ARTICLE

Dosing Exercise to Regulate Cardiometabolic Risk Among People Requiring Cardiac Rehabilitation

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GORDON, B.A., E.B. PARR, and M.G. SCHULTZ. Dosing exercise to regulate cardiometabolic risk among people requiring cardiac rehabilitation. *Exerc. Sport Sci. Rev.*, Vol. 53, No. 3, pp. 141–149, 2025. *Exercise is a crucial component of cardiac rehabilitation; however, lack of physical assessment and consideration of the full cardiovascular risk profile limits individualization and potentially effectiveness. We propose a model to prescribe exercise dose, dosing, and dosage that considers cardiorespiratory fitness, strength, blood pressure, glucose, and cholesterol concentrations, along with medications and nutrition to improve individual outcomes from cardiac rehabilitation.* **Key Words:** cardiovascular disease, exercise, blood pressure, cholesterol, glucose, cardiac rehabilitation

KEY POINTS

- There is a need for tailoring exercise programs based on an initial assessment of physical capacity, considering both aerobic and resistance exercises, along with nutritional and pharmacological interactions.
- Exercise intensity may not be the most crucial factor; rather, the appropriate mode and duration of exercise are key to improving cardiovascular health and reducing cardiac event risk.
- Aerobic exercise benefits those with moderate to high cardiorespiratory fitness and lower blood pressure, whereas resistance exercise is recommended for individuals with low fitness and high blood pressure.
- Although beneficial, high-intensity interval exercise can induce physiological stress affecting lipid metabolism and should be carefully considered for those with elevated cholesterol levels.
- It is important to consider the full profile of cardiorespiratory fitness, muscle strength, blood pressure, and cholesterol/glucose concentrations for exercise prescriptions. Regular re-evaluations are necessary to adjust exercise dosages and ensure continued effectiveness.

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INTRODUCTION

Exercise is considered an integral component of cardiac rehabilitation, which has developed in its approach since the 1960s (1). Guidelines for providing cardiac rehabilitation have been developed within most countries and regions around the world; however, despite a significant amount of investigation and research, a lack of consensus to the approach remains (2). To prescribe exercise for optimal benefit, the approach should be individualized, and this is indeed emphasized in guidelines. However, the implementation of outpatient cardiac rehabilitation appears to be driven more by the diagnosed condition or provided cardiac intervention, rather than an individual's physical ability (3). It is likely that prescribing exercise based on the condition or intervention is guided by the desire to do no harm and reduce risk, driven through a lack of facilities and resources to deliver the best possible and most efficacious care.

Recent evidence demonstrates that high-intensity interval exercise does not induce any greater cardiovascular risk than moderate-intensity continuous training (4,5), and including resistance training in conjunction with aerobic training improves physical function and blood pressure (BP) more than aerobic training alone (6,7). Despite the evidence for prescribing high-intensity interval exercise and resistance exercise, high-intensity interval exercise is rarely prescribed within cardiac rehabilitation (8,9) and resistance training appears infrequently in guidelines (2), reinforcing the clinical approach to do no harm. The reasons for not fully considering all client data are not clear, but to achieve the best possible outcomes for individuals undertaking cardiac rehabilitation, evidence-informed exercise prescription is necessary, which requires careful and comprehensive individual assessment and evaluation.

Although there is good evidence for exercise-based cardiac rehabilitation to reduce cardiovascular risk, attendance is poor and rates of subsequent cardiac events are increasing (10). Therefore, a new or revised approach to prescribing and implementing exercise for the purpose of cardiac rehabilitation needs to be determined. We propose that this revised approach should focus primarily on current physical capacity and markers of cardiometabolic risk, and we will demonstrate their importance throughout this brief review. Depending on the individual risk profile, it is possible that low- to moderate-intensity, high-duration exercise might be more beneficial in comparison to high-intensity, low-volume exercise, and vice versa. The physiological responses to prescribed exercise could be influenced by the pharmacological recommendations and nutritional practices of the individual, which do not appear to be considered in current guidelines for exercise prescription within cardiac rehabilitation. Therefore, this brief review will present evidence to support the hypothesis that exercise for therapeutic reasons within cardiac rehabilitation should be prescribed in a medicalized way to consider dose, dosing, and dosage that utilizes various objective data to ensure individualization and consider interactions between pharmaceutical agents and nutrition.

