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ACTIVE MUSCLE MASS AFFECTS ENDURANCE PHYSIOLOGY: A REVIEW ON SINGLE VERSUS DOUBLE-LEG CYCLING

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Review
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Abstract:

This review gives an overview of methods and outcomes of studies that compared circulatory, ventilatory, energetic or hormonal responses evoked by single-leg cycling and double-leg cycling at sub-maximal and maximal intensities. Through a systematic search, 18 studies were identified in the databases PubMed, Embase and Web of Science. Additionally, one study was added after a check of references. Critical analysis of each study showed that their quality was low to moderate. Between studies, widely divergent study procedures were present, such as different intensities, incremental or constant workloads, and different cycling frequencies. Moreover, a large variety of outcome variables was found and thereby comparison was hard. Nevertheless, results showed a tendency to higher hormonal levels of catecholamines as well as circulatory and ventilatory responses during double-leg cycling compared to one-leg cycling. Additionally, at similar normalized sub-maximal workloads, blood lactate levels tended to be lower during double-leg cycling, suggesting that more type II muscle fibers were recruited. From the reviewed studies the tentative conclusion is that active muscle mass seems a crucial factor in the regulation of endurance performance. Consequently, exercise regimens that recruit a larger active muscle mass, for example combined arm and leg exercise, would optimally stress the release of biochemicals and hence the modulation of central training adaptations, which may positively affect physical capacity in, for example, persons that have diminished leg muscle mass available. However, it also became clear that more information is needed to further understand the contributions of active muscle mass. The experimental possibilities of comparing one-legged and two-legged cycling is promising, but future studies should aim to provide complete quantitative data on the muscle mass recruited, as well as on the specific contribution of anaerobic/aerobic metabolism. They should also aim to include blood parameters such as PCO_2, pH, myokines and physiological responses such as heart rate and ventilation.

Key words: *exercise test, physical exertion, skeletal muscle, muscle fatigue, review of literature*

Introduction

The role of active muscle mass in bodily physiological responses to endurance performance, including circulatory, ventilatory, energetic and hormonal changes, has been the subject of debate (Abbiss, et al., 2011; Jensen-Urstad, Svedenhag, & Sahlin, 1994; Kjaer, Kiens, Hargreaves, & Richter, 1991; Neary & Wenger, 1986; Vianna, Oliveira, Ramos, Ricardo, & Araujo, 2010). While several studies have shown that exercise regimens involving less active muscle mass induce lower physiological responses at the whole body level compared to exercise regimens involving more active muscle mass (Kjaer, et al., 1991; Vianna, et al., 2010), others have reported opposite results and have other recommendations for practical use (Abbiss, et al., 2011; Neary & Wenger, 1986). Clarification of this issue, by means of a literature review, may deepen our understanding of physiological processes in the body and benefit the tailored design of sport programs, guidelines for exercise behavior and hence physical fitness of the population.

Such knowledge may be particularly helpful for certain patient populations that have diminished muscle mass available, such as amputees, wheelchair users (Hettinga, et al., 2013) and patients with rheumatoid arthritis (Cooney, et al., 2011) or burns (Disseldorp, et al., 2012; Willis, et al., 2011). Many of these patients suffer from unexplained fatigue that disturbs regular physical activity (Disseldorp, et al., 2012; Franklin & Harrell, 2013; Yeung, Leung, Zhang, & Lee, 2012). Low levels of physical activity lead to a decrease in functional status and participation in daily life, which will lead to a further decrement of physical capacity (van den Berg, de Groot, Swart, & van der Woude, 2010). Understanding the physiological processes related to active muscle mass might explain the problems associated with fatigue.

Conversely, such evidence may give rise to improvements of rehabilitation programs and thereby physical fitness, mobility and participation of persons who have diminished muscle mass available. When initiating specific guidelines for exercise behavior, it is important to keep in mind what rehabilitation or training result is being pursued and what training adaptations will have positive effects on the disability-related symptoms. Central training adaptations such as increased cardiac output or oxygen delivery to the muscle are transferable to different exercise regimens (Hettinga, Hoogwerf, & van der Woude, 2016). On the other hand, some training adaptations such as increased oxygen utilization by specific muscles, are local and exercise specific (Hettinga, et al., 2016). Given that in some populations more central and/or local training adaptations might be preferable, it would be useful to deepen our understanding of physiological processes related to active muscle mass and its possible effects on training adaptations.

In order to understand the role of active muscle mass in the regulation of endurance performance, the broad notion that skeletal muscles co-function as secretory organs during exercise may be considered. First and foremost, it has been long known that biochemicals such as carbon dioxide, lactic acid and vasodilatory metabolites including adenosine are released by working muscles. These biochemicals mediate homeostatic circulatory and ventilatory responses to meet the increased demand for oxygen and nutrients, as well as remove metabolic waste products (Powers & Howley, 2012). That is, circulatory and ventilatory responses are linked to the release of biochemicals by working muscles.

Following this view, we hypothesized that the magnitude of homeostatic circulatory and ventilatory responses to exercise is related to the amount of active muscle mass. A possible way to test this hypothesis is to compare physiological outcomes during one-legged (1-leg) and two-legged (2-leg) cycling exercise in able-bodied people. To date a number of such studies have been performed. However, any overview of their findings has been lacking. In the present review, the methods and outcomes of studies that compared circulatory, ventilatory, energetic or hormonal responses during sub-maximal and maximal 1-leg versus 2-leg cycling exercise are presented and discussed.

