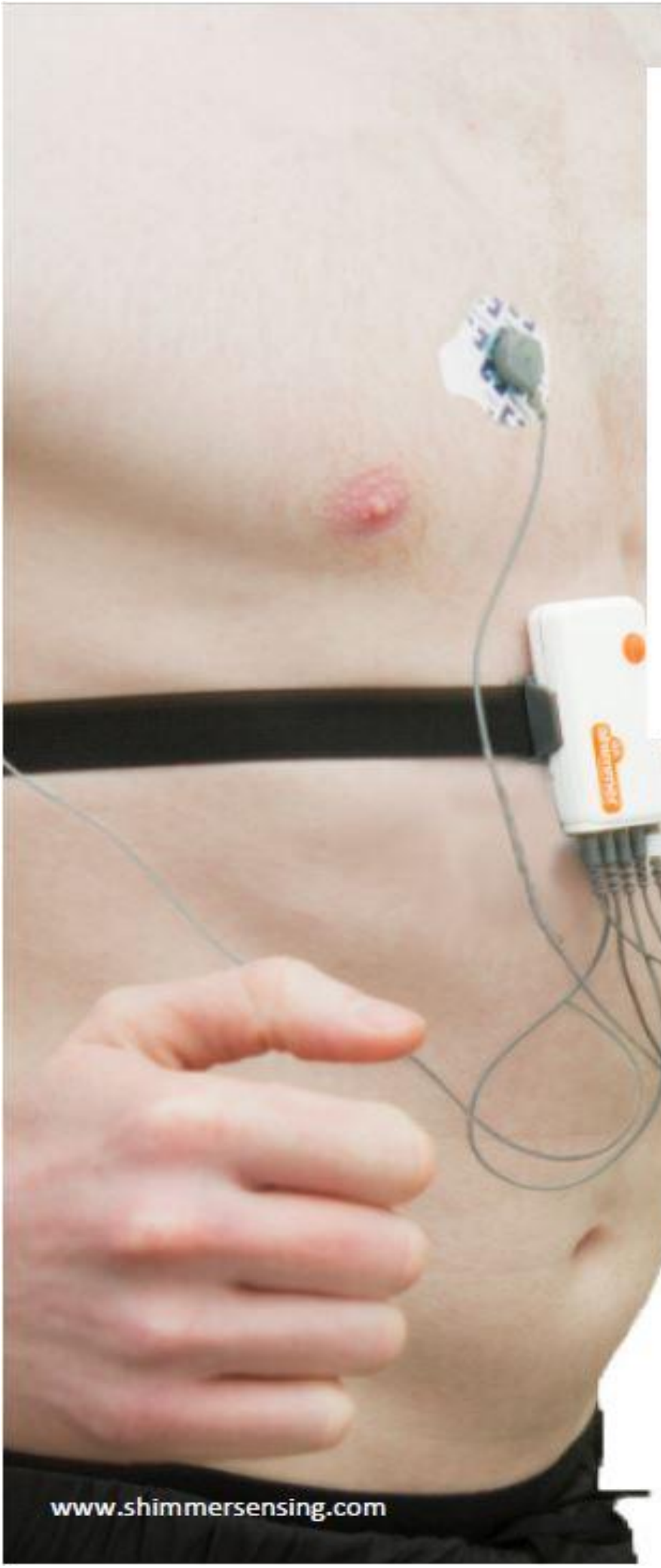

WHITE PAPER

Shimmer3 EBio Sensor for COVID-19 Clinical Trials

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By Shimmer Research Inc

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1. Introduction

COVID 19 virus is now a global pandemic. The COVID 19 virus causes an illness which is asymptomatic or mild in most cases (81%), serious in a minority (14%), severe in 5% and fatal in 2 - 3%. Respiration issues are associated with the vast majority of serious, severe, and fatal cases. In addition, there are reports of long-term damage to the lungs in non-fatal cases, but it is too early to obtain reliable statistics on long-term effects. Some of the challenges of measuring outcomes in the current environment include:

- Rapidly changing treatment protocols mean that outcomes defined by clinical treatment paths (e.g., use of mechanical ventilation) may be difficult to assess
- Patient reported outcomes (PRO) may not be reliable in many cases. For example, symptomless hypoxia where patients are not even aware of respiratory problems appears to have high incidence.
- Long-term effects of the disease are currently uncertain and will take a long time to measure.

