



Objective Measures for the Assessment of Energy Expenditure: A Historical Overview

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Authors' contributions

This work was carried out in collaboration between all authors. Author MA designed the methodological approach and wrote the first draft of the manuscript. Authors MA, KZ, KK and MK managed the literature searches and contributed in drafting the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Accurate measurement of energy expenditure and estimate physical activity is extremely important in terms of health outcome and effectiveness of intervention programs. However, total energy expenditure, apart from physical activity, includes basal energy expenditure and food thermogenesis. Energy expenditure can be determined objectively by criterion methods, using direct and indirect calorimetry and doubly labeled water (DLW). Indirect calorimetry is frequently applied in laboratory settings, while DLW is the reference for energy expenditure under free-living conditions. These techniques have been used in both clinical and research settings. This review includes a historical overview of these techniques, with more emphasis on the indirect calorimetry and DLW, with particular reference to their validity. These criterion methods are the most valid and reliable measurements against which all other energy expenditure assessments methods should be validated. However, they have important limitations, which are addressed in the present review. The preferred method to determine energy expenditure is likely to depend principally on the number of study participants to be monitored, the time of measurements and the finances

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available. New technologies have evolved, such as accelerometry, and additional studies are needed to examine the accuracy of these methods and the possibility of improving the accuracy of measurement by combining two methods or more.

Keywords: Physical assessment; methodologies; human energy expenditure; objective measurement techniques; criterion measures; doubly labeled water; calorimetry; energy intake.

1. INTRODUCTION

Energetics, the consumption and utilization of energy by living organisms, is a unifying aspect of biology. For every organism, regardless of how complex this might be, energy expenditure is an inevitable occurrence since it is an unavoidable consequence of existence. Total energy expenditure is the energy required by the organism daily and it is determined by the sum of three main components: Basal energy expenditure, food thermogenesis and muscular activity [1]. Managing rates of energy expenditure is often fundamental to every organism's fitness [2]. Monitoring energy expenditure is important for surveillance and for assessing the effectiveness of interventions or public health initiatives aimed at increasing physical activity levels.

Clearly, some techniques for measuring and estimating energy expenditure are more popular than others, while others are quickly developing. Presently the two most widely used techniques often described as 'golden standards', are respirometry, otherwise known as indirect calorimetry, and doubly labeled water method (DLW). Direct calorimetry, a technique very similar to respirometry, is the only direct method of measuring energy expenditure as it measures metabolic heat production. However, its application is less common despite its high accuracy and is considered an almost lost art [3]. The aim of this study was to address the historical evolution of energy expenditure assessment in humans. Special emphasis will be given to these three research techniques, direct and indirect calorimetry and DLW, which are considered the criterion measures for assessing the energy expenditure validity of newly developed activity motion trackers and wearable physical activity monitors.

2. METHODOLOGY

This review was performed using a variety of medical and scientific databases including Medline, PubMed, Scielo, Scopus and *Lilacs* to identify relevant articles focused on objective

energy expenditure measurement methods in humans. The following key words, in English, were used: Energy expenditure, criterion (and golden standard) energy expenditure assessment, bioelectrical impedance, direct calorimetry, indirect calorimetry, doubly labeled water, circulatory indirect calorimetry, physical activity energy expenditure, food and exercise thermogenesis. Other sources were identified by journal article citations. Relevant articles and books were selected after an abstract or chapter pre-reading and independently of their publication year, since we were interested in articles that described original methodologies for measuring energy expenditure, and we specially focused on the historical overview of these methods.

3. HISTORICAL PERSPECTIVE

Every metabolic process occurring in all living organisms results in the production of heat [4]. Approximately 40% of the total energy realized during the glucose and fat metabolism is used for ATP production, while the remaining 60% is converted into heat [5]. Therefore, the calculation of heat produced provides a measure of energy metabolism. The primary heat unit, and thus energy unit, is the kilocalorie (kcal) and is defined as the amount of energy needed to raise the temperature of one kilogram of water by one degree Celsius at a pressure of one atmosphere. In the International System of Units it is used the kilojoule (kJ) and 1 kcal equals to 4176 kJ [5,6].

