

# A NOVEL OXIGRAPHY SYSTEM BASED ON OXYGEN LUMINESCENCE QUENCHING

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## ABSTRACT

A system suitable for real-time measurement of oxygen partial pressure ( $pO_2$ ) in respiratory gas (oxigraphy) that is based on oxygen's ability to quench the phosphorescence of a lumiphore is described. A description of currently used  $pO_2$  technologies is provided followed by a description of the luminescence quenching  $pO_2$  technology. A comparison of the technologies is made. The description of luminescence quenching  $pO_2$  technology includes the operational theory and the advantages of the use of phosphorescence lifetime as opposed to phosphorescence intensity for  $pO_2$  measurement. The clinical benefits of oxigraphy as well as a possible space-based application of luminescence quenching  $pO_2$  technology are proposed.

*Key Words:  $pO_2$ , paramagnetism, susceptibility, polarographic, galvanic, zirconium oxide, mass spectrometry, Stern-Volmer, lumiphore, luminescence, photoexcitation, quenching, oxigraphy.*

### Introduction

In the medical field, the monitoring of respiratory oxygen may have applications not only in the monitoring and study of respiratory patterns, but in maintenance of correct gas mixtures during mechanical ventilation and anesthesia delivery, as well as in the treatment and diagnosis of cardiopulmonary disorders. A new oxygen partial pressure ( $pO_2$ ) technology, based on the measurement of phosphorescence lifetime has been developed and will be described herein. Currently available techniques of  $pO_2$  measurement include electrochemical sensors including polarographic and galvanic cells, paramagnetic cells, zirconium oxide cells, and mass spectrometry. A review of these technologies follows.

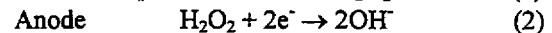
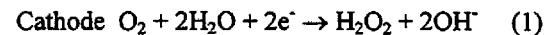
### Electrochemical $pO_2$ Sensors

Electrochemical sensors, in which a chemical reaction takes place between a cathode and an anode, are commonly used in both gas phase and blood-gas analysis. The two commonly used sensors are polarographic (Clark) cells and fuel (galvanic) cells.

### Polarographic Cells

In 1954, Leland Clark conceived of and built the first oxygen sensing electrode which consisted of an anode and cathode behind an oxygen permeable polyethylene membrane. The Clark or polarographic cell (Fig. 1.) can be used in both

gas phase and blood-gas analysis. The electrode consists of four components, a platinum cathode, a silver anode, an electrolyte solution (e.g. KCl) and an oxygen permeable membrane. A negative voltage is applied to the silver anode and a positive voltage applied to the platinum cathode. Electrical contact is maintained between the anode and cathode via the electrolyte solution. Oxygen molecules pass through the membrane where they are electrolyzed at the platinum surface in accordance with the following reactions:



Oxygen reduction rate alters the conductivity of the electrolyte solution. The resulting current flow is proportional to the concentration of  $O_2$  in the electrolyte solution.

Polarographic electrodes are typically slow with response times of 3 seconds and longer<sup>1</sup>. Rapid response time polarographic electrodes have been reported<sup>2,3</sup>, and are typically constructed by reducing the distance between the cathode and the membrane, thus reducing the diffusion pathlength for oxygen. Unfortunately, these electrodes suffer from a short lifespan (2-3 days<sup>3</sup>) and are vulnerable to electrolyte evaporation, gas bubbles in the electrolyte, pressure and temperature effects at the membrane<sup>4</sup>, and possible errors due to interaction with anesthetic agents such as halothane<sup>5</sup> and nitrous oxide<sup>6</sup>.

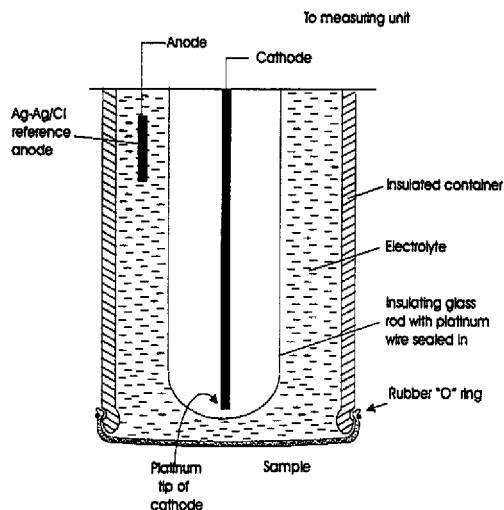


Fig. 1. Details of Polarographic (Clark) cell. (Redrawn from Crampton Smith, A., and Hahn, C.E.W.: Electrodes for the measurement of oxygen and carbon dioxide tensions, Br. J. Anaesth. 41:732, 1969.