Accurately measuring lung function is therefore critical to assessing the efficacy of any treatment. Thoracic Bioimpedance, as an indicator of total fluid in the chest, has been studied extensively in Chronic Heart Failure (CHF) and the Acute Respiratory Distress Syndrome (ARDS). In these settings, thoracic bioimpedance monitors can provide a number of useful biometrics including respiration rate, respiratory [tidal] volume, and *bioimpedance* which is inversely related to the amount of fluid in the thoracic cavity. Tomographic applications of bioimpedance have been able to assess the distribution of fluid within the chest. A selected bibliography appears in the appendix.

The wearable Shimmer3 EBio sensor continuously measures thoracic bioimpedance, ECG, and acceleration, enabling continuous:

- Data to identify trends, variations and opportunities that can be missed with intermittent monitoring
- Relevant and highly specific respiratory assessments through the use of thoracic bioimpedance – RR, depth (tidal volume), minute ventilation, and respiratory pattern (I:E ratio)
- Assessments that correlate with acute illness – HR (average, range, trend, activity contextualized) and HRV which may show shift to sympathetic tone dominance
- Activity and posture assessments that may signal fatigue, asthenia, and increasing severity of illness

In short, continuous monitoring with the Shimmer3 EBio can provide specific quantitative assessment of respiratory function and other symptoms that can act as outcome measures to address some of the challenges of measuring more traditional outcome measures.

2. Equipment

The Shimmer3 EBio sensor was introduced in 2014 and has been used successfully in literally thousands of studies in over 70 countries. It is CE marked for safety but is not a registered medical device. However, Shimmer is a registered ISO 13485:2016 medical device manufacturer and will seek additional regulatory clearance as appropriate.

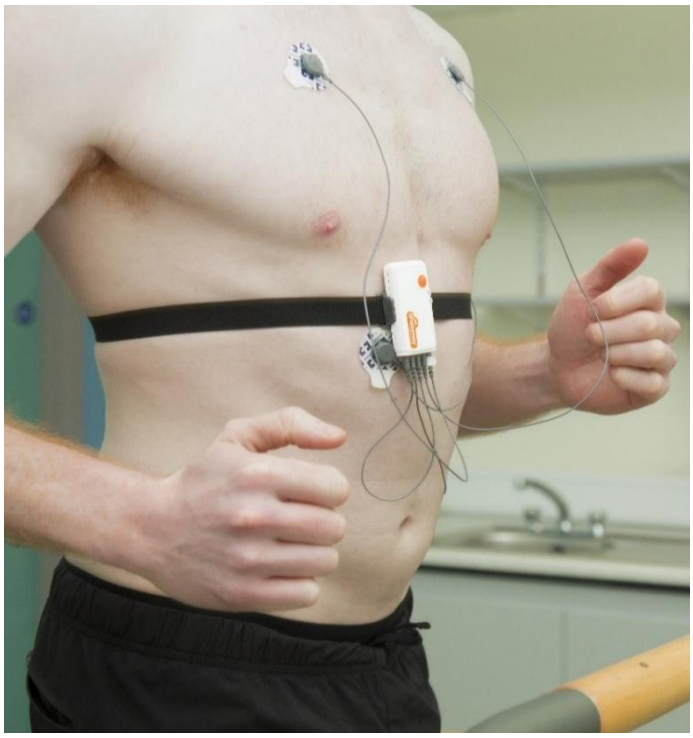

Figure 1: *Shimmer3 ECG/Bioimpedance Sensor*

Figure 1 shows a photo of the sensor *in situ* on a subject. Figure 2 shows the recommended placement of electrodes when used in the bioimpedance mode. Only three electrodes are required to obtain bioimpedance measurements (V6, RA, LA). The LL and Vx electrodes are used to capture ECG signals. Raw sensor data from all of the sensors are available to the researcher.

