of care given to other babies who needed intensive care. The follow-up exam will not add any expense. While your baby may not benefit directly from being in this study, the final results of this research will benefit other babies by showing whether or not the high frequency ventilators are better than standard breathing machines.

The standard breathing machines push air into the lungs at a normal breathing rate, about 30 to 60 times a minute for babies. The high frequency ventilators push a much smaller breath into the lungs at a very high rate, around 900 times a minute (15 times a second). High frequency ventilation has been used in a number of babies and the initial short term results have been encouraging. The direct risks with the high frequency machine are thought to be the same as the risks with the standard breathing machines. These risks include possible damage to the lungs, such as leaks of air (pneumothorax) and long term breathing

problems (bronchopulmonary dysplasia or BPD). The smaller breath used in high frequency ventilation may decrease these risks. Since high frequency ventilation is a relatively new form of treatment, there may be other risks that are not known at this time.

Records on your baby will be kept completely confidential although they may be shared with the U.S. Food and Drug Administration.

Taking part in this study is entirely voluntary. You may refuse to take part in the study or take away your consent at any time during the study and we will continue to give your baby the best medical and nursing care that we can. The _____ will not repay you for injuries that happen because of your baby being in this study. You may call _____ for more information about this or to report problems that come up because of this study.

SUBJECTS STATEMENT

Dr. _____ and/or his coworkers have explained this study to me and answered my questions. I understand the above information and agree to have my baby in the study. If I have any more questions or if I have problems that come up because of this study, I can contact Dr. _____ of his coworker at _____.

Parent/Guardian _____ Date _____

Witness _____

APPENDIX C

APPENDIX C: STRATEGY FOR VENTILATOR UTILIZATION

Situation	Regular HFV Available	Backup HFV Available	Machine on "3-Day Reserve"	Machine To Be Used	Impact
1. Breakdown or crossover	yes	yes or no	yes or no	regular	may stop enrollment
2. Breakdown or crossover	no	yes	yes or no	backup	reduce or deplete backup pool
3. Breakdown or crossover	no	no	yes	3-day reserve	may result in weaned baby being forced onto CMV if further ventilation required
4. Breakdown or crossover	no	no	no	CMV until HFV available	results ambiguous
5. Weaned less than 3 days	yes or no	yes or no	yes-this baby	3-day reserve	none
6. Weaned, any time *	yes	yes or no	yes-other baby or no	regular	may stop enrollment
7. Weaned, any time *	no	yes	yes-other baby or no	backup	reduce or deplete backup pool
8. Weaned, any time *	no	no	yes-other baby	3-day reserve	may result in weaned baby being forced onto CMV is further ventilation required
9. Weaned, any time *	no	no	no	CMV until HFV available	results ambiguous

* NOTE: It is possible that a particular baby's "3-day reserve" machine could be unavailable if used in breakdown/crossover situation #3.

APPENDIX D

ABSTRACT

The mechanical performance of eight neonatal high frequency ventilators (HFV) operating under identical conditions was compared. The ventilators were coupled to in vitro models of the neonatal respiratory system in varying severity of disease. The principal physiological characteristics examined were tidal volume delivered, frequency dependence of the volume delivered, load dependence of volume delivered, peak inspiratory flow rate, waveform characteristics of volume delivered, flow, distal pressure and proximal pressure. Substantial differences were observed between devices with regard to these measures, but some common features emerged. Tidal volume increased with endotracheal tube size, but was invariant with changes in respiratory system compliance in 7 of 8 devices; tidal volume diminished with increasing frequency in 7 of the 8 devices. Peak inspiratory flow rates for a given tidal volume and frequency were smallest in the group of oscillators as compared with jets and flow interrupters. The oscillators were judged to be physiologically equivalent.

Introduction and Rationale

This report deals with the mechanical performance of eight neonatal high frequency ventilators considered for use in the High Frequency Intervention (HIFI) Trial. The major purpose of this report is to characterize the ventilators in question with respect to pertinent physiological inputs delivered to the patient.

Conventional mechanical ventilators (CMV) are readily characterized. Little uncertainty remains concerning the nature of CMV therapy after specifying pressure cycled or volume cycled mode of operation, pressure limits, tidal volume, and inspiratory and expiratory duration. The measurement of timing, pressures, and volumes are straightforward. The mechanics of the lung ventilated at slow rates are well studied, and the physiology and pathophysiology of gas exchange during CMV are well developed. In contrast, in the case of high frequency ventilation of the neonate the only quantity that has been reported with certainty is ventilatory rate. The terms "jet", "oscillator", and interrupter" are descriptive of devices, but say little about the physiological outputs.

Delivered tidal volumes in infants have not been reported to date because of technical difficulties in obtaining reliable measurements during high amplitude high frequency flows in uncuffed endotracheal tubes. Pressures upstream and downstream of the endotracheal tube have been reported, but these data have been of limited significance or difficult to interpret for several reasons: substantial inertial and resistive pressure drops across the endotracheal (ET) tube guarantee that upstream pressure swings will be a poor indicator of central airway pressure swings (Frantz, 1985); resonant amplification phenomena produce alveolar pressure swings that exceed those in the central airway by several fold at some frequencies (Fredberg, et al., 1984); mean pressure in the alveolar zone can exceed mean pressure at the airway opening, a phenomenon called dynamic hyperinflation (Simon, et al., 1984), and can be nonhomogeneous as well (Allen, et al., 1984). The mechanics of the neonatal lung at high frequencies have been studied little (Dorkin, et al., 1983), and in the face of these uncertainties the physiology and pathophysiology of gas exchange during HFV have proven to be elusive and controversial, even in the case of well controlled animal investigation (Chang, 1984).

Acknowledging the substantial uncertainties that will arise in applying HFV in the clinical trial, it is important to characterize and control the physical/physiological inputs to which the infant might be exposed. In so doing the therapy will be as consistent and well defined as possible. To this end the specific attributes by which these ventilators have been characterized are described below. The first aim was to relate readily monitored variables such as ventilator settings, bias flow rates, and proximal pressures, to the less readily assessed but more important physiological inputs to which the infant is exposed, such as distal pressure, tidal volume, and flow waveform. These physiological inputs are seen to be of considerably greater import than the device from which they issue forth. Such characterization should facilitate retrospective estimation of pertinent physiological inputs, and more importantly, should permit prospective control, comparable use, and functional equivalence of ventilators of the same or different types as used within and between clinical centers. A second aim of this study was to compare the mechanical performance of these eight ventilators

under the condition of a common mechanical load, whereby differences between devices could be assessed in a controlled manner.

Methods

The method employed an in vitro model of the intubated neonatal respiratory system coupled to a ventilator in question. A tube-bottle system was employed in which respiratory system inertance and resistance were modeled by tubing of varying diameter (2.5 - 3.5 mm ID), and compliance was modeled by gas compressibility using containers of varying volume (250 - 4000 ml). Tidal volume delivered to the lung was determined by pressure plethysmography. Thus, the pressure plethysmograph served a double function: volume measurement and variable elastic load. The input impedance of these models spanned much of the range of data reported by Dorkin, et al. (1983) for infants with respiratory distress syndrome (RDS) and pulmonary interstitial emphysema (PIE). The nominal values and ranges of parameters studied are given in Table 1.

Table 1. PARAMETER RANGES

Parameter	Nominal State	Range
ET ID (mm)	3.0	2.5 - 3.5
C_L (ml/cm$H_2$0)	1.5	0.4 - 2.9
f (Hz)	15.0	7.5 - 30.0
V_T (ml)	2.0	0.5 - 10.0

The ventilators in question are listed in Table 2.

Table 2. VENTILATORS

Oscillators	Jets	Flow Interrupters
Emerson (Oscillator)	Bunnell (Life Pulse)	Bird (Military)
Gould (Texas Research)		Emerson (Interrupter)
Senko (Hummingbird)		Infrasonics (Infant Star)
Metrex (Flutter II)		

Of these the first four are oscillators, the fifth is a jet, and the last three are flow interrupters. Other important characteristics of these devices are summarized in Tables 3-6.