EXERCISE DOSE, DOSING, AND DOSAGE IN CARDIAC REHABILITATION

The evidence that we present in this brief review demonstrates that physiological adaptation and subsequent health outcome improvements are associated with exercise stimulus (intensity and time), commonly quantified as exercise dose (11). Unfortunately, exercise dose varies widely within rehabilitation programs and the prescription of exercise is often dictated by available resources rather than best available evidence (12). One of the primary reasons for fluctuations in exercise dose is a lack of agreement regarding the definition of this term. Some consider exercise dose to be time based, others consider it intensity based. A volume-based exercise dose considers both intensity and time, and utilizing a medical model, dose is the amount of something taken at a single point in time.

For exercise, we propose exercise dose should consider intensity and time (considered to be exercise volume) and mode. However, frequency (or dosing) should also be considered (Fig. 1). It is possible that a smaller prescribed dose two or three times a day is as, or more, beneficial than a larger prescribed dose once per day. An important consideration that differs from pharmacological prescribing is that it usually takes much longer to complete an exercise bout than to administer a pharmaceutical agent. Traditionally, cardiac rehabilitation is completed in a group environment at a health facility one to three times a week. The logistics surrounding this means it is difficult to prescribe anything other than a larger dose, with single dosing (*i.e.*, once a day) for individuals, at least within a supervised setting.

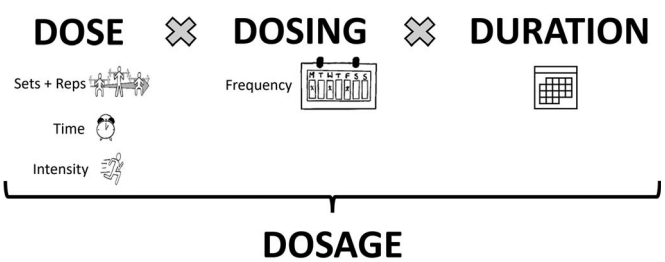

Figure 1. Proposed model for prescribing exercise dosage, which considers dose (mode, volume/time, intensity), dosing (frequency), and duration.

The final element of the prescription matrix is duration, which allows for a total dosage to be prescribed. There is general acceptance that progression of exercise needs to occur every 4–12 wk to promote continued adaptation; however, there is a dearth of evidence to provide guidance on what is an appropriate duration, and, therefore, dosage. Although it is important that exercise be encouraged to be a lifelong pursuit, within a rehabilitation context it is important to understand the desired effect and how to achieve that, including adjusting the prescription periodically. There are many approaches to exercise progression that are implemented, most of these based on clinician feel or historical approaches, and we have demonstrated the inconsistencies in this practice (13). However, adjusting exercise prescription is challenging due to the lack of follow-up testing, amplified by the lack of initial testing, of exercise capacity and other cardiovascular risk factors (8,9). In currently unpublished data from our group (Collins, BE. Unpublished data, 2024) evaluating exercise dosage for people with cardiovascular disease, there is no clear optimal dosage that results in further improvements to peak oxygen uptake ($\dot{V}O_{2peak}$), with something being better than nothing. Although, the lack of an incremental response is possibly due to the chronic lack of investigation of alternate doses, dosing, and dosages from what is considered effective.