Data can be collected at a variety of sampling rates, from 1Hz to more than 1kHz. We recommend a minimum 200Hz data sampling rate for bioimpedance. Data can be either stored on board the sensor and/or wirelessly transmitted via Bluetooth. At 200Hz, the sensor has onboard storage for up to 29 days. For the remote monitoring application, data can be stored on the device and uploaded upon return to the site.

The Shimmer3 EBio system uses standard ECG electrode to capture the ECG and bioimpedance signals. (We work with Research Sites to select the most appropriate skin sensors for the study.

In addition to ECG and bioimpedance data, the sensor can simultaneously collect 9 degrees of freedom IMU data (3-axis accelerometer, 3-axis gyro, and 3-axis magnetometer). Activity and position data provide important contextual information, such as the posture of the patient (supine, prone, or upright) as well as activity levels, bouts and intensity. These signals are also important in identifying periods of motion artefact to enhance signal processing.

The sensor's battery will last for 2+ days without recharging in the local data storage mode. In the streaming mode, the battery life is 8+ hours.

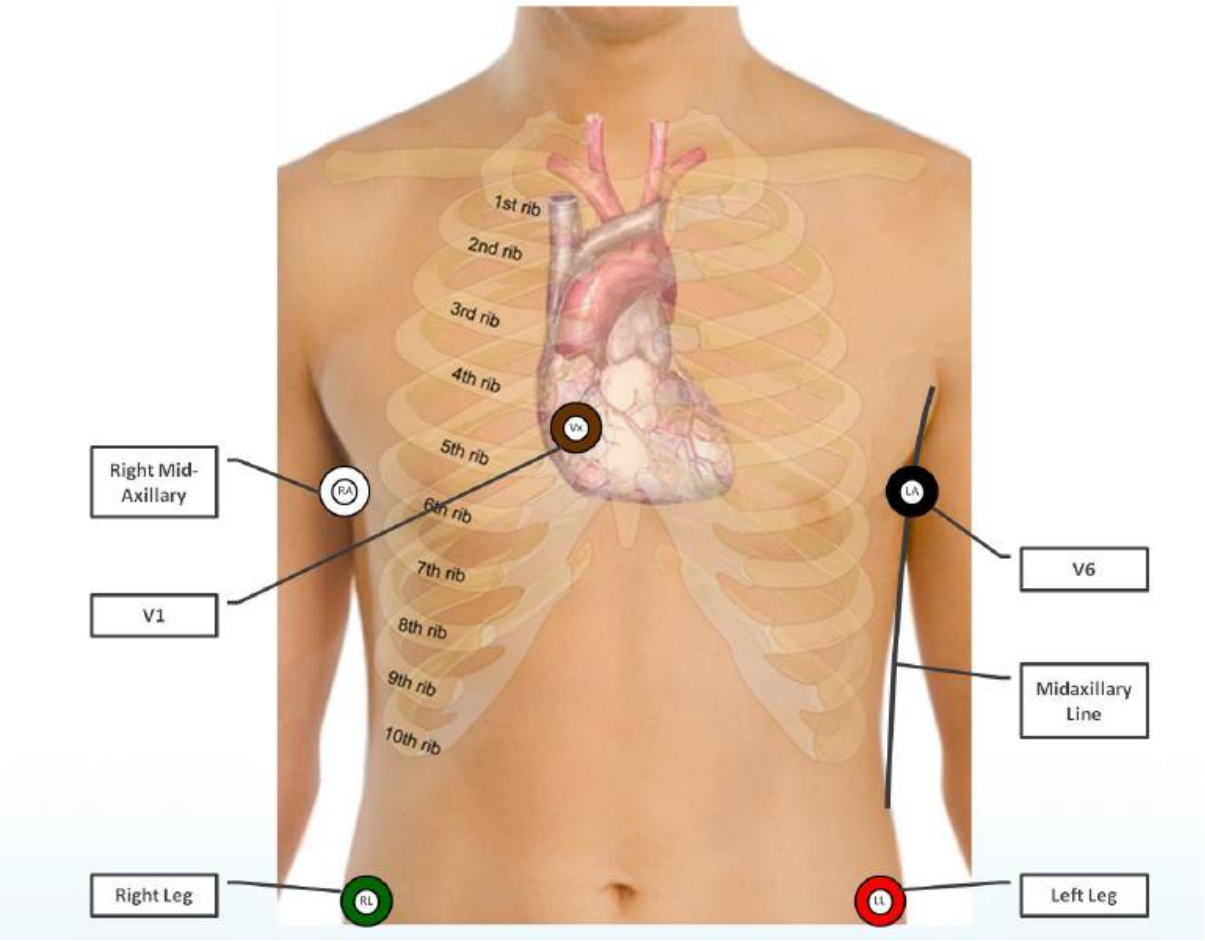

Figure 2 *Recommended Bioimpedance Electrode Placement*

3. The Signals

