Use of a non-invasive method to verify changes in small airways.

Summary

We have investigated the possibility of using a non-invasive method to verify changes in the airways (atelectasis formation in the lungs) after hyperoxygenation during generally anesthesia. Fifteen health patients were chosen and their lung function before and after generally anesthesia were measured by TremoFlo C-100. The measurement shows increased resistance in the airways which can be interpreted as atelectasis.
Abstract

**Background.** Hyperoxygenation during anesthesia lead to development of atelectasis. The purpose of the study was to demonstrate that a non-invasive measurement method can visualize changes in the small airways.

**Methods.** This is a clinical trial including fifteen healthy patients undergoing minor orthopedic surgery between November 2017 and December 2017. All patients were oxygenated during general anesthesia following the standard regime at the hospital. All patients were preoxygenated with 100 percent of oxygen prior to surgery and during surgery the patients were treated with 50 percent of oxygen. Lung function was investigated before and after general anesthesia using a non-invasive method. The non-invasive measurement method was used to measured resistance in total, large and small airways. Data were analyzed for normality and non-parametric or parametric statistical methods were used depending on the distribution of the data. A p < 0.05 was considered statistically significant

**Results.** Comparing before to after measurements hyperoxygenation showed an increased resistance in large airways in 12 out of 15 patients (p = 0.011).

**Conclusions.** The observed changes in resistance may be due in part to hyperoxygenation. It can lead to postoperatively clinical important morbidity such as respiratory complication, longer recovery and increased mortality. Therefore, it is important to focus on oxygen treatment side effects.

Resumé

**Baggrund.** Hyperoxygenering under anæstesi fører til udvikling af atelektase. Formålet med undersøgelsen var at påvise, at en ikke-invasiv målemetode kan visualisere ændringer i de små luftveje.

**Metoder.** Dette er et klinisk forsøg omfattende femten raske patienter, der gennemgår mindre ortopedikirurgi i perioden november 2017 til december 2017. Alle patienter blev behandlet med ilt under general anæstesi efter hospitalets standardinstruks. Alle patienter blev præoxygeneret med 100 procent ilt. Under operationen blev patienterne behandlet med 50 procent ilt. Lungefunktion blev undersøgt før og efter generel anæstesi ved anvendelse af en ikke-invasiv metode. Den ikke-invasiv målemetode blev brugt til at måle modstand i total, store og små luftveje. Data blev analyseret for normalfordeling, og ikke-parametriske eller parametriske statistiske metoder blev brugt afhængigt af fordelingen af data. Resultat er signifikant ved en p-værdi <0,05

**Resultater.** Sammenligning af før og efter målinger viser stigning i resistens i de store luftveje. Stigning ses hos 12 ud af 15 patienter (p = 0,011).

**Konklusion.** De observerede ændringer i resistens kan skyldes hyperoxygenering. Det kan føre til postoperativ klinisk betydelig morbidity såsom respiratorisk komplikation, længere genopretning og øget dødelighed. Derfor er det vigtigt at fokusere på bivirkninger i forbindelse med iltbehandling.
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Introduction

Atelectasis, which is collapse of the small airways, is a common perioperative complication caused by high percentage of inspired oxygen, mechanical ventilation and posture. Previous studies have shown that ventilation using 80 – 100 percent of oxygen lead to development of atelectasis\textsuperscript{1,2,3}. However, in 2017 WHO and von Bormann et al recommended very high concentration of oxygen during and after surgical procedures to reduce or prevent surgical site infection\textsuperscript{4,5,6}. Moreover, oxygenation with 100 percent oxygen is used prior to intubation and in all emergency situations as time to arterial desaturation down to 90 percent in doubled when using preoxygenated with 100 percent oxygen compared with 60 percent oxygen\textsuperscript{3}.

Oxygen is essential to life. The atmosphere contains 21 percent oxygen\textsuperscript{7,8,9}. But oxygen given in concentration exceeding 21% is to be considered as a drug and thus part of a medical treatment. Therefore, the use of oxygen above 21 percent, should be individualized taking into account the benefits and side effects.

Mechanism of atelectasis

Main mechanisms underlying the atelectasis formation are compression, loss of surfactant or impaired surfactant function and absorption of gas (oxygen) from alveoli behind closed or intermittently closed airways\textsuperscript{10,11}.

Atelectasis refers to the partial or complete collapse of the lung tissue. There are many different types of atelectasis, absorption atelectasis being one such type. Absorption atelectasis refers to the condition where the reduction of nitrogen concentration in the lungs causes a collapse, nitrogen washout\textsuperscript{10}. Under normal circumstances, the air you breathe contains the same amount of nitrogen as blood in human body\textsuperscript{7}. It is the nitrogen that helps keep the alveoli or air sacs in the lungs open and functioning properly. Nitrogen provides a certain amount of surface tension that prevents the collapse of the alveoli. When people are hospitalized or have undergone surgery and general anesthesia, large amounts of oxygen are usually administered. This decreases the nitrogen concentration in the air and leads to absorption atelectasis\textsuperscript{10,11,12}.

Resorption atelectasis is another type of atelectasis that occurs when an obstruction in the lungs prevents air from reaching the airways. The air is absorbed into the surrounding areas and the alveoli collapse. Depending on the size of the obstruction, the collapse could be partial or complete and involve segments of a lobe, the whole lobe or even the entire lung. The most common cause of resorption atelectasis is the presence of a mucus plug in the bronchioles. Such mucus plugs may develop as a side effect of anesthesia or surgery or as a complication of other respiratory diseases such as asthma or chronic bronchitis. Young children may suffer from this type of atelectasis after inhaling a foreign object such as a marble or a peanut that then gets stuck in the airways\textsuperscript{11,10,12}.

Every day supplemental oxygen is given routinely to patients undergoing general anesthesia and is considered to be safe. In Denmark, patients undergoing general anesthesia, are preoxygenated with 100% pure oxygen for three minutes before they are intubated or most commonly also prior to extubation (Appendix 1). During
surgery the inspired fraction of oxygen is at least 0.50 percent (Appendix I). Atelectasis is a respiratory complication in the perioperative period which is important to investigate, verify and prevent, because the atelectasis can cause morbidity and mortality13,14,15,10.

Different studies have used computed tomography (CT) of thorax to verify atelectasis in patients undergoing general anesthesia15,2,16. Thereby, it has been shown that atelectasis is present in the postanesthesia period and that oxygen concentration has an influence on the formation of atelectasis. The higher the oxygen concentration, the greater the risk of atelectasis formation. However high cost, risk to the patient due to radiation and the time it takes to make a CT-scan lead to the investigation of another, cheaper and quicker method to verify the atelectasis.

Aim and hypothesis of the study

The aim of this study was to look on a non-invasive method to verify the changes in the airways. The hypothesis was that treatment with high concentration of inspired oxygen will lead to collapse of the small airways.

Searching strategy

To find the literature for this project the following electronic databases were used: PubMed, Cinahl, Medline, Google.com, Google scholar, PRI. The following keywords were used: Oxygen, Atelectasis, Pulmonary Atelectasis, Pulmonary Collapse, Lung, Anesthesia, General Anesthesia, Intubation, and Complication. Results were limited to human subjects, Danish- and English- language and free/available full text articles. Publication date was not specified, because the historical use and understanding of oxygen and atelectasis was of interest for this project.

Patients and Methods

This study is a small part of a larger study (Metabolic Changes during Minor Orthopedic Surgery in otherwise Healthy Patients) approved in the Research Ethics Committee (N-20170062).

Information material was extradited to all patients and informed consent was obtained from all enrolled subjects. The patients included in this study are adult, non-smokers or ex-smokers with no smoking for at least 2 years prior to the study and otherwise healthy persons selected for same-day surgery in the Orthopedic Unit between November 2017 and December 2017. Important to avoid comorbidities, the patients must not had any respiratory infection in the past three months, any alcohol intake the last 24 hours or be pregnant. All patients included in this study underwent surgery in general anesthesia with an expected duration of at least 40 minutes.
Measurement of oxygen treatment

The measurements of lung function was performed using TremoFlo C-100 Airwave Oscillometry System (AOS). TremoFlo C-100 (THORASYS Thoracic Medical Systems Inc. Canada) is a non-invasive device used to verify the central lung obstruction, peripheral obstruction and dynamic lung collapse. Size and mobility of this device makes it suitable to perform the measurement of lung function fast and easy and bedside. Measurements are obtained during tidal breathing and without patient effort. The TremoFlo provide the possibility of performing a pulmonary function test on patients of all ages, from preschoolers to the elderly\textsuperscript{17,18} (Appendix 2).

The measurements was performed before and after general anesthesia. Each patient performed four measurements before and after general anesthesia. All four measurements were processed in AOS software to a single numeric value. The AOS sends a spectrum of electrical impulses in spectrum ranging from 5 to 37 Hz (other Oscillometry system use also the spectrum ranging from 0 to 100 Hz)\textsuperscript{19}. According to manufacturer of TremoFlo 100-C the waveform 5 to 37 Hz performs better than harmonic or pseudo-impulse waveforms in the presence of so-called “nonlinearities” in the lungs. Nonlinearities exist in all lungs and become more dominant with decreased lung function. (Appendix 3).

AOS measures lung function by overlaying a gentle oscillatory pressure and flow wave on the patient's spontaneous breathing, while they seated in the bed and wearing a nose clip and were told to press the palms of their hands against the cheeks. Every subjects performed spontaneous breathing 4 times of 20-second duration. AOS superimposes a small, higher frequency oscillation onto the breathing waveforms. The oscillatory waves are sometimes referred to as “pseudo-random noise” in recognition of the fact that the resulting waveforms have the appearance of a “noisy” breathing waveform. Sophisticated signal processing techniques are then used to separate the recorded waveforms into their slower breathing pattern components and their faster respiratory mechanics components. (Appendix 3).