A very interesting timeline of the inventions used for energy expenditure calculation is presented by Halsey [7]. The scientific study of animal respiration was first recorded in the 1600s. Probably the first device to measure energy expenditure, called respirometer or calorimeter, was constructed either by John Mayrow in 1668 [8], or by Joseph Black in 1761 [9]. During that time, the French chemist Antoine Lavoisier (1743-1794) was the first to observe that living organisms could produce heat. In 1777 he invented a calorimeter and measured for the first time the energy metabolism in animals [4,6,9,10]. From 1782 to 1784, Lavoisier collaborated with

the mathematician Laplace in order to measure heat production with the use of a modified Black device [9]. By placing the test animal in the calorimeter, which was a sealed chamber containing ice, and measuring the weight of water derived from the melted ice, they could calculate the calorific energy produced by the animal based on the fact that 80 kcal of energy are required for melting 1000 gr ice.

The following years, Lavoisier and his colleagues measured oxygen and carbon dioxide consumption in humans through a device called spirometer [9]. This device was a cylindrical vessel with an inverted bottom and open nozzle, which was deposited over a mercury layer. By placing the testing animal in the spirometer they observed that it consumed an element, namely oxygen, and produced another, carbon dioxide, in equal amounts. Lavoisier was the first to name the generated element 'oxygen', even though Joseph Priestly had already discovered it [9]. Lavoisier made several important discoveries about oxygen consumption and energy production; such as larger people consume more oxygen than smaller ones and oxygen consumption is elevated after a meal. Also Lavoisier established the methodology of indirect calorimetry that remained the benchmark for quantifying animal and human energy expenditure to this day [10].

4. DIRECT CALORIMETRY

Modern era has been evolved on these precursor discoveries and opened the way for direct calorimetry and the production of calorimetric spirometers, which measure generated heat, oxygen consumption and carbon dioxide production. According to a historical approach, two chemists, namely Atwater (1844-1907) and Benedict (1870-1957), and the physicist Rosa (1861-1921), used the first human calorimeter in the late 1890s [11,12]. This device functioned according to the law of energy conservation, confirming the relation between direct and indirect calorimetry [13]. They also established the indirect calorimetry method, which is widely used nowadays for the estimation of energy expenditure in humans [4,9]. A second historical approach indicates Zuntz and Hagemann as the first individuals in the late 19th century to describe and created the first human calorimeter [5].

The calorimeter used by humans (Atwater-Rosa calorimeter) consisted of an airtight chamber filled with oxygen, in which an individual could

live and work for an extended period of time. Each Atwater and Rosa's experiment lasted from several hours up to 13 days and needed at least 16 assistants. Through a series of coils located at the top of the chamber, a previously known volume of water with a specified temperature circulated. The entire chamber was well insulated, the generated and radiated heat from the individual was absorbed by the water in circulation. The water temperature change, for a given amount of time, was directly proportional to the energetic metabolism of the observed individual. The caloric loss was estimated from the weight of the water vapor absorbed by the system and the calculation was based on the caloric equivalent, which was 586 kcal per kg. In order to provide sufficient ventilation, the exhaled air was constantly absorbed inside the chamber and passed by chemical substances that removed humidity and restrained carbon dioxide, and in the same time oxygen was added in the chamber [4,6,9,14].

Over 110 years passed from the first application of direct calorimetry and presently other methods have been developed to count energy expenditure, such as airflow, water flow, gradient layer and storage calorimeters. While the direct measurement of body heat production has important theoretical applications, its practical usefulness is very limited [6]. Accurate measurement requires much time, is very expensive, adequately qualified staff is needed and may provide inaccurate results during intense muscular work and exercise [6]. Today this method has mainly historical interest in the development of Exercise Physiology, however we should not underestimate its significant contribution to the establishment of indirect calorimetry.

5. INDIRECT CALORIMETRY

In the last few decades the human body energy expenditure has been estimated by the indirect calorimetry method [15,16]. This method is based on the triadic relationship between consumed oxygen, produced carbon dioxide and energy released during the combustion of caloric substances in the mitochondria. During the combustion of 1 gr of carbohydrate, 828 ml of oxygen are consumed and an equal amount of carbon dioxide is produced, as well as 4.2 kcal of energy [5,14]. It is therefore possible to estimate indirectly energy expenditure by measuring only oxygen uptake [1,5,7,14,17]. Under controlled laboratory conditions, indirect calorimetry may be

used to distinguish between the three different components of energy expenditure, namely basal metabolic rate, thermogenic foods and muscular activity thermogenesis [18]. Of these, the energy consumed during muscular activity is considered the most volatile and depends on gender, body size, type and intensity of physical activity [19]. It may range from 15% to 30% of total daily energy expenditure, while in overly physically active people this may reach 50% [14].