Methods

Selection procedure

A literature search without date restrictions was conducted on April 7th, 2015 and an additional search from this date to January 18th, 2018 in the electronic databases PubMed, Web of Science and Embase. In all the three databases the same search strategy was used (Table 1). Studies that met the following six eligibility criteria were included in the review when: 1. a comparison between 1-leg versus 2-legs was made, 2. the experiment included cycling, 3. the study focussed on circulatory, ventilatory, energetic or hormonal exercise responses during cycling, 4. 1-leg and 2-leg cycling was performed by the same participants, 5. the protocol for 1-leg and 2-leg cycling was similar for all participants, containing equally defined workloads, and 6. sub-maximal intensity was specified in Watts, the percentage of peak oxygen uptake (%$\dot{V}O_{2peak}$), or could be calculated from the given data. Studies were excluded when: 1. non-healthy persons were involved, 2. the study took place at altitude, or 3. the full text was not available.

Risk of bias assessment

Risk of bias assessment was performed independently by two reviewers (MV and FH) with a checklist specifically developed for this review. The checklist was based on the Cochrane Collabora-

Table 1. The search strategy used in the databases PubMed, Web of Science and Embase

1-leg		AND	2-leg		AND	cycling	
OR	1-legged		OR	2-legged		OR	cycle
OR	one-leg		OR	2-legs		OR	bicycling
OR	one-legged		OR	two-leg		OR	bicycle
OR	single-leg		OR	two-legged		OR	exercising
OR	single-legged		OR	two-legs		OR	exercise
OR	single		OR	double-leg			
OR	one		OR	double-legged			
OR	1-leg-cycling		OR	2-leg-cycling			

Table 2. Assessment model risk of bias (ROB)

ROB domain	Explanation	Judgment of risk
ROB participants	Participants performed no or minimal physical activity prior to the measurements. Physical activity level and ingestion of food, drinks or stimulants prior to the measurements were similar between 1-leg and 2-leg cycling.	Low: fully considered Moderate: partly considered High: not considered or not mentioned
ROB study confounders	Participants had time to become familiar with the test conditions. Enough time was scheduled between 1-leg and 2-leg cycling (min. an hour and max. 5 hours). The sequence of the test conditions was randomized.	Low: fully considered Moderate: partly considered High: not considered or not mentioned
ROB outcome measures	The results are related to relative intensity (%VO_{2peak}).	Low: all results are related Moderate: partly related and/or can be calculated from given data High: could not be related
ROB reporting	The results are presented in tables and/or text and not only visually presented in graphs. Findings are presented with significance levels.	Low: fully fulfilled Moderate: partly fulfilled High: not fulfilled
Other ROB	Other potential bias which do not obviously fit into any other category.	No judgment

Note. ROB, risk of bias, %$VO_{2peak,}$ percentage of peak oxygen uptake.

tion's tool (Higgins, et al., 2011) and consisted of risk of bias in 5 domains (Table 2). The selected publications were rated for each domain as high risk of bias (+), moderate risk of bias (+-) or low risk of bias (-). Disagreements were settled by consensus.

Comparison of 1-leg and 2-leg exercises

Comparing circulatory, ventilatory, energetic, and hormonal responses of 1-leg vs. 2-leg cycling as found in the literature, might give insight into the relation between the amount of active muscle mass and the magnitude of exercise responses.

For the comparison of 1-leg and 2-leg exercise in this review a distinction was made between studies that have tested participants at sub-maximal workloads and maximal workloads. It has been well established that the maximal oxygen uptake cannot be attained in exercise regimens involving a limited active muscle mass (Hettinga, et al., 2013; Ogita, Stam, Tazawa, Toussaint, & Hollander, 2000). Performance during 1-leg cycling at maximal intensities is thus limited, in contrast to 1-leg cycling at sub-maximal intensities. Moreover, the reliance on anaerobic glycolysis increases with the exercise intensity (Plowman & Smith, 2007). These two phenomena can cause different responses to maximal and sub-maximal intensities during 1-leg and 2-leg cycling.

Furthermore, in comparing 1-leg and 2-leg exercises, relative intensity (%$\dot{V}O_{2peak}$) and absolute intensity (in Watts) were distinguished. Logically, exercises involving less muscle mass will elicit larger exercise responses compared to exercises involving more muscle mass when the same absolute intensity in Watts is maintained. As less active muscle mass is recruited to perform the same workload, more energy is needed per unit muscle mass. As a consequence, the active muscle mass is metabolically and mechanically stressed at a relatively higher rate. Therefore, a comparison between 1-leg and 2-leg cycling based on relative intensities, as a percentage of a person's $\dot{V}O_{2peak}$ achieved during 1-leg or 2-leg cycling, will give a better indication of differences in exercise responses between 1-leg and 2-leg cycling.

Results

Full-text selection

The initial search in the electronic databases PubMed, Web of Science and Embase identified 768 articles (Figure 1). After removing 358 duplicates, 410 records were examined by title and abstract of which 357 irrelevant records were excluded. The remaining 53 records were retrieved and assessed for eligibility. Three full-text versions were not available and 32 articles did not meet the inclusion criteria, leaving 18 eligible articles for appraisal. The reference lists of the eligible studies were checked for other potentially eligible articles and one article was added. Ultimately, 19 articles were included in this review. One out of the 19 reviewed studies tested participants at sub-maximal and maximal workloads, but did not fulfil the inclusion criteria completely as the sub-maximal intensities were random for all participants (Gleser, 1973). Therefore, only the results from the maximal tests of this study were used in this review.

Risk of bias

The included articles scored high or moderate risk of bias on the category participants and study confounders, frequently because of lacking information or too much time between the testing conditions (Table 3). In five sub-maximal studies, the outcome measures were not related to relative intensities (%$\dot{V}O_{2peak}$) (Burns, Pollock, Lascola, & McDaniel, 2014; Few, Cashmore, & Turton, 1980; Freyschuss & Strandell, 1968; Ogita, et al., 2000; Stamford, Weltman, & Fulco, 1978).

