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Innovations in energy expenditure assessment

Najate Achamrah, Taku Oshima, and Laurence Genton

Purpose of review

Optimal nutritional therapy has been associated with better clinical outcomes and requires providing energy as closed as possible to measured energy expenditure. We reviewed the current innovations in energy expenditure assessment in humans, focusing on indirect calorimetry and other new alternative methods.

Recent findings

Although considered the reference method to measure energy expenditure, the use of indirect calorimetry is currently limited by the lack of an adequate device. However, recent technical developments may allow a broader use of indirect calorimetry for in-patients and out-patients. An ongoing international academic initiative to develop a new indirect calorimeter aimed to provide innovative and affordable technical solutions for many of the current limitations of indirect calorimetry. New alternative methods to indirect calorimetry, including CO₂ measurements in mechanically ventilated patients, isotopic approaches and accelerometry-based fitness equipments, show promises but have been either poorly studied and/or are not accurate compared to indirect calorimetry. Therefore, to date, energy expenditure measured by indirect calorimetry remains the gold standard to guide nutritional therapy.

Summary

Some new innovative methods are demonstrating promises in energy expenditure assessment, but still need to be validated. There is an ongoing need for easy-to-use, accurate and affordable indirect calorimeter for daily use in in-patients and out-patients.

Keywords

energy expenditure, indirect calorimetry, innovation, nutritional therapy

INTRODUCTION

Many methods are available for energy expenditure assessment in humans. Apart from costly and/or invasive methods used in specialized research centers (e.g. direct calorimetry and Fick method), indirect calorimetry is a noninvasive technique to measure energy expenditure in patients with various diseases and conditions, spontaneously breathing or mechanically ventilated. More than 100 years ago, basic technical principles started with the concept of gas exchange related to combustion and heat production. Indirect calorimeters measure their oxygen consumption (VO₂) and carbon dioxide production (VCO₂) and derive energy expenditure by the Weir's equation: energy expenditure (kcal/day) = $1.44 \times [3.94 \times \text{VO}_2(\text{ml/min}) + 1.11 \times \text{VCO}_2(\text{ml/min})]$. The ratio of VCO₂ to VO₂ (VCO₂/VO₂), called the respiratory quotient, is considered as an indicator of measurement adequacy (physiological between 0.67 and 1.3) and of substrates oxidation in stable state individuals [1].

However, there are currently many limitations to the routine use of indirect calorimeters in clinical

settings worldwide. First, there is clearly a lack of knowledge about the importance of feeding patients according to their needs for their clinical outcomes. Optimal nutritional therapy to avoid underfeeding or overfeeding has been recently associated with better clinical outcomes in ICU patients [2[•],3]. Second, the need of sufficient knowledge to interpret the indirect calorimetry results may also be a limiting factor. Indeed, clinical conditions deeply influence energy expenditure measurements. Third, the lack of an adequate device largely limits the use of indirect calorimetry. The Deltatrac Metabolic Monitor (Datex, Finland) produced 35 years ago is often viewed as the reference device [4]. However,

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KEY POINTS

- Indirect calorimetry remains the gold standard for energy expenditure assessment in humans despite many limitations.
- Method to calculate energy expenditure based on CO₂ measurements (EEVCO₂) has been proposed as an alternative to indirect calorimetry in mechanically ventilated patients but remains controversial.
- New technologies to measure ratio of stable carbon isotopes (¹³C/¹²C expressed as δ¹³CO₂) in exhaled breath are showing promise to objectively indicate type of metabolic fuel use.
- Wearable devices initially developed for fitness settings may be helpful for the monitoring of physical activity energy expenditure during clinical interventions and rehabilitation programmes.
- Predictive equations are often inaccurate and should not be considered as a reliable alternative method to indirect calorimetry.

this device went out of production and off the market 10 years ago. Furthermore, currently available calorimeters are usually costly and cumbersome, requiring warm-up and calibration before energy expenditure measurement (almost 30 min), a separate computer to export and analyze the results, and extensive disinfection of the device after measurements. Therefore, there is an ongoing need for easy-to-use, accurate and affordable indirect calorimeters for daily use in in-patients and out-patients. Meanwhile, new alternative methods to indirect calorimetry have been proposed.