For each ventilator the bias flow circuit was set up in a fashion consistent with clinical application. In cases where the complete circuit was provided by the manufacturer, that circuit was employed. Otherwise a circuit similar to that described by Frantz, et al. (1983) or Boynton, et al. (1984), was employed. Each ventilator was operated as suggested by the manufacturer.

The time histories of proximal pressure, distal pressure, volume delivered, and flow were recorded. Volume delivered was computed from the plethysmographic pressure signal calibrated for adiabatic gas compression, and flow rate was computed from the time derivative of the volume signal. All pressures were measured using Endevco 8510-2 piezoresistive pressure sensors (San Juan Capistrano, CA), which have flat frequency response from DC to 35,000 Hz, and are linear response to ± 140 cm H_2O. These signals were bandpass filtered from 0.1 Hz to 100 Hz (Tektronix AM502 bandpass amplifier). Load dependence of tidal volume was determined by varying the elastic load (plethysmograph compliance, 0.42 - 2.6 ml/cm H_2O) and by varying endotracheal tube size (Portex, 2.5 - 3.5 mm ID) and thereby, system resistance and inertance.

The following issues were not tested: safety or safety features, efficacy for promoting gas exchange during high frequency ventilation, ease of clinical management, between-unit variability, temporal stability, wear, or durability.

Limitations of the in vitro model: Dorkin, et al. (1983) studied the high frequency mechanics (4-40 Hz) of six neonates with RDS, some of whom also had PIE. They reported that the respiratory system/endotracheal tube combination could be modeled as a series inertance-resistance-compliance system. Endotracheal tube resistance was equivalent to about 50% of the respiratory system resistance distal to the tip of the endotracheal tube. Virtually all of the system inertance resided within the endotracheal tube, while virtually all of the system compliance resided distal to the tip of the endotracheal tube.

To model the essential mechanical characteristics of the RDS neonatal lung a tube-bottle combination as described above and as suggested

Table 3. CONTROLS

	Frequency	Variable I/E	PIP	PEEP	Other AMP Control	Bias Flow	Gas Temp.									
1 Metrex	●			●	●	●										
2 Emerson Interrupter	●				●											
3 Infrasonics	●	(1)		●	●											
4 Emerson Oscillator	●				●											
5 Bird	●	●														
6 Bunnell	●	●	●				●									
7 Gould	●	●			●											
8 Senko	●			●	●	●										

(1) For HFV, INSP fixed at 10 m.sec.

Table 4. INDICATORS

	Frequency	I/E	PIP	PEEP	ΔP	Map	Other Amplitude	Bias Flow	Temperature	Humidifier Liquid ml/min						
1 Metrex	●				●	●		●								
2 Emerson Interrupter	●															
3 Infrasonics	●			●			●									
4 Emerson Oscillator	●															
5 Bird																
6 Bunnell	●	●	●	●	●	●			●	●						
7 Gould	●	●					●									
8 Senko	●		●	●	●	●										

Table 5. ALARMS

	Low Supply Gas Pressure	Low Supply O_2 Pressure	Loss of PIP	High PIP	Cannot Meet PIP	Low PEEP	High MAP	Low MAP	Obstructed Tube	Ventilator Fault	Valve Fault	Low Temperature	Humidifier Liquid Level	Humidifier Circuit Fault		
1 Metrex				●		●										
2 Emerson Interrupter																
3 Infrasonics	●	●				●			●	●						
4 Emerson Oscillator																
5 Bird																
6 Bunnell	●		●	●	●		●	●		●	●	●	●	●		
7 Gould	N/A	N/A														
8 Senko			●	●												

Table 6. OTHER FEATURES

	Low Frequency (Hz)	High Frequency (Hz)	Integral Bias Flow	Integral Humidifier	Integral Gas Temperature	Sigh Function	O_2 Air Blend	Internal Battery Backup	Clinical Experience	Low Tidal Volume (ml)	High Tidal Volume (ml)	CMV	Circuit Supplied	High Pressure Dump		Tidal Volume Affects Frequency
1 Metrex	5	35	●			●			●	.5	8.		●	●		
2 Emerson Interrupter	2	35							●	.6	6.3					
3 Infrasonics	2	30	●(1)			●	●	●		1.	4.2	●	●	●		
4 Emerson Oscillator	14	>30							●	3.9	5.1					
5 Bird	<1	>50						N/A		1.94	6.3	●	●			●
6 Bunnell	2	15		●	●				●	2.46	>8.0		●	●		
7 Gould	1	50				●			●	4.2	5.82					
8 Senko	2	22				●	●			.3	>80		●	●		

(1) Fixed at 4 L/min.

by Dorkin, et al. was employed. This system shares the following mechanical features with the intubated RDS infant: it behaves as a series inertance-resistance-compliance system; nearly all of the inertance resides within the endotracheal tube; nearly all of the compliance resides peripheral to the tip of the endotracheal tube; the compliances and inertances are readily matched to physiological values. The major departure of this in vitro model from the RDS lung is that there is little resistance peripheral to the tip of the endotracheal tube, whereas the resistance in an RDS lung can be about twice as great as endotracheal tube resistance. This discrepancy was tolerated for three reasons. First, the endotracheal tube diameter can be varied to compensate for the overall system resistance. Second, little is known about the mechanical origins of flow resistance in the small and collapsible airways of the neonate, so development of a more detailed model is somewhat problematical. Third, Dorkin's data shows that while flow resistive pressure differences are important, their importance is somewhat limited compared to the roles of inertial and elastic pressure differences. The impedance of the intubated RDS respiratory system is controlled by elastic pressures associated with lung compliance at lower frequencies, and by inertial pressures associated with endotracheal tube and airway inertance at higher frequencies. The impedance is contolled by resistive pressures at intermediate frequencies where inertial and elastic pressure differences are of comparable magnitude but of opposite sign, and hence mutually cancelling. Overall, this leads to an impedance vs. frequency characteristic that matches real data well with respect to both frequency dependence and magnitude of impedances, except near resonance where the impedance minimum is about 50% of that observed in the patient population. The implications of this approximation is addressed in the Discussion.

While these models are thought to embody the many essential physical features known to be of importance, they should not be expected to mimic the detailed mechanics of the RDS lung. They do provide a reasonable and relevant object of study and guide for thought for evaluating ventilator performance. It is also noteworthy that these studies make no assumption of system linearity, and accordingly, engender whatever flow nonlinearities might arise in the ventilator, the circuit, or the endotracheal tube.

Results

Frequency Dependence of V_T: Each ventilator was set to a rate of 15 Hz, and the amplitude of oscillation was adjusted to produce a tidal volume of 2 ml for the nominal respiratory system load (Table 1). In some cases (Bunnell and Emerson oscillator) tidal volumes this small could not be achieved. The frequency was then altered and the ensuing changes in tidal volume were noted. In all but two machines tidal volume fell with increasing frequency (Figure 1). The tidal volume delivered by the Bunnell device increased with frequency, while the Infrasonics output was least at 15 Hz and slightly greater at 7.5 and 30 Hz. These same data could be expressed as mechanical efficiency, V_T/Pao, the tidal volume per unit pressure cost (Figure 2). All units exhibited diminishing efficiency with increasing frequency, but the Infrasonics unit exhibited far less frequency dependence than the others. Three of the oscillators (Metrex, Emerson, and Senko) exhibited similar behaviors and higher efficiencies.

Load Dependence: At nominal settings (Table 1) the amplitude was adjusted to produce a tidal volume of 2 ml as closely as possible. Thereafter endotracheal tube size was varied and resulting changes in tidal volume were noted (Figure 3a). All ventilators exhibited increasing tidal volume with increasing endotracheal tube size. Similar results were observed when the initial tidal volume was set at 4 ml (Figure 3b).