After first AOS measurement the patients were transferred to the operating room where they all were treated according to the standard procedure at the Department of Anesthesia, Aalborg University Hospital. The patients were pre-oxygenated with 100 percent of oxygen for 5 minutes followed by insertion of a laryngeal mask allowing controlled ventilation. During surgery the all patients were normoventilated with 50 percent of oxygen. Before removal of the laryngeal mask the all patients were oxygenated with 100 percent of oxygen for 5 minutes. On arrival to the recovery room all patients were treated with 3 liters of oxygen per minute through a nasal catheter for half an hour. Second AOS measurement was performed five minutes after oxygen treatment was switched off and patients were sufficiently awake to cooperate to the measurement.

Moreover, in all patients an atrial blood sample was taken before surgery, during surgery and after surgery. The patients did not receive any oxygen treatment during blood sampling before and after surgery. Blood samples were examined for pH, partial pressure of arterial carbon dioxide (PaCO\textsubscript{2}), partial pressure of arterial oxygen (PaO\textsubscript{2}), standard base excess (SBE), bicarbonate (HCO\textsubscript{3}), Hemoglobin, p-Lactate, p-Glucose.
The data is stored on a laptop computer (DELL Latitude 3450). The following data was collected and analyzed; R5 representing total airway resistance and R20 representing resistance of the large airways. Subtracting R20 from R5 (R5-R20) represents the resistance in the small airways\textsuperscript{20,21}. The X5 represent low frequent reactance reflecting changes to the lung periphery, but is, however, not specific\textsuperscript{21}. The reactance (AX) depends on the capacitance, which reflects elastic of the lung and inertive force characteristic of the respiratory system\textsuperscript{21}. The reactance (AX) is an expression of the respiratory reactance between 5 Hz and higher thus reflects the mainly capacitance part of the reactance. This makes AX a good index for changes to degree of peripheral involvement\textsuperscript{21}.

**Statistical methods**

For data analysis the SPSS (IBM Corporation, New York, United States) and the Stata (Metrika Consulting AB, Stockholm, Sweden) software was used. Data were tested for normality using histograms, QQ-plots and Shapiro-Wilks test. Normal distributed data are presented as mean and standard deviation and non-normal distributed data are presented as median and quartiles (25\textsuperscript{th} – 75\textsuperscript{th}). The before and after measurements are compared using paired t-test if data are normal distributed or Wilcoxon if data are non-normal distributed. A two-sided P value of less than 0.05 will be considered statistical significant.

**Results**

**Subjects**

A total of 15 otherwise healthy patients distributed into seven men and eight women were included in this study. Fourteen patients were of Caucasian origin and one female patient was of Asian origin. The mean age of patients is 33.7 ± 15.4 years. Mean weight and height are respectively 77.9 ± 10.7 kg and 174 ± 9.3 cm. Mean BMI is 25.7 ± 2.9. The mean surgery time is 87.5 ± 39.6 minutes. The patients were recruited from the Department of Orthopedic Surgery where they were scheduled for minor extremity surgery.

**Data**

Table 1 shows the subject characteristics AOS variables before end after general anesthesia and oxygen exposure. Colon Time is an expression of time between pre-oxygenation prior to insertion of the laryngeal mask and until the removal of the laryngeal mask.
Table 2 shows the results from the arterial blood samples taken before, during and after general anesthesia and oxygen exposure. Blood samples was a control of oxygen treatment under anesthesia. The PaCO₂ and pH value from Table 2 shows that all patients was normally ventilated before, under and after generally anesthesia. PaO₂ values show that all patients has a normal value before generally anesthesia. During surgery and controlled ventilation all patients are treated with high concentration of oxygen this is reflected in high PaO₂ values in all patients. After surgery and end of oxygen treatment, all patients have a normal PaO₂ value.

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Average: 13.2, 29.7, 12.3
St. deviation: ±1.98, ±6.91, ±1.76

Table 2: Blood samples before, during and after general anesthesia
Figures 1, 2 and 3 shows a graphical presentation of R5, AX and R5-R20 before and after general anesthesia.

The Q-Q plot shows that data for resistance in total (R5) and large (R20) was normally distributed, while data for small (R5-R20) airways, low frequent reactance (X5) and reactance (AX) is not normally distributed.

The collected data shows increase resistance in total airways in 13 out of 15 patients. The total airway resistance increased with average 0.55 cmH₂O from $3.82 \pm 1.03$ cmH₂O before to $4.37 \pm 1.90$ cmH₂O after generally anesthesia ($p = 0.06$), respectively.

Data for large airways shows increase resistance in 12 out of 15 patients. The resistance in large airways increased with average 0.81 cmH₂O from $2.84 \pm 0.54$ cmH₂O before to $3.65 \pm 1.34$ cmH₂O after generally anesthesia ($p = 0.011$), respectively.

Similar trends were seen for resistance in small airways where an increase was observed in 11 out of 15 patients. The resistance in small airways increased with average 0.17 cmH₂O. Data for resistance in small airways is not normally distributed with median 0.54 cmH₂O ($0.07 \text{ cmH}_2 \text{O} – 1.06 \text{ cmH}_2 \text{O}$) before and median 0.61 cmH₂O ($0.16 \text{ cmH}_2 \text{O} – 0.92 \text{ cmH}_2 \text{O}$) after generally anesthesia ($p = 0.36$).
Data for reactance and low frequent reactance is not normally distributed with median 5.92 cmH2O (2.23 cmH2O – 12.16 cmH2O) before and median 4.95 cmH2O (2.33 cmH2O – 10.31 cmH2O) after generally anesthesia for reactance (p = 0.23) and median -0.10 cmH2O (-0.2 cmH2O – 0.32 cmH2O) before and median -0.20 cmH2O (-0.21 cmH2O – 0.22 cmH2O) after generally anesthesia (p = 0.495) for low frequent reactance. Both reactance and low frequent reactance is increased after generally anesthesia. The reactance is increased in 9 out of 15 patients with average 2.91 cmH2O while low frequent reactance increased in 9 out of 15 patients with average 0.23 cmH2O.

Discussion

This is to our best knowledge the first study to investigate AOS possibility to detect damages/changes in the airways upon exposure to high concentrations of oxygen. The changes in small airways were not significant (p = 0.33) but data for total airways was nearly significant (p = 0.06) while data for large airways were significant (p = 0.011). AOS data shows moreover an insignificant tendency towards an increased reactance and low frequent reactance. The study performed by Shiota et al., where they investigate the IOS reliability of Japanese adult healthy subjects shows the average value of total, large airways and low frequent reactance for non-smokers and smoker’s lies close to our results. According to Shiota et al. lies data for non-smokers total airways resistance at 2.86 cmH2O, data for large airways resistance lies at 2.45 cmH2O and data for low frequent reactance lies at -1.12. For smokers the resistance in total airways lies at 2.75 cmH2O, data for large airways resistance lies at 2.35 cmH2O and data for low frequent reactance lies at -1.02 cmH2O\(^19\). It can be concluded that our AOS data is reliable and useful.

Our AOS data showed a large variation between the otherwise healthy patients. Mainly total airways resistance and reactance shows a large variation. According to Bill Brashier and Sundeep Salvi, women have higher resistance and lower reaction values compared to men. They also shows age-related changes in small airways resistance and reactance. The low frequent reactance values showed only age-related changes only in women. The body weight were a significant predictor for most AOS parameters in women but not males. Obesity was found to cause an increase in low frequent reactance and reactance values\(^20\). Female patients with high age and/or weight, included in this study had higher R5 and AX.

Unfortunately, there are not so many attempts to develop normal AOS values for adults as it is for children. Moreover, we also needed a knowledge about AOS measurement day to day variability in healthy adults and AOS measurement in healthy smokers and healthy non-smokers. Goldman et al. shows day variability in AOS measurement in children with asthma\(^22\) and According to Fisher et al\(^23\) and Landser et al\(^24\) the are no difference in AOS Measurement between smokers and no-smokers. However, Faria et al\(^25\) concludes in his study that amount of package has influence on lung function and AOS value, while Berger et al\(^26\) could only detect changes in IOs measurement in 9 of 16 healthy smokers. The patients in the present study was non-smokers.
Moreover, the second AOS measurement was preformed 45 – 60 minutes after controlled ventilation with 50 percent of oxygen as the patients should be awake enough to cooperate with the TremoFlo equipment.

**Strengths and Limitation**

There are several strengths and limitations in our study that we would like to acknowledge and expand on here.

A non-invasive, portable measurement method which can be used quickly and without the big costs to detect changes in lung parameters is a strengths side of this study.

A limitation is the small number of patients showing large variation despite the fact of being non-smokers and otherwise healthy. It is unknown whether some of the patients suffered undiagnosed pulmonary diseases as a lung function (spirometry) test was not part of the study. The AOS results stands alone with no comparison to golden standards, CT scan of lung to visual the atelectasis after generally anesthesia\(^1\),\(^4\). The CT scan could have confirmed the changes in airways.

Patients should be completely awake to complete the study and that meant that the distance from oxygen treatment to the measurement might be too large and the changes/atelectasis had disappeared.