The oxygen uptake can be readily converted to a value that corresponds to the energy expenditure. Approximately 4.82 kcal of energy are released when 1 lt of oxygen is consumed by combustion of carbohydrates, lipids and proteins. The ratio of 4.82 kcal per lt of oxygen has a minimal fluctuation of 2% to 4% and these minimal fluctuations depend mainly on the food mixture that is oxidized. For practical convenience, during the conversion of consumed oxygen into energy expenditure the conversion coefficient of 5 kcal per lt of oxygen is used [6,14,16].

The oxygen uptake is estimated by two different methods, the close and open circuit spirometry. During the close circuit process the individual breathes 100% oxygen from a spirometer filled beforehand with pure oxygen. The individual breathes only through this device, without the atmospheric air been able to enter the circuit. This method is used only in hospitals and research laboratories, however it is not considered suitable for measuring energy expenditure during exercise [4,14].

During physical activity the open circuit spirometry is used, in which oxygen consumption is calculated by measuring the volume and the exhaled air composition of oxygen and carbon dioxide [1]. The individual inhales the environmental air which has a constant composition of 20.9% oxygen, 0.03% carbon dioxide 79.04% nitrogen and some inert residues [6,14]. The difference between the rates of oxygen and carbon dioxide in the exhaled air, compared with the same components of the inhaled air, indirectly reflects the ongoing energy metabolism process [14]. Presently three techniques of open circuit spirometry are the most common: a. Douglas bag, b. portable spirometer, c. automatic gas analyzer [14,15,20].

Regardless of the complexity of these systems, data estimated reflect the accuracy of each method and measuring device. Therefore, the

validity and reliability of the devices require careful and frequent adjustments, with the use of standardized reference data [14]. In the past, all calibrations of oxygen and carbon dioxide levels were made by Scholander and Haldane chemical analysers [6,14]. For a detailed presentation of the Haldane conversion one may follow the Kenney, Wilmore and Costill's [5] report. In order to implement these methods during an experiment, hundreds time-consuming analyses were required, limiting the number of participants in one or two people for each experiment [10,20]. Now computer analysers perform the calibration of these devices [6,14].

Over the last 40 years a significant number of automatic systems have been developed, with over 12 commercial manufacturers having produced more than 20 spirometers-calorimeters [15]. Nowadays there are laboratory based spirometers, which are too bulky and not suitable for outdoor testing, as well as portable metabolic analysers, for measurement of oxygen consumption under free-living conditions. However, both types of spirometers are extremely expensive, with prices reaching well above \$20000 [20].

5.1 Portable Metabolic Analyzer Cosmed K4b2

The portable metabolic analyzer and the doubly labeled water method (DLW) of hydrogen and oxygen radioisotopes are used in modern studies as the 'golden standards' of objectively measured energy expenditure and all other methods are compared against these [1,7,17,21]. In the present section of our report, the portable metabolic calorimeter Cosmed K4b2 (Rome, Italy), which is the most commonly analyzer used in many free-living studies, will be presented.

Cosmed K4b2 is used in numerous studies as the reference device to which other methods and devices are compared and evaluated. This is a telemetric, lightweight (600 gr) and portable spirometry system. It has a specially constructed breath mask (Hans Rudolf, Kansas City, MO) which contains a. a turbine meter for measuring of pulmonary ventilation and b. a capillary tube for sampling of the exhaled air. The air subsequently is analyzed into oxygen and carbon dioxide with the use of specific polarographic electrodes. The device carries a radio transmitter that communicates with the installed computer software within a range of 1000 m.

Cosmed K4b2 was the first portable device manufactured by Cosmed Company in order to measure the respiratory gases breath-by-breath. K4b2 technology allows the measuring and processing of physiological parameters, such as maximum rate of oxygen consumption and energy expenditure, during short-term and high intensity outdoor physical activities, as well as recording and storing of these parameters for one to five hours [10]. K4b2 counts extremely accurately up to 30 physiological parameters, including oxygen uptake, carbon dioxide consumption, heart rate, pulmonary ventilation etc [10,22].