### Fuel Cells

The fuel or galvanic cell (Fig. 2.) is an electrochemical cell which consists of two electrodes: a gold cathode and a lead anode. The

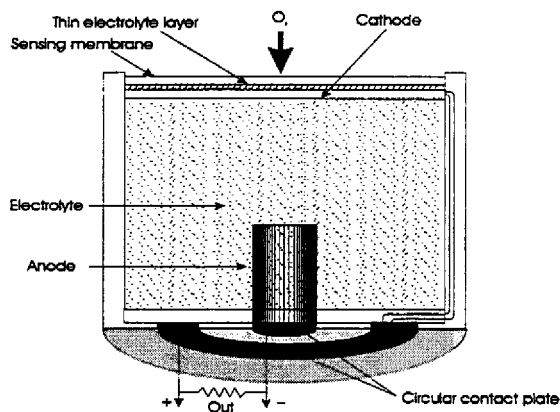
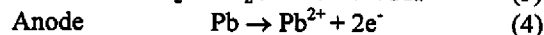
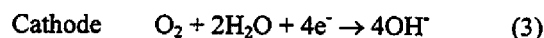


Fig. 2. Details of fuel cell. Redrawn from Merilainen PT. Sensors for oxygen analysis: paramagnetic, electrochemical, polarographic, and zirconium oxide technologies. Symposium, Nov. 1989.

gold cathode is exposed to oxygen through a polymer membrane. The electrolyte is typically a

solution of potassium hydroxide. Oxygen diffuses through the membrane and a thin electrolyte layer to the cathode where it is electrochemically reduced as follows:

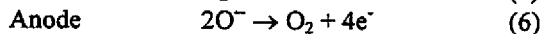
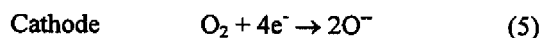


The electrical current from this reaction is proportional to  $p\text{O}_2$ . This reaction proceeds spontaneously in the presence of oxygen, thus requiring no external power source.

Fuel cells are inexpensive and in wide clinical use, however they suffer from poor response times<sup>7,8</sup> ( $T_{10}-T_{90}$  of 9 to 48 seconds for a 100-21%  $\text{O}_2$  step change) and are subject to output errors in the presence of condensing water vapor<sup>7,1,9</sup>.

### Zirconium Oxide Cells

Zirconium oxide cells are solid electrolyte fuel cells (Fig. 3.). The cell consists of a zirconium oxide ( $\text{ZrO}_2$ ) tube which is typically stabilized with yttria ( $\text{Y}_2\text{O}_3$ ). The internal and external surfaces of the  $\text{ZrO}_2$  tube are coated with platinum film to form separate electrodes on either side of the tube. The cell is heated to approximately 700-1000°C. The sampled gas is drawn through the tube where it is ionized. The electrolyte acts as a semi-permeable membrane; permeable to the oxygen ions but impermeable to electrons. The outside of the tube is exposed to a reference gas of known  $p\text{O}_2$ . The platinum electrode which is exposed to the higher  $p\text{O}_2$  becomes the anode and the following reaction takes place:



The voltage generated across the cell follows the Nernst equation:

$$E = RT/nF \cdot \log(P_1/P_2) \quad (7)$$

Since the output voltage is a logarithmic function of the ratio of  $p\text{O}_2$  on either side of the cell (approximately 50 mV per decade of oxygen concentration) the cell has a high dynamic range allowing determinations of a broad range of  $p\text{O}_2$  differences. The zirconium oxide cell will combust many operating room gases at the temperature at which it operates. This renders the

cell unusable for analysis of respiratory  $pO_2$  in the OR. However, this cell may be used for metabolic monitoring in the absence of such combustible gases. Breath-to-breath analysis is possible due to the adequate response of the cell ( $T_{10}-T_{90}$  of 0.030 seconds for a 12% to 21% concentration change - Servomex Model 728). Unfortunately, the cell suffers from fragility<sup>10</sup> and requires a warm-up period.