**Conclusion**

We have demonstrated that the TremoFlo/AOS test can be used as non-invasive method to show changes in the airways. Unfortunately, we were unable to confirm our hypothesis that exposure to high oxygen concentration will lead to changes in small airways but we could detect changes in major airways. Our AOS data shows only a significant increased resistance in large airways, but with a tendency towards changes in small airways.

Unfortunately, we do not know the patients lung function (spirometry) before surgery. The spirometry could possible reveals lung diseases or other airways abnormality that could explain the large spread we gets in our AOS measurements. We can conclude that the small number population and the variation in age, height and weight might have had an impact on the results. Moreover, it can be concluded that the prolonged time from exposure to high concentration of oxygen to the second measurement could be a contributing factor to decreased atelectasis in small airways.

**Perspectivation**

This study is a pilot study showing significant changes in airways using a non-invasive measurement method. Use of TremoFlo could have a clinical importance to detects and prevents possible airway complications in healthy but also in sick patients. It is too early to say whether the use of the TremoFlo can be as promising.
Therefore, it is necessary to perform other studies with greater populations, to find the normal value for AOS, to identify day to day variability and AOS values for heavy smokers. Simultaneously to repeat the present study in a larger population.

Several studies using CT scan show that anesthesia and use of high oxygen leads to atelectasis therefore it would be an advantage to perform a small TremoFlo study using CT scan as a control of airways before and after anesthesia.
References

16. Lundquist, H., Hedestrierna, G., Strandberg, A., Tokics, L. & Brismar, B. CT-assessment of


Oxygenering på H-anæstesi i forbindelse med intubation og ekstubation af voksne patienter i generel anæstesi

Baggrund

Formål
Af hensyn til patientsikkerheden er der behov for strukturerede ensartede guidelines for denne patientkategori.

Praöxygenering før generel anæstesi
Alle patienter skal praöxygeneres med 100% ilt, flow på minimum 10 l/min og tætsluttende maske. Optimalt tilstræbes end-tidal oxygen fraktion på 0.87-0.9 (anbefaling fra DASAIM/Difficult Airway Society 2015 guidelines)

I enkelte tilfælde kan en end-tidal oxygenfraktion på 0.7 accepteres.

Ved optimal praöxygenering kan man forlænge apnøperioden uden saturationsfald fra 2 minutter til 8 minutter.

Transnasal Humidified Rapid Insufflation Ventilatory Exchange: THRIVE
Man kan yderligere opnå forlænget apnøperiode uden væsentlig saturationsfald ved at anvende næsekateter både under praöxygenering med en tætsluttet maske, og under apnøperioden, hvor intubationsforsøg gennemføres. Der gives ilt 10-15 l/min via næsekateteret. Dette anbefales som standardbehandling hos højrisikopatienter.

Praöxygenering i forbindelse med ekstubation
Der er øget risiko for vanskelige luftveje hos kæbekirurgiske patienter, som har gennemgået osteotomi samt øre-næse hals patienter som har gennemgået operation i luftvejene, mundhulen eller halsen.


Patienterne skal praöxygeneres med 100 % ilt i 3 til 5 minutter før ekstubation.

Hos patienter som ikke har gennemgået større kæbekirurgiske indgreb, og heller ikke er opereret i luftvejene, mundhulen eller halsen, og som under anæstesiindledning har haft uproblematiske luftveje, kan patienten praöxygeneres med 80 % ilt i 3-5 minutter før ekstubation.

Referencer

Up to date DAS intubation guidelines 2015
https://www.das.uk.com/content/update_on_new_das_guidelines_2015_3
Discover the tremoFlo C-100 Airwave Oscillometry System

+ **No patient effort**
  Just keep breathing normally.

+ **Captures small airways**
  And peripheral airway heterogeneities.

+ **Fast & easy**
  Complete tests in a couple of minutes.

+ **Normal values**
  Intuitive green-to-red gauge scales.

+ **Adult & pediatric**
  From 2 years up, perfect for the elderly.

+ **Resistance, Reactance, ΔX**
  More insight for obstructive diseases.

+ **Bronchodilator support**
  Efficient reversibility testing.

+ **Light, compact & portable**
  Take it to where your patients are.

Find out more!
Contact us today at **1-855-THORASYS** or visit [www.thorasys.com](http://www.thorasys.com)
tremoFlo C-100 AOS

Key Characteristics

**Measurement Principle**  Oscillometry (Forced Oscillation Technique, FOT)

**Oscillator Technology**  Breathe-through Vibrating Mesh (Patented)

**Measurement Modes**  AOS: Pseudo-random noise (adult/pediatric)
                        SPOS: Harmonic soft impulse Oscillometry

**Measurement Duration**  Adjustable, typ. 16 to 30 s, 3 repetitions

**Patient Interface**  Bacterial/viral filter with integrated mouthpiece

**Dimensions & Weight**
- 19 x 13 x 14 cm, 0.7 kg (handheld only)
- 21 x 14 x 24 cm, 1.7 kg (handheld & cradle)


**Selected Certifications**  Health Canada, CE Mark, ARTG

Selected Outcome Parameters

- **R5**  Low-frequency Resistance (5 Hz), reflects overall resistance.
- **R19**  Mid-frequency Resistance (19 Hz), reflects mostly conducting airways.
- **R5-19**  Frequency dep. of Resistance, reflects heterogeneity and shunts.
- **Xs**  Low-frequency Reactance (5 Hz), refl. compliance & small airways.
- **ΔXs**  Intra-breath variation of Xs, reflects dynamic collapse.
- **fres**  Resonance frequency, increases in small airway disease.
- **AXs**  Reactance Area (5 Hz to fres), increases in small airway disease.

Contact us to locate your nearest distributor and to obtain further product information, technical specifications and literature listings.

THORASYS Thoracic Medical Systems Inc.
6560 avenue de l’Esplanade, Suite 103
Montréal, Québec H2V 4L5
Canada
tel: +1-514-384-8555
toll-free: 1-855-THORASYS (North-America)
email: info@thorasys.com

www.thorasys.com
Appendix 3

tremoFlo C-100 Airwave Oscillometry System User Manual
Custom Edition for AstraZeneca Mesos Study, English (102392-CA-EN), Rev. 1.0, 17-Aug-15

Caution: Please read this manual in its entirety before using your tremoFlo C-100 Airwave Oscillometry System or the tremoFlo software. Failure to read and respect the content of this manual may lead to equipment damage or potential health risk.

This User Manual is intended ONLY for participant sites of the AstraZeneca Mesos Study in Canada, Denmark and the United Kingdom. Please contact THORASYS Technical Support for the appropriate documentation for any other use.

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The tremoFlo C-100 Airwave Oscillometry System is manufactured by

THORASYS Thoracic Medical Systems Inc.
6560 Avenue de l’Esplanade, Suite #103
Montreal, Quebec H2V 4L5 Canada

represented in Europe by

THORASYS Europe UG (haftungsbeschränkt)
Tscheulinstr. 21
D-79331 Teningen
Germany

Symbols

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>🚨</td>
<td>This symbol indicates that this device protects the patient against electric shock-Type BF.</td>
</tr>
<tr>
<td>📚</td>
<td>This symbol warns that the user must read all instructions carefully before use.</td>
</tr>
<tr>
<td>⚡️</td>
<td>This symbol shows that this device complies with the Medical Devices Directive of the European Economic Community.</td>
</tr>
<tr>
<td>⚨</td>
<td>This symbol means that when you discard this equipment you should not mix it with general waste. For proper treatment, recovery and recycling, please contact your dealer or supplier for further information.</td>
</tr>
<tr>
<td>🌐</td>
<td>This symbol informs that Intertek has tested this product to conform to safety standards for Canada and USA.</td>
</tr>
</tbody>
</table>
### Warnings & Cautions

<table>
<thead>
<tr>
<th>Icon</th>
<th>Warning</th>
</tr>
</thead>
<tbody>
<tr>
<td>!</td>
<td>Warning: To avoid risk of electric shock, the tremoFlo C-100 must be connected to supply mains with protective earth.</td>
</tr>
<tr>
<td>!</td>
<td>Warning: Stop using the tremoFlo C-100 immediately if the device emits smoke. Inhaling smoke can cause lung irritation.</td>
</tr>
<tr>
<td>!</td>
<td>Warning: If any part of the tremoFlo C-100 or its accessories and cables, appears damaged, do not use the device. Use of a damaged device could cause injury to the patient or operator.</td>
</tr>
<tr>
<td>!</td>
<td>Warning: The tremoFlo C-100 is not suitable for use in the presence of explosive or flammable gasses.</td>
</tr>
<tr>
<td>!</td>
<td>Warning: Do not position the tremoFlo C-100 in a way that would make it difficult to disconnect the power cord in an emergency.</td>
</tr>
<tr>
<td>!</td>
<td>Warning: Do not modify the tremoFlo C-100 in any way. Modification to the device may make it unsafe or cause measurement error.</td>
</tr>
<tr>
<td>!</td>
<td>Warning: A qualified medical practitioner must interpret test results from the tremoFlo C-100. Test results are not a substitute for examination and qualified diagnosis. Before using the tremoFlo C-100, users must read and understand this manual and all product labels and markings.</td>
</tr>
<tr>
<td>!</td>
<td>Caution: Only qualified persons may service the tremoFlo C-100. Do not open the device as this may lead to damage or inaccuracy.</td>
</tr>
<tr>
<td>!</td>
<td>Caution: Do not insert anything into the tremoFlo C-100’s opening, damage to the mesh screen inside may cause measurement errors.</td>
</tr>
<tr>
<td>!</td>
<td>Caution: Testing with the tremoFlo C-100 should not interfere with patient breathing; stop testing if the patient shows or reports signs of discomfort.</td>
</tr>
<tr>
<td>!</td>
<td>Caution: Use only the accessories and cables provided with your tremoFlo C-100. Use of other accessories or cables may have undesirable effects on the performance of the device or on the test results.</td>
</tr>
<tr>
<td>!</td>
<td>If function stops during electrostatic discharge to the device, reset the system by unplugging the device waiting for several seconds then plugging back in and following normal start-up procedures.</td>
</tr>
</tbody>
</table>

### License & Operating Conditions

By using the tremoFlo C-100 Airwave Oscillometry System and the tremoFlo Software, you agree to the THORASYS License and Operating Conditions, a copy of which is available upon request.