Similarly, the elastic load was varied and the resulting changes in tidal volume were noted (Figure 4). For the most part, all devices delivered tidal volumes which were independent of the elastic load, down to the smallest compliances studied (0.4 ml/cm H_2O). The notable exception was the Bunnell device, whose tidal volume increased as compliance increased.

Waveform Shapes: Waveform shapes of the volume delivered, flow rate, and upstream pressure were recorded for the nominal settings. By virture of the plethysmographic relations, distal pressure is merely the volume signal scaled by a constant, the terminal compliance. Remarkable differences in waveform shapes were observed between devices, but three of the four oscillators (Metrex, Emerson, Senko) exhibited similar waveform shapes (Figure 5). For equivalent values of frequency and

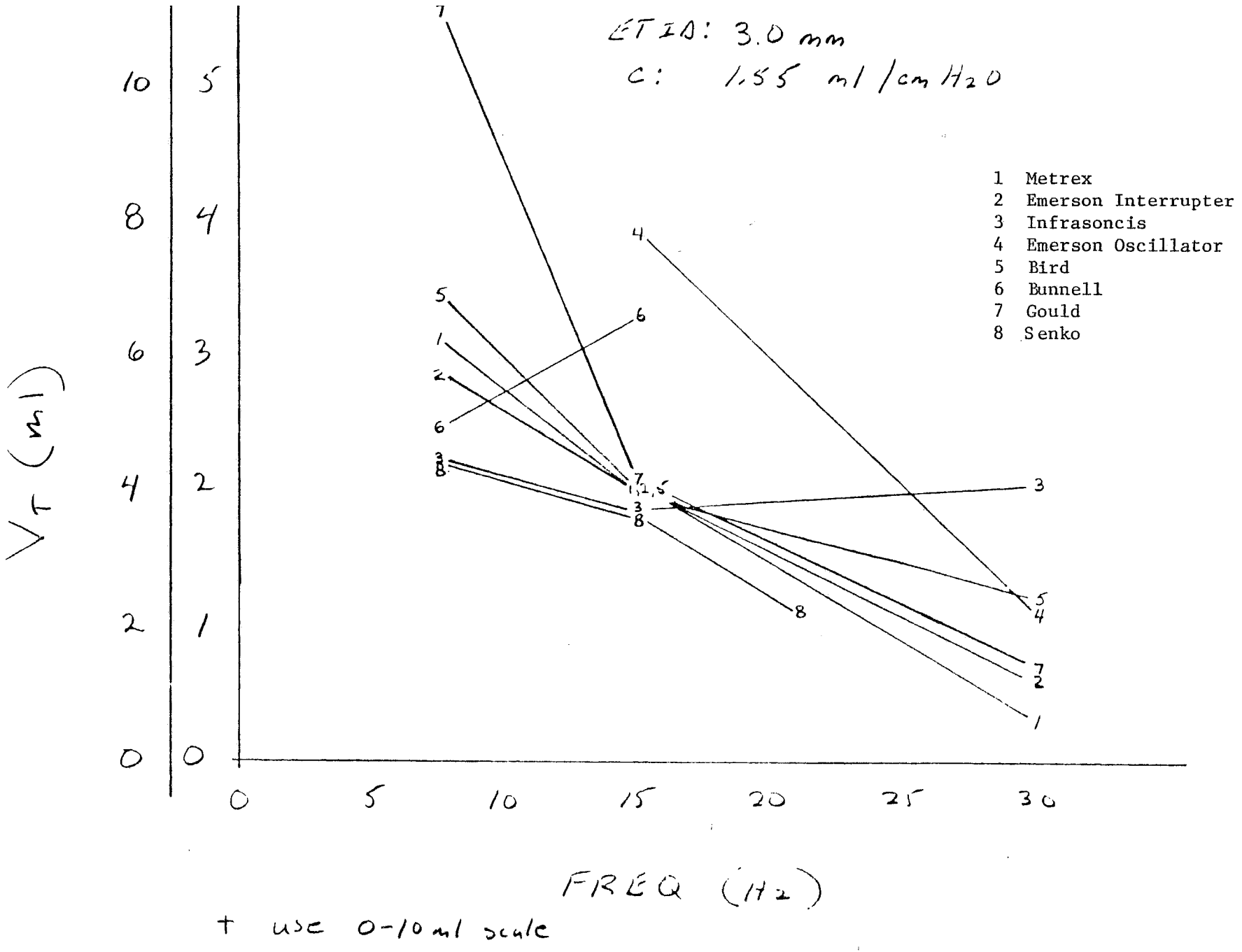

ETID: 3.0 mm
C: 1.55 ml/cm H2O
1 Metrex
2 Emerson Interrupter
3 Infrasoncis
4 Emerson Oscillator
5 Bird
6 Bunnell
7 Gould
8 Senko
VT (ml)
FREQ (Hz)
0
5
10
15
20
25
30
+ use 0-10 ml scale

Figure 1.