The ECG-Bioimpedance monitor captures ECG, thoracic bioimpedance, and activity/position from a 9 degree-of-freedom inertial measurement unit (IMU. Because the electrodes are in non-standard locations for ECG and the bioimpedance signals generate high frequency noise, the morphology of the ECG waveform may be affected although fully able to capture accurate heart rate and peak-to-peak intervals after filtering. Figure 3 below shows the ECG and bioimpedance signals before and after filtering.

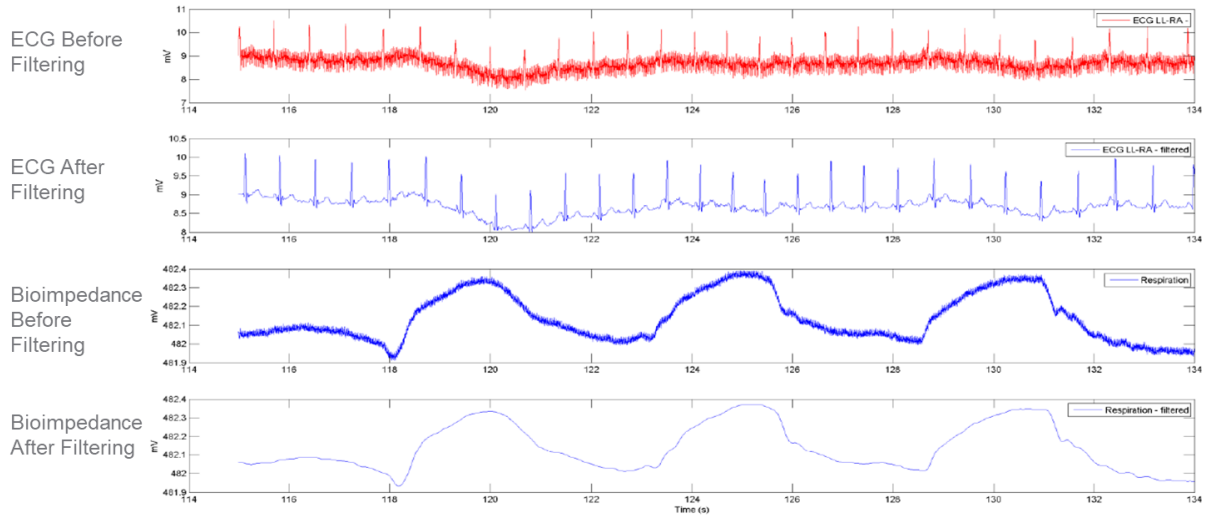

Figure 3 *ECG and Bioimpedance before and after filtering*

As shown above, the R waves stand out very clearly even before filtering the raw ECG. The change in the bioimpedance signals are driven by the lungs' tidal exchange of air. Since air is less conductive than bodily fluids, when the lungs fill with air or other gases, the impedance increases. When the subject exhales, the impedance returns to baseline at FRC (functional residual capacity). The rate of the peaks is equivalent to the respiration rate (RR) and the width of the peaks indicates time and can thus yield an I:E (inspiration to exhalation) ratio. Furthermore, the height of the peaks is related to the depth of breathing. Figure 4 below shows some different breathing patterns and how they appear on bioimpedance monitoring. There is clearly a relationship between the depth of breathing (tidal volume) and the height of the peaks. Whether this relationship is linear remains to be seen in practice.