Cycling protocols

The protocols that have been used for sub-maximal and maximal studies were incremental, with increasing intensities up to exhaustion, or the participants were tested at constant workloads (Table 3). Although the cycling frequency ranged from 45-98 revolutions per minute (rpm), 60 rpm was mostly used. Furthermore, in eight studies a counterweight was attached to the pedal of the resting limb during 1-leg cycling or another method was used to return the pedal of the resting limb, to minimize the muscular contractions during the pedal-up phase and to match the exercise more closely to the 2-leg cycling exercise (Freyschuss & Strandell, 1968; Gleser, 1973; Jensen-Urstad, et al., 1994; Koga, et al., 2001; Kounalakis, Nassis, Koskolou, & Geladas, 2008; MacInnis, et al., 2017; Shephard, Bouhlel, Vandewalle, & Monod, 1988; Weyand, Cureton, Conley, & Higbie, 1993). The feet were fastened to the pedals with a toe clip or strap in seven studies (Table 3) (Bond, Balkissoon, Caprarola, & Tearney, 1986; Davies & Sargeant, 1974; Davies & Sargeant, 1975; Jensen-Urstad, et al., 1994; Lewis, Taylor, & Graham, 1983; Neary & Wenger, 1986; Weyand, et al., 1993).

Single- versus double-leg cycling at sub-maximal intensities

Fourteen studies compared 1-leg and 2-leg cycling at sub-maximal intensities (Table 4). The studies were performed world-wide and mostly included 5-12 men, aged 21-30 years. The maintained workload ranged considerably, varying from 20 to 95% $\dot{V}O_{2peak}$. Five of the studies tested participants at equal relative workloads during 1-leg and 2-leg cycling (Bond, et al., 1986; Davies & Sargeant, 1974; Few, et al., 1980; Klausen, Secher, Clausen, Hartling, & Trap-Jensen, 1982; Lewis, et al., 1983), four at lower (up to 70%) (Jensen-Urstad, et al., 1994; Koga, et al., 2001; Kounalakis, et al., 2008; MacInnis, et al., 2017) and one (Neary & Wenger, 1986) at higher (up to 200%) relative workload during 1-leg cycling.

Heart rate (HR), cardiac output, stroke volume, oxygen uptake ($\dot{V}O_2$), respiratory minute volume ($\dot{V}_E$) and arteriovenous oxygen differences were lower during 1-leg cycling compared to 2-leg cycling at comparable relative exercise intensities (Table 5). However, four studies that tested participants at higher absolute workloads per leg during

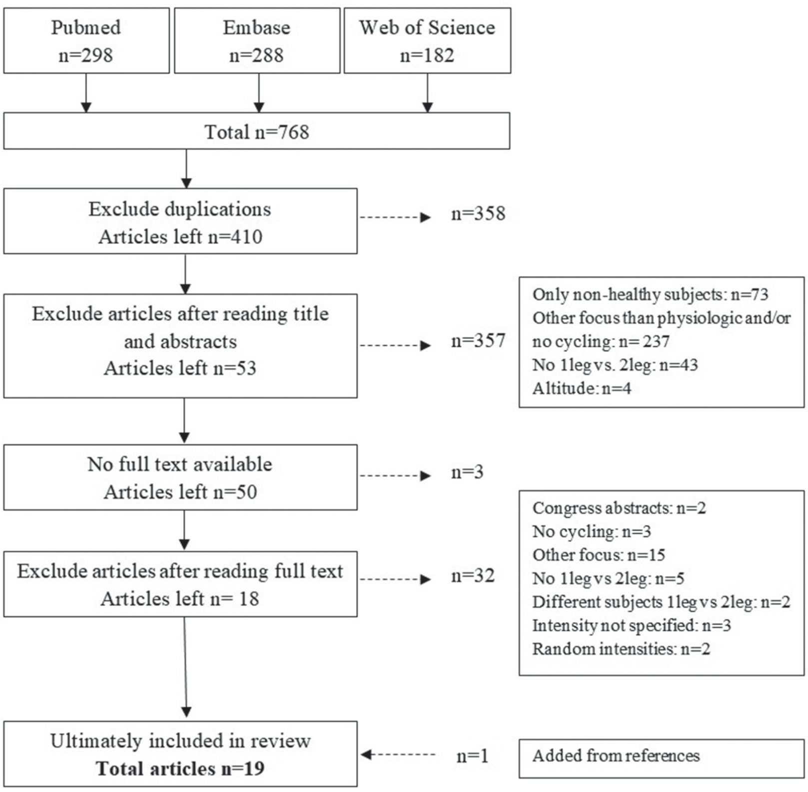

Figure 1. Flow diagram of the literature search (n – number of studies).