We review here the current innovations in energy expenditure assessment in humans, focusing on indirect calorimetry and other new alternative methods as wearable devices.

METHODOLOGY OF INDIRECT CALORIMETRY: WHAT IS NEW?

Guidelines on how to perform indirect calorimetry measurements in healthy and noncritically ill adults were recently updated, but there are still some issues that need to be clarified [1]. During resting energy expenditure (REE) measurement using indirect calorimetry, gas exchanges are commonly recorded during 30 min, from which the first 5 min of recorded data is discarded. The steady state (STS) period, defined as a period in which gas exchange variables (VO₂ and VCO₂) present low variation (usually < 10%), increases the validity of the measurements [5]. However, as STS is not always achieved, other methods for data analysis have been

proposed, such as predefined time interval selection [5]. Sanchez-Delgado *et al.* [6] recently showed that REE is consistently lower when following STS approach than when following time interval methods in healthy young adults. This suggests that achieving STS could provide a more valid REE measurement, given that REE is considered the lowest energy expenditure in an awake person [5]. However, further studies are needed to assess the best method for analyzing indirect calorimetry measurements if STS is not achieved. According to Sanchez Delgado *et al.* [6], the selection of the five most stable minutes should be the method of choice for analyzing indirect calorimetry measures in healthy young adults. Indeed, although no significant differences were found between different durations of STS (3, 4, 5 and 10 min), 5 min STS presented the lowest REE [6]. Borges *et al.* [7] reported that the first 5-min interval should be discarded because of high variations of REE during a standard 30-min indirect calorimetry measurement, according to their evaluation on healthy young adults. However, no significant difference was found between the second 5-min interval and the REE averaged over the last 20 min. Finally, the recent guidelines suggested that once STS is achieved, measurements of only 4 min need to be averaged to determine the energy expenditure [1]. However, this finding should be confirmed according to the technology of indirect calorimeters used, that is 'breath-by-breath' or mixing chamber, as explained in the next section.

MODERN INDIRECT CALORIMETERS

Recent indirect calorimeters have used the 'breath-by-breath' technology for measuring gas exchanges: O₂ and CO₂ concentrations measured continuously by gas analyzers are synchronized with expiratory flow measurements by the in-line flow meter to allow for gas exchange calculations for every breath. Although this method allows rapid measurements and conception of small devices, it is prone to errors because of the response time of the gas analyzers and software [8]. Calorimeters using a mixing chamber generate more stable measurements because the expiratory gas is physically 'averaged' before being analyzed (Fig. 1). However, limitations of this technology include the volume of the mixing chambers (3–5 l) which makes difficult the conception of small devices and the need for stabilization of gas concentrations in the mixing chamber, which limits the validity of short duration measurements (e.g. 3–5 min).

Nevertheless, an ongoing international academic initiative supported by two major academic organizations (The European Society for Clinical Nutrition and Metabolism and The European