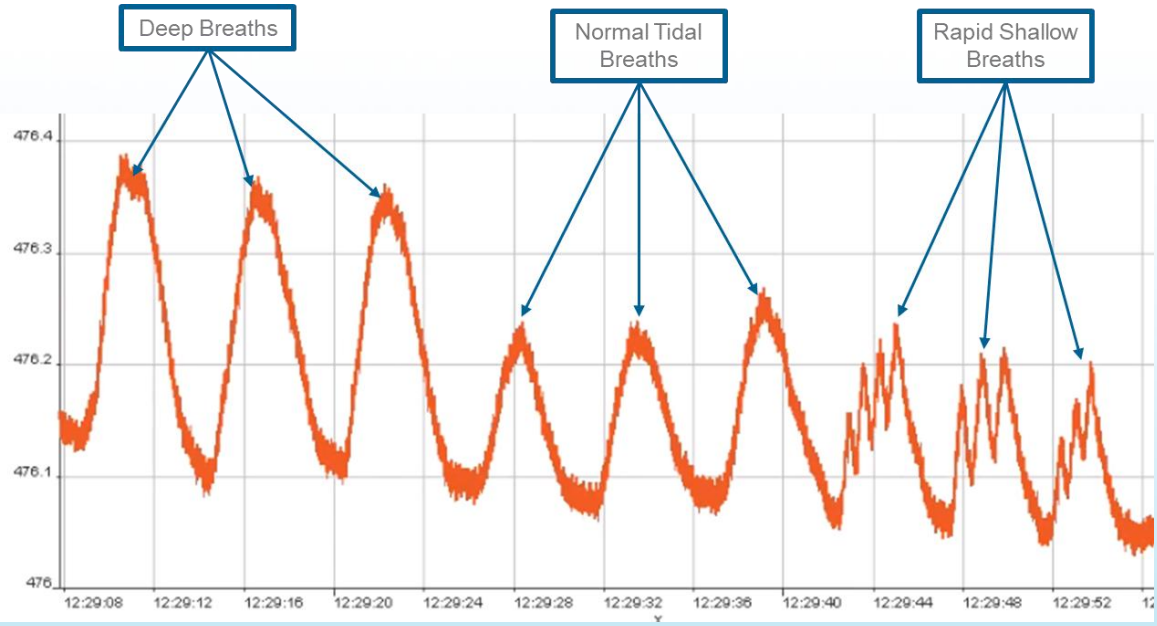

Figure 4 *Bioimpedance with different breathing patterns*

In addition to the electrical signals, the IMU can provide measurements of activity, body position, posture, and sleep. Algorithms for these biometrics are well known and can be applied to the raw data streams generated.

4. Monitoring COVID-19

With these sensors, the Shimmer3 ECG-Bioimpedance monitor can assess a very wide range of COVID-19 symptoms. The table below outlines the systems and sensing modalities of the system.

Symptom	Digital Biomarker	Sensing Modality with Shimmer3 ECG-Bioimpedance Sensor
Fever	Elevated HR Elevated RR Δ HRV	ECG Thoracic Bioimpedance ECG
Cough	Thoracic Cage Movement Thoracic Volume Pattern	Accelerometer Thoracic Bioimpedance
Fatigue	Body Position and Posture Active Time and Intensity Δ Sedentary Time	Accelerometer Accelerometer Accelerometer
Respiratory Distress	Rapid Shallow Breathing Elevated RR Elevated HR Disrupted sleep	Thoracic Bioimpedance Thoracic Bioimpedance ECG Accelerometer

An example of actual data from a patient with COVID-19 is displayed in Figure 5 below. As can clearly be identified with the 3-axis accelerometer data, the patient was placed in a prone position for a little over two hours. During this period, the patient's respiration eased from 35+ breaths per minute to ~20 breaths per minute, suggesting a significant improvement in respiration. Heart rate was also reduced, consistent with improving respiration (as were other indicators that collected by the hospital). Because we can get moment by moment data, the impact of the position (and potentially other treatments) can be seen easily.