Table 3. Cycling protocols and risk of bias (ROB) in five domains

			Pedaling			ROB in five domains				
Author(s)	Year	Protocol	frequency (rpm)	counter-weight	foot was fastened	ROB participants	ROB study confounders	ROB outcome measures	ROB reporting	other ROB
Sub-maximal intensities (n=14)										
Freyschuss and Strandell	1968	constant	45-75	x		+	+–	+	+–	Cycling in supine position
Davies and Sargeant	1974	NS	NS		x	+–	+–	+–	+–	
Stamford et al.	1978	incremental	60			–	+–	+	+–	Many results from graphs
Few et al.	1980	constant	NS			+–	+	+	–	
Klausen et al.	1982	constant	60			+	+–	–	+–	
Lewis et al.	1983	constant	60		x	–	+–	–	+–	
Bond et al.	1986	incremental	60		x	–	+–	+–	–	
Neary and Wenger	1986	incremental	60		x	+–	+–	+–	–	
Jensen-Urstad et al.	1994	constant	60	x	x	–	+–	–	+–	
Ogita et al.	2000	incremental	80			+	+–	+	–	
Koga et al.	2001	constant	60	x		+	+	+–	–	
Kounalakis et al.	2008	constant	80	x		–	+–	–	–	
Burns et al.	2014	constant	80			+	+–	+	–	
MacInnis et al.	2017	constant, interval	80	x		–	+–	–	–	
Maximal intensity (n=14)										
Gleser	1973	NS	NS	x		+	+–	–	+–	1-leg: 2 persons at each side of bicycle
Davies and Sargeant	1974	NS	NS		x	+–	+–	–	+–	
Davies and Sargeant	1975	NS	NS		x	+	+–	–	+–	
Stamford et al.	1978	incremental	60			–	+–	+–	+–	Many results from graphs
Klausen et al.	1982	constant	60			+	+–	–	+–	
Lewis et al.	1983	constant	70		x	–	+–	–	+–	
Bond et al.	1986	incremental	60		x	–	+–	–	–	
Neary and Wenger	1986	incremental	60		x	+–	+–	–	–	
Bell et al.	1988	incremental	90			+–	+	–	+–	
Shephard et al.	1988	NS	50	x		+	+–	–	–	
Weyand et al.	1993	incremental	98	x	x	+	+	–	+–	
Ogita et al.	2000	incremental	80			+	+–	–	–	
Koga et al.	2001	incremental	60	x		+	+	–	–	
MacInnis et al.	2017	incremental	80	x		+–	+–	–	–	

Note. +: high ROB, +–: moderate ROB,–: low ROB, NS, not specified, rpm, revolutions per minute, ROB, risk of bias.

1-leg cycling compared to 2-leg cycling, noticed higher HR, $\dot{V}O_2$ and $\dot{V}_E$ responses during 1-leg cycling (Burns, et al., 2014; Neary & Wenger, 1986; Ogita, et al., 2000; Stamford, et al., 1978). Furthermore, the total peripheral resistance (Kounalakis, et al., 2008; Lewis, et al., 1983) and venous oxygen saturation (Freyschuss & Strandell, 1968; Jensen-Urstad, et al., 1994; Kounalakis, et al., 2008) were found to be higher and the $\dot{V}O_2$ at the ventilatory threshold (Bond, et al., 1986; Koga, et al., 2001) and arteriovenous oxygen difference (Freyschuss & Strandell, 1968; Jensen-Urstad, et al., 1994; Kounalakis, et al., 2008; Lewis, et al., 1983) were found to be lower during 1-leg cycling compared to 2-leg cycling.

Table 4. Characteristics of the studies on sub-maximal 1-leg and 2-leg cycling

Author(s)	City	n		$\%VO_{2peak}$			W (watt)		
Year	Country	men (%)	Age	2-leg	1-leg*	1-leg/2-leg (%)	2-leg	1-leg	1-leg/2-leg (%)
Freyschuss and Strandell	Stockholm	8	22	–	–	–	102-204†	51-102†	50
1968	Sweden	100							
Davies and Sargeant	London	5	30	26-88†	27-85†	100	47-235†	25-121†	50
1974	England	100							
Stamford et al.	Louisville	10	28	–	–	–	75-150	75-150	100
1978	USA	100							
Few et al.	London	12	21	95‡	95‡	100	–	–	–
1980	England	100							
Klausen et al.	Copenhagen	6	23	70	70	100	–	–	–
1982	Denmark	100							
Lewis et al.	Dallas	6	26	50-75	50-75	100	–	–	–
1983	USA	100							
Bond et al.	Washington	8	24	70	70	100	168	105	60
1986	USA	100							
Neary and Wenger	Victoria	8	21	19-38†	32-79†	168-208	50-150	50-150	100
1986	Canada	100							
Jensen-Urstad et al.	Stockholm	8	30	80	65	80	228	114	50
1994	Sweden	100							
Ogita et al.	Kagoshima	9	23	–	–	–	80-160	80-160	100
2000	Japan	100							
Koga et al.	Kobe	6	–	50 -80†	40 -70†	85	93-190	36-62	35
2001	Japan	100							
Kounalakis et al.	Athens	12	23	60	40	70	126	57	45
2008	Greece	–							
Burns et al.	Kent	10	22	30-50	–	–	40-120	40-120	100
2014	USA	100							
MacInnis et al.	Hamilton	12	21	69**	61**	88	182**	103**	57
2017	Canada	100							

Note. – not specified, * peak oxygen uptake measured during 1-leg cycling, ** mean constant and interval exercise, † calculated from information in the article. 1 watt = 6,12 kpm/min, ‡ nearly maximal, interpreted as 95% of VO_{2peak}. VO_{2peak}, peak oxygen uptake.

Table 5. Comparison of the circulatory and ventilatory responses found during sub-maximal 1-leg vs. 2-leg cycling

Author(s)	Load 1-leg/2-leg (%)		Circulatory							Ventilatory								
Year	$\%VO_{2peak}$	Watt	HR	Q	SV	MAP	LBF	TPR	LVR	VO_2	VCO_2	VE	VO_2 at VT	P_AO_2	P_ACO_2	a-v O_2	P_VO_2	SVO_2
Freyschuss and Strandell 1968	–	50	↓			↑*				↓↓		↓↓				↓		↑
Davies and Sargeant 1974	100	50	↓	↓	↓¶					↓↓		↓↓						
Stamford et al. 1978	–	100	↑†	↑†						↑¶	↑¶	↑¶				≈¶		
Few et al. 1980	100	–	↑†							≈								
Klausen et al. 1982	100	–	≈	↓	↓*	≈	↑		↓¶	↓		↓		≈	↓	≈		
Lewis et al. 1983	100	–	↓†	↓§	≈	≈		↑†		↓†	↓↓	↓↓				↓§		
Bond et al. 1986	100	60											↓†					
Neary and Wenger 1986	168-208	100	↑†							↑†		↑†	≈					
Jensen-Urstad et al. 1994	80	50	↓				≈			↓↓						↓	↑	↑↑
Ogita et al. 2000	–	100								↑‡		↑†						
Koga et al. 2001	85	35	↓†										↓†					
Kounalakis et al. 2008	70	45	↓†	↓‡	↑¶	≈		↑†								↓‡		↑‡
Burns et al. 2014	–	100	↑§			↑†				↑§								
MacInnis 2017	88	57	↓§							↓§	↓§	↓§						