THE INFLUENCE OF PHYSICAL CAPACITY ON PRESCRIBED EXERCISE

Low cardiorespiratory fitness is an identified risk factor for initial and subsequent cardiac events. Therefore, initial physical capacity should be evaluated. Tests such as a cardiopulmonary exercise test (CPET) or the 6-minute walk test (6MWT), are commonly conducted to gain insights into an individual's aerobic capacity, functional status, and potential physical limitations (14). However, the 6MWT does not always provide an accurate indicator of function. Such evaluations at the onset of rehabilitation contribute to risk stratification and are vital for determining the initial exercise intensity that a patient can safely tolerate (15). Risk stratification ensures that exercise prescription aligns with the individual risk profile, enhancing safety and effectiveness, while facilitating alignment with guidelines for cardiac rehabilitation, which generally recommend starting exercise at 40%–60% of $\dot{V}O_{2peak}$. Personalized exercise prescription following appropriate assessment and risk stratification considers an individual's initial physical capacity and tends to yield better adherence and outcomes compared to more generalized approaches (16). Although the EXercise Prescription in Everyday practice & Rehabilitative Training (EXPERT) tool has attempted to bring a number of the proposed personal data together to inform exercise prescriptions (16), there remains limitations in the completion of appropriate exercise testing within rehabilitation programs to properly inform the tool inputs, and the tool is yet to be widely adopted within clinical practice.

We have identified that exercise prescription as part of the clinical delivery of cardiac rehabilitation is not routinely based on exercise testing outcomes (13), with individuals having low exercise capacity being prescribed exercise intensities that were

high or vigorous relative to their baseline capacity (beyond the current recommendations) (3). Data from the United States suggest that less than 20% of participants complete a CPET, and that physical assessment data are used to guide exercise prescription in only 16% of individuals (8). In Australia, more than 90% of cardiac rehabilitation participants have their physical capacity evaluated by the 6MWT (9). The 6MWT is appropriate to determine prognosis for morbidity and mortality, but it is not reliable for determining exercise capacity due to the lack of progressive increases in intensity. Therefore, the default for prescribing exercise within cardiac rehabilitation is to use heart rate-based formulas or rating of perceived exertion to prescribe exercise intensity (8). This is not an evidence-informed approach and is not likely to achieve systematic improvements in physical capacity or cardiovascular risk, and a modification to the current approach is required. It is apparent that individual cardiovascular risk factors are not widely considered when prescribing exercise within cardiac rehabilitation, and, therefore, we propose an approach that recommends a battery of objective measurements be completed as routine practice to be considered and used to guide exercise prescription as demonstrated in Figure 2.

THE EFFECT OF EXERCISE ON BLOOD PRESSURE REGULATION

It is well understood that exercise has extensive acute and chronic effects on the cardiovascular system. Although difficult to view in isolation from cardiac structure and function, acute and chronic exercise of various forms will directly modify arterial structure and function. The direct mechanisms and mode of action of exercise on the vasculature have been extensively reviewed elsewhere (17). However, it has been hypothesized that it is the chronic/repeated exposure to acute exercise-induced changes in blood flow, BP, and arterial shear stress that alter endothelial and smooth muscle cell function and drive structural arterial changes (18). Broadly speaking, vascular changes may be region specific and appear sensitive to the type and intensity of the exercise dose. For example, endurance-trained individuals show large changes in brachial arterial diameter, with individuals undertaking mixed training (endurance and resistance) showing greater diameter change in the femoral artery (19). This suggests that arterial adaptations to chronic exercise may result from localized arterial differences, with vascular remodeling occurring because of specific hemodynamic functions that depend on exercise modality (20). Arterial