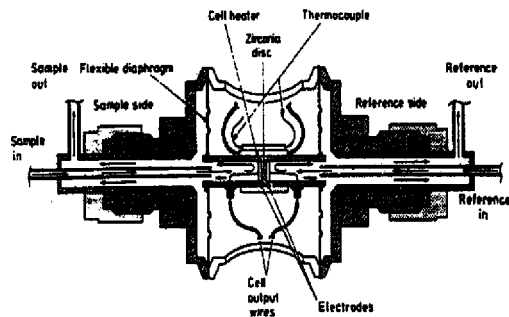


Fig. 3. Details of zirconium oxide fuel cell. Reproduced from Servomex product literature.

#### Paramagnetic Cell Background

In 1845, Faraday discovered that substances other than iron could be attracted by magnetic fields<sup>11</sup>. In one experiment, he found that a glass sphere filled with oxygen and supported by silk fibers was displaced in the presence of a strong, non-uniform magnetic field. Faraday called this phenomenon paramagnetism. The paramagnetic nature of oxygen was later determined to be due to the presence of two unpaired electrons in the outer shell of the oxygen molecule. These unpaired electrons produce a magnetic moment which gives rise to oxygen's paramagnetism.

The strength of interaction of a material with a magnetic field is known as magnetic susceptibility<sup>12</sup>. Materials with a positive susceptibility, such as oxygen, are termed paramagnetic and those with a negative susceptibility, such as nitrogen, are termed diamagnetic. The effects of oxygen paramagnetism can be described by a physical law which relates the force (F) on the molecule to susceptibility (K) and the magnitude and gradient of the magnetic field (H):

$$F = K \cdot H \cdot dH/dx \quad (8)$$

The susceptibility of oxygen is greater than that of other operating room respiratory gases. Two

types of technologies based on oxygen paramagnetism are commonly used for determination of  $pO_2$ . The original technology developed in 1940 by Linus Pauling<sup>13</sup> utilizes a mechanical device which takes advantage of the differential magnetic behavior of paramagnetic and diamagnetic gases in a static, non-uniform magnetic field. The second technology, originally presented by Heinz Hummel<sup>14</sup> in 1968 uses a dynamic principle based on the differential behavior of paramagnetic and diamagnetic gases in an electrically switched magnetic field.

#### The Pauling Paramagnetic Cell

The paramagnetic cell developed by Pauling consisted of a sealed glass dumbbell containing a diamagnetic gas (usually nitrogen). The dumbbell is suspended between two wedge shaped permanent magnets (Fig. 4.), which by virtue of their shape provide a non-uniform magnetic field. When a paramagnetic gas such as oxygen enters the cell, it will be attracted to the area where the magnetic field is the strongest. By contrast, the diamagnetic gas in the glass spheres of the dumbbell will be attracted to the area in which the magnetic field is the weakest. This generates a torsional force on the dumbbell

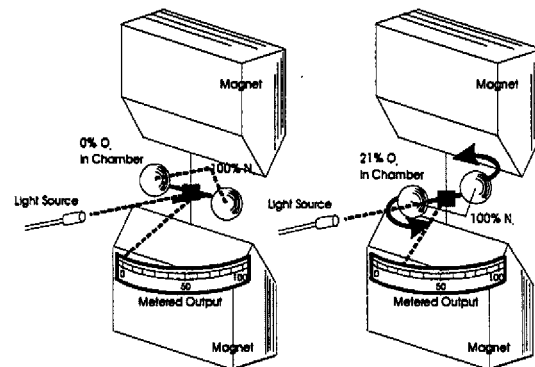


Fig. 4. Details of Pauling cell showing torsional force on dumbbell resulting from oxygen in sampling chamber.

roughly proportional to the  $pO_2$  of the surrounding gas, thus rotating the dumbbell vertically about its horizontal axis. The degree of rotation is measured optically using a photosensor based on the reflection of a light beam off a mirror mounted to the dumbbell assembly. In the early cells, the degree of dumbbell rotation was taken as a measure of  $pO_2$ . However, rotation of the dumbbell

produced a non-linearity due to the movement of the dumbbell spheres into areas of differing magnetic gradients. This non-linearity problem was later solved by C.W. Munday of Servomex Controls Limited. Munday introduced a feedback system which prevented the dumbbell from rotating by introducing current to coils surrounding the spheres. The current required to maintain the dumbbell in position is linearly related to  $pO_2$ .