### Copyright Notice

The tremoFlo Software is copyright to THORASYS. The software may not be copied, decompiled or disassembled in any way. All rights and ownership of the software remain with THORASYS at all times. Only those parties indicated on the license agreement are entitled to use the software.
Patents
The tremoFlo Airwave Oscillometry System is protected by U.S. and International Patents. Contact THORASYS for
detailed patent number listings.

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1 Introduction

1.1 Welcome to the tremoFlo!
Welcome, and congratulations for the acquisition of a new tremoFlo C-100 Airwave Oscillometry System (AOS)!
The tremoFlo is a state-of-the-art medical device, and we hope that it will be able to aid and assist you in your work as you strive to provide the best possible care to your patients. On behalf of the entire THORASYS team and all our partners and representatives, we thank you for the trust you have put into us by deciding to acquire a tremoFlo system. We will work hard to continue to earn your trust and recognition, and we look forward to working with you as we support you in your use of the device.

1.2 About this Manual
This User Manual is specifically prepared for sites participating in the Mesos clinical trial study sponsored by AstraZeneca. Several sections of this manual have been modified to match specific configuration details that are unique to the protocol of this study, and that differ from the tremoFlo default configuration. Moreover, some information contained in the standard user manual has been omitted because it was considered not relevant for the Mesos configuration. As such, this is not a complete tremoFlo user manual, and the functionality presented is a subset of that offered by standard tremoFlo installations.

1.3 Indications for Use
Indications for Use are provided in Appendix A.

2 Operating Principles

2.1 Airwave Oscillometry
Airwave Oscillometry (AO) is one of the most advanced implementations of Oscillometry, which in the literature is also referred to as the Forced Oscillation Technique. AO measures pulmonary function, more specifically respiratory mechanics, by superimposing a gentle oscillatory pressure and flow wave onto the patient’s spontaneous breathing. The frequencies of oscillation are higher than those contained in normal quiet breathing, but lower than audible sound waves.

As illustrated in Figure 2-1, breathing is a slow oscillatory process. The tremoFlo C-110 Airwave Oscillometry System (AOS) superimposes a small, higher frequency oscillation onto the breathing waveforms. The oscillatory waves are sometimes referred to as “pseudo-random noise” in recognition of the fact that the resulting waveforms have the appearance of a “noisy” breathing waveform. Sophisticated signal processing techniques are then used to separate the recorded waveforms into their slower breathing pattern components and their faster respiratory mechanics components.
Unlike most other Oscillometry systems, the tremoFlo AOS utilizes an oscillatory waveform that contains only prime number frequencies ranging from 5 to 37 Hz. This waveform performs better than harmonic or pseudo-impulse waveforms in the presence of so-called “nonlinearities” in the lungs. Nonlinearities exist in all lungs and become more dominant with decreased lung function.

2.2 Resistance & Reactance

The primary, non-parametric outcome of Oscillometry is a pair of curves referred to as Resistance (R) and Reactance (X), each of which is plotted against frequency.

**Resistance (R)** is a measure of the energy dissipation in the respiratory system. A large portion of R can be attributed to the friction within the breathing gases as they make their way through the airways. Here, resistance is defined as the ratio of the pressure drop across an airway segment and the flow through that segment, and it increases rapidly as the airway narrows. However, overall R also contains contributions from energy dissipation in the lung and chest wall tissues.

**Reactance (X)** captures energy conservation in the respiratory system, which includes both the elastic fibres in the lung, i.e. those elements determining lung compliance (C), and the inertive forces related to the acceleration and deceleration of the column of air in the airway tree as well as the lung tissues.
As illustrated in Figure 2-2, R for a healthy lung is expected to be frequency-independent, resulting in a horizontal line. On the other hand, X is a negative number at low frequencies, but crosses into positive territory as frequency increases. If X were determined by C only, it would remain entirely negative. In contrast, if C were absent and X were entirely determined by the inertance (I) of the mass being oscillated, X would be positive only. Since C and I coexist in reality, and given their individual characteristics, we find that in the healthy lung,

- at low frequencies, X is dominated by C;
- at high frequencies, X is dominated by I; and
- there exists an intermediate frequency called the resonance frequency (fres) at which C and I make equal and opposite contributions to X, so that X becomes equal to zero.

2.3 Assessment of Small Airways
A variety of invasive studies in animals and post-mortem lungs, along with computer simulations, have demonstrated that R and X change in different patterns depending on the type of airway obstruction.

Specifically, as illustrated in Figure 2-3,

- **Central Obstruction** leads to a frequency-independent increase in R, i.e. a parallel upward shift, without significant changes to X;
- **Homogeneous Peripheral Obstruction** may cause a similar frequency-independent change in R that is accompanied by a downward-and-right shift in X;
- **Heterogeneous Peripheral Obstruction** also results in a downward-and-right shift in X, but in this case the increase in R is greater at low frequencies than at higher frequencies, therefore R becomes characteristically frequency-dependent.

Therefore, Oscillometry can uniquely and distinctly capture peripheral obstruction as indicated by a shift in X, and the heterogeneity of such peripheral obstruction as indicated by a newly introduced or greatly amplified frequency-dependence of R.

2.4 Outcome Parameters
A variety of numerical outcome parameters may be derived from the non-parametric measurements of R and X. The most commonly reported key outcome parameters are listed in Table 2-1 and their relationship to the R and X curves is illustrated in Figure 2-4.

Table 2-1: Key Outcome Parameters of Airwave Oscillometry
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Abbr.</th>
<th>Units</th>
<th>Indicative of</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistance at 5 Hz</td>
<td>R₅</td>
<td>kPa.s/L</td>
<td>Overall respiratory system resistance</td>
</tr>
<tr>
<td>Resistance at 20 Hz</td>
<td>R₂₀</td>
<td>kPa.s/L</td>
<td>Central airway resistance</td>
</tr>
<tr>
<td>Frequency dep. of Resistance, 5 – 20 Hz</td>
<td>R₅-2₀</td>
<td>kPa.s/L</td>
<td>Heterogeneity of airway obstruction</td>
</tr>
<tr>
<td>Reactance at 5 Hz</td>
<td>X₅</td>
<td>kPa.s/L</td>
<td>Compliance, small airway obstruction</td>
</tr>
<tr>
<td>Reactance Area</td>
<td>Aₓ</td>
<td>kPa/L</td>
<td>Small airway obstruction</td>
</tr>
<tr>
<td>Resonance Frequency</td>
<td>fₚₑₛ</td>
<td>Hz</td>
<td>Small airway obstruction</td>
</tr>
</tbody>
</table>

Note that since the tremoFlo AOS waveform contains only prime number frequencies, values at 20 Hz are obtained by linear interpolation between neighbouring prime number frequencies (19 and 23 Hz).

2.5 Quality Control Parameters

Coefficient of Variation

The primary test for the goodness of a patient test as per the 2003 ERS guideline for Oscillometry is that the coefficient of variation (CV) between three valid measurements must not exceed 15%.

Coherence

Coherence (Coh) is also frequently found in the literature as a quality control parameter. Coh results from the tremoFlo analysis and captures the stability of the relationship between the different raw data waveforms used for analysis. Because Coh depends on analysis settings, there is no globally valid threshold for accepting or rejecting data based on Coh.
3 Setup Instructions

3.1 Unpacking & System Components

Unpacking & Inspection
Before opening, inspect the tremoFlo packaging for damage during shipping. If the box appears damaged, do not open the box and immediately contact THORASYS Technical Support or your local representative.

Open the tremoFlo packaging carefully without allowing sharp objects to protrude into the box. Remove packing foam and carefully remove all items from the box. Be sure to take out the tremoFlo C-100 cradle and handheld unit together. Visually inspect all items, and make sure that you obtained all system components (see below).

| ! | Warning: If any part of the tremoFlo C-100, or its accessories and cables, appears damaged, do not use the device. Use of a damaged device could cause injury to the patient or operator. |

tremoFlo C-100 AOS Components
Every tremoFlo C-100 AOS system provided for AstraZeneca Mesos Study sites includes the parts listed in Table 3-1. The parts shown in Table 3-1 are reusable unless otherwise indicated. Disposables and computer systems are packaged separately from the tremoFlo System.

