

<Original Article>

Assessment of energy expenditure: an association between heart rate and oxygen uptake in daily physical activity

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Summary Purpose: This study aimed to investigate the association between heart rate (HR) and oxygen uptake (VO_2) in daily physical activity and to assess the usefulness of estimated energy expenditure (EE) derived from actual HR and VO_2 .

Subjects and Methods: The subjects consisted of 40 healthy university students (males, $n = 20$; mean age of 21.5 ± 1.5 years). A portable gas analyzer (AT-1100, Anima, Co., Japan) measured HR and VO_2 while the students undergoing 20 different types of exercise. Estimated HR and VO_2 were calculated on a basis of age and the intensity of daily physical activity for the comparison between measured EE and estimated EE.

Results: Significant and positive correlations were found between measured EE and estimated EE ($y = 0.89x + 1.23$, $R^2 = 0.99$) as well as between HR and VO_2 ($y = 0.20 - 9.98$, $R^2 = 0.60$).

Conclusion: This study result demonstrated the association between oxygen transport and cardiac pump function, suggesting that the estimation formula might be practical as an indicator of EE adjusted for age and daily physical activity in Japanese.

Key words: VO_2 , METs, HR, %HRR, % VO_2R

1. Background

The importance of daily physical activity in health maintenance and prevention of chronic disease has been reported. An appropriate method to determine the intensity of physical daily activity is required for better understanding of the relation between daily physical activity and health, leading to health maintenance and its improvement. A simple and non-invasive method for measuring the intensity of daily physical activity has not been fully established yet^{1,2}; thus,

heart rate (HR) has been widely employed for objective assessments^{3,4,5,6}. HR has a strong correlation with energy expenditure (EE)⁷ and high reliability in electrocardiography⁸. HR is a low cost and non-invasive method for monitoring the intensity of daily physical activity. A commercially available HR monitor can record data for days or even weeks; average HR is used as a predictor of EE. In the moderate or more intensity of daily physical activity, the correlations between HR and oxygen uptake (VO_2) and between oxygen reserve (VO_2R) and estimated

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percent HR reserve (%HRR) have been reported^{9,10}. To date, only a handful of studies in this field have been conducted in Japanese.

2. Subjects

The present study aimed to evaluate the association between HR and VO₂ in daily physical activity and the usefulness of estimated EE derived from actual EE. Totally, 40 healthy students in Saitama Prefectural University who had no medical history limiting physical activities and those who were not extremely mean or obese were enrolled into this study. Of these, 20 students were male (mean age of 21.1 ± 0.7 years; mean height of 172.4 ± 5.8 cm; mean weight of 61.2 ± 7.1 kg) and the remaining 20 students were female (mean age of 21.3 ± 0.4 years; mean height of 156.5 ± 5.0 cm; mean weight of 48.7 ± 4.0 kg).

3. Methods

VO₂ was continuously measured according to a breath-by-breath method using a portable gas analyzer (AT-1100, Anima, Co., Japan)¹¹; carbon dioxide

emission and minute volume were also obtained. A WearLink Transmitter (Polar, Co.) monitored and measured HR and VO₂ during exercise. An ultrasonic flow meter measured volumetric flow as well (Figure 1).

The students underwent the following physical activities at or above 2 metabolic equivalent level (METs): 1) jump rope, 2) 4 km/h walking, 3) 6 km/h walking, 4) 10 km/h jogging, 5) 4 km/h walking while wearing 5 kg weights, 6) 4 km/h walking while wearing 10 kg weights, 7) ergometer, 8) futsal, 9) basketball, 10) volleyball, 11) badminton, 12) tennis, 13) table tennis, 14) playing catch, 15) basic boot camp training using DVD (Billy's boot camp), 16) aerobic dance, and resistance training using 17) Rotary Hip, 18) Leg magic, 19) Leg press, and 20) sit-ups.