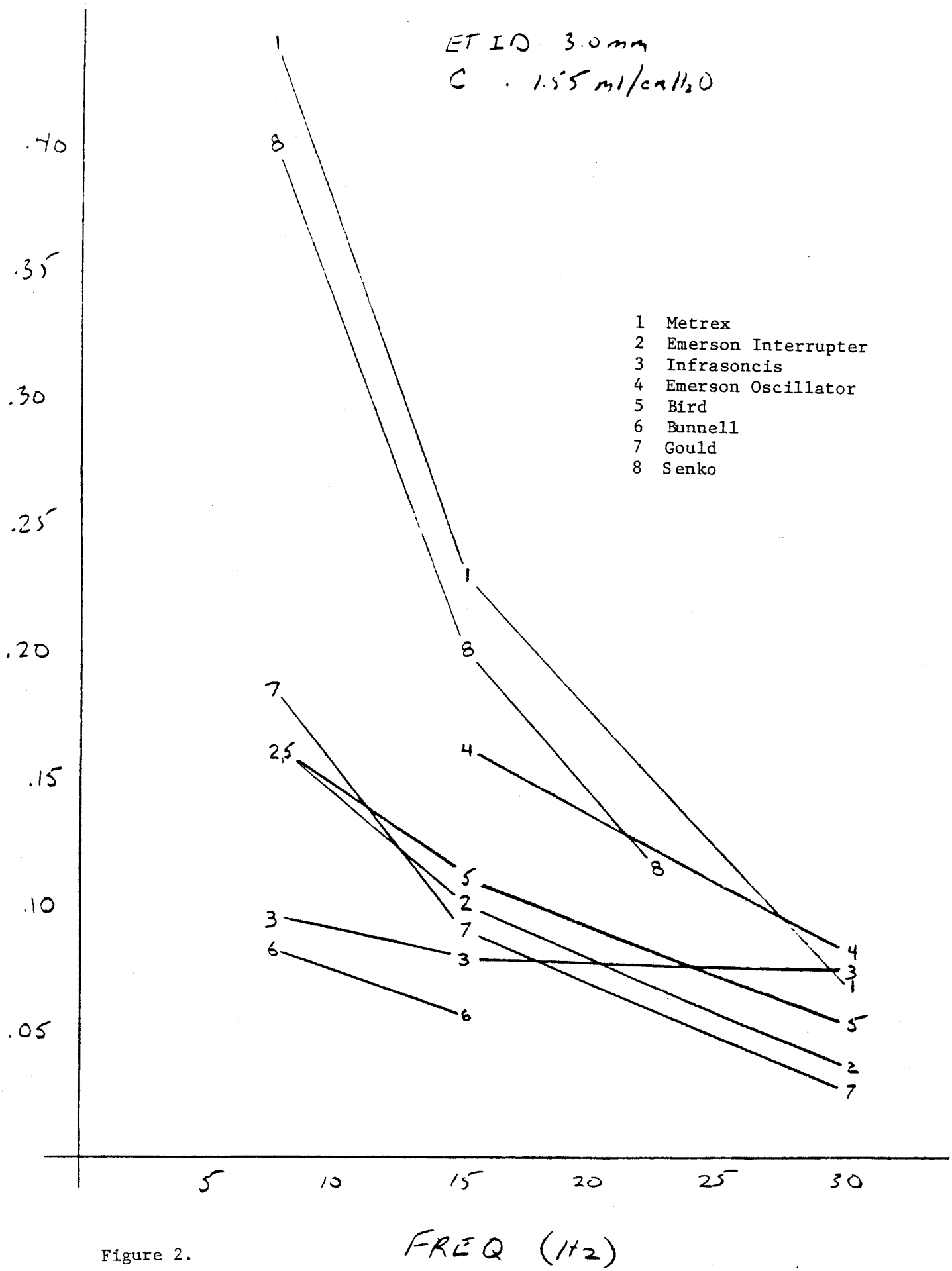

ET ID 3.0 mm
C . 1.55 ml/cm H2O
1 Metrex
2 Emerson Interrupter
3 Infrasoncis
4 Emerson Oscillator
5 Bird
6 Bunnell
7 Gould
8 Senko
.40
.35
.30
.25
.20
.15
.10
.05
5
10
15
20
25
30
FREQ (Hz)

Figure 2.

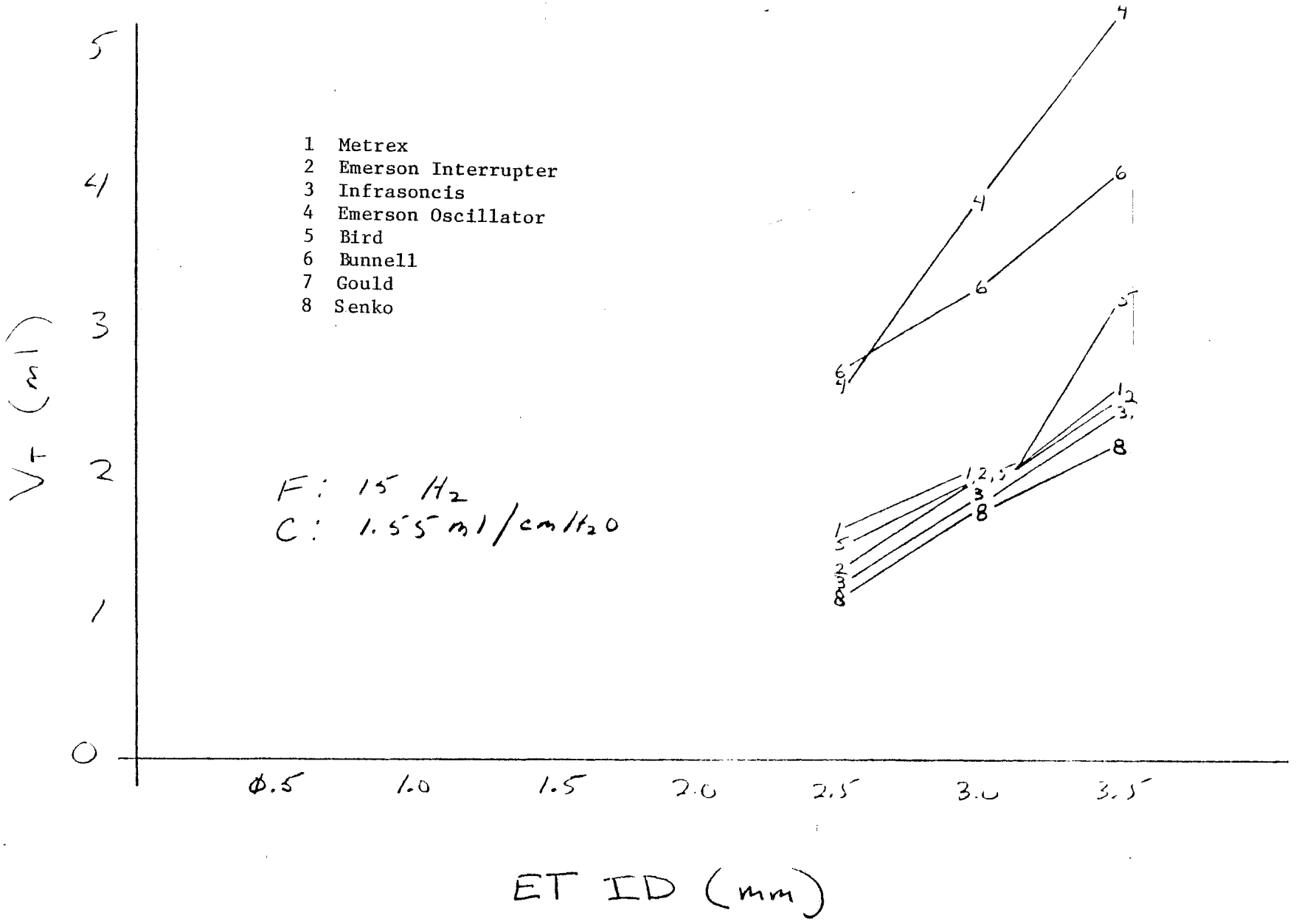

1 Metrex
2 Emerson Interrupter
3 Infrasoncis
4 Emerson Oscillator
5 Bird
6 Bunnell
7 Gould
8 Senko
F: 15 Hz
C: 1.5-5 ml/cm H2O
VT (l)
0
1
2
3
4
5
Φ.5
1.0
1.5
2.0
2.5
3.0
3.5
ET ID (mm)

Figure 3a.