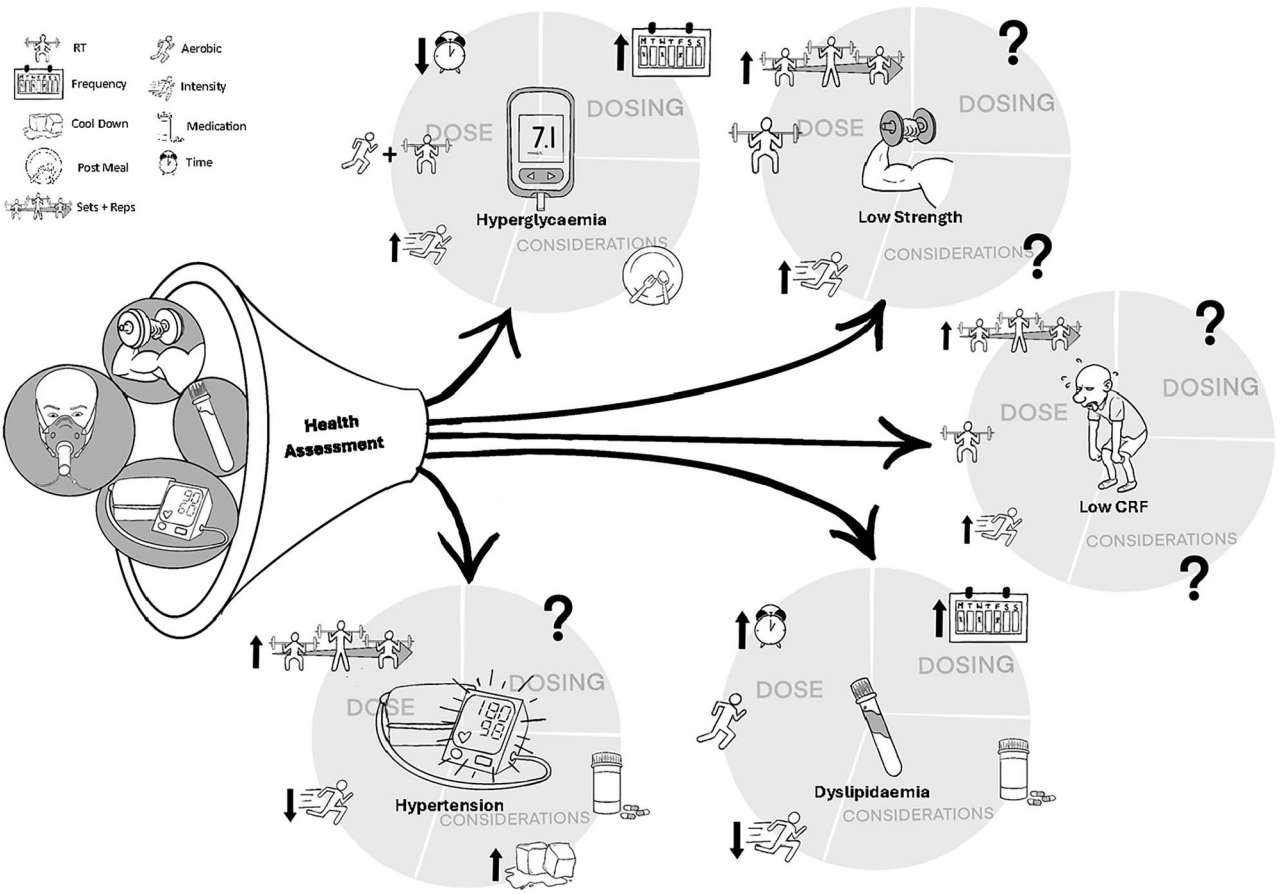

Figure 2. Proposed model for prescribing exercise dose and dosing with consideration of objective health data (cardiorespiratory fitness, muscle strength, blood lipids and glucose, blood pressure) and other factors such as medication and nutrition. The guidance provided surrounding the prescription factors for each outcome (the central icon) are based on various outcomes from studies referenced elsewhere in this manuscript. Where there is no clear evidence to make a recommendation, the prescription factor is either not represented or a question mark is identified. *The prescription factors should be considered as being on a continuum, with arrow representing the direction, *i.e.*, higher or lower, rather than absolutes of high and low. Clinical decision-making is still required for multiple risk factors and comorbidities.

diameter contributes to systemic vascular resistance and, in turn BP, and, therefore, increased arterial diameter is a critical outcome to achieve and should be measured through reduced BP. Ultimately though, it is important to evaluate BP to guide the mode of exercise to be prescribed to achieve the desired hemodynamic function and provide cardioprotective benefits.