1. HR and VO₂ assessment

VO₂ (mL/min/kg) and HR (beat/min) in sedentary were monitored for 10 minutes; then, the students underwent 5-minute exercise. VO₂ during the last 2 minutes of the exercise was averaged. In the present study, 1 MET was considered equivalent to the consumption of 3.5 mL/min/kg and derived from the resting consumption of a healthy, 40-year-old, 70 kg,

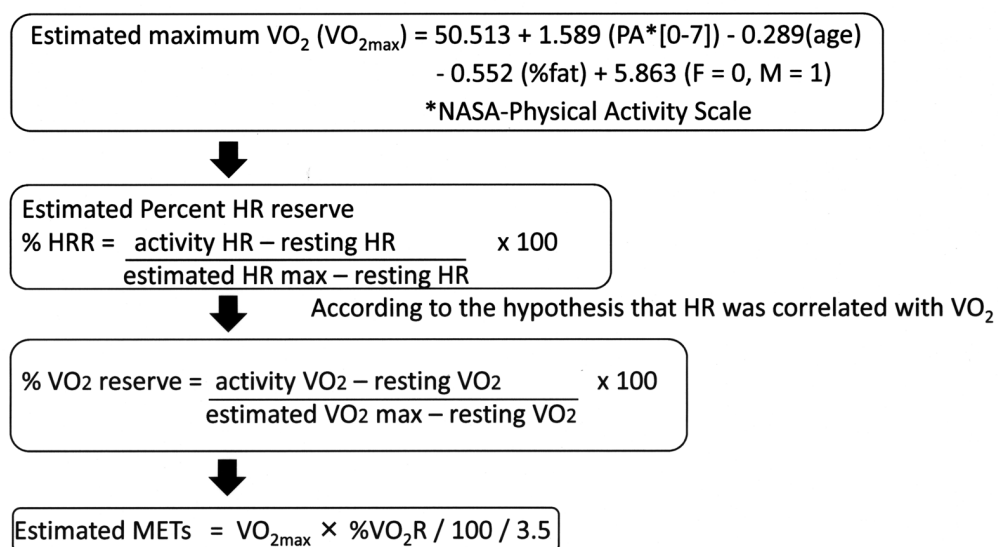


Fig. 1 Flow diagram demonstrating the calculation of estimated metabolic equivalent level based on heart rate and oxygen uptake.
HR, heart rate; %HRR, estimated percent heart rate reserve; %VO₂R, estimated present oxygen reserve; VO₂, oxygen uptake; METs, metabolic equivalent level.

and Caucasian subject. Data were expressed as mean \pm standard deviation. This study protocol was approved by the Ethic Committee of Saitama Prefectural University.

2. Measured EE and estimated EE

Each parameter was obtained according to the following estimation formula (Figure 1).

- 1) Estimated maximum HR (HR_{max}) = 220 - age
- 2) Estimated maximum VO_2 (VO_{2max}) = 50.513 + 1.589 (PA*[0-7]) - 0.289(age) - 0.552 (%fat) + 5.863 (F = 0, M = 1)

*NASA-Physical Activity Scale

$$3) \%HRR = \frac{HR \text{ during exercise} - HR \text{ at rest}}{HR_{max} - HR \text{ at rest}} \times 100$$

4) According to the hypothesis that HR was correlated with VO_2 ,

Estimated percentage VO_2 reserve

$$(\%VO_2R) = \frac{VO_2 \text{ during exercise} - VO_2 \text{ at rest}}{VO_{2max} - VO_2 \text{ at rest}} \times 100$$

- 5) Estimated EE = $VO_{2max} \times \%VO_2R/100/3.5$

4. Results

1. HR, VO_2 , and $\%VO_2R$ in daily physical activity (Table 1)

1) HR (bpm)

HR significantly differed in sit-ups (male, 105.9 \pm 11.4; female, 125.8 \pm 21.6, $p < 0.019$), badminton (male, 119.5 \pm 20.9; female, 135.9 \pm 19.1, $p < 0.013$), ergometer (male, 129.1 \pm 13.2; female, 144.8 \pm 14.1, $p < 0.019$), and 4 km/h walking while wearing 10 kg weights (male, 104.1 \pm 9.5; female, 114.6 \pm 8.5, $p < 0.013$) between the male and female students.

2) VO_2 (ml/min/kg)

VO_2 significantly differed in sit-ups (male, 13.0 \pm 2.5; female, 9.5 \pm 1.4, $p < 0.001$), aerobic dance (male, 12.9 \pm 1.8; female, 10.7 \pm 1.8, $p = 0.031$), futsal (male, 24.6 \pm 8.8; female, 18.7 \pm 7.5, $p = 0.029$), and basketball (male, 31.1 \pm 4.1; female, 25.8 \pm 3.7, $p = 0.007$) between the male and female students.