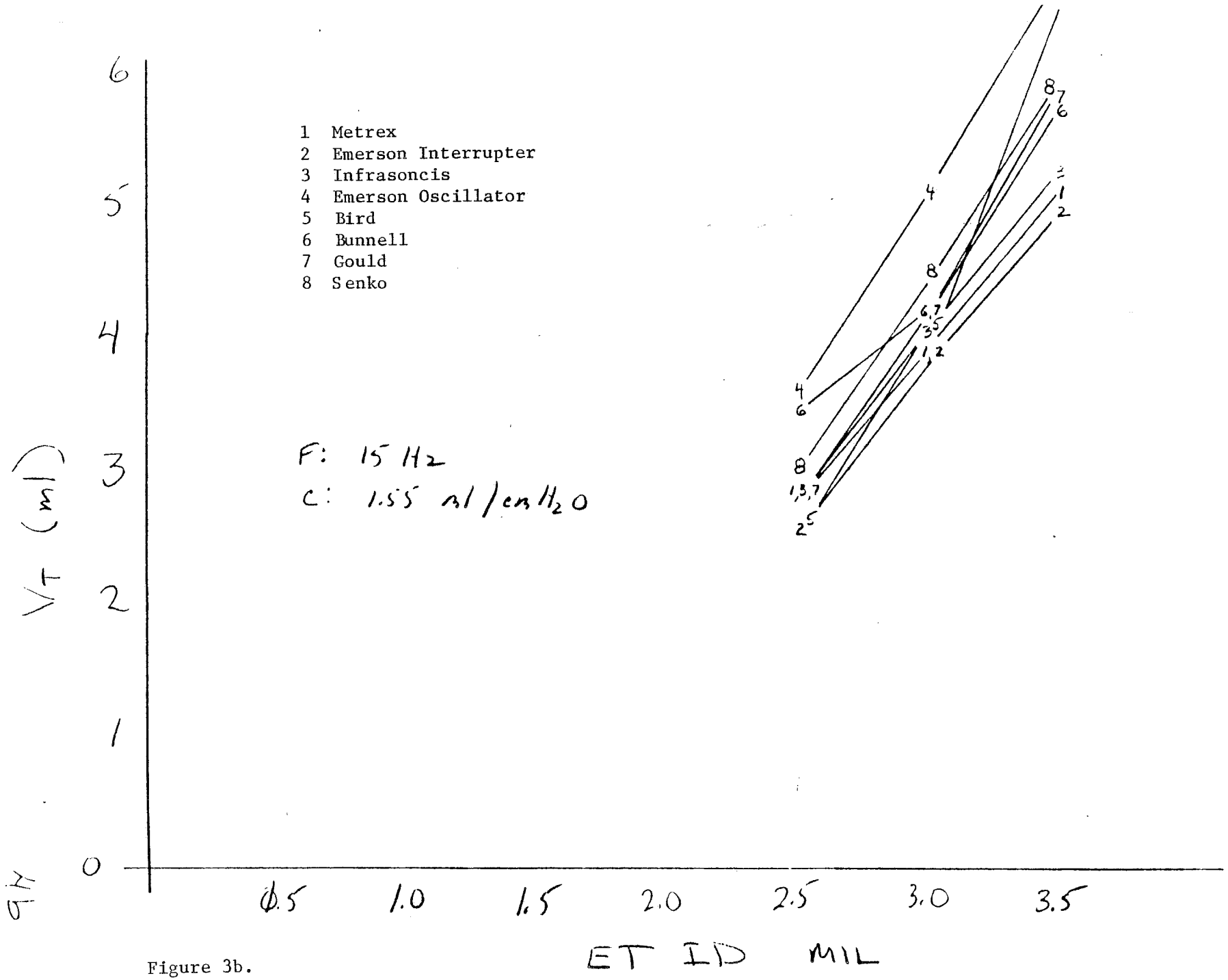

1 Metrex
2 Emerson Interrupter
3 Infrasoncis
4 Emerson Oscillator
5 Bird
6 Bunnell
7 Gould
8 Senko
F: 15 Hz
C: 1.55 ml/cm H2O
VT (ml)
0
1
2
3
4
5
6
0.5
1.0
1.5
2.0
2.5
3.0
3.5
ET ID MIL

Figure 3b.

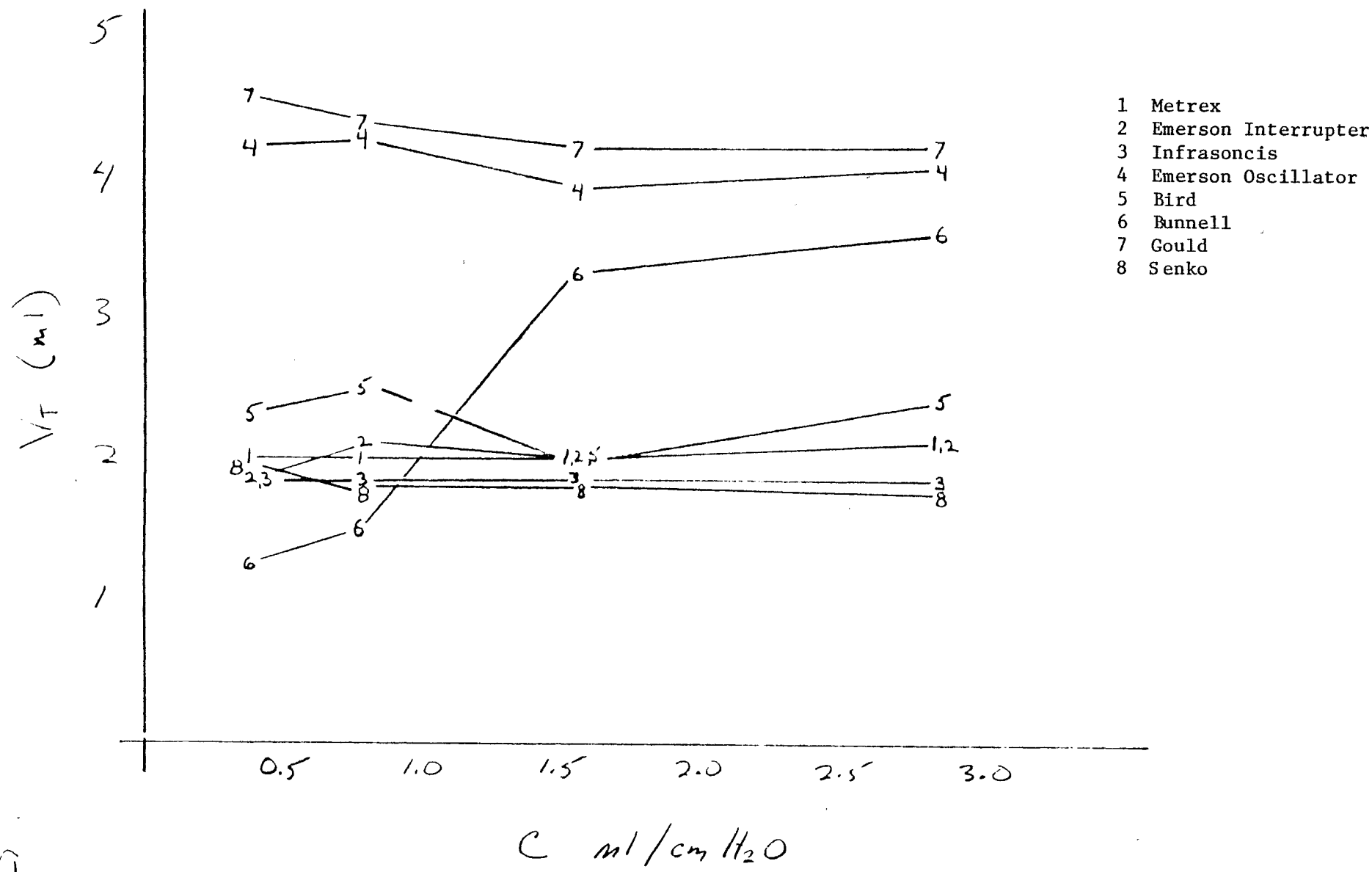
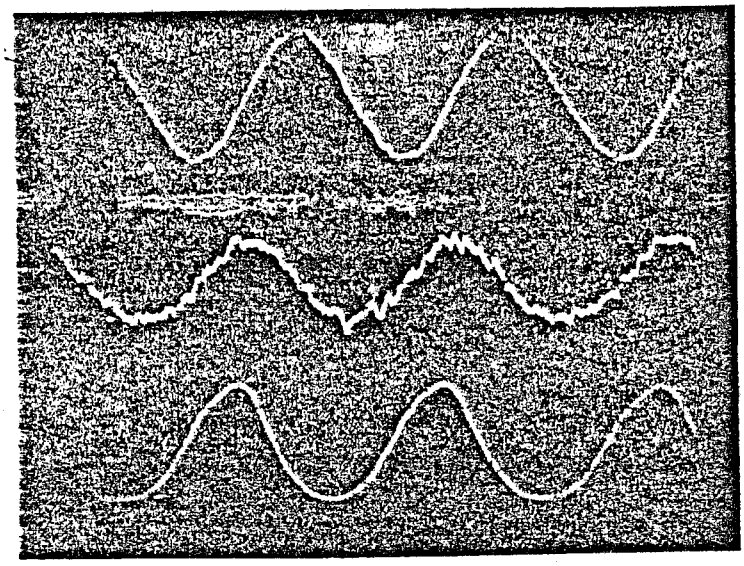
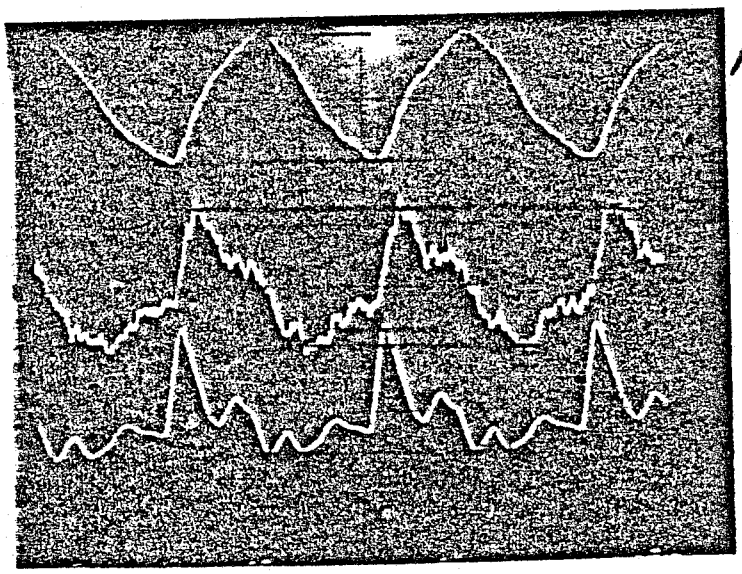

F: 15 Hz
LT IO: 3.0 mm
VT (ml)
5
4
3
2
1
0.5
1.0
1.5
2.0
2.5
3.0
C ml/cm H2O
1 Metrex
2 Emerson Interrupter
3 Infrasoncis
4 Emerson Oscillator
5 Bird
6 Bunnell
7 Gould
8 Senko

Figure 4.