Note. ↑ or ↓: higher or lower in 1-leg vs. 2-leg, – not specified, * scaled to same oxygen uptake for both 1-leg and 2-leg, † p<.05, ‡ p<.01, § p<.001 1-leg vs. 2-leg, ↑↑ or ↓↓: > 20% , ↑ or ↓: 5-20% , ≈: < 5% higher or lower than 2-leg, ¶ no information about exact difference. HR, heart rate, Q, cardiac output, SV, stroke volume, MAP, mean arterial pressure, LBF, leg blood flow, TPR, total peripheral resistance, LVR, leg vascular resistance, VO_2, oxygen uptake, VCO_2, carbon dioxide production, VE, respiratory minute volume, VT, ventilatory threshold, P_AO_2, arterial oxygen pressure, P_ACO_2, arterial carbon dioxide pressure, a-vO_2, arteriovenous oxygen difference, P_VO_2, venous oxygen pressure, SVO_2, venous oxygen saturation.

Table 6. Comparison of energetic and hormonal responses during sub-maximal 1-leg and 2-leg cycling

Author(s)	Load 1-leg/2-leg (%)		Energy								Hormones		
			Efficiency	CrP	ADP	Lactate		NADH	NH_3	Δgluc	C	aldosteron	cortisol
Year	$\%VO_{2peak}$	Watt				Art	Ven						
Freyschuss and Strandell 1968	–	50	$\downarrow^{\S}$			$\uparrow^{*\ddagger}$	$\uparrow^{*\S}$						
Davies and Sargeant 1974	100	50					$\uparrow^{*}$						
Stamford et al. 1978	–	100					↑¶						
Few et al. 1980	100	–					$\uparrow\uparrow^{\dagger}$					↑↑	$\uparrow\uparrow^{\S}$
Klausen et al. 1982	100	–				↑	↑↑						
Lewis et al. 1983	100	–									↓↓		
Neary and Wenger 1986	200	100					$\uparrow^{\dagger}$						
Jensen-Urstad et al. 1994	80	50		↑¶	$\downarrow^{\ddagger}$	↓↓		↓¶	↓¶	↑	↓↓		
Burns et al. 2014	–	100	$\downarrow^{\ddagger}$										

Note. ↑ or ↓: higher or lower in 1-leg vs. 2-leg, – not specified, * scaled to same oxygen uptake for 1-leg and 2-leg, † p<.05, ‡ p<.01, § p<.001 1-leg vs. 2-leg, ↑↑ or ↓↓: > 20% , ↑ or ↓: 5-20% , higher or lower than 2-leg, ¶ no information about exact difference. CrP, creatine phosphate, ADP, adenosine diphosphate, Art, arterial, Ven, venous, NADH, nicotinamide adenine dinucleotide, NH_3, ammonia, C, catecholamines, Δgluc, glucose uptake.

Lactate content of arterial and venous blood was higher during 1-leg cycling compared to 2-leg cycling in six studies (Table 6) (Davies & Sergeant, 1974; Few, et al., 1980; Freyschuss & Strandell, 1968; Klausen, et al., 1982; Neary & Wenger, 1986; Stamford, et al., 1978). However, one study (Jensen-Urstad, et al., 1994) that had tested participants at a lower relative workload during 1-leg cycling compared to 2-leg cycling, noticed a lower blood lactate content during 1-leg cycling. Furthermore, in two studies (Burns, et al., 2014; Freyschuss & Strandell, 1968) 1-leg cycling was found to be less efficient compared to 2-leg cycling and in two others (Jensen-Urstad, et al., 1994; Lewis, et al., 1983) the increase in catecholamines was lower during 1-leg cycling.

Single- versus double-leg cycling at maximal intensity

Studies that compared 1-leg and 2-leg cycling at maximal intensities are performed world-wide (Table 7). Nine out of 14 studies included 5-12 subjects, all male, aged 21-30 years (Bond, et al., 1986; Davies & Sergeant, 1974; Gleser, 1973; Klausen, et al., 1982; Lewis, et al., 1983; MacInnis, et al., 2017; Neary & Wenger, 1986; Ogita, et al., 2000 Stamford, et al., 1978). Only six studies provided information about the workload maintained by test subjects (Bond, et al., 1986; Koga, et al., 2001; MacInnis, et al., 2017; Ogita, et al., 2000; Shephard, et al., 1988; Stamford, et al., 1978). While all maximal studies have tested subjects with a workload of 100% $\dot{V}O_{2peak}$ for 1-leg and 2-leg cycling, the absolute workload during 1-leg cycling varied from 30-60% of the 2-leg cycling workload in these six studies.

Peak HR, cardiac output, $\dot{V}O_{2peak}$, peak $\dot{V}_E$, the carbon dioxide production ($\dot{V}CO_2$) and arterial and venous blood lactate were lower during maximal 1-leg cycling compared to maximal 2-leg cycling (Table 7). In two studies the arteriovenous oxygen difference was lower during maximal 1-leg cycling compared to maximal 2-leg cycling (Lewis, et al., 1983; Stamford, et al., 1978).