3) $\%VO_2R$

$\%VO_2R$ also significantly differed in Leg magic

(male, 23.6 \pm 8.9; female, 7.8 \pm 13.4, $p = 0.012$), sit-ups (male, 22.9 \pm 4.4; female, 17.1 \pm 5.1, $p = 0.015$), basic boot camp training using DVD (male, 46.3 \pm 14.5; female, 57.8 \pm 6.2, $p = 0.034$), jump rope (male, 57.6 \pm 5.2; female, 69.4 \pm 11.8, $p = 0.013$), badminton (male, 33.9 \pm 13.1; female, 45.9 \pm 16.5, $p = 0.015$), tennis (male, 55.9 \pm 10.9; female, 65.7 \pm 9.4, $p = 0.046$), table tennis (male, 29.3 \pm 9.9; female, 38.9 \pm 5.8, $p = 0.017$), playing catch (male, 23.5 \pm 7.9; female, 31.9 \pm 8.5, $p = 0.033$), ergometer (male, 31.2 \pm 3.6; female, 42.7 \pm 3.9, $p < 0.001$), 4 km/hr walking (male, 14.1 \pm 1.3; female, 19.7 \pm 3.3, $p < 0.001$), 6 km/h walking (male, 28.3 \pm 3.7; female, 40.7 \pm 5.8, $p < 0.001$), 10 km/h jogging (male, 55.6 \pm 8.4; female, 72.7 \pm 8.3, $p < 0.001$), 4 km/h walking while wearing 5 kg weights (male, 18.1 \pm 2.9; female, 22.3 \pm 3.2, $p < 0.001$), and 4 km/h walking while wearing 10 kg weights (male, 18.9 \pm 2.7; female, 24.3 \pm 3.1, $p < 0.001$) between the male and female students. Significant correlations between HR and VO_2 were found in male ($y = 0.21x - 10.00$, $R^2 = 0.58$), female ($y = 0.20x - 10.47$, $R^2 = 0.68$), and all participants ($y = 0.20x - 9.98$, $R^2 = 0.60$; Figure 2), respectively.

2. Measured EE and estimated EE (Table 2)

1) Estimated EE (METs)

Estimated EE significantly differed in sit-ups (male, 2.8 \pm 0.5; female, 1.6 \pm 0.5, $p < 0.001$), futsal (male, 6.4 \pm 2.8; female, 4.8 \pm 2.4, $p = 0.049$), and basketball (male, 8.5 \pm 1.2, female, 7.8 \pm 1.2, $p = 0.015$) between the male and female students.

2) Measured EE (METs)

Measured EE significantly differed in sit-ups (male, 3.7 \pm 0.5; female, 2.7 \pm 0.4, $p < 0.001$), aerobic dance (male, 3.7 \pm 0.7; females, 3.1 \pm 0.5, $p = 0.031$), futsal (male, 7.0 \pm 2.5; female, 5.3 \pm 2.2, $p = 0.029$) and basketball (male, 8.9 \pm 1.1; female, 8.0 \pm 1.1, $p = 0.007$) between the male and female students.

The significant and positive correlations between measured EE and estimated EE were also found in the males ($y = 0.91x + 1.16$, $R^2 = 0.99$), females ($y = 0.86x + 1.13$, $R^2 = 0.99$), and all participants ($y = 0.89x + 1.23$, $R^2 = 0.99$), respectively (Figure 3).