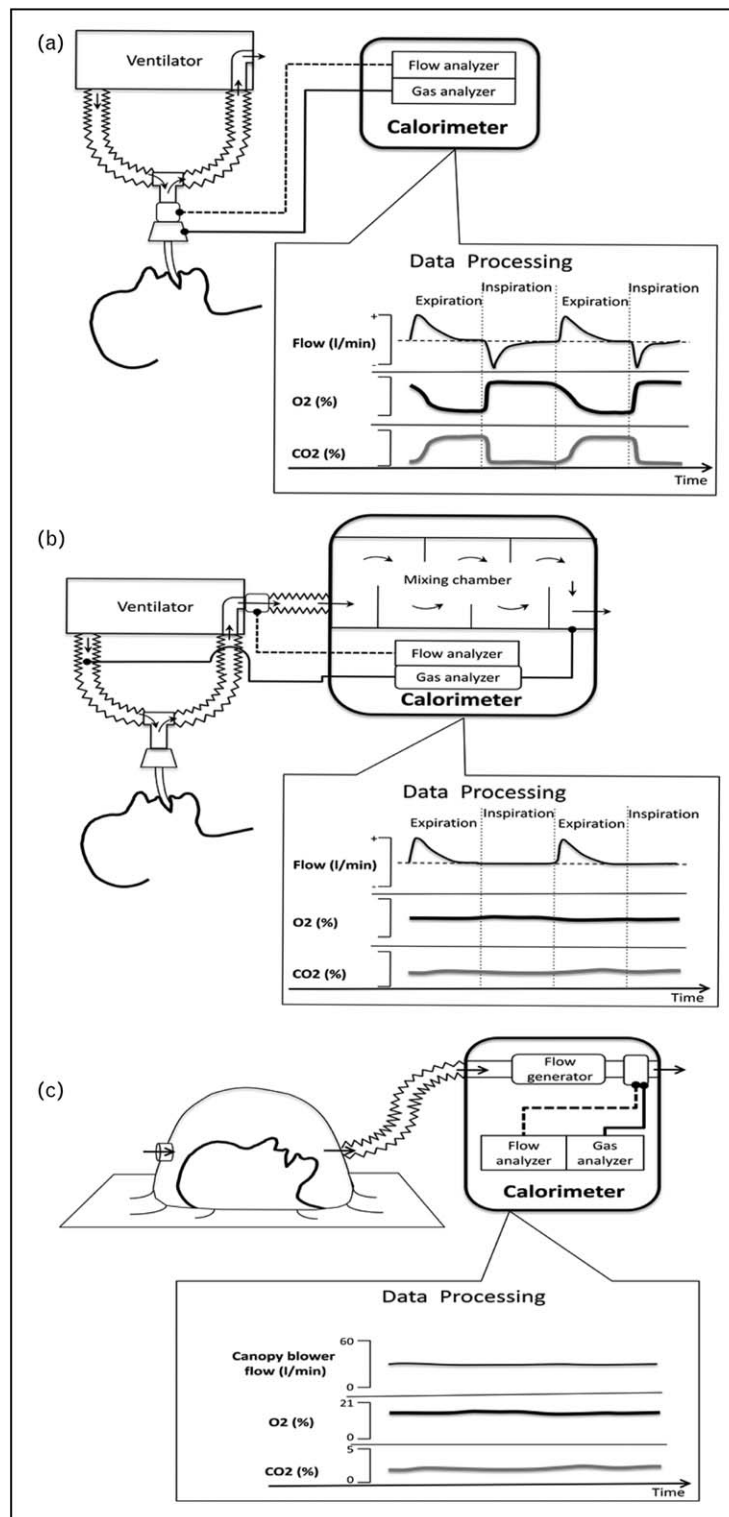


FIGURE 1. Indirect calorimeter technologies. (a) Breath-by-breath system in a mechanically ventilated patient. (b) Mixing chamber system in a mechanically ventilated patient. (c) Canopy system in a spontaneously breathing individual.

Society for Intensive Care Medicine) aimed to develop a new accurate, easy-to-use and affordable indirect calorimeter (Q-NRG, COSMED) [8]. The overall performance of this calorimeter consists of

a newly developed dynamic micromixing chamber (2 ml) which reduces time stabilization of gas concentrations and VO₂, VCO₂ variability. The Q-NRG has been validated *in-vitro* against the gold standard

technology for gas composition measurements, that is mass spectrometer (MAX300-LG, Extrel, Pittsburgh, USA) [9]. The accuracy and practical characteristics of this new calorimeter are being evaluated in a multicenter study which started in 2017.

PORTABLE INDIRECT CALORIMETRY

Over the last 110 years, the portable gas analysis systems have experienced many significant advances for the estimation of energy expenditure [10[¶]]. Latest Cosmed's K5 IntelliMET module (174 × 64 × 114 mm, 4 h battery, ≈ 900 gm) (Cosmed, Roma, Italy) permits sampling via breath-by-breath or dynamic mixing chamber technologies. Measured VO₂ and VCO₂ values by the Cosmed's K5 IntelliMET module have been compared to a metabolic simulator (VACUMED) by the company in a first validation study. The metabolic simulator produces an exact, simulated VO₂ and VCO₂ to verify the accuracy of a metabolic measurement system. This study reported a low relative percentage of difference for VO₂ (1.6%) and VCO₂ (2.2%) [11]. In the same way, recently, Cortex has incrementally updated their MetaMax 3B (Cortex, Leipzig, Germany) to include dynamic flow sampling breath-by-breath that ensures a more constant control of sample line flow even with changes in resistances of air flow. However, no data appear available yet on its updated validity or reliability. Furthermore, the National Aeronautics and Space Administration Glenn Research Center (NASA GRC) developed a very innovative, patent-pending, system for the ISS. The Portable Unit for Metabolic Analysis (PUMA) could rapidly monitor VO₂ and VCO₂ over prolonged periods in flight crew and astronauts without being tethered to a base unit [12]. Inspired and expired flow is measured by a modified commercial ultrasonic sensor and sampled