Table 3-1: tremoFlo System Components

<table>
<thead>
<tr>
<th>Description</th>
<th>Image</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Handheld Unit (HU)</strong></td>
<td></td>
</tr>
<tr>
<td>Core component of the tremoFlo C-100 AOS. Contains the patented vibrating mesh oscillator as well as all sensors required to obtain a measurements. Permanently attached to the Cradle by a highly flexible cable. Supplied with a dust cap.</td>
<td><a href="image">Handheld Unit Image</a></td>
</tr>
<tr>
<td><strong>Cradle</strong></td>
<td></td>
</tr>
<tr>
<td>Contains electronics and supports the HU during calibration or when the system is not in use.</td>
<td><a href="image">Cradle Image</a></td>
</tr>
<tr>
<td><strong>Power Supply</strong></td>
<td></td>
</tr>
<tr>
<td>External medical grade power supply with wide input range for safe connection to mains in any locale.</td>
<td><a href="image">Power Supply Image</a></td>
</tr>
<tr>
<td><strong>Power Supply Cord</strong></td>
<td></td>
</tr>
<tr>
<td>Medical grade power supply cord, as indicated by green dot, according to the standards of your locale.</td>
<td><a href="image">Power Supply Cord Image</a></td>
</tr>
</tbody>
</table>
**Ethernet Cable**
Ethernet cable used to connect the Cradle to the computer system.

<table>
<thead>
<tr>
<th>Description</th>
<th>Image</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Calibration Test Load</strong></td>
<td><img src="calibration_test_load.png" alt="Image" /></td>
</tr>
<tr>
<td>Calibrated mechanical test load used for Field Calibration. Supplied with two red dust caps.</td>
<td></td>
</tr>
<tr>
<td><strong>Test Load Adapter</strong></td>
<td><img src="test_load_adapter.png" alt="Image" /></td>
</tr>
<tr>
<td>Adapter to permit insertion of the test load into the HU during field calibration check.</td>
<td></td>
</tr>
<tr>
<td><strong>Computer System</strong></td>
<td><img src="computer_system.png" alt="Image" /></td>
</tr>
<tr>
<td>Laptop computer system with power supply and accessories, tremoFlo software preinstalled, configured according to study protocol and verified.</td>
<td></td>
</tr>
<tr>
<td><strong>Bacterial/Viral Filters &amp; Nose Clips</strong></td>
<td><img src="bacterial_viral_filters.png" alt="Image" /></td>
</tr>
<tr>
<td>One box of supplies containing 100 ClearFlo F-100 bacterial/viral filters with integrated mouthpiece and 100 nose clips is provided to each study site. These items are for single use and not reusable.</td>
<td>(Not shown)</td>
</tr>
<tr>
<td><strong>User Manual</strong></td>
<td><img src="user_manual.png" alt="Image" /></td>
</tr>
<tr>
<td>This user manual.</td>
<td>(Not shown)</td>
</tr>
</tbody>
</table>

3.2 Installation

**Operating Conditions**
The tremoFlo C-100 AOS is intended for indoor testing at elevations below 2000 m, temperatures between 10 and 35°C, and relative humidity between 15 and 85%, noncondensing. Please contact THORASYS for information on acceptable electromagnetic environments.

**Electrical Safety**

Warning: IEC 60601-1-1 requires that any equipment connected to a power outlet without medical grade insulation, including computers, be located at least 1.5 m away from the patient. In cases where this minimum distance cannot be maintained, such equipment must be connected to the power outlet via medical grade isolation transformers.
Caution: Use only the power supply provided with your tremoFlo C-100. Use of another power supply may damage the device or put patients at risk.

Caution: Use only the Ethernet cable provided with your tremoFlo C-100 and only connect the device directly to a supported PC. Use of another cable, an indirect connection of the device to the PC through network devices or a connection of the tremoFlo C-100 to other unsupported devices may damage the device or put patients at risk.

Placement

Place the tremoFlo C-100 Handheld Unit and Cradle on a desk or other flat surface within easy reach of the intended patient location during a measurement, as shown in Figure 3-1. Place the computer system at least 1.5 m away from the intended patient location. Orient the computer such that the operator can easily view the patient and the computer screen simultaneously.

Connections

To provide interconnections between the tremoFlo system components, computer and power outlets, proceed as follows:

1. Connect one end of the Ethernet cable to the Ethernet port on the tremoFlo Cradle. Note that the tremoFlo’s Ethernet port features medical grade isolation.
2. Connect the other end of the Ethernet cable to the Ethernet port of your computer. If the computer has multiple Ethernet cards make sure to connect the cable to the port that is configured for use with the tremoFlo.
3. Connect the tremoFlo power supply to the power port of the tremoFlo Cradle.
4. Connect the device end of the medical grade power supply cord to the tremoFlo power supply.
5. Connect the other end of the medical grade power supply cord to a suitable wall outlet.
6. Connect the power supply of the computer as per the instructions of the computer manufacturer, subject to the warnings, minimum distances and electrical safety instructions provided above.

Software Installation

Your tremoFlo system is provided with a computer on which the tremoFlo software is installed, configured according to the required study protocol and verified. No further software installation is necessary, and no special actions are required during first use.
4 Operating Instructions

4.1 Power Switch & Indicators

To power up the tremoFlo system, briefly press the power button on the tremoFlo Cradle. The power button will light up, briefly alternating between green, yellow and red before settling to a steady yellow colour.

The tremoFlo C-100 AOS has two power indicator lights. On the cradle, a power and status indicator light around the power button can light up in green, yellow or red, wherein each colours has the significance indicated in Table 4-1. The second power indicator, located on the top of the Handheld Unit, lights up in blue when power is supplied to the Handheld Unit and does not change colour with system status.

<table>
<thead>
<tr>
<th>Colour</th>
<th>Status</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unlit/Gray</td>
<td>Off</td>
<td>The tremoFlo is powered down.</td>
</tr>
<tr>
<td>Flashing</td>
<td>Starting</td>
<td>The tremoFlo firmware is booting.</td>
</tr>
<tr>
<td>Green</td>
<td>Ready</td>
<td>The tremoFlo is powered up, communicating with the software, fully initialized and ready for use.</td>
</tr>
<tr>
<td>Yellow</td>
<td>Standby</td>
<td>The tremoFlo is powered up and either waiting to connect to the software or being initialized.</td>
</tr>
<tr>
<td>Red</td>
<td>Error</td>
<td>The tremoFlo is powered up, but a critical error has occurred and the system is not ready for use. Refer to section 0 for possible causes and solutions.</td>
</tr>
</tbody>
</table>

4.2 Software Start-up Sequence

Starting the Software

With the computer running, start the tremoFlo software by either clicking the tremoFlo icon in the task bar or double-clicking the tremoFlo icon on the desktop.

User Logon

Upon startup, the tremoFlo software will display a user logon dialog as shown in Figure 4-1. Enter your user name and password, then click the Log in button. All data collected during the session will be associated with the user account corresponding to the credentials entered on this screen.
Welcome Dialog

Next, the software shows a Welcome Dialog (Figure 4-2) offering three main actions:

- **Calibrate**: Click to perform a Field Calibration Check (see section 4.3) before patients arrive to be measured. If you omit this step at the start of a session, the software will automatically prompt you prior to the first measurement.

- **New Patient**: Click to add and test a new patient (see section 4.4).

- **Select Patient**: Click to select an existing patient from the database to either perform a new test on that patient or review previous test data (see section 4.4).

4.3 Field Calibration

**Overview**

Each tremoFlo system is factory calibrated to offer maximal measurement accuracy. The tremoFlo’s sensors and electronics possess excellent long-term stability characteristics, therefore calibration factors do not change significantly under normal circumstances. Nonetheless, it is good practice to perform a quick Field Calibration on a daily basis to ensure continued system accuracy and detect any change or damage to the system that may inadvertently have occurred.

The tremoFlo software contains features to regularly prompt the user for Field Calibration in predefined intervals, typically daily. A Field Calibration Wizard guides the user through the calibration process, which typically takes less than a minute to complete. When the Wizard is first displayed (Figure 4-3), click Next to start the calibration process.
Step 1: Waveform Selection

Step 1 of the Field Calibration Wizard displays the Oscillometry waveforms that are loaded in the current configuration along with the time since last calibration for each waveform. If calibration is required, the waveform will be displayed in red colour. Make sure the checkboxes are checked next to the waveforms you intend to calibrate and use for measurement, then click Next.

![Figure 4-4: Field Calibration Wizard, Waveform Selection Screen](image)

Step 2: Calibrator ID Entry

Step 2 of the wizard allows you to enter the Calibrator ID printed on the Calibration Test Load (see Table 3-1) that you will use for calibration. Note that each Calibration Test Load has a unique Calibrator ID that communicates to the software the exact characteristics of this particular Calibration Test Load.

If you are performing the Field Calibration for the first time after a new software installation, or if you are changing test loads, enter the Calibrator ID as shown in Figure 4-5. The Calibrator ID contains a checksum to protect against typographic errors, and a green checkmark is displayed when a valid Calibrator ID is entered. Click Next to continue.

If you have already performed Field Calibration with the same Calibration Test Load, the software has retained the Calibrator ID and you can immediately click Next.

![Figure 4-5: Field Calibration Wizard, Calibrator ID Screen](image)

Step 3: Calibration Test Load Attachment

In Step 3 (Figure 4-6), the Field Calibration Wizard reminds you to attach the Calibration test load to the tremoFlo. Make sure to remove the two red dust caps from the Calibration test load prior to attaching it to the tremoFlo system as show in Figure 4-7, then click Next to start the calibration.
Step 4: Calibration

In Step 4, the tremoFlo software measures the Calibration Test Load (Figure 4-8). This step typically takes 8 to 16 seconds for each waveform that is loaded. Upon completion of this step, the software automatically proceeds to the Results screen.
Results

The final screen of the Field Calibration Wizard displays the results of the Field Calibration. If the measured values for the Calibration Test Load match the nominal values contained in the Calibrator ID based on predefined acceptance criteria, the software displays a green checkmark (Figure 4-9). Click Finish to complete the calibration.