Figure 5.


V
2.0 ml
ETREX
V̇
P_{AO}
8.8 cm H_2O
←20 ms→


V
2.04 ml
MERSON
NTERRUPTER
V̇
P_{AO}
19.8 cm H_2O

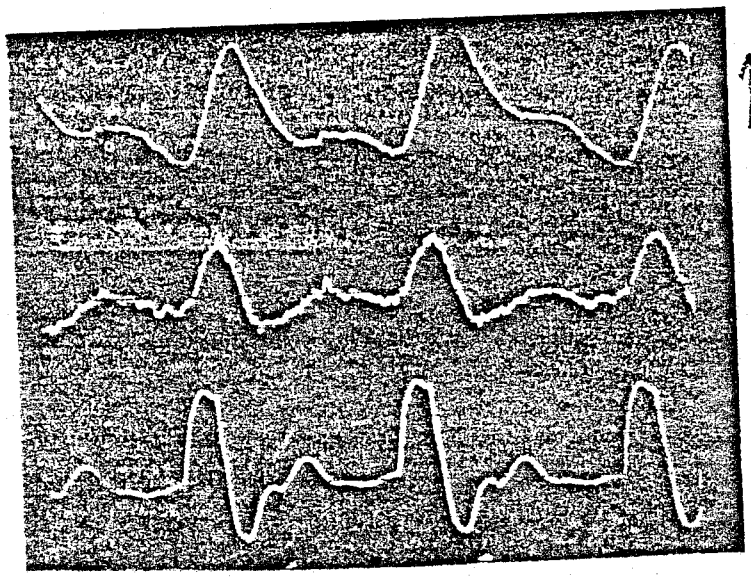
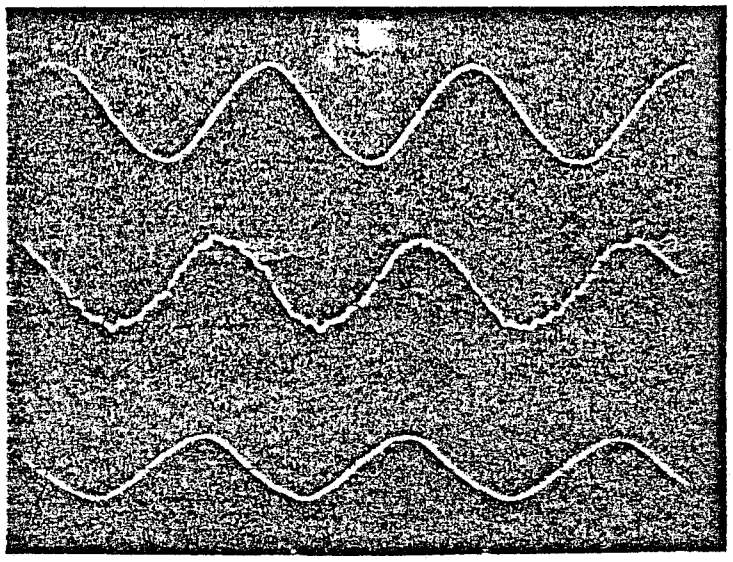
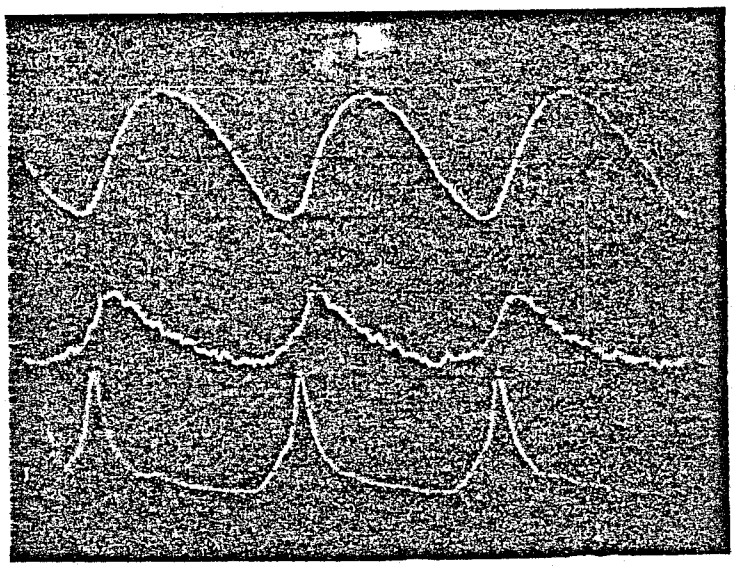

V
1.86 ml
NFRASONICS
V̇
P_{AO}
23.4 cm H_2O

Figure 5. continued





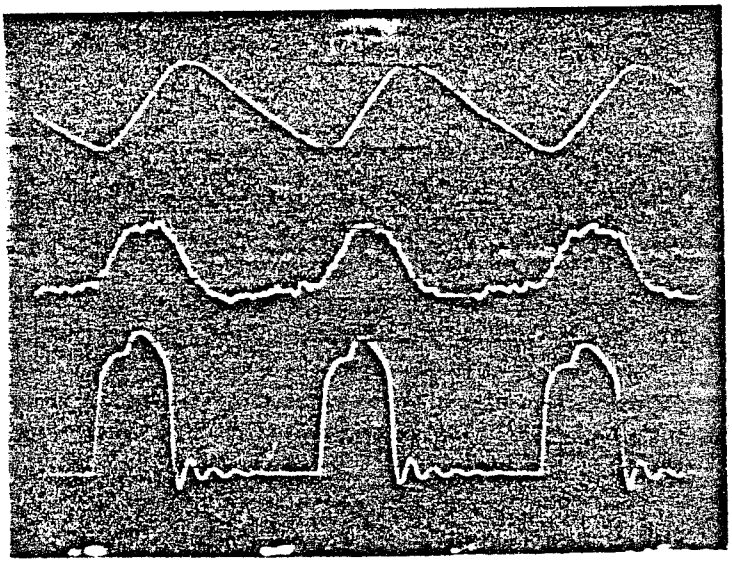
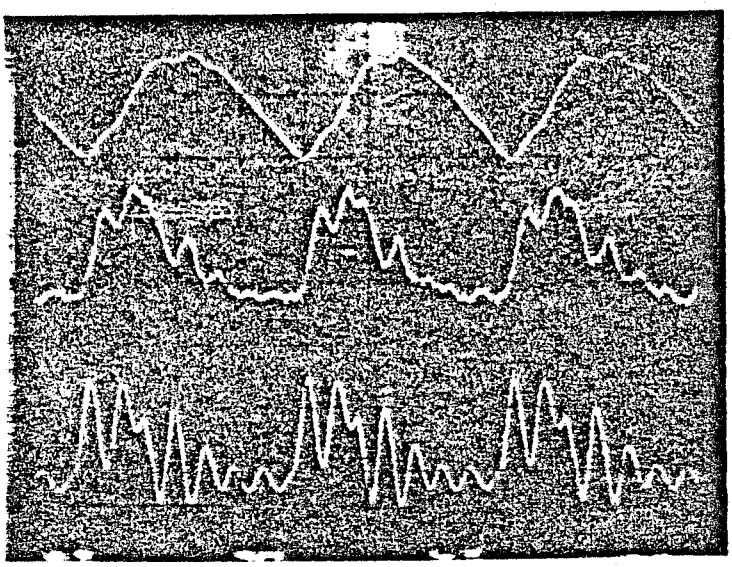
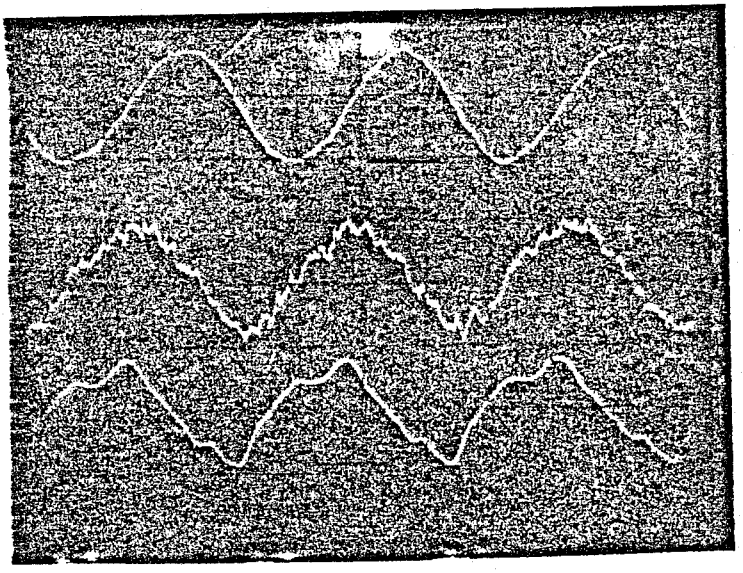