In the context of cardiac rehabilitation, it is perhaps of most relevance to understand the regulation of vascular risk markers that can be easily measured and monitored over time. The leading risk factor for cardiovascular disease is high BP (hypertension) (21). Although BP may be considered a "surrogate" vascular risk marker, the expectation is that most patients referred to cardiac rehabilitation would have high BP and be undergoing pharmacological antihypertensive treatment. BP is also perhaps one of the simplest arterial/vascular markers available for routine measurement in cardiac rehabilitation to assist in guiding exercise prescription. Importantly, exercise, both acute and chronic, of various modalities is unique in the context of BP regulation in that it can aid in the prevention, identification, and management of cardiovascular disease risk (as discussed next). Thus, a thorough awareness of BP status prior to participation within cardiac rehabilitation and monitoring throughout exercise sessions (both at rest and during exercise) will enable individualized exercise prescription that targets appropriate cardiovascular regulation and risk reduction.

Prevention

There exists a dose-response relationship between cardiorespiratory fitness and relative risk of hypertension, where a one-metabolic equivalent (MET) improvement in fitness is associated with an 8% reduction in risk of hypertension (22). Importantly, there is also likely no upper limit to physical activity (in terms of dose [intensity or volume]) detrimental in those with established hypertension (23). In terms of secondary prevention, higher fitness protects against progression from prehypertension to hypertension (24), as well as cardiovascular mortality among those with established hypertension or undergoing assessment for coronary artery disease via exercise stress testing (25). Although improved cardiorespiratory fitness following cardiac rehabilitation is an important goal (current targets set at one-MET), there is minimal reported difference in MET improvements of ~0.33 METs with exercise ranging from moderate to vigorous intensity (26). Therefore, the prescription of exercise intensity should be made in consideration of vascular risk and known responses, although manipulating volume (for adjustment of dose) and dosing to optimize improvements in vascular health and cardiovascular risk.

Identification of the Acute BP Exercise Response

Through a hemodynamic lens, BP in its simplest form can be viewed as the product of cardiac output and systemic vascular resistance, and as such is sensitive to exercise-induced changes in either parameter. Upon initiation of acute dynamic aerobic exercise, cardiac output will increase and, under normal circumstances, systemic vascular resistance will decline, with the combined effect of raising systolic BP and maintenance of diastolic BP. As reviewed elsewhere (27), the increase in cardiac output is mediated though the interplay of cardiovascular processes including parasympathetic withdrawal, metabolic and endothelium-dependent vasodilation, and systemic sympathetic activation to ensure an adequate balance in blood flow to active skeletal muscle (and to a lesser extent cardiac muscle) and maintenance of systemic perfusion pressure to supply other physiological systems. Alterations in vascular structure and/or function (including endothelial dysfunction, decreased large artery compliance, and coronary artery flow reserve) that can occur with aging and the disease process (likely common among participants referred to cardiac rehabilitation) can result in a disruption to the complex balance in cardiac output and systemic vascular resistance during exercise, affecting BP regulation (28–30). Indeed, these alterations underlie a stiffened vascular system and may impair blood flow runoff and reductions in systemic vascular resistance during dynamic aerobic exercise, which will be insufficient to buffer exercise-induced increases to cardiac output. As a result, although diastolic BP will remain largely unchanged with exercise, systolic BP may dramatically increase. This condition is termed a hypertensive response to exercise (31), and is often defined as a systolic BP exceeding 210 mm Hg for males, and 190 mm Hg for females at maximal/peak intensity aerobic exercise. Although extensively discussed elsewhere (31,32), a hypertensive response to exercise is also possible during submaximal exercise of light-to-moderate intensities. When recorded at submaximal exercise intensities, a hypertensive response to exercise is a sign of uncontrolled high BP and is associated with poor cardiovascular outcomes, irrespective of cardiovascular disease and BP status (31). Thus, a hypertensive response to exercise is a useful marker upon which to follow up care for management of cardiovascular risk related to hypertension (32), however, is one that is not commonly measured or considered in prescribing exercise within cardiac rehabilitation. We propose that exercise BP should become an important marker to be evaluated when entering cardiac rehabilitation, alongside resting BP, to inform both exercise mode and intensity and to guide BP management.