If the Calibration fails, a warning message will pop up, and a red X will be displayed instead of the green checkmark. In this case, you can click on each waveform to visualize additional details for troubleshooting and technical support purposes. Provided that the cause of failure is readily identified (see section 0), you can click Start Over to restart the calibration.

End of Calibration

When you click Finish on the Results screen of the Field Calibration Wizard, the calibration is stored into the database and the wizard closes.

If the Field Calibration was started from the Welcome Dialog (see section 4.2), the tremoFlo software will return to the Welcome Dialog so that the user can continue to add a new subject to the database or select an existing subject to be tested anew.

4.4 Starting a Patient Test

About Patient Tests

The tremoFlo software is designed to assess respiratory function in accordance with the 2003 ERS guideline for Oscillometry. Thus, a complete tremoFlo patient test is required to include at least three separate, valid measurements. The overall results of a test are calculated as the average of the three tests.

Accordingly, the tremoFlo software maintains constructs for Subjects, Patient Tests and Measurements, where each subject can have a multitude of Patient Tests, and each Patient Test can contain a multitude of Measurements.

Adding Subjects to the Database

The first step when starting a patient test is to add the subject to be measured to the database, or to select an existing subject.

If the subject you intend to assess is not yet in the database, select New Patient either from the Welcome Dialog or from the tremoFlo toolbar on the Patient tab to display the New Patient Dialog (Figure 4-10). Enter the subject information as per Table 4-2.
<table>
<thead>
<tr>
<th>Subject Code</th>
<th>E-Code</th>
<th>As per study guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male/Female</td>
<td>From drop-down list</td>
</tr>
<tr>
<td>Date of Birth</td>
<td>Date Of Birth</td>
<td>As per computer settings</td>
</tr>
<tr>
<td>Weight</td>
<td>Body Weight</td>
<td>In kg</td>
</tr>
<tr>
<td>Height</td>
<td>Body Height</td>
<td>In cm</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Subject’s Ethnicity</td>
<td>From drop-down list</td>
</tr>
</tbody>
</table>

Caution: To protect patient privacy, you must not enter patient names or any information other than what is listed in Table 4-2.

![Patient Details](image)

Figure 4-10: New Patient Dialog

Selecting Existing Subjects

If the subject you wish to study is already in the database, choose Select Patient either on the Welcome Dialog or on the tremoFlo toolbar on the Patient tab to display the Patient List Dialog (Figure 4-11).

A selection of search modes may be selected at the top of the Patient List Dialog to facilitate rapidly locating the desired record. Available choices include:

- **All Patients** – all patients are displayed.
- **Recently Tested Patients** – the specified number of recently test patients are displayed.
- **Search Patient** – patients whose name or subject code starts with the specified search string are displayed.

In addition, the buttons at the top left of the Patient List Dialog permit adding a new patient, editing the selected record or deleting a patient for whom no measurements are contained in the database. Patients with measurement data cannot be deleted.
Once the correct patient record is selected, the buttons on the bottom of the Patient List Dialog may be used to select one of the following two actions:

- **Test Patient** – Start a new Patient Test for the selected Patient. Note that if a recent open patient test exists, the software will ask whether you prefer to continue that test or start a new one.

- **Review Data** – Review historic Patient Tests for the selected Patient. Note that the software may stay in offline mode, and the light on the tremoFlo may remain yellow in this case.

### Test Properties

In general, the tremoFlo software supports different test types including standard baseline measurements and reversibility testing. However, for the current study, the test type is preselected and only baseline measurements are permitted.

Once a new Patient Test is started, the Test Properties Dialog is displayed (Figure 4-12). In the Title field, enter the Visit Code formatted as per study guidelines, then click OK.

Closing the Test Properties Dialog completes the startup sequence of the tremoFlo software. At this point, the screen will display the main window of the tremoFlo software.
4.5 tremoFlo Main Window

Screen Layout
The tremoFlo main window features a tabbed “ribbon” toolbar at the top of the screen (Figure 4-13). The Ribbon has three tabs labelled 1 | Patient, 2 | Test and 3 | Results. Below the Ribbon is the large client area that changes appearance depending on which tab is selected on the Ribbon, but generally displays a combination of graphical or tabular data, selected numerical readouts and meta-data.

1 | Patient
When this tab is selected, the Ribbon offers buttons to add, select or edit patients, or to start a new Patient Test. The client area displays historic test results for the current patient, which may be formatted as graphs or table views.

2 | Test
This tab is used for collection of new measurements, as described in further detail in section 4.6. The Test tab is only available when an open test exists for the current patient. The client area on this tab shows a live data feed from the tremoFlo system. Once available, the software may also display real-time measurement outcomes, along with data from previous measurements in the same test. The toolbar on the Test tab displays commands to control the measurement or repeat calibrations if needed.

3 | Results
The Results tab is designed to review complete test results, overread data for quality control, drill down into individual measurements as needed and produce final reports.

As shown in Figure 4-13, the client area for the Results tab features a vertical side bar on the left side of the screen allowing users to navigate between current and historical patient tests and measurements for the current patient. Depending on the display mode selected, the remainder of the client area may show a chart showing R and X versus frequency, timecourse charts permitting visualization of intra-breath variation, a table of outcome parameters or a report preview. For the two graphical display modes, a vertical side bar on the right side of the screen displays selected outcome parameters relative to their normal values on green-to-red gauge scales.

The Ribbon on the Results tab provides a variety of different commands as needed to perform these tasks and described in detail in sections 0 and 4.9.
Menu
To the left of the Patient tab, the tremoFlo software features a pull-down menu that can be accessed by clicking the word “tremoFlo”. This menu provides access to less frequently used features, such as motor calibration and user management.

4.6 Measurement Collection

Measurement Preparation
After you have added and/or selected the subject and started a new patient test as described above, perform the following steps in order to prepare the subject for the measurement. Upon completion of these steps, the subject should be positioned and prepared as shown in Figure 4-14, and the subject’s breathing should be visible on screen as shown in Figure 4-15.

1. **Test Screen** – Make sure that the tremoFlo software is showing the Test screen. To switch to the Test screen, click the corresponding tab or press one of the buttons on the tremoFlo Handheld Unit. Note: Upon entering the Test screen, the software may re-zero the flow and volume channels, therefore the subject must not be breathing through the device at that time.

2. **Mouthpiece** – Remove a new, originally packaged ClearFlo F-100 bacterial/viral filter from its wrapping. Without touching the oval mouthpiece portion, insert the round end into the corresponding port on the cradled tremoFlo Handheld Unit.

3. **Posture** – Place the subject in an upright seated position.

4. **Nose Clip** – Provide a nose clip to the subject and instruct the subject to apply the nose clip to fully seal the nasal passage.

5. **Cheek Support** – Instruct the subject to use both hands to support facial soft tissues, such that the thumbs support the mouth floor while the remaining fingers support the cheeks. Elbows should be relaxed and aiming slightly outward, without pressure against the chest. In patients unable to support their own cheeks such as young children, cheek support may be provided by a third person standing behind the subject, such as a parent or another health care professional.

6. **Mouth Seal** – Take the tremoFlo Handheld Unit off the Cradle and hold it in front of the subject’s mouth, so that the subject can take place and seal his or her lips around the mouthpiece without leak or discomfort.

7. **Face 15° Upward** – Gently position the tremoFlo such that the subject faces approximately 15° upwards from the horizontal plane to ensure that there is no compression on the upper airways that could lead to elevated resistance readings.

8. **Three Quiet Breaths** – Once the above steps have been completed, observe the subject’s breathing. If the subject’s breathing is unusually shallow, heavy or otherwise abnormal, ask the subject to correct accordingly. Abort and restart if needed.

9. **Inform the Patient** - Once the subject is breathing steadily and quietly through the device for at least three breaths as shown in Figure 4-15, inform the subject that they will soon feel a gentle oscillation, then press one of the two buttons on the tremoFlo Handheld Unit to start the measurement.

| Caution: Proper cheek support is an essential element of a properly performed Oscillometry measurement. Failure to properly support the cheeks may lead to measurement errors and invalid measurements that may be difficult to detect post-hoc. |
| Caution: Compression on upper airways, glottis and/or vocal cords may lead to abnormally elevated resistance values. Ensure that patient faces approximately 15° upward to prevent such errors. |
Figure 4-14: Subject preparation showing upright posture facing slightly upwards, nose clip, seal around the mouthpiece and cheek support.

Figure 4-15: Quiet breathing in preparation for a measurement.

Measurement Collection

Measurements are initiated by briefly pressing one of the two buttons on the device, or by clicking the corresponding button on the Ribbon toolbar. Upon initiating a measurement, a mesh inside the tremoFlo that is within the subject’s flow pathway starts oscillating gently according to a carefully designed multi-frequency waveform. The oscillation is both audible and perceivable by the patient and the operator, but it should be neither loud nor unpleasant to either person.

At the beginning of the measurement, the screen on the tremoFlo software resets, and the horizontal axis is scaled to the configured measurement duration. Therefore, a complete measurement will exactly fill the chart from left to right, as shown for a 30 second measurement in Figure 4-16. Numerical readings are displayed live on the right side of the screen. During the measurement, coach the patient to continue breathing quietly and steadily with a normal tidal volume.

The tremoFlo automatically ceases oscillating when the measurement is complete. Measurement data are automatically stored without need for user intervention.
Repetitions
According to the 2003 ERS guideline, a minimum of three valid Measurements is required for a valid Patient Test. Especially in more difficult and/or severe patients, it is common practice to collect additional Measurements and exclude possible outliers. Remove the mouthpiece from the patient’s mouth between measurements to allow for a moment of relaxation.