The main unit of this device can store breath-by-breath data in the available high capacity memory card and up to 16000 breaths. After completion of the data recording, these can be transferred to a computer for analysis and presentation. By using the telemetry system, K4b2 breath-by-breath data can be transferred to the computer from distance, enabling real-time monitoring of previously mentioned physiological parameters during outdoor exercise. Furthermore, K4b2 can be used as a conventional stable metabolic analyzer, upon connecting it directly to the computer via usb to PC cable. The evaluation and calibration can be executed either via computer or through the built-in device keyboard. Before testing, the device has to be calibrated according to a. room air, b. reference gas, c. delay, and d. turbine calibration methods [22].

An extensive list of over 23 pages of all researches carried out with Cosmed K4b2 from 1996 to 2015 can be retrieved from the manufacturer's website [23]. It has been used in many studies over the last 20 years and is considered a highly valid and accurate method for energy expenditure estimation. The first empirical attempt to validate K4b2 was back in 1997 [24]. This research showed that K4b2 provided accurate measurements of oxygen uptake at many different activity levels, from resting to high intensity activities. Similar results yield the following two research attempts [25,26], who compared K4b2 with the Douglas airbag method. In both studies the results of oxygen consumed, carbon dioxide elimination and respiratory quotient ($RQ = \text{CO}_2 \text{ eliminated} / \text{O}_2 \text{ consumed}$) ranged within acceptable limits of agreement, even though it was made obvious that the device slightly overestimates oxygen uptake during specific exercise intensities. Small deviations in metabolic parameters during low

and moderate intensity activities were observed in a subsequent study, however they were also within acceptable limits of agreement [27]. Finally, Shrack, Simonsick and Ferrucci [28] compared K4b2 with the stationary, traditional metabolic analyzer Medgraphics D-Series and concluded that both devices provided comparable energy expenditure estimates in stable, submaximal exercise intensities.

Although it is widely used in studies with children and adolescents, only one published research regarding its validity on these populations exists [29]. The sample consisted of 14 children, aged eight to 14 years, and the data produced by K4b2 were compared against the standard laboratory metabolic analyzer Parvo Medics Truemax 2400 during rest, walking ($4.0 \text{ km} \cdot \text{h}^{-1}$) and running ($8.0 \text{ km} \cdot \text{h}^{-1}$). A small positive bias of $5.1 \text{ mL} \cdot \text{min}^{-1}$ at rest, $32.7 \text{ mL} \cdot \text{min}^{-1}$ while walking, and $43 \cdot 9 \text{ mL} \cdot \text{min}^{-1}$ when running was observed, while the overall measurement error between the two oxygen uptake methods did not exceed 6% ($p > 0.05$).

5.2 Doubly Labeled Water (DLW) Method

Presently the most acceptable and reliable method for energy expenditure estimation over a long period of time in free-living conditions, which can range from three days up to four weeks, is the DLW technique which is an isotope-based method that measures the energy expenditure of unencumbered subjects from the divergence in enrichments of two isotopic labels in body water, ^2H and ^{18}O [1,4,5,21,30,31,32]. The minimum use of three days is suggested when energy expenditure from very physically active individuals is recorded, while four weeks are recommended for elderly people who lead a mostly sedenteray life [19].

The term 'isotope' was initially introduced by Soddy in 1913 and refers to variants of a particular chemical element, which differ in neutron number and have different atomic weights [9]. The term isotope is formed by the Greek roots isos ('equal') and topos ('place'), meaning 'the same place'. DLW technique was invented by Lifson, Gordon and McClintock [33] and implemented in a 12 mice experiment. The researchers observed that the exhaled carbon dioxide was in complete isotopic equilibrium with the oxygen included in body water. Therefore, each isotope detector of oxygen inserted into the body water would be eliminated not only by the continuous water flow within the body, but also

by the continuous oxygen consumption and carbon dioxide production [34]. Basically this method depends on the details of carbon metabolism in living organisms' bodies and the first study in humans was published 30 years ago [35]. This delay for some 30 years between animal and human experiments with DLW occurred because improvements in analytical instrumentation were necessary in order to make such investigations feasible.