very close to the mouth at 10 Hz, and then analyzed by very rapidly responding sensors. Although commercialization of the NASA PUMA system for the fitness market has been announced recently, no date has been provided and no validity or reliability data have been published.

NEW ALTERNATIVE METHODS TO INDIRECT CALORIMETRY

CO₂ based calorimetry in ICU patients

Methods to calculate energy expenditure based on CO₂ measurements (EEVCO₂) have been proposed as a surrogate to indirect calorimetry in mechanically ventilated ICU patients. Table 1 [13–15,16[¶]] shows the studies which compared REE derived from EEVCO₂ vs. indirect calorimetry (Table 1). The 10% accuracy rate was achieved in only 44–89% of the patients, which is not enough for clinical practice. This method measures only the VCO₂ derived from measurements of exhaled gas volume in each breath. The approach assumes that the respiratory quotient value is fixed (e.g. 0.85) in order to derive the unknown oxygen consumption (VO₂) needed to calculate energy expenditure according to the Weir formula. However, Oshima *et al.* [16[¶]] reported that EEVCO₂ was not sufficiently accurate to consider the results as an alternative to measured energy expenditure by indirect calorimetry, as the variability of respiratory quotient is likely to influence the accuracy of the results. Finally, whether EEVCO₂ could be an appropriate alternative method to indirect calorimetry in ICU patients remains still controversial. Recently, Stapel *et al.* [17] consider EEVCO₂ useful to assess energy expenditure continuously [13], whereas De Waele *et al.* [18] argue that the most accurate and precise estimation of energy expenditure in ICU patient can only derived from

Table 1. CO₂ measurement in mechanically ventilated ICU patients (EEVCO₂) compared to measured energy expenditure by indirect calorimetry

	Patients	IC devices	10% accuracy rate vs. IC ^a
Stapel <i>et al.</i> [13]	n = 84 adults (58 men and 26 women), APACHE II = 24 ± 8	Deltatrac (mixing chamber)	EEVCO ₂ : 61%
Rousing <i>et al.</i> [14]	n = 18 adults (13 men and 5 women), APACHE II = 16 ± 7	Compact Airway module, E-CAiOVX (breath-by-breath)	EEVCO ₂ : 89%
Kerklaan <i>et al.</i> [15]	n = 41 children (23 boys and 18 girls), PRISM = 10 (5–16)	Deltatrac (mixing chamber)	EEVCO ₂ : 44% in overall patients EEVCO ₂ : 70% in patients ≤ 15 kg
Oshima <i>et al.</i> [16 [¶]]	n = 278 adults (191 men and 87 women), APACHE II = 24 ± 7	Deltatrac (mixing chamber)	EEVCO ₂ : 77%

APACHE II, acute physiology and chronic health evaluation, scored from 0 to 71; PRISM, Pediatric Risk of Mortality Score, from 0 to 76.

^a10% accuracy rates defined as the proportion of calculated EEVCO₂ values within the clinically relevant limits, that is +/– 10% of the measured energy expenditure.

EE, energy expenditure; IC, indirect calorimetry; PE, predictive equation.

sampling of inspired and expired O₂/CO₂ concentrations and measuring expired gas flow.