Figure 5. continued

GOULD



SENKO



tidal volume, the inspiratory durations were largest and the peak inspiratory flow rates were smallest in this oscillator group (Table 7). The data of Table 7 are referenced to the nominal settings specified in Table 1. Where tidal volumes of 2 ml were not achievable in a particular device, results were extrapolated to a tidal volume of 2 ml. As an index of the potential for fluid-dynamically induced damage to the tracheal wall, the peak value of the dynamic head of the inspiratory gas stream at the tip of the endotracheal tube is given as well (Table 7). Dynamic head also represents fluid kinetic energy per unit volume.

Table 7. PEAK INSPIRATORY FLOW RATES AT NOMINAL SETTINGS

	Peak Inspiratory Flow (ml/s)[1/]	Peak Dynamic Head (cmH_2O)[2/]
Gould[3/]	114	1.6
Emerson Oscillator[3/]	98	1.2
Senko	85	0.9
Metrex	92	1.0
Bunnell[3/]	104	1.3
Bird[3/]	159	3.0
Emerson Interrupter	129	2.0
Infrasonics	177	3.7

1/ Tidal volume = 2 ml, frequency = 15 Hz, endotracheal tube 3.0 mm.
2/ Gas density times square of linear velocity divided by two, calculated at the tip of the endotracheal tube.
3/ These devices could not meet nominal tidal volumes. Peak inspiratory flow rates extrapolated to 2 ml tidal volume.

Other Features: The relationship between peak-to-peak proximal pressure and tidal volume was nonlinear and varied widely between devices. The frequency set on the ventilator control had good correspondence with the actual frequency of oscillation. Characteristics including alarm, pressure dumps, clinical exposure, etc., are summarized in Table 8.

Table 8. SUMMARY

Ventilator	Control	Monitor	Alarm	Dump	Clinical Experience	Character-izibility
Gould	+	+	--	--	++/-	-
Emerson Oscillator	+	-	--	--	++	++
Senko	++	++	++	++	--	++
Metrex	++	++	++	++	++	++
Bunnell	++/-	++	++	++	++/-*	+
Bird	--	--	--	--	+/--	+
Emerson Interrupter	-	-	--	--	+	-
Infrasonics	++	++	++	++	--	+

* Unpublished

Discussion

The principal findings of this report are as follows. Delivered tidal volume 1) fell with increasing frequency of oscillation in 6 of the 8 ventilators examined; 2) increased with increasing endotracheal tube size in all 8 ventilators; and 3) was largely insensitive to changes in elastic load in 7 of the 8 ventilators. The efficiency of volume delivery, V_T/Pao, decreased as frequency increased in all eight ventilators, but the magnitudes were variable between devices. Three oscillators exhibited similar behaviors, smaller peak inspiratory pressures, and higher mechanical efficiencies than the others. The waveforms of volume delivered and flow were highly variable among ventilators, but three oscillators exhibited essentially similar waveforms of flow and pressure.

A substantial dependence of tidal volume delivered upon frequency differentiates these ventilators from more familiar CMV devices, in which minute ventilation (fV_t) increases in direct proportion to frequency, all other factors being equal. No such simple relation exists for this group of high frequency ventilators, in which the changes in the frequency control always engendered changes in tidal volume as well.

Indeed, in some increasing rate increases minute ventilation, leaves it unaltered in others, and even reduces minute ventilation in still others. Thus, even if a simple model of gas exchange were to prevail, it would be difficult to predict in any general way how gas exchange might vary as the frequency control is altered.

The dependence of tidal volume upon endotracheal tube size was consistent among the ventilators tested. To the degree that changes in endotracheal tube size model changes in pulmonary airway size or patency, these data suggest that tidal volume delivered might diminish with the deterioration of airway state, and vice versa. These data also suggest that accumulation of slight amounts of secretion in the endotracheal tube is likely to diminish volume delivered.

The independence of volume delivered from compliance is an intriguing finding, but may represent an oversimplification compared with clinical conditions. In the in vitro model at 15 Hz this arises because the overall pressure difference across the endotracheal tube is much greater than the pressure generated peripherally, which is purely elastic. Accordingly, it is the pressure difference across the endotracheal tube that controls tidal volume, independent of the elastic load. This simple and desirable behavior may not prevail in the clinical situation for two reasons. First, in the extremely stiff lung, with compliances substantially smaller than 0.4 ml/cm H_2O, the elastic pressures may well exceed the pressure difference across the endotracheal tube, and hence tend to diminish tidal volume with decreasing lung compliance and vice versa. Thus the plateau values indicated in Figure 4 may represent an upper bound. Second, these data do not reflect any possible changes in airway properties, as described above. Dorkin's data at 15 Hz indicates that resistance distal to the endotracheal tube is comparable to endotracheal tube resistance. This suggests that increases in lung resistance would tend to decrease tidal volume when lung resistance is large, but quantitative estimation is difficult.

Physiological Equivalence: While it cannot be predicted, even with modest accuracy, what tidal volume may be delivered to an infant with RDS in any specific situation with any one of the ventilators, the model data do suggest how tidal volume might vary with frequency, endotracheal tube size, and changes in lung mechanics. With regard to such mechani-

cal behavior, the Senko, Emerson, and Metrex oscillators are physiologically indistinguishable. To the degree that the nearly sinusoidal waveforms produced by these devices are readily characterized, they ought to be readily reproducible by other investigators using other devices capable of producing similar waveforms.

Each of the remaining devices was unique in one way or another. The differences in behaviors of these systems is attributable in part to the broader frequency content of the waveforms compared with oscillators. Because the endotracheal tube offers increasingly high impedance to higher frequency components of the waveform, waveform shapes upstream and downstream of the endotracheal tube are quite different when the upstream waveform is not sinusoidal. Furthermore, to the degree that the inspiratory/expiratory (I/E) ratio is smaller than unity, peak inspiratory flow rates are larger for the same tidal volume delivered, minute ventilation and frequency. It has been reported that small I/E ratios may be associated with improved gas exchange, but it has been speculated that small I/E ratios may also be associated with airway damage induced by fluid dynamical factors in the vicinity of the tip of the endotracheal tube.