DLW may be administered by injection or orally, which is the usual route in humans. Participants taking part in similar experimental procedures are given a previously specified quantity of radioactive isotopes ^2H and ^{18}O dissolved in water, which in a few hours are distributed and equilibrated with the water already present in the human body. The time required for the whole process is about five hours. The heavy, radioactive hydrogen is gradually eliminated from the body in form of water, perspiration and water vapor breathing, while the premarked oxygen is lost as both water and carbon dioxide. After correction for isotopic fractionation, the excess disappearance rate of ^{18}O relative to ^2H is a measure of the carbon dioxide production rate and is calculated with a high accuracy mass spectrometer [31,36]. This rate can be converted to an estimate of total energy expenditure by using a known or estimated respiratory quotient and the classical principle of indirect calorimetry [4,37]. The administration and the calculation of radioisotopes are described in detail in Montoye, Kemper, Saris and Washburn's book [9].

The validity of this method has been extensively described by Schoeller and Hnilicka [37] and although there is some debate over the precise calculation protocols that should be used, the differences between alternative calculations result in minor effects on total energy expenditure estimates of about 6% [32]. The DLW technique has a validity range between 2% and 10% in adults [16,19] and within subject variation 7.8% [37]. It can be used in vulnerable groups such as children, pregnant women, nursing mothers, patients and overweight individuals. Furthermore, it is considered the most valid method of energy expenditure under free-living conditions (three to 14 days), because it is not affected by individuals' daily activity patterns, and is used as the criterion measurement for comparison with other energy expenditure methods [1,16,18,21]. Its use in humans is completely safe, as the water is labeled with stable isotopes, ^{18}O and ^2H in low

abundances. Both ^{18}O and ^2H are naturally occurring isotopes, which are present in the body prior to the administration of DLW. Their natural abundance is 2000 ppm of ^{18}O and 150 ppm of ^2H , respectively [19].

Nevertheless, DLW technique is not without limitations and disadvantages. According to Buchowski [30], the limitations are that it uses several assumptions such as a constant rate of carbon dioxide production and constant size of body water pool throughout the measurement period. In addition, not all researchers use the same methods to calculate the isotope pool spaces, the constant elimination rate, the fractionation factors, and the mode of carbon dioxide conversion to energy expenditure.

A main disadvantage is that it can only estimate total energy expenditure and not activity energy expenditure and does not provide information about the intensity, the frequency and the duration of physical activity [38]. In addition, it does not estimate energy expenditure for shorter periods (e.g. for a few hours) and cannot distinguish the three categories of energy expenditure, namely basal metabolic rate, food thermogenesis and muscular activity thermogenesis [10]. Furthermore, the radioisotopes' production and analysis is very expensive, with a cost of \$1500 per participant that makes it an inappropriate method for large population studies. It also requires extremely sophisticated equipment, highly skilled, well trained personnel, and is in general a very complex procedure [1,20].

6. CONCLUDING REMARKS

Objective estimation techniques, with emphasis on their historical development, have been the primary focus of this review. With so many approaches available, the accurate assessment of energy expenditure can be very challenging. It is very important to understand that irrespective of the apparent sophistication of techniques, they all have inherent strengths and limitations. Their main weaknesses are that these methods are very expensive, require trained personnel and are limited to a small number of participants.

Nowadays, the trend in health care and energy expenditure estimation is clear. Newly, easy to wear activity monitors with motion sensors that provide users with real time data and objective information about the wearer's lifestyle, such as distance travelled and steps made, offer many

possibilities. These are mainly accelerometers, pedometers, heart rate monitors, GPS monitors and multisensor devices [20]. These devices are small, incorporate many sensors and tend to become more accurate over time. However, these consumer-based wearable devices, until these days, are not a valid alternative in energy expenditure estimation [39-41]. The main reason for the large errors computed in these validation studies is that they are inappropriate for the quantification of activities other than walking and running. For example, most wearable activity monitors are not able to quantify movement in swimming and cycling and their resting energy expenditure algorithms are still very inaccurate.

Probably the ideal scenario is the combination of various methods and approaches for measuring energy expenditure. This is perhaps most valuable when measuring individuals in the field over long periods, where different measurement methods may be more suitable in particular situations. More research is clearly needed to examine the possibility of improving the validity and reliability of measurements by combining two or more techniques. The accurate estimation of daily energy expenditure is crucial for determining current physical activity levels, understanding the dose-response relationship between energy consumption and health, developing and evaluating the effectiveness of physical activity intervention programs.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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