Isotopic techniques

The doubly labeled water is the method of choice for measuring total energy expenditure (TEE) in free-living individuals [19]. This approach is based on the principle that the different elimination rates of nonradioactive isotopic labels of hydrogen (deuterium ²H) and oxygen (¹⁸O) provide a measurement of CO₂ production. Briefly, after a bolus dose of water labeled with both isotopes, the ²H is lost as water (mainly in urine) and the ¹⁸O as both water and exhaled CO₂. This excess elimination of ¹⁸O relative to ²H reflects the CO₂ production rate. This rate can be converted to an estimate of TEE by assuming a given respiratory quotient. However, this method is limited by several assumptions such as steady-state CO₂ and constant body water pool size during the measurement period, as well as the costs of the isotopic labels, and the challenges related to sample collection, preparation and analysis using isotope ratio mass spectrometry. The delay to obtain the results limits the routine use of the DLW method, but allows long period measurements of TEE.

Doubly labeled water can be combined with other isotopic techniques. Half a century ago, researchers demonstrated that the ratio of stable carbon isotopes (¹³C/¹²C expressed as δ¹³CO₂) in exhaled breath of humans could reveal the oxidation of labeled substrates *in vivo* [20]. Multiple methods have been developed to measure this ratio including isotope ratio mass spectrometry, the gold standard and most widely used. Recently, Butz *et al.* [21] developed a noninvasive δ¹³CO₂-breath test which derives concentrations of ¹³CO₂ and ¹²CO₂ in the expired breath using a novel mid-infrared dual beam technique. The authors suggested that this tool could noninvasively and rapidly monitor energy balance and allow a biofeedback during nutritional therapy. However, although δ¹³CO₂-breath test could guide and provide feedback on nutritional interventions, it was not validated against indirect calorimetry so far and further studies are needed to validate this method.

Energy expenditure assessment by fitness equipment

Devices wearable on the arm, wrist or waist are widely used in the fitness setting as they are user-friendly, relatively low-cost, noninvasive. They provide information on duration of the exercise, heart rate, speed, distance and altitude covered during a training session, and can also help maintain the

patient's motivation to pursue physical activity. They may be useful not only for athletes but also for patients with malnutrition, obesity and diabetes [22]. We will focus on wearable devices relying on accelerometry which measures the body accelerations along reference axes. Energy expenditure is derived from acceleration data and personal parameters (age, sex, height, weight, heart rate...) using companies' confidential algorithms. The energy expenditure derived from these devices generally overestimates or underestimates energy expenditure measured by indirect calorimetry by at least 10%, showing their inaccuracy to measure absolute values (Table 2) [23,24,25²⁶,26].

Sardinha and Jucice [27] reviewed the accuracy of different accelerometers to estimate physical activity energy expenditure and TEE against doubly labeled water. They found correlation coefficients ranging from 0.06 to 0.89, and from 0.23 to 0.88, for the estimation of activity energy expenditure and TEE, respectively, against doubly labeled water. The highest correlation compared with doubly labeled water was obtained with the Polar Activity Recorder and ActivPAL (*r*=0.8 and 0.7, respectively). Addition of weight, fat-free mass and heart rate to accelerometry data was reported to improve the estimations of physical activity and TEE [28]. A noninvasive and nonobtrusive (i.e. without a face mask) wearable device called the 'Device for Reliable Energy Expenditure Monitoring' (DREEM) [29³⁰] also combines measurements of heart rate, acceleration data and VO₂. The DREEM is worn around the waist during active exercises (treadmill or stationary bike), sedentary periods. In 42 healthy people, athletes and obese patients, instantaneous VO₂ measured by this device and an indirect calorimetry (Cosmed K4b²) showed a promising good correlation (*r*=0.93).

IS THERE A PLACE FOR PREDICTIVE EQUATIONS?

Many predictive equations providing estimated energy expenditure using anthropometric data (height, weight, fat mass, fat-free mass...) have been developed. However, the accuracy of equations is often low when applied to patients who differ from those for whom predictive equations have been initially developed.