Table 1 Heart rate and oxygen uptake in each physical activity

		Men (n=20)		Women (n=20)		t (40)	P	ES
		M	SD	M	SD			
Rotary Hip								
Exercise	HR (bpm)	125.2	23.7	122.6	15.5	0.282	0.781	0.09
	VO ₂ (ml/min/kg)	11.3	3.8	10.5	1.6	0.593	0.561	0.19
	VO ₂ R	18.3	8.8	20.8	4.7	0.783	0.444	0.25
Leg Maagic								
Exercise	HR (bpm)	139.2	25.4	144.0	15.0	0.507	0.619	0.16
	VO ₂ (ml/min/kg)	13.2	3.6	15.3	3.3	1.347	0.195	0.43
	VO ₂ R	23.6	8.9	37.8	13.4	2.796	0.012	0.88
Leg Press								
Exercise	HR (bpm)	105.1	15.7	100.0	12.8	0.792	0.439	0.25
	VO ₂ (ml/min/kg)	10.1	2.4	9.6	1.1	0.565	0.579	0.18
	VO ₂ R	15.4	5.9	17.7	4.5	0.952	0.354	0.30
Abs								
Exercise	HR (bpm)	125.8	21.6	105.9	11.4	2.574	0.019	0.81
	VO ₂ (ml/min/kg)	12.9	1.8	9.5	1.4	4.767	0.001>	1.51
	VO ₂ R	22.9	4.4	17.1	5.1	2.682	0.015	0.85
Aerobic dance (standing)								
Exercise	HR (bpm)	101.9	9.8	98.9	8.4	0.701	0.492	0.22
	VO ₂ (ml/min/kg)	13.0	2.5	10.7	1.8	2.344	0.031	0.74
	VO ₂ R	21.9	5.9	21.3	7.1	0.223	0.826	0.07
Billy's Boot Camp dance								
Exercise	HR (bpm)	140.4	27.6	147.9	7.1	0.793	0.438	0.25
	VO ₂ (ml/min/kg)	21.8	4.9	20.9	1.4	0.574	0.537	0.18
	VO ₂ R	46.3	14.5	57.8	6.2	2.301	0.034	0.73
Jump rope								
Exercise	HR (bpm)	175.4	19.6	176.3	10.9	0.119	0.907	0.04
	VO ₂ (ml/min/kg)	26.3	1.9	24.1	3.1	1.940	0.068	0.61
	VO ₂ R	57.6	5.2	69.4	11.8	2.880	0.013	0.91
Futsal								
Exercise	HR (bpm)	151.9	36.6	143.2	37.5	0.735	0.467	0.23
	VO ₂ (ml/min/kg)	24.6	8.8	18.7	7.5	2.272	0.029	0.72
	VO ₂ R	52.4	22.8	49.7	27.7	0.331	0.742	0.10
Volleyball								
Exercise	HR (bpm)	159.8	22.0	166.1	19.1	0.679	0.506	0.21
	VO ₂ (ml/min/kg)	25.6	3.7	22.1	4.6	1.825	0.085	0.58
	VO ₂ R	55.6	9.3	61.9	16.5	1.056	0.305	0.33
Badminton								
Exercise	HR (bpm)	119.5	20.9	135.9	19.1	2.594	0.013	0.82
	VO ₂ (ml/min/kg)	17.5	4.9	18.1	4.1	0.402	0.690	0.13
	VO ₂ R	33.9	13.1	45.9	16.5	2.562	0.015	0.81

M: mean, SD: Stsandard deviation, P values by unpaired t-test

Table 1 (Continued)

		Men (n=20)		Women (n=20)		t (40)	P	ES
		M	SD	M	SD			
Basketball								
Exercise	HR (bpm)	177.1	12.5	183.1	7.5	1.252	0.228	0.40
	VO ₂ (ml/min/kg)	31.1	4.1	25.8	3.7	3.056	0.007	0.97
	VO ₂ R	69.7	8.4	75.3	13.7	1.115	0.280	0.35
Tennis								
Exercise	HR (bpm)	153.1	23.5	160.1	14.9	0.808	0.430	0.26
	VO ₂ (ml/min/kg)	25.8	4.6	23.1	2.3	1.629	0.121	0.51
	VO ₂ R	55.9	10.9	65.7	9.4	2.138	0.046	0.68
Table Tennis								
Exercise	HR (bpm)	119.6	21.9	133.2	12.5	1.635	0.120	0.52
	VO ₂ (ml/min/kg)	15.3	3.5	15.6	1.9	0.246	0.808	0.08
	VO ₂ R	29.3	9.9	38.9	5.8	2.642	0.017	0.83
Play catch								
Exercise	HR (bpm)	111.7	14.3	115.6	9.5	0.741	0.468	0.23
	VO ₂ (ml/min/kg)	13.7	2.8	12.7	2.4	0.898	0.381	0.28
	VO ₂ R	23.5	7.9	31.9	8.5	2.313	0.033	0.73
Ergometer								
Exercise	HR (bpm)	129.1	13.2	144.8	14.1	2.574	0.019	0.81
	VO ₂ (ml/min/kg)	16.2	1.7	16.7	1.2	0.804	0.432	0.25
	VO ₂ R	31.2	3.6	42.7	3.9	6.954	0.001>	2.20
Walking (4 km/hr)								
Exercise	HR (bpm)	98.5	9.5	101.2	7.2	0.694	0.496	0.22
	VO ₂ (ml/min/kg)	10.1	1.0	9.4	1.1	1.601	0.127	0.51
	VO ₂ R	14.1	1.3	19.7	3.3	5.018	0.001>	1.59
Walking (6 km/hr)								
Exercise	HR (bpm)	122.1	17.5	127.8	7.1	0.958	0.351	0.30
	VO ₂ (ml/min/kg)	15.7	1.8	14.9	1.3	1.000	0.330	0.32
	VO ₂ R	28.3	3.7	40.7	5.8	5.680	0.001>	1.79
Jogging (10 km/hr)								
Exercise	HR (bpm)	163.8	19.3	174.3	14.6	1.994	0.059	0.63
	VO ₂ (ml/min/kg)	25.9	3.5	24.4	2.4	1.674	0.102	0.53
	VO ₂ R	55.6	8.4	72.7	8.3	6.515	0.001>	2.06
Package of 5 kg (4 km/hr)								
Exercise	HR (bpm)	101.1	9.2	107.9	6.4	1.953	0.067	0.63
	VO ₂ (ml/min/kg)	11.5	1.4	11.1	1.1	0.636	0.533	0.20
	VO ₂ R	18.1	2.9	22.3	3.2	3.126	0.006	0.99
Package of 10 kg (4 km/hr)								
Exercise	HR (bpm)	104.1	9.5	114.6	8.5	2.631	0.017	0.83
	VO ₂ (ml/min/kg)	12.1	0.9	12.2	1.7	0.306	0.763	0.10
	VO ₂ R	18.9	2.7	24.3	3.1	4.054	0.001	1.28