Although it is beyond the scope of this article to extensively review the acute BP response to resistance exercise, it is suggested that BP will respond in a similar way (albeit possibly with a higher elevation) to aerobic exercise (33). The elevation in BP response with resistance training could be due to a pressor effect, associated with the Valsalva maneuver (33). The Valsalva maneuver can drive large elevations to intrathoracic pressure and both systolic and diastolic BP. However, the large muscular arteries are able to withstand large distending pressures (34), and so resistance training supervised and with emphasis on technique remains a safe and efficacious therapeutic modality in those with cardiovascular disease and high BP. Importantly, from the limited evidence available, lower intensity resistance training might produce a higher BP response than higher intensity (33), meaning that all clinical and prescription factors should be considered when designing an exercise program for cardiac rehabilitation.

Management of the Chronic BP Profile

Increasing $\dot{V}O_{2peak}$ improves both systolic and diastolic BP, in turn reducing cardiovascular risk. Thus, guidelines have traditionally emphasized dynamic (endurance based) aerobic exercise up to and including a moderate intensity as the most efficacious type of exercise to improve cardiovascular risk related to BP (35,36). However, evidence from meta-analyses of randomized controlled trials suggest that training consisting of various

intensities, durations, and modalities can induce large reductions in BP. These changes, on average, are 2–4 mm Hg in those with normal BP and prehypertension, and appear greater [reductions up to 8/5 mm Hg in-clinic (office) BP] among those with established hypertension (37,38). Both endurance exercise and dynamic resistance exercise in isolation or combined appear to have similar effects on lowering both systolic and diastolic BP (7). There is emerging evidence of the antihypertensive effects of isometric resistance training, and although BP reductions appear profound (with reductions in systolic BP >8 mm Hg demonstrated) (7), caution has been suggested for the application of isometric resistance training in isolation to other modalities (39). Recent data also indicate that high-intensity interval exercise is safe among those with established cardiovascular disease, and if prescribed under close supervision may provide comparable BP reductions to that of moderate-intensity and continuous aerobic exercise training (5). Such findings suggest that it may not be intensity per se that is the important modulating factor in relation to BP, but the combination of mode, intensity, and time (exercise dose) that becomes important to consider when prescribing exercise. Making appropriate evaluations of an individual, rather than a specific risk factor, considering objectives other than simply to reduce BP are important to guide the exercise prescription to provide an appropriate balance of modalities, dose, and dosing.

THE EFFECT OF EXERCISE ON GLUCOSE AND LIPID REGULATION

As reviewed extensively elsewhere (40,41), the acute and chronic effects of aerobic exercise improve both glucose and lipid regulation. Metabolic status (type 1 or 2 diabetes) and high blood lipids are both risk factors for cardiovascular disease. There is consensus that the effects of a single exercise session are experienced for 24–48 h for systems that influence blood glucose. For individuals with type 1 diabetes attending cardiac rehabilitation, there is generally evaluation of blood glucose concentrations prior to exercise and checking of meal status. For individuals with elevated blood lipid (hypercholesterolemia), the evidence supporting exercise is less clear and there is a strong reliance for treatment placed on statin therapies. Due to limitations on point of care measures, cholesterol profiles are not frequently measured during cardiac rehabilitation.

Identification of the Acute Metabolic Exercise Response

Glucose

Specifically, acute (30–60 min) submaximal exercise induces insulin-independent pathways for increased glucose oxidation (42), lowering glucose concentrations in people with elevated glucose concentrations (*i.e.*, insulin resistant, prediabetes, type 2 diabetes). Similarly, high-intensity exercise increases glucose utilization for periods of 24–72 h (43). Acute continuous moderate-intensity aerobic exercise also lowers postexercise glucose levels, but the reduction does not persist through until the next day (44). The acute glycemic response might not be dependent on exercise intensity but on energy expenditure, which is a function of intensity and time (45) and is considered exercise dose in our proposed model.