Artefacts
The tremoFlo software has the ability to isolate and exclude well-delimited artefacts originating from brief episodes of swallowing, speaking, laughing, light coughing or letting go of the mouth seal. In many cases, the remainder of datasets containing such artefacts can be analyzed to produce a valid Measurement. However, Measurement should be excluded if too large a portion of the Measurement is affected by artefacts, and often such exclusions will happen automatically.

The occurrence of a strong cough during a Measurement may interfere with the operation of the tremoFlo and result in an error message. Such cases are detected by the software and indicated by an error message on the screen, and the device needs to be reset before further Measurements can be attempted.

Aborted Measurement
Measurements may be cut short or aborted by pressing one of the two buttons on the tremoFlo Handheld Unit for a second time while the measurement is ongoing. In such cases, the tremoFlo software will prompt the user whether the partial measurement should be stored or discarded. Note that a configuration-dependent minimum amount of valid data is required, otherwise the measurement will be automatically and irrevocably excluded.

Closing a Patient Test
When the patient test has been completed, the test should be marked as closed in the tremoFlo software. The software will automatically prompt for closing of the test if a new test is started, a different patient is selected or the software is shut down.

Disposal of Supplies
Upon completion of a patient test, also be sure to dispose the single-use supplies, namely the ClearFlo F-100 bacterial/viral filter and the nose clip, in a suitable waste collection container as per your institutions guidelines and regulations.
4.7 Data Review

Overview
As briefly mentioned in section 4.5, the Results tab of the tremoFlo software offers comprehensive functionality to review test results and overread data for quality control before producing final reports. Data review can be performed during or immediately after a test as well as at a later time.

![Figure 4-17: Results Navigation Pane and Toolbar](image)

When first navigating to the Results screen, the tremoFlo software shows the Chart View shown in Figure 4-13. Using the buttons on the toolbar (Figure 4-17), you may then navigate to the Timecourse View, Table View or Report Preview. The first three views are described in detail in the remainder of this section, and the Report Preview is detailed in section 4.9.

Navigation Pane
The Navigation Pane is a vertical side bar on the left side of the Results screen that displays a blue rectangular card for each patient tests that exists for the currently loaded patient (Figure 4-17). Tests are sorted in reverse chronological order, so that the most recent test appears at the top. Once a test is selected, it is “expanded” to show additional lighter coloured cards for each measurements contained in the test.

As shown in Figure 4-17, the cards representing tests and measurements display a variety of meta-data such as titles and timestamps. Measurement cards also include three controls permitting the actions listed in Table 4-3 to be taken with respect to the corresponding measurement.

<table>
<thead>
<tr>
<th>Icon</th>
<th>Action</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Add/Edit Comment</td>
<td>Add a comment to a measurement, or edit an existing comment. Icon appears darker when a comment is available.</td>
</tr>
<tr>
<td>Include/Exclude</td>
<td>Controls inclusion of the measurement in the test average. Set by automatic validation, but may be changed to force inclusion or exclusion.</td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Show/Hide</td>
<td>Show or hide the selected measurement.</td>
<td></td>
</tr>
</tbody>
</table>

Gauge Scales

In a variety of views and reports, the tremoFlo software uses green-to-red Gauge Scales (Figure 4-18) to easily visualize the state of a subject’s respiratory mechanics relative to their normal values according to tabulated reference data. Gauge scales are typically located on the right side of the screen and may be configured via the program options.

Each Gauge Scale Card visualizes the abbreviation and value for one single outcome parameter in large font. A text line in smaller font further provides the units, reference value, Z score and in select cases, the coefficient of variation (CV) of that parameter. Finally, a diamond indicator on a horizontal gauge ranging from green to yellow to red visually illustrates the patient’s outcome relative to normal. The significance of the individual colours is as follows:

- **Green** – Outcome well within the 95% confidence interval of normal.
- **Yellow** – Close to the upper or lower limit of normal, as defined by 95% confidence interval around normal value.
- **Red** – Outside of the 95% confidence interval around normal value, i.e. above the upper limit of normal (ULN) or below the lower limit of normal (LLN).

![Figure 4-18: Gauge Scales](image)

When a Patient Test is selected in the Navigation Pane, as shown in Figure 4-17, the Gauge Scales display the average outcome values for this test. In this case, the title at the top of the Gauge Scale Pane reads “Test Results”, as shown in Figure 4-18.
When a Measurement is selected in the Navigation Pane, the Gauge Scales will display the outcome values for the selected measurement only. Accordingly, the title at the top of the Gauge Scale Pane reads “Selected” in this case (not shown).

Impedance Chart

When in Chart View, a graph visualizing R and X versus frequency is displayed between the Navigation Pane and the Gauge Scale Pane. As illustrated in Figure 4-19, this impedance chart contains the following graphical elements:

- **Measurements** – Each individual measurement contained in the selected test is represented by uniquely coloured symbols connected with thin hairlines.

- **Test Average** – The test average is represented by dark blue symbols connected by a thicker line.

- **Normal Values** – The normal values for the patient’s age, sex, height and weight is displayed as a thin black line. The source of the reference values is displayed at the bottom of the chart.

- **Limits of Normal** – The ULN for R and LLN for X are displayed as dashed lines.

![Figure 4-19: Impedance Chart](image)

Table View

The Table View permits visualization of the numerical outcome values for the selected patient test. As shown in Figure 4-20, the parameter abbreviations, units and reference values are shown in the leftmost section of the table, followed by the test average, standard deviation, coefficient of variation, Z-score and % predicted. The individual measurements are shown in the rightmost columns of the table.

Note that some Oscillometry outcome parameters have normal values very close to zero. CV and % predicted cannot be evaluated for these parameters because they would not being meaningful and risk divisions by zero. Moreover, Z-scores and % predicted can be evaluated only for parameters for which reference values exist.
The Timecourse View permits the visualization of the raw pressure, flow and volume waveforms as well as the temporal variations in R and X over the course of a measurement (Figure 4-21). The Timecourse View is valuable both for quality control and to visualize intra-breath changes in R and X that are characteristic for certain lung diseases such as COPD.

Figure 4-20: Table View

### 4.8 Quality Control

#### Overview

The tremoFlo software employs a number of different criteria to automatically assess the quality of data as they pass through the different stages of data analysis. These algorithms have proven to reliably detect and exclude most common artefacts while avoiding excessive data exclusion that would lead to unnecessary repetitions.

However, because we are dealing with living systems, automated validation and the resulting inclusion/exclusion decisions will not be perfect in all circumstances, and some degree of human assessment and adjustment is required to achieve the best possible results.
This section describes the automatic validation and exclusion mechanisms contained in the tremoFlo software as well as the means available to adjust and override automated decisions.

**Raw Data Validation**

In the first stages of data analysis, the tremoFlo software assesses the quality of the raw data collected from the tremoFlo system. If a problem such as a clipped raw data channel is detected, the measurement is automatically excluded.

Raw data validation errors are rare, but when they occur they typically prevent further analysis, and they cannot be overridden.

**Artefact Detection**

To identify artefacts contained within a measurement, the tremoFlo scans the resistance and reactance curve for irregularities such as negative resistances and excessive outliers. Such irregularities typically signify the presence of one of the artefacts listed in Table 4-4. Most of these artefacts can be readily identified visually in the Timecourse View, as shown in Figure 4-22.

<table>
<thead>
<tr>
<th>Artefact</th>
<th>Appearance</th>
<th>Detection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swallowing, Tongue Blockage</td>
<td>Flat flow and volume curves; suppressed oscillation amplitude on flow; large random swings in R and X.</td>
<td>High</td>
</tr>
<tr>
<td>Leak</td>
<td>Flat volume curve; increased oscillation amplitude on flow; R and X near zero.</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Cough</td>
<td>Large swings in flow, volume, R and X.</td>
<td>High</td>
</tr>
<tr>
<td>Vocal Expression</td>
<td>Irregular breathing pattern with extended, noisy expiration; random excursions in R and X; negative R values</td>
<td>High</td>
</tr>
</tbody>
</table>

The automatic artefact identification and exclusion may be edited and overridden in the Timecourse View as follows:

- To exclude an artefact not detected by the software, click into a valid (blue) part of the curve and drag the mouse to mark the bad segment.
- To include a data segment incorrectly marked as artefact, click into an excluded (gray) part of the curve and drag the mouse to mark the segment to be included.

You must click Apply on the Ribbon toolbar to apply your changes and recalculate the measurement and test outcomes. Click Undo if you do not wish to apply your changes, or to reset prior edits.
Measurement Validation
Next, the tremoFlo software will validate the measurement as a whole based on the criteria shown in Table 4-5. A failure to meet these criteria will result in exclusion of the measurement. Visualization of the measurement validation criteria in the Chart View is illustrated in Figure 4-23.

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Pass Criteria</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum Duration</td>
<td>≥ 20 sec.</td>
<td>Total valid data as shown in Timecourse.</td>
</tr>
<tr>
<td>Valid Percentage</td>
<td>≥ 70%</td>
<td>Portion of valid data points across all frequencies.</td>
</tr>
<tr>
<td>Coherence</td>
<td>≥ 0.8</td>
<td>See section 2.5.</td>
</tr>
</tbody>
</table>

Figure 4-23: Quality Control Parameters on Chart View
Test Validation

Finally, the tremoFlo software validates the patient test based on the criteria shown in Table 4-6. A failure to meet these criteria will result in a warning triangle being displayed on the test’s card in the Navigation Pane, Figure 4-23.