M: mean, SD: Stsndard deviation, P values by unpaired t-test

5. Discussion

The result of this study demonstrated the significant correlation between HR and VO₂. Rodahl et al.⁴ investigated HR and VO₂ using Douglas Bag technique in Norwegian coastal fisherman and demonstrated approximately 15% differences between measured VO₂ and estimated VO₂. Davis et al.¹¹ reported the influence of gender, age and exercise habits on the association between HR and VO₂. Exercise habits have been reported to affect HR¹². A significant difference in gender as exercise intensity increased is considered due to the differences in muscle volume and cardio-pulmonary function between men and women.

HR is most commonly used to measure exercise intensity. %HRR has a strong correlation with %VO₂R. The percent of the maximal heart rate actually underestimates %VO₂R by approximately 15%; thus, compared to %HHR, it does not precisely indicate exercise intensity in lower physical activity. The relationship between markers of relative intensity (%HRR and %VO₂R) is much tighter than the relationship between HR and VO₂^{9,10}. Therefore, we applied the well-established equations for age-predicted HRmax¹³ and nonexercise estimates of VO₂max¹⁴ to allow the relative intensity of the activity to be expressed. A limitation of the present study was that we did not directly measure maximal exercise values.

However, this might be impractical and/or unfeasible in larger stud particularly those studies where

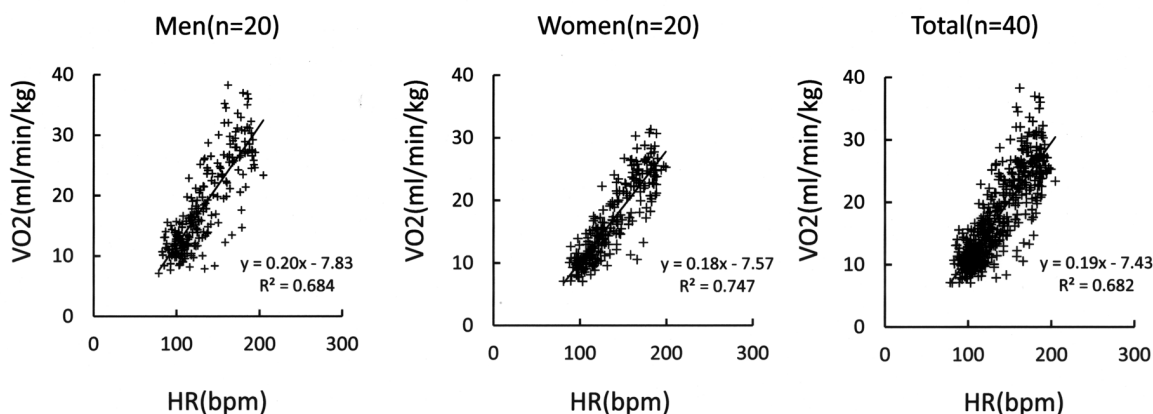


Fig. 2 Relationship between HR and VO₂. Significant correlations between HR and VO₂ were found in the males ($y = 0.21x - 10.00$, $R^2 = 0.58$), females ($y = 0.20x - 10.47$, $R^2 = 0.68$), and all participants ($y = 0.20x - 9.98$, $R^2 = 0.60$), respectively.