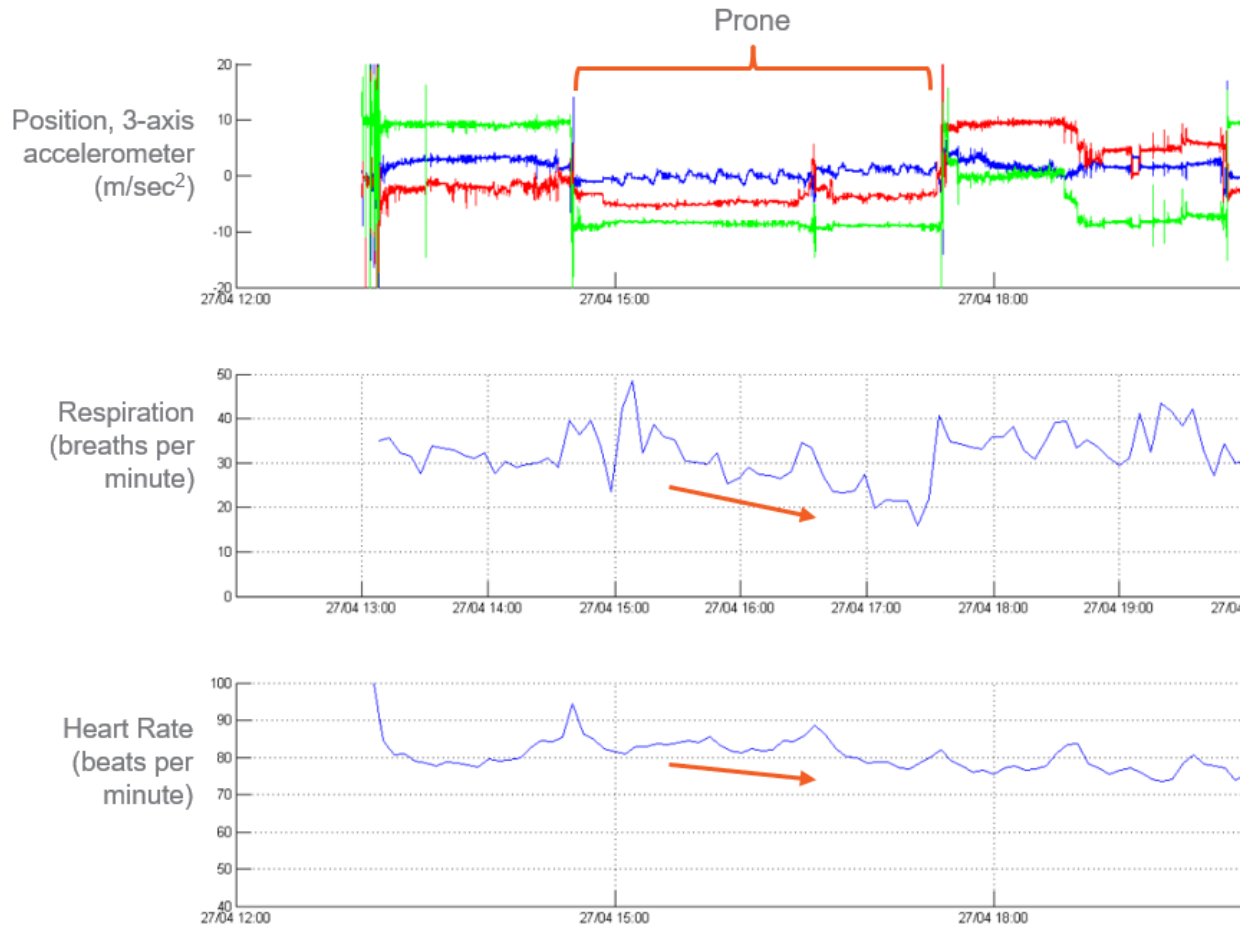

Figure 5: *Respiration and Heart Rate Improvement of COVID Patient in Prone Position*

5. Summary

The Shimmer3 EBio sensor is a fully validated, CE marked and extensively used off-the-shelf product that offers the opportunity to measure critical indicators of disease severity with special emphasis on lung health, a primary concern for COVID-19 patients. Shimmer has initiated research to discover, validate and use digital biomarkers to predict the course and outcome of COVID-19, and we expect other researchers to join in this effort to accelerate progress and provide independent validation.