The drawbacks of this  $pO_2$  technology include the inherent fragility of the mechanical device and its susceptibility to contamination by particulate matter. In addition, slow response times ( $T_{10}-T_{90}$  of 0.5 seconds at 90 ml/min flow for the Servomex Model 1111) render the sensor useless for spirographic (breath-by-breath) recording.

#### The Hummel Paramagnetic Cell

Hummel constructed a paramagnetic cell based on an electromagnet. This cell mixed two gas streams (a reference gas stream and a sample gas stream) inside a homogenous magnetic field. By alternating this magnetic field it is possible to measure the pressure difference upstream of the sample inlets using a differential pressure transducer (Fig. 5.). The amplitude of the differential pressure signal is proportional to the difference in  $pO_2$  of the sample and reference gases.

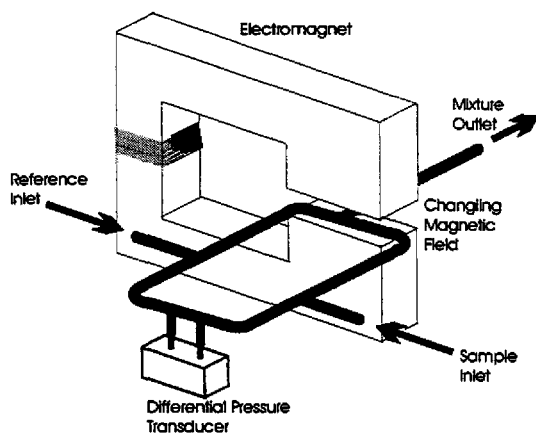


Fig. 5. Details of Hummel cell showing pneumatic path of sample and reference gases through the electromagnet gap and differential pressure measurement technique.

The major advantage of this configuration is the improved response time of the system ( $T_{10}-T_{90}$  of 0.150 seconds at 100 ml/min flow for the Datex sensor) which allows for spirographic recording. In addition, the  $pO_2$  of the sample gas can be altered allowing for accurate differential analysis of the sample and reference gases which is advantageous for measurement of metabolic oxygen consumption. The primary disadvantage of this configuration is the need for continuous reference gas which, when ambient air is used as a reference gas, results in a slow accumulation of nitrogen in closed-circuit anesthesia systems. In addition, water vapor partial pressure differences between the reference and sample gases as well as background acoustic noise can produce inaccuracies<sup>12</sup>.

#### Mass Spectrometry

Mass spectrometry can be used for the analysis of respiratory gases such as oxygen. Mass spectrometry separates ionized gas molecules by their ionic mass/charge ratios. Gas is sampled into the system by means of an inlet system through the use of a vacuum pump. A portion of this gas is drawn into a high-vacuum source where it is ionized via bombardment with an electron beam. The ions are then passed through a magnetic field oriented normal to the direction of ion travel. As a result, ion streams follow separate circular trajectories based on their aforementioned ionic mass/charge ratios. The ion streams are captured by collector electrodes and the resulting current is amplified and displayed.

Mass spectrometry can be used for analysis of partial pressures of a variety of respiratory gases including oxygen. Response times ( $T_{10}-T_{90}$  of 0.100 seconds for oxygen)<sup>4</sup> are adequate for breath-to-breath analysis. Unfortunately, the technology is bulky and expensive.

#### Oxygen Luminescence Quenching

Phosphorescence (and fluorescence) results from photon emission of an excited-state lumiphore. Lumiphores, or aromatic molecules capable of photoexcitation, can be excited from a ground state to an excited state by photon absorption. The ground and excited energy states are illustrated graphically in the Joblinski Diagram (Fig. 6.). Photoexcitation (photon absorption) of a lumiphore in the ground state ( $S_0$ ) will excite the molecule to a higher energy state (singlet state) such as  $S_1$  or  $S_2$ . The excited molecule

will then relax to the lowest energy state of  $S_1$  by means of loss of thermal energy known as vibrational relaxation. Since the energies associated with the lower energy singlet states  $S_2$  and higher energy states of  $S_1$  are similar, a change of singlet state from  $S_2$  to  $S_1$  is possible. This process is known as internal conversion. The vibrational relaxation and possible internal conversion of an excited molecule from a higher energy level of the  $S_1$  or  $S_2$  states to the lowest energy level of the  $S_1$  state typically occurs in approximately  $10^{-12}$  seconds<sup>15</sup>.