Lipids

Although not always observed, acute exercise can reduce circulating lipid concentrations (total cholesterol and low-density lipoprotein), while increasing high-density lipoproteins (46). There is evidence though of increased metabolic fat oxidation after high-intensity exercise that might contribute to lipid adaptations (47). There are also known anti-inflammatory properties of exercise, which help mitigate dyslipidemia, and we have demonstrated a potential difference in response of inflammatory biomarkers following exercise of different modalities (high-intensity interval vs resistance exercise) (48). Therefore, it is important to consider that individuals with elevated circulating blood lipids will have increased systemic inflammation, and the prescription of modality and intensity of exercise is important to not elevate stress and inflammatory makers more than necessary while promoting the highest intensity and duration of exercise possible.

Management of the Chronic Metabolic Profile

Glycemia

Extensive dosing of aerobic exercise induces normalization of blood glucose in those without diabetes and plays an integral role in supporting appropriate time in range glucose concentrations for those with type 2 diabetes (49). Further, we have demonstrated that more frequent (3 times daily) short (10 min) bouts of moderate-intensity walking after meals is more effective to modulate glucose response than a single 30-minute bout each day (50). Combined, these data suggest that the frequency of exercise should be somewhat dependent upon the intensity of exercise that is prescribed, with the initial glucose concentration and metabolic status (insulin resistant, prediabetes, diabetes) important to be considered. These considerations further highlight a need for routine blood glucose monitoring in cardiac rehabilitation to guide the adaptation of exercise dose and dosing.

Lipidemia

Lipid utilization during exercise is upregulated following regular exercise. Such responses are attributed to enhanced lipid metabolism and increased activity of enzymes like lipoprotein lipase, which contributes to metabolizing triglycerides (51). Although an adaptation of poor metabolic health is to have lipids/fat stored within the muscle, ironically an adaptation to high amounts of exercise training (*i.e.*, in athletes who typically have good metabolic health) is also to have high concentrations of intramuscular triglycerides, even in people with pathologies (52). Consequently, high concentrations of intramuscular triglycerides enable lipid stores to be preferentially utilized during exercise, thus, reducing the formation of blood lipids (total cholesterol and low-density lipoproteins) and promoting better lipid homeostasis. The intensity and duration of exercise play crucial roles in these lipid adaptations. Higher intensity and longer duration exercise are associated with more significant improvements in lipid profiles (53). It is likely that improved lipid profiles are related, in part at least, to energy expenditure and, therefore, exercise dose becomes an important consideration. Because elevated fat oxidation seems to occur with increased exercise intensity, a careful consideration of exercise intensity and volume is required to promote lipid metabolism

without stimulating an inflammatory response to contribute to further dyslipidemia.

INFLUENCE OF PHARMACOLOGIC AGENTS ON EXERCISE DOSE

Despite oral antihypertensive and hypoglycemic agents existing since the 1950s and 1960s (*i.e.*, thiazides and metformin), there is still limited knowledge of how the pharmacotherapy timing affects exercise responses and vice versa.

Cardiac Effects

The most relevant considerations to performing exercise in those prescribed common antihypertensive and cardioprotective medications is a requirement to consider appropriate cool-down periods in those taking vasodilator drugs, calcium channel, or alpha blockers to reduce the risk of hypotensive (excessive BP lowering) episodes (54). These cool-down periods might need to be manipulated dependent on exercise dose. Beta-blockers, besides their obvious heart rate-limiting effects, may impair thermoregulation during exercise (55), and, thus, appropriate mitigation steps to ensure exercise in a cool (or at least not hot) environment should be taken. In some climates, this could involve avoiding exercise at certain times of the day, which might