Table 7. Comparison of circulatory, ventilatory and energetic exercise responses during maximal (100% $\dot{V}O_{2peak}$) 1-leg and 2-leg cycling

Author(s)	City	n	Age	Load (watt)			Circulatory							Ventilatory						Energy		
																				Lactate		C
Year	Country	men (%)		2-leg	1-leg	%1-leg/2-leg	HR_{peak}	Q	SV	MAP	LBF	TPR	LVR	VO_{2peak}	VCO_2	VE_{peak}	P_AO_2	P_ACO_2	a -vO_2	Art	Ven	
Gleser	Massachusetts	6	21	–	–	–	↓	↓§						↓↓								
1973	USA	100																				
Davies and Sargeant	London	5	30	–	–	–	↓							↓↓		↓						
1974	England	100																				
Davies and Sargeant	London	7	29	–	–	–	↓							↓		↓						
1975	England	–																				
Stamford et al.	Louisville	10	28	300	175	60	↓†	↓†	≈¶					↓¶	↓¶	↓¶			↓¶		↓¶	
1978	USA	100																				
Klausen et al.	Copenhagen	6	23	–	–	–	≈	↓		≈	↑		↓¶	↓		↓	≈	↓	≈	↓	↓	
1982	Denmark	100																				
Lewis et al.	Dallas	6	26	–	–	–	↓†	↓§	↓	↑		↑↑		↓†	↓↓	↓↓			↓§			↓↓
1983	USA	100																				
Bond et al.	Washington	8	24	266	158	60	↓†							↓†		↓†						
1986	USA	100																				
Neary and Wenger	Victoria	8	21	–	–	–	↓†							↓†		↓†						
1986	Canada	100																				
Bell et al.	Victoria	9	26	–	–	–	↓							↓								
1988	Canada	90																				
Shephard et al.	Toronto	16	31	214*	107*	50	↓‡							↓‡		↓‡				↓‡		
1988	Canada	50																				
Weyand et al.	Georgia	20	24	–	–	–								↓								
1992	USA	55																				
Ogita et al.	Kagoshima	9	23	324	204	65	↓‡							↓‡		↓‡						
2000	Japan	100																				
Koga et al.	Kobe	6	–	292	95	30	↓†							↓†								
2001	Japan	100																				
MacInnis et al.	Hamilton	12	21	315	177**	55	↓§							↓§	↓§	↓§						
2017	Canada	100																				

Note. ↑ or ↓: higher or lower in 1-leg vs. 2-leg, – not specified, * mean men and women, ** mean right and left leg, † p<.05, ‡ p<.01, § p<.001 1-leg vs. 2-leg, ↑↑ or ↓↓: > 20%, ↑ or ↓: 5-20%, ≈: < 5% higher or lower than 2-leg, ¶ no information about difference. HR_{peak}, peak heart rate, Q, cardiac output, SV, stroke volume, MAP, mean arterial pressure, LBF, leg blood flow, TPR, total peripheral resistance, LVR, leg vascular resistance, VO_{2peak}, peak oxygen uptake, VCO_2, carbon dioxide production, VE_{peak}, peak respiratory minute volume, P_AO_2, arterial oxygen pressure, P_ACO_2, arterial carbon dioxide pressure, Δa-vO_2, arteriovenous oxygen difference, Art, arterial, Ven, venous, C, catecholamines.

Discussion and conclusions

The aim of the present review was to gain more understanding of the relation between active muscle mass and the magnitude of bodily physiological responses to endurance performance. In order to achieve this aim, methods and outcomes of physiological studies on circulatory, ventilatory, energetic or hormonal responses during 1-leg and 2-leg cycling were searched and analyzed.

Results showed that sub-maximal and maximal cycling involving more active muscle mass tended to induce higher levels of catecholamines and higher circulatory and ventilatory exercise responses compared to cycling involving less muscle mass. In addition, blood lactate levels were typically higher during sub-maximal 1-leg cycling compared to sub-maximal 2-leg cycling. These findings and their implication for training and rehabilitation of subjects that have a relatively small muscle mass available are discussed below.

Physiological responses to exercise

In response to exercise, the cardiovascular system rapidly adapts to the increased metabolic demands of working muscles for oxygen and nutrients as well as removal of metabolic waste products including carbon dioxide and lactic acid in order to minimize disturbances in the myocellular internal environment (Jeneson & Bruggeman, 2004; Powers & Howley, 2012). The endocrine system and nervous system constitute major control systems involved in the bodily coordination of these homeostatic responses, modulating circulatory and ventilatory flows and mobilizing substrate flows for muscle contraction (Figure 2) (Powers & Howley, 2012).

Homeostatic disturbances during exercise are ultimately the end result of changes in arterial blood pressure, carbon dioxide concentration, acidity level and neural signals originating from contracting muscles (Powers & Howley, 2012) and the brain (central command) (Kounalakis, et al., 2008). As such, any definitive testing of the relationship under investigation would require quantitative knowledge of the changes in arterial blood pressure, carbon dioxide concentration and acidity level during 1-leg versus 2-leg exercise in addition to $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$. However, such comprehensive datasets for these exercise regimens have typically not been collected and reported in the literature (Tables 5-7). Therefore, the analysis was limited in relating the magnitude of bodily physiological responses to exercise and active muscle mass.