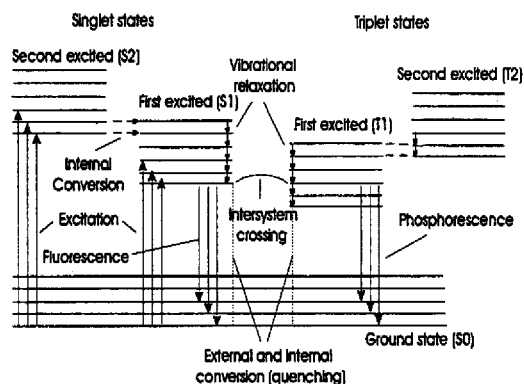


Fig. 6. Joblinski diagram, redrawn from Lewis, Kasha, 1944; Lott and Hurtubise, 1974.

From the lowest energy level of  $S_1$ , two events may transpire, first the molecule may relax to the  $S_0$  ground state. This relaxation to the ground state can occur by internal conversion or by emission of a photon (fluorescence). The latter event is more likely as internal conversion is a relatively slow process owing to the large energy difference between the  $S_1$  and  $S_0$  states. The second event which may transpire from the lowest energy level of  $S_1$  is intersystem crossing to the triplet state  $T_1$ . A molecule in the  $T_1$  state may then return to the  $S_1$  state by intersystem crossing, or return to the  $S_0$  state by a low probability vibrational relaxation or, finally, by emission of a photon (phosphorescence).

### Phosphorescence

Photon emission from the  $T_1$  state to the  $S_0$  state involves a change in electron spin. This event has a low probability of occurrence and as a result, phosphorescence is a long lived phenomenon ( $10^{-5}$  to 10 seconds)<sup>15</sup>. Further, the lowest energy level of the  $T_1$  state is lower than that of the  $S_1$  state and as a result, the wavelength of photons emitted from the triplet state during

phosphorescence are longer than those emitted from the singlet state during fluorescence. The long lifetime of phosphorescence renders the molecule vulnerable to outside influences such as the presence of oxygen. Oxygen, which has two unpaired electrons in different orbitals is a triplet state molecule. This makes the oxygen molecule reactive with other molecules in the triplet state and, thus a good quencher of such molecules. Quenching is the deactivation of an excited state lumiphore from the  $S_1$  or  $T_1$  state to the  $S_0$  ground state. The drawback of using phosphorescence, as opposed to fluorescence for detection of  $pO_2$  is that excited state triplet molecules are, in effect, di-radicals and therefore photolabile<sup>16</sup>. As a consequence, a progressive photo-bleaching of excited state triplet molecules leads to a reduction in phosphorescence with time. The advantage of using excited state triplet molecules for  $pO_2$  measurement is the long lifetime of phosphorescent radiative decay which makes quenching phenomenon quantifiable with current low cost signal processing electronics.

### The Modified Stern-Volmer Equation

The quenching of phosphorescence (and fluorescence) is described by a modified version of the Stern-Volmer equation as follows:

$$I_0/I = \tau_0/\tau = 1 + k_q\tau_0[O_2] \quad (9)$$

where the ratio of  $I_0/I$  represents the intensity in the presence and absence of oxygen, respectively, and  $\tau_0/\tau$  represents the lifetime of luminescence in the presence and absence of oxygen, respectively. The variable  $k_q$  specifies the quenching rate constant and  $O_2$  the oxygen concentration. Thus, this equation describes both the intensity drop and the lifetime change resulting from the presence of oxygen on a lumiphore.

### Phosphorescence Lifetime vs. Intensity

As described above, both lifetime and intensity changes of a phosphorescent molecule in the presence of oxygen are affected equally ratiometrically. However, for measurement of  $pO_2$ , the use of phosphorescent lifetime is preferred as intensity measurements may be affected by variations in excitation light source intensity, photobleaching, leaching of the lumiphore from its immobilized point of reference, and external factors such as the presence of water or sputum.