Recently, several studies have assessed the validity of these equations in overweight and obese individuals compared with indirect calorimetry, showing a wide variation in the equations [30]. Bedogni *et al.* [31³²] reported that the accuracy of equations decreased with increasing values of BMI, whereas Orozco-Ruiz *et al.* [32] validated a new equation in adults with overweight and obesity (with a mean bias of 25 Kcal/day compared to

Table 2. Measured energy expenditure with wearable devices relying on accelerometry vs. indirect calorimetry

Authors	Study population	Accelerometer (wearable site)	IC	Protocol	Results
Bai <i>et al.</i> [23]	52 healthy adults (28 men and 24 women)	ActiGraph GT3X+ (waist) BMC Bodymedia (arm) Fitbit (wrist) JU24 Jawbone (wrist) Misfit Shine (wrist) Polar Loop (wrist) Nike+ Fuelband (wrist)	Oxycon Mobile, breath-by-breath	20 min sedentary activity 25 min running 25 min resistance exercise	Mean overestimation vs. IC: +30% Misfit Shine <+20% except for the other accelerometers
Roos <i>et al.</i> [24]	20 healthy adult runners (12 men and 8 women)	Suunto Ambit2 (wrist) Garmin Forerunner920XT (wrist) Polar V800 (wrist)	Moxus Modular Metabolic System, breath-by-breath	Running 4–11 km/h Running 14–17 km/h	Mean overestimation vs. IC: At 4–11 km/h: Suunto Ambit2 +38% Mean underestimation vs. indirect calorimetry At 4–11 km/h: Garmin Forerunner920XT: -25% Polar V800: -12% At 14–17 km/h: Suunto Ambit2: -32% Garmin Forerunner920XT: -49% Polar V800: -39.5%
Wahl <i>et al.</i> [25]	20 healthy and active sport students (10 men and 10 women)	Bodymedia Sensewear armband (arm) Beurer AS80 (wrist) Polar Loop (wrist) Garmin : Vivofit, Vivosmart, Vivoactive, Forerunners 920XT (wrist) Fitbit: Charge, Charge HR (wrist) Xaomi MiBand (wrist) Withings Pulse Ox (waist or wrist)	Metamax 3B, breath-by-breath	Walking/running 4.3, 7.2, 10.1 and 13.0 km/h Intermittent velocity Outdoor run 10.1 km/h	Mean absolute percentage error vs. IC: 4.3 km/h: -27 to +83% 7.2 km/h: -19 to +54% 10.1 km/h: -33 to +51% 13.0 km/h: -43 to +41% Intermittent velocity: -49 to +25.5% Outdoor run: -48 to +22%
Santos-Lozano <i>et al.</i> [26]	23 healthy adults (56.5% women)	Bodymedia SenseWear (arm)	Oxycon Pro, breath-by-breath	Walking 3 km/h Walking 5 km/h Running 7 km/h Running 9 km/h	AUC ^a : 3 km/h: 0.67 ($P<0.001$) 5 km/h: 0.57 ($P<0.05$) 7 km/h: 0.61 ($P<0.003$) 9 km/h: 0.5 (0.92)

AUC, area under the receiver operating characteristic (ROC) curve.

^aValues ≥ 0.90 are considered excellent, ≥ 0.80 – 0.90 are good, 0.8 – 0.70 are average and <0.70 are poor. Studies published between 2016 and 2017.

indirect calorimetry). A large variation in equations accuracy has been reported recently in 2588 obese patients (from 3 to 67% of accurate predictions), according to the use or not of body composition data, the method of body composition assessment (bioelectrical impedance analysis or dual-energy X-ray absorptiometry), the BMI class and the sex [33].

Furthermore, various equations based on body weight have been recently compared to indirect calorimetry (Deltatrac II) in ICU patients [34]. No equation had sufficient accuracy to be considered clinically acceptable when compared to indirect calorimetry, regardless of the body weight used (anamnesic body weight, measured body weight, adjusted body weight and ideal body weight for BMI at 22.5 and at 25 kg/m²). However, body weight had a significant impact on estimated energy expenditure and the use of measured body weight or ideal body weight (at 22.5 kg/m²) was associated with the best energy expenditure prediction.

In summary, predictive equations are inaccurate and should not be considered as an alternative method to indirect calorimetry.

CONCLUSION

Promising new and innovative energy expenditure assessment methods are CO₂-based calorimetry in mechanically ventilated patients, isotopic approaches ($\delta^{13}\text{CO}_2$ -breath test) and accelerometry-based wearable devices. However, further studies are needed to validate their accuracy in clinical practice. To date, indirect calorimetry measuring both VO₂ and VCO₂ to derive energy expenditure remains the reference method to target caloric needs of patients, but the complexity of its use, the length of the measurement and the costs still limit its use in clinical routine all over the world.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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