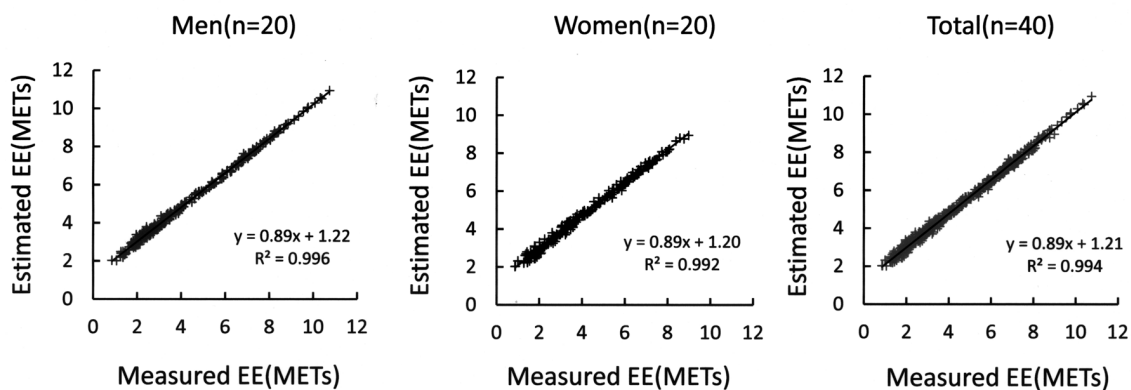


Fig. 3 Relationship between measured METs and estimated METs. Favorable correlations between estimated energy expenditure (EE) and measured EE were found in the males ($R^2=0.996$), females ($R^2=0.992$), and all participants ($R^2=0.994$), respectively.