## Oxygen Luminescence Quenching Sensor

A sensor has been developed which measures the phosphorescent lifetime of an oxygen quenched lumiphore. This lifetime provides an accurate measurement of  $pO_2$ . This sensor is a main-stream respiratory  $pO_2$  sensor. Main-stream  $pO_2$  sensors are sensors which can obtain oxygen measurements directly from the patient breathing circuit without the need to sample or remove gas to an external device.

Table 1. Qualitative comparison of oxygen sensing technologies.

Oxygen Sensing Technology	Controlled Ambient Light	No. Yrns of Pre-Analytic	No. Anesthesia Indications	No. Blood Gas Analyses	Low Temperature Operation	Adequate Response	Not Toxic	Low Cost
Polarographic Cell	X		X	X	X	X	X	X
Fuel Cell	X	X	X	X	X	X	X	X
Zirconium Oxide Cell	X	X	X			X	X	
Paramagnetic Cell - Pauling	X	X	X	X	X			X
Paramagnetic Cell - Hummel	X		X	X	X	X	X	X
Mass Spectrometer		X	X	X	X	X		
O <sub>2</sub> Luminescence Quenching	X	X	X	X	X	X	X	X

The luminescence quenching  $pO_2$  sensor is comprised entirely of solid-state components. The lumiphore is immobilized on a temperature controlled polymer film which is encapsulated in a disposable cuvette placed in the patient circuit. The lumiphore used is non-toxic to the patient and provides clinically acceptable operational and shelf life. A non-disposable light emitter/detector module snaps onto the cuvette and provides for photoexcitation and phosphorescent lifetime detection. The detector is optically filtered to reduce external lighting effects on sensor performance. The light emitter/detector also contains a proportional-integral-derivative (PID) controlled temperature control circuit to provide for thermostating of the cuvette's lumiphore/polymer assembly thus reducing temperature induced measurement inaccuracies resulting from the temperature sensitive nature of oxygen diffusivity. The sensor is lightweight and rugged and may combined with other mainstream respiratory gas analysis devices such as infrared based capnography systems. Finally, the sensor provides for response times adequate to allow for breath-to-breath analysis of respiration. Table 1. outlines the advantages of this sensor over previously described  $pO_2$  technologies.

## Oxigraphy

The use of oxygen sensors for graphical display of breath-to-breath respiratory traces is known as oxigraphy. Oxigraphy may have important clinical benefits. Oxigraphy allows for detection of interruption of respiration (apnea) well before such events are detectable by blood oximetry. Oxigraphy may prove helpful in tracking the preoxygenation of patients prior to cessation of ventilation for the induction of anesthesia<sup>17,18</sup>. Oxigraphy may provide an indicator of cardiac output during cardiopulmonary resuscitation. Mainstream oxigraphy may be helpful in identifying patient circuit leaks during mechanical ventilation which could result in lower than intended  $F_{I}O_2$  levels delivered to the patient. Finally, oxigraphy is an important component of indirect calorimetry systems.

## Indirect Calorimetry

Indirect calorimetry is a technique for measuring patient energy expenditure. This technique determines the quantity of oxygen being consumed ( $VO_2$ ) and the quantity of carbon dioxide being produced ( $VCO_2$ ) by patient metabolic processes. Using these values, the respiratory quotient ( $RQ = VCO_2/VO_2$ ) which is an important indicator of a patient's metabolic state may be obtained and used to alter the patient's nutritional support regimen. The respiratory quotient can easily be converted to an estimation of daily energy expenditure (EE) in kcal/day using a number of formulas including the Weir formula:

$$EE = 1.44 * (3.796 * VO_2 + 1.214 * VCO_2) \quad (10)$$

These indices are good measures of the nutritional state of critically ill patients. Malnutrition is associated with a poor outcome<sup>19,20,21</sup> and thus, indirect calorimetry is an important preventative clinical tool.

The potential integration of the oxygen quenching oxigraphy technology into an existing mainstream capnography/spirometry system such as the Novamatrix Cosmo+, may provide for real-time main-stream indirect calorimetry which would be a valuable tool in the ICU.

## Space Oxigraphy Applications

A lightweight metabolic monitor could be constructed using an IR capnography/spirometry

system. This may be of value in providing a small and lightweight means of monitoring/trending exercise physiology of astronauts during space missions.

#### Acknowledgements

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