BIBLIOGRAPHY

Allen J; Frantz ID; Fredberg J. "Mean alveolar pressures during high frequency oscillations." Physiologist 27:212, 1984.

Boynton BR; Mannino FL; Davis RF; Kopotic RJ; Friederichsen G. "Combined high-frequency oscillatory ventilation and intermittent mandatory ventilation in critically ill neonates." J. Pediatr. 105:297-302, 1984.

Chang HK. "Mechanism of gas transport during ventilation by high frequency oscillation." J. Appl. Physiol. 56:553-563, 1984.

Dorkin HL; Stark AR; Werthammer JW; Strieder DJ; Fredberg JJ; Frantz ID. "Respiratory system impedance from 4 to 40 Hz in paralyzed intubated infants with respiratory disease." J. Clin. Invest. 72:903-910, 1983.

Frantz ID; Close RH. "Alveolar pressure swings during high frequency ventilation in rabbits." Pediatr. Res. 19:162-166, 1985.

Frantz ID; Werthammer JW; Stark AR. "High frequency ventilation in premature infants with lung disease: adequate gas exchange at low tracheal pressure." Pediatrics 71:483-488, 1983.

Fredberg JJ; Keefe DH; Glass GM; Castile RG; Frantz ID. "Alveolar pressure nonhomogeneity during small amplitude high frequency oscillation." J. Appl. Physiol. 57:788-800, 1984.

Simon BA; Weinmann GG; Mitzner W. "Mean airway pressure and alveolar pressure during high frequency ventilation." J. Appl. Physiol. 57:1069-1078, 1984.

PROTOCOL REVISIONS

7-16-85

Appendix D	Totally revised.

PROTOCOL REVISIONS
5-6-85

Title Page ... revised

Table of Contents ... revised

I. page 8 ... 1st paragraph ... slightly revised

II. page 9 & 10 ... 'one year' changed to '18 months' and this change made throughout the rest of the protocol

III. page 13 ... Section C - new
page 14 ... Section E ... last sentence added

IV. page 16 ... criteria #5 and #7 revised somewhat

IX. page 39 ... Section D - new

XII. page 47 ... first paragraph added
page 47 ... Section A - last sentence added

XIV. page 54 ... name of Boston participating institution changed

App. B. Full Study Conset Form ... six months changed to nine months

PROTOCOL REVISIONS
4-9-85

Title Page ... new date

Table of Contents ... revised

I. page 6 ... 2nd paragraph ... new

II. page 9 ... Objective Ib revised, Ic deleted
All references to 12 months changed to 18 months

III. page 13 ... Section B - new

IV. page 15 ... Section A4 revised

V. pages 18-19 ... data to be collected on all forms ... revised

VI. page 21 ... new last paragraph
flow diagram moved to Chapter IX

IX. page 37 ... Section A ... slightly revised
... Section B ... Condition Worsens, revised
page 38 ... Figure 1 ... revised
page 39 ... Section C - new

X. page 42 ... Section H. - Title changed
... Section L - new

XI. page 44 ... data to be collected ... revised

XII. page 45 ... follow-up completely revised
page 47 ... Section B - new

XVI. page 62 ... References revised

App. B. Pilot Study Consent Form added, Full Study Consent Form revised

App. C. new

App. D. new

PROTOCOL REVISIONS
3-12-85

Title Page ... new date

Table of Contents ... revised

I. Page 6 ... 2nd paragraph - new

II. Page 9 ... objective 1.a - revised

III. Page 12 ... Section A ... revised slightly

IV. Page 14 ... paragraph 1 ... last sentence expanded
... Section A.4 revised

VI. Page 19 ... paragraph 1 ... numbers revised slightly
Page 20 ... last paragraph ... backup within three days
Page 21 ... flow diagram slightly revised

VII. Page 22 ... sentence 1 slightly revised

IX. Page 35 ... Section A ... paragraph 2 ... slightly revised
... Section B.1 ... revised
Page 36 ... paragraph 2 ... last sentence revised
... paragraph 3 ... last sentence eliminated
... Section L ... new

X. Title Changed
... Section D ... title changed and fluid criteria changed
... Section E ... title changed
... Section H ... title changed

XII. completely revised

XVI. Page 59 ... references revised

Appendix B ... completely revised

PROTOCOL REVISIONS
2-5-85

Title Page ... new date

Table of Contents ... revised

I. page 4 ... Section B ... MAP changed to $\bar{P}aw$ and this change is made throughout the protocol.

II. page 9 ... Objective 1, revised slightly
page 11 ... Sections B and C deleted

III. page 12 ... Section A... paragraph 1 ... new sentence added
paragraph 2 ... replaced
page 13 ... Section C ... last sentence added.

IV. page 14 ... "multiple births" changed to "twins"
"a similar form" changed to "the same form"
... Section A 1 ... 751 grams changed back to 750 grams and this change is made throughout the protocol
... Section A 4 ... revision reflecting birthweight strata
... Section A 5 ... deleted
page 15 ... Section B. Exclusion Criteria #6 replaced, #7 added

VI. page 19 ... paragraph 1 ... defined birthweight groups
page 20 ... last paragraph ... "immediately" changed to "twenty-four hours"

VII. page 22 ... chapter revised slightly

VIII. page 23 ... new chapter added

IX. page 35 ... paragraph 1 ... revised
Sections A and B added

XVI. page 58 ... references revised

Appendix B ... page 67 ... added

PROTOCOL REVISIONS
1-8-85

TITLE PAGE ..... High Frequency Ventilation changed to High Frequency Intervention (HIFI) Trial and through the rest of the protocol

TABLE OF CONTENTS ..... Revised

I. A. Several paragraphs revised.
B. Several paragraphs revised.
C. Several paragraphs revised.

II. page 9 ... first section revised
page 10 ... Section A ... hypothesis c changed
page 11 ... 750 grams changed to 751 grams and this change is made throughout the protocol.

III. Completely new chapter added.

IV. page 15 ... Section C ... new section added.

VI. page 20 ... new final paragraph.

VII. Completely new chapter added.

IX. Several paragraphs revised.

XIII. page 36 ... Section 3 ... line 11 ... "through the Structure and Function Branch" eliminated

page 43 ... Article 13 ... an additional sentence added stating that this committee reviews proposals and make recommendations regarding ancillary studies.

References - Revised

PROTOCOL REVISIONS
12-11-84

TITLE PAGE ..... New Date
TABLE OF CONTENTS ..... Revised

I. A. Completely Revised
C. Completely Revised

II. Completely Revised

III. A. Completely Revised
B. Completely Revised

IV. page 14 ... A.4 ... line 6 ... insert word "diabetes"

V. page 17 ... line 7 ... insert word "strata" instead of blocking variables

page 17 ... line 9 ... insert word "strata" instead of fixed blocks

VI. page 19 ... line 10 ... "60" instead of 50 torr
... line 11 ... "65" instead of 60 torr
... line 12 ... "45" instead of 50 torr
... $\bar{P}\bar{a}\bar{w}$ of "20-25" instead of > 24
... lines 13-16 ... new
page 20 ... line 4 ... "duration of 0.5 to 1.0 sec" instead of 1:2 to 1.1

VII. Completely Revised

VIII. page 24 ... "Type of Ventilator" included
Frequency requirements changed

IX. Completely Revised

XI. page 32 ... #3 ... first four lines changed
... the word "Panel" has been replaced with the word "Board" and throughout the rest of the protocol

page 34 ... the word "Publication" has been replaced with "Publications and Ancillary Studies" and throughout the rest of the protocol

page 36 ... Section 3 ... line 2 ... delete the words "the principal investigator"

page 39 ... Article 10 ... line 1 ... one sentence deleted stating that this subcommittee reviews and makes recommendations regarding ancillary studies

page 39 ... Article 11 ... line 4 ... add "of usage"

References - Revised