With continuous objective data, the Shimmer EBio sensor can provide quantitative and highly sensitive measurements of the severity and course of the disease.

6. Appendix 1: Examples of Changing Treatment Protocols

Treatment protocols are evolving rapidly. For example, a recent report for Sun et al. (Sun et al. Ann. Intensive Care (2020) 10:33) outlines the mortality and resource utilization benefits of twice daily monitoring of straightforward clinical signs such as tachycardia, tachypnea and falling oxygen saturation, to indicate which COVID 10 pneumonia patients need more aggressive measures (high flow oxygen, non-invasive ventilation, proning). Through the monitoring and intervention the authors were able to see a cure rate of 96.67% while keeping the rate of endotracheal intubation to less than 1%.

The authors demonstrated remarkable sensitivity, specificity and area under the ROC curve (0.962), for this constellation of monitoring parameters. As a result, these approaches are starting to be implemented widely.

Another example is the recent clinical experience at Massachusetts General Hospital (see https://youtu.be/cEHXdoUlJaQ) that indicates there are at least two different phenotypes (L and H) that respond differently to treatments such as mechanical ventilation. If this experience is confirmed with systematic research, it will likely significantly change the protocol for a significant fraction of COVID patients.

7. Appendix: Recent Data on COVID 19 and Use of Bioimpedance to Monitor Intrathoracic and Lung Water

COVID-19

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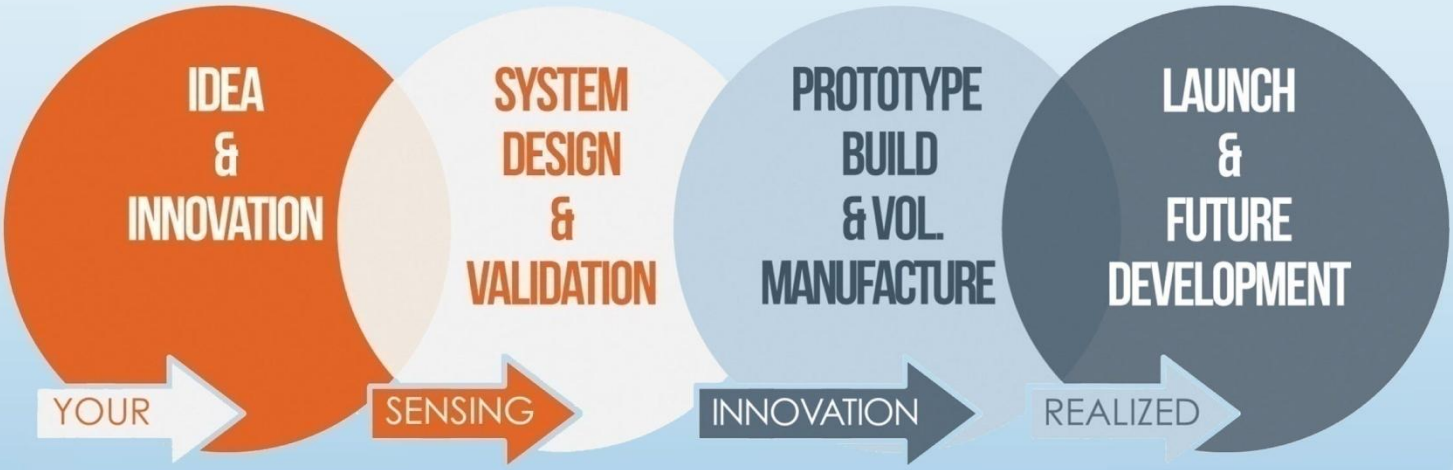

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