Physiological responses to exercise at sub-maximal intensities

At similar relative intensities, circulatory and ventilatory responses were lower during sub-maximal 1-leg cycling compared to 2-leg cycling, but the blood lactate concentration was higher (Davies & Sargeant, 1974; Klausen, et al., 1982). An explanation for the higher blood lactate concentration during sub-maximal 1-leg cycling, might be that more type II muscle fibers were recruited during 1-leg cycling compared to 2-leg cycling. Type II muscle fibers are activated when more power is needed, have higher anaerobic capacity and are less efficient compared to type I muscle fibers (Ament & Verkerke, 2009; Keyser, 2010). This is in line with findings of Freyschuss and Strandell (1968) and Burns et al. (2014) who found a lower mechanical efficiency during 1-leg cycling. When energy is generated by the anaerobic energetic pathways, lactic acid will accumulate (Gastin, 2001), explaining the higher blood lactate concentration during 1-leg cycling observed in the reviewed studies. Moreover, a lower $\dot{V}O_2$ at the ventilatory threshold (Bond, et al., 1986; Koga, et al., 2001) during 1-leg cycling suggested an earlier switch from aerobic energy supply to anaerobic energy supply during 1-leg cycling compared to 2-leg cycling (Ghosh, 2004). A smaller arteriovenous oxygen difference and higher venous oxygen saturation during 1-leg cycling

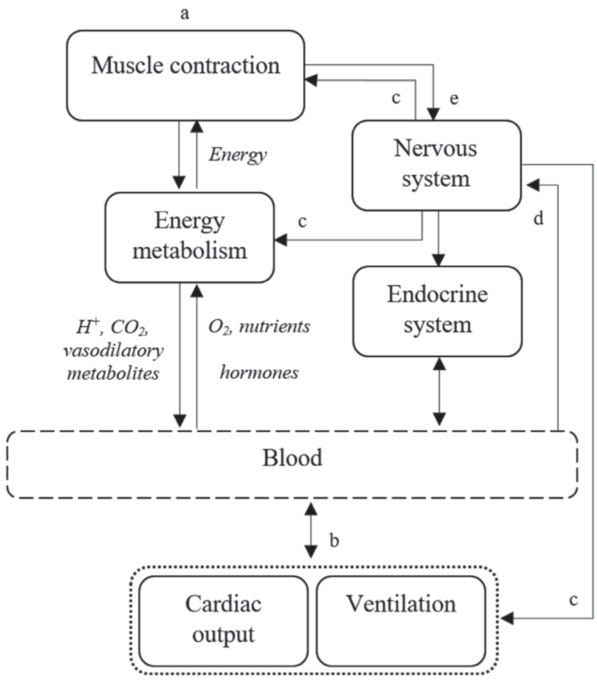

Figure 2. Proposed scheme of short-term physiological responses to exercise.
In response to muscle contraction (a), the respiratory and circulatory system will work together by increasing the ventilation and cardiac output (b). This enhances the delivery of O_2 and nutrients and the removal of waste products. The nervous system stimulates muscle contraction, ventilatory, circulatory and energetic responses via neurotransmitters (c) or the endocrine system and is triggered by mechanoreceptors (e.g., muscle spindles) (e), chemoreceptors (e.g., changes in H^+ concentrations and PCO_2) and baroreceptors (changes in arterial blood pressure) (d). The nervous system and endocrine system control the energy metabolism by increasing synthesis of glucose in the liver and mobilizing fatty acids from adipose tissue. (Created with data from Powers & Howley, 2012)

(Freyschuss & Strandell, 1968; Jensen-Urstad, et al., 1994; Kounalakis, et al., 2008; Lewis, et al., 1983), implied that less oxygen was used by the leg muscles during 1-leg cycling compared to 2-leg cycling.

Normally, the accumulation of lactic acid increases partial carbon dioxide pressure, which is counteracted by the stimulation of $\dot{V}_E$ in order to control pH (Burton, Stokes, & Hall, 2004; Powers & Howley, 2012). Apparently, the lactate and carbon dioxide blood contents were not high enough during 1-leg cycling to stimulate $\dot{V}_E$, as $\dot{V}_E$ was lower during 1-leg cycling compared to 2-leg cycling at sub-maximal intensities (Davies & Sargeant, 1974; Freyschuss & Strandell, 1968; Klausen, et al., 1982).

Physiological responses to exercise at maximal intensity

Findings from studies that compared 1-leg and 2-leg cycling at maximal intensities were similar to those from sub-maximal studies, except for the blood lactate contents which were lower during maximal 1-leg cycling compared to maximal 2-leg cycling, instead of higher. During maximal 2-leg cycling, more type II muscle fibers are likely recruited compared to sub-maximal 2-leg cycling (Burton, et al., 2004). As twice as many muscles are involved in 2-leg cycling compared to 1-leg cycling, blood lactate levels are likely higher during maximal 2-leg cycling compared to 1-leg cycling (Klausen, et al., 1982; Shephard, et al., 1988; Stamford, et al., 1978).

Exercise responses in hormonal metabolism

Responses of hormonal metabolism were measured in three of the reviewed studies. Few et al. (1980) showed that the increase of plasma cortisol and aldosterone were higher during sub-maximal 1-leg cycling compared to sub-maximal 2-leg cycling. As a raise in these hormone levels is related to physical stress (Nepomnaschy, Lee, Zeng, & Dean, 2012; Powers & Howley, 2012), these findings suggest that exercises involving low muscle mass are physically more stressful than exercises involving more muscle mass. However, Lewis et al. (1983) and Jensen-Urstad et al. (1994), showed that the level of catecholamines increased more during 2-leg cycling compared to 1-leg cycling. Release of catecholamines is also associated with physical stress and catecholamines and cortisol both increase the mobilization of fatty acids from adipose tissue (Powers & Howley, 2012; Zouhal, Jacob, Delamarche, & Gratas-Delamarche, 2008). Moreover, catecholamines increase HR, stroke volume and stimulate respiratory functions (Powers & Howley, 2012; Zouhal, et al., 2008). Therefore, higher levels of catecholamines during 2-leg cycling explain the higher ventilatory and circulatory responses during 2-leg cycling observed in the reviewed studies.