Table 2 Estimated EE and measured EE in physical activities

		Men (n=20)		Women (n=20)		Total (n=40)		P*	ES
		M	SD	M	SD	M	SD		
Rotary Hip	Estimated EE (METs)	2.3	1.1	2.0	0.5	2.1	0.9	0.445	0.25
	Measured EE (METs)	3.2	1.1	3.0	0.5	3.1	0.8	0.561	0.19
Leg Magic	Estimated EE (METs)	2.9	1.1	3.5	1.2	3.2	1.2	0.216	0.41
	Measured EE (METs)	3.8	1.0	4.4	1.0	4.1	1.0	0.195	0.43
Leg Press	Estimated EE (METs)	1.9	0.7	1.7	0.4	1.8	0.6	0.401	0.27
	Measured EE (METs)	2.9	0.7	2.7	0.3	2.8	0.5	0.579	0.18
Abs	Estimated EE (METs)	2.8	0.5	1.6	0.5	2.2	0.8	0.001>	1.77
	Measured EE (METs)	3.7	0.5	2.7	0.4	3.2	0.7	0.001>	1.51
Aerobics dance (standing)	Estimated EE (METs)	2.7	0.7	2.2	0.6	2.5	0.7	0.089	0.57
	Measured EE (METs)	3.7	0.7	3.1	0.5	3.4	0.7	0.031	0.74
Billy's Boot Camp dance	Estimated EE (METs)	5.6	1.6	5.6	0.4	5.6	1.1	0.723	0.11
	Measured EE (METs)	6.2	1.4	6.1	0.4	6.1	1.0	0.573	0.18
Jump rope	Estimated EE (METs)	7.0	0.6	6.5	1.0	6.8	0.8	0.158	0.47
	Measured EE (METs)	7.5	0.6	6.9	0.9	7.2	0.8	0.068	0.61
Futsal	Estimated EE (METs)	6.4	2.8	4.8	2.4	5.6	2.7	0.049	0.64
	Measured EE (METs)	7.0	2.5	5.3	2.2	6.2	2.5	0.029	0.72
Volleyball	Estimated EE (METs)	6.8	1.1	5.8	1.5	6.3	1.4	0.129	0.50
	Measured EE (METs)	7.3	1.1	6.3	1.3	6.8	1.3	0.085	0.58
Badminton	Estimated EE (METs)	4.2	1.6	4.5	1.3	4.3	1.4	0.512	0.21
	Measured EE (METs)	5.0	1.4	5.2	1.2	5.1	1.3	0.690	0.13
Basketball	Estimated EE (METs)	8.5	1.2	7.8	1.2	7.8	1.4	0.015	0.85
	Measured EE (METs)	8.9	1.1	8.0	1.1	8.0	1.3	0.007	0.97
Tennis	Estimated EE (METs)	6.8	1.4	6.1	0.8	6.5	1.2	0.186	0.43
	Measured EE (METs)	7.4	1.3	6.6	0.6	7.0	1.1	0.121	0.51
Table Tennis	Estimated EE (METs)	3.5	1.1	3.6	0.6	3.6	0.8	0.776	0.09
	Measured EE (METs)	4.4	1.0	4.5	0.5	4.5	0.8	0.808	0.08
Play catch	Estimated EE (METs)	2.9	0.9	2.8	0.7	2.9	0.8	0.797	0.08
	Measured EE (METs)	3.9	0.8	3.6	0.7	3.8	0.7	0.381	0.28
Ergometer	Estimated EE (METs)	3.8	0.5	4.0	0.4	3.9	0.4	0.308	0.33
	Measured EE (METs)	4.6	0.5	4.8	0.3	4.7	0.4	0.432	0.25
Walking (4km/hr)	Estimated EE (METs)	1.8	0.2	1.7	0.3	1.8	0.2	0.755	0.10
	Measured EE (METs)	2.9	0.3	2.7	0.3	2.8	0.3	0.127	0.51
Walking (6km/hr)	Estimated EE (METs)	3.5	0.5	3.6	0.4	3.6	0.4	0.868	0.05
	Measured EE (METs)	4.5	0.5	4.3	0.4	4.4	0.5	0.330	0.32
Jogging (10km/h)	Estimated EE (METs)	6.9	1.1	6.6	0.7	6.8	0.9	0.397	0.27
	Measured EE (METs)	7.4	1.0	7.0	0.7	7.2	0.9	0.102	0.53
Package of 5kg (4km/hr)	Estimated EE (METs)	2.3	0.4	2.4	0.3	2.3	0.3	0.560	0.19
	Measured EE (METs)	3.3	0.4	3.2	0.3	3.2	0.3	0.533	0.20
Package of 10kg (4km/hr)	Estimated EE (METs)	2.4	0.3	2.6	0.4	2.5	0.4	0.256	0.37
	Measured EE (METs)	3.4	0.3	3.5	0.5	3.5	0.4	0.763	0.10

M: mean, SD: Standard Deviation, P values by unpaired t-test.

elderly participants are involved. Despite this limitation, our findings were in agreement with those of Swain et al.^{9,10}, who demonstrated a strong numerically

similar relationship between %HRR and %VO₂R in the laboratory. Had we actually measured HR_{max} and VO₂max, it would have most likely improved the

estimate of EE. An important advantage of using HR over motion sensors is that HR monitoring provides an index of both the relative (%VO₂R), as well as the absolute intensity (METs) of the physical activity performed. The importance of relative intensity can be seen when classifying different individuals on the basis of exercise intensity.

The Karvonen formula determines target HR as follows: target HR = (maximum HR – resting HR) × %HRR + resting HR. The American College of Sports Medicine categorizes exercise intensity as follows based on %VO₂R or %HR: very light, <20%; light, 20-39%; moderate, 40-59%; hard, 60-84%; very hard, ≥85%; maximum, 100%.

In the present study, there was a tendency that measured EE was greater than estimated EE calculated using the estimation formula, although, a favorable correlation was found between measured EE and estimated EE (R²=0.99), supporting the study result of Scott et al.¹² If the regression equation is employed as a correction method, physical activity intensity can be calculated from HR and METs; the assessments based on expensive calculation apparatus and the complexity of the technique required for accurate measurements of VO₂ are not necessary. The result of this study suggested that the estimation formula would provide appropriate EE in individual physical activity.

Conclusion

Actual EE and estimated EE were derived from HR and VO₂ while healthy and young subjects performing various physical activities. Further investigation and data collection including larger study population are required for the more detailed and clinical evaluation.

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