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Pass Criteria</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valid Measurements</td>
<td>≥ 3</td>
<td>After measurement validation.</td>
</tr>
<tr>
<td>Coefficient of Variation</td>
<td>≤ 15%</td>
<td>After exclusion of outliers.</td>
</tr>
</tbody>
</table>

4.9 Generating Reports

To generate a report click the View Report button on the Results tab of the Ribbon toolbar. A preview of the report for the selected patient test will be displayed in the client area of the main window, as shown in Figure 4-24.

To produce and save a copy of the report in Portable Document Format (PDF), click the Print button on the Ribbon toolbar. Note that by default, tremoFlo reports are saved to the folder “C:\Users\Public\Documents\Thorasys\tremoFlo 1.0\Reports”.

![Report Preview](image)

Figure 4-24: Report Preview

4.10 System Shut-Down

Closing the Software

To close the software, click the red X on the top right corner of the tremoFlo screen, or select Exit from the tremoFlo menu. There is no need to click Save before closing the software, all data are stored automatically as soon as they are collected.

Hardware Power-Down

When you are done with your tremoFlo session and after you have closed down the tremoFlo software, the power/status indicator on the Cradle should return to yellow. At this point, press and hold the power button on the Cradle for three to five seconds, until all power indicators turn off.
5 Software Reference Manual

5.1 Device Connectivity
On computer systems provided for use in the Mesos Study, device connectivity is fully configured and tested and should not be altered.

5.2 User Management
On computer systems provided for use in the Mesos Study, user accounts are configured during installation and should not be altered.

5.3 Data Storage & Management

Database Storage
The tremoFlo software stores data in a relational Client/Server database. For standard stand-alone installation, the database is typically located in the Windows Program Data area under C:\ProgramData\Thorasy\Database. This directory is not readily visible and accessible to Windows users unless they have administrator or similar privileges.

Backups & Data Transfers
The tremoFlo software includes a database utility that permits database backups as well as transfer of selected types of data, including individual patient tests, from or to another database. The database utility is accessed from the System Settings menu.

Data Storage Locations
Default data storage locations are provided in Table 5-1. The file locations for reports and data export can be modified under Customize Reports and in the Export Wizard, respectively. Note that a shortcut to the reports folder is provided on the Windows desktop.

During normal operation, there should not be a need to directly access database or log files. Information contained in these files is normally accessed and maintained via the tremoFlo software.

<table>
<thead>
<tr>
<th>File Type</th>
<th>Folder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reports</td>
<td>C:\Users\Public\Public Documents\Thorasy\tremoFlo 1.0\Reports</td>
</tr>
<tr>
<td>Exported Data</td>
<td>C:\Users\Public\Public Documents\Thorasy\tremoFlo 1.0\Export</td>
</tr>
<tr>
<td>Study Database</td>
<td>C:\ProgramData\Thorasy\Database</td>
</tr>
<tr>
<td>Database Template</td>
<td>C:\ProgramData\Thorasy\Database\Empty</td>
</tr>
<tr>
<td>System Log File</td>
<td>C:\ProgramData\Thorasy\tremoFlo 1.0</td>
</tr>
</tbody>
</table>
6 Care & Maintenance

6.1 Storage & Transport

Dust Cover & Packaging
When the tremoFlo system is not used for an extended period of time, be sure to place the dust cover over the filter port on the Handheld Unit. For long-term storage or transport, please retain and use the original tremoFlo packaging.

Environmental Conditions
Store the tremoFlo C-100 in a location where the temperature is between -25 and 50 degrees Celsius and the relative humidity is between 10 and 85%, non-condensing. Do not store the tremoFlo C-100 in direct sunlight. The above environmental conditions apply for both transport and storage. Do not subject the tremoFlo C-100 to impact or excessive vibration during transport and storage.

Acclimatization
After storing or transporting your tremoFlo in a cold, or warm environment, allow several minutes for the device to acclimatize to room temperature before taking any measurements. This will ensure maximum accuracy of reported results.

6.2 Routine Cleaning
The use of a disposable anti-bacterial/anti-viral filter prevents transmission of diseases and infection between patients during regular use of the device. Proper use and disposal the filters means that it is not necessary to perform special cleaning procedures to sterilize your tremoFlo.

However, it is important to regularly clean the exterior surfaces of the tremoFlo C-100 using a mild detergent of neutral pH. Detergents that assist in the removal of organic soil are ideal. Use warm tap water with the detergent to moisten a clean, soft cloth. Wipe the exterior body and the edges of the tremoFlo’s filter port, but take care not to press against or otherwise damage the mesh screen inside. Do not use harsh chemical or abrasive cleaners as these may damage your device.

Caution: Do not immerse any part of the tremoFlo C-100 in liquid or sterilize any part with hot water, steam, ETO or Gamma Rays; doing so may damage the device.

6.3 Scheduled Maintenance
The tremoFlo system should be serviced by certified service personnel every 24 months.

6.4 Disposal
At the end of product’s life dispose of the tremoFlo in accordance with all local regulations regarding electrical and electronic waste. Where required, return the tremoFlo to the place of purchase for safe disposal.
Appendix A. Indications for Use

The tremoFlo Airwave Oscillometry System (AOS) is a portable medical device intended to monitor lung function and help in the assessment of human respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD) in adults and children. The device produces measures of airway resistance, reactance and other lung function parameters to assist physicians in diagnosis, treatment selection and evaluation of treatment efficacy. The principle technology of the AOS is based on a compact implementation of the Forced Oscillation Technique (FOT), a non-invasive technique that assesses lung function by superimposing a multi-frequency airwave on top of the patient’s spontaneous breathing. The technique requires virtually no patient effort: patients breathe normally into the tremoFlo for a short period of time while supporting their cheeks and blocking nasal airflow with a nose clip. Cheek support may be provided by a parent or medical assistant for patients who require assistance (e.g. children, elderly). All tests are performed via an anti-viral/bacterial mouthpiece connected to the device. Test results are displayed in the software and available in a printable report. The tremoFlo should be used with the patient sitting in a natural position with the back straight and the chin up.  The tremoFlo is safe for use in all patients capable of spontaneous breathing, including geriatric, pregnant, and mobility impaired patients as well as children as young as 2 years of age with and without respiratory illness. Young or sick patients may require rest between measurements; abnormal breathing, such as hyperventilation, may cause errors in test results and normal breathing must be restored before testing patients experiencing breathing difficulty. Patients that experience shortness of breath, tightness in the chest, chronic cough, wheezing, or exposure to dust or chemicals must be capable of sustaining normal breathing for the duration of a measurement. Bronchodilator testing may be evaluated through the assessment of key parameters before and after administration of bronchoconstrictor or bronchodilator drugs. Measurements are performed by specialized users, such as respiratory therapists, pulmonologists, researchers or other health practitioners, under the direction of a trained physician. The tremoFlo is intended for use in a hospital environment, pulmonary function testing clinic/laboratory, physician’s office or similar settings. The device may also be used in a home, clinic, workplace or other location under the supervision of a specialized user.

Appendix B. Troubleshooting

Power Problems

<table>
<thead>
<tr>
<th>Problem</th>
<th>Possible Cause</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unit does not turn on, all power indicators remain unlit.</td>
<td>Power cable not connected.</td>
<td>Verify all power connections.</td>
</tr>
<tr>
<td></td>
<td>No power on outlet.</td>
<td>Verify that power is available, try a different outlet.</td>
</tr>
<tr>
<td></td>
<td>Power button not fully pressed.</td>
<td>Press the power button for one full second.</td>
</tr>
<tr>
<td>Only one power indicator (Cradle or Handheld Unit) turns on while the other remains unlit.</td>
<td>Internal error (rare).</td>
<td>Disconnect and reconnect power supply, reboot the tremoFlo. Contact Technical Support if the problem persists.</td>
</tr>
<tr>
<td>Power/status indicator on Cradle is yellow.</td>
<td>Software is not running.</td>
<td>Start the software and complete the software start-up sequence.</td>
</tr>
<tr>
<td></td>
<td>Software is not fully initialized.</td>
<td>Complete the software start-up sequence.</td>
</tr>
<tr>
<td></td>
<td>Software is in offline mode (reviewing historic data).</td>
<td>Start a new patient test.</td>
</tr>
</tbody>
</table>
Power/status indicator on Cradle is red. | Ethernet cable disconnected. | Reconnect Ethernet cable, software normally recovers and light returns to green.

| Software error. | Check error messages on screen and proceed accordingly.

| Internal error (rare). | Disconnect and reconnect power supply, reboot the tremoFlo. Contact Technical Support if the problem persists.

## Calibration Problems

<table>
<thead>
<tr>
<th>Problem</th>
<th>Possible Cause</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unable to attach Calibration Test Load.</td>
<td>Dust cap still on unit.</td>
<td>Remove the dust cap before attaching the test load.</td>
</tr>
<tr>
<td></td>
<td>Incorrect Calibrator Adapter.</td>
<td>Verify that the calibrator adapter matches the filter diameter.</td>
</tr>
<tr>
<td>Calibration produces error message.</td>
<td>No Calibration Test Load attached.</td>
<td>Attach the calibration test load (without dust caps) and click Start Over.</td>
</tr>
<tr>
<td></td>
<td>Dust caps still on Calibration Test Load.</td>
<td>Remove the dust caps, reattach the test load and click Start Over.</td>
</tr>
<tr>
<td></td>
<td>None of the above.</td>
<td>Click Start Over and try again. If the problem persists, contact Technical Support.</td>
</tr>
</tbody>
</table>