Theoretical background

Results showed that sub-maximal and maximal cycling involving more active muscle mass induced higher levels of catecholamines and higher circulatory and ventilatory exercise responses compared to cycling involving less muscle mass. These results are in line with the broad notion that exercising skeletal muscles co-function as secretory organs, producing and releasing biochemicals that are involved in the bodily coordination of homeostatic responses to exercise. It has been suggested that myokines are likewise important signals towards improved homeostasis (Pedersen, Akerstrom, Nielsen, & Fischer, 2007). However, no results of studies comparing myokine production during 2-leg versus 1-leg exercise protocols have been described in the literature. As such, we omitted any in-depth analysis of the role of these bioactive compounds in this subject matter.

We do acknowledge that by taking this focus, we are leaving an important parameter that is relevant for endurance performance unattended: central command (Figure 2). It has been shown that active muscle mass affects cardiovascular drift, that is the progressive rise in HR accompanied by a decline in stroke volume, followed often by a drop in cardiac output and mean arterial pressure (Kounalakis, et al., 2008). A larger cardiovascular drift was found in 2-leg compared with 1-leg exercise at the same oxygen uptake per leg, suggesting that central command plays a role on cardiovascular regulation during steady state exercise performed with large muscle mass (Kounalakis, et al., 2008). For static isometric handgrip exercise, on the other hand, several experiments have been conducted on active muscle mass and skin sympathetic nerve responses (Wilson, Dyckman, & Ray, 2006), where no effects of muscle mass were found. Similar results were found for isometric knee-extensor exercise (Ray & Wilson, 2004). These contradictory findings raise doubt about the relation between active muscle mass and central command. On the other hand, this also stresses the necessity to look into endurance performance and whole body exercise as a separate area, as done in the present study.

Limitations

Comparison of results was complicated due to the fact that for both sub-maximal and maximal cycling tests the protocols varied considerably between different studies. Specifically, the cycling workload was either incremental or constant, workloads for 1-leg cycling ranged from 70 to 200% of the relative 2-leg workload (in $\%\dot{V}O_{2peak}$) and from 35 to 100% of the absolute 2-leg workload (in Watts), cycling frequency ranged from 45 to 98 rpm, a counterweight was used or not and feet were strapped to the pedals or not.

Any of these disparities may have influenced the outcome. For instance, it is not surprising that studies that tested participants at higher relative workloads during 1-leg cycling, noticed higher physiological responses during 1-leg cycling (Neary & Wenger, 1986; Ogita, et al., 2000). This was also demonstrated in a study by Abbiss et al. (2011), who reported superior training benefits in maximal self-paced 1-leg cycle training compared to 2-leg cycle training. Significantly more work was performed during 1-leg cycle training and the training effects were likely the result of higher individual leg power outputs. Furthermore, varying cycling frequencies between studies might result in different muscle activation patterns during pedaling, and thus differences in physiological responses. With respect to the use of counterweights, Burns et al. (2014) stated that the use of a counterweight during 1-leg cycling induces comparable circulatory responses as during 1-leg cycling without a counterweight. However, this statement cannot be confirmed by the results of the present review. In fact, it will be likely to assume that other muscles, such as muscles in the upper body and flexors in the legs, need to work harder during 1-leg cycling without a counterweight compared to 1-leg cycling with counterweight. This large range of exercise protocols showed the necessity of standardizing the exercise protocols in future studies in order to compare and interpret the results.

Practical implications

Understanding the role of active muscle mass in the regulation of endurance performance can be particularly helpful for training and rehabilitation of subjects that have a relatively small muscle mass available, as it can result in evidence-based improvements of exercise programs. While the included studies were difficult to compare due to protocol variations, the present review seems to suggest that exercises involving less muscle mass induce less physiological responses compared to exercises involving more muscle mass. Such smaller responses likely lead to limited central adaptations, and might partly explain the relatively low physical capacity and higher fatigue complaints of persons who have less active muscle mass available. These findings imply that able-bodied persons as well as persons with a diminished available active leg muscle mass might benefit from exercise regimens that also recruit arm muscle mass, such as use of a combined arm-leg ergometer (Simmelink, Wempe, Geertzen, & Dekker, 2009; Simmelink, et al., 2015). This optimally stresses the release of biochemicals and hence the modulation of central adaptations to exercise, which will probably increase physical capacity and decrease fatigue. In addition, during exercises involving low muscle mass, energy seemed to be produced less efficiently, possibly due to recruitment of more type II muscle fibers. Anaerobic exercise induces peripheral adaptations in the active muscles and will improve the oxidative potential and metabolic profile (Abbiss, et al., 2011), which could be helpful for persons exercising with diminished active muscle mass. Because of the different physiological responses in 2-leg and 1-leg cycling, exercises involving limited muscle mass likely require different training strategies. When formulating specific training guidelines for able-bodied persons or particular patient populations, it is necessary to consider whether central versus peripheral training adaptations, or a combination of both, is desired. The desired training adaptations should be leading in electing exercises involving different amounts of muscle mass.

Conclusions

Results of the present literature review seem to indicate that active muscle mass might be a crucial factor in the regulation of endurance performance, potentially requiring different strategies in sports performance as well as in daily life activities. Results suggest that anaerobic training or exercise regimens recruiting more muscle mass, such as combined arm and leg exercise, could be beneficial for patient populations who have limited muscle mass available. Lastly, a large range of exercise protocols was found in the present literature review, which hampered comparison and coming to unequivocal conclusions. Standardization of the exercise protocols in future studies is therefore recommended, in particular for sub-maximal intensity.

Author contribution

MV wrote the first draft of the manuscript and MV and LM conducted the literature search. MV and FH performed the risk of bias assessment. MV, FH and LM contributed in acquisition and presenting data, and FH, JJ and MV contributed to the interpretation and conception of the work. All authors (MV, FH, LM, JJ) were involved in drafting, editing and final approval of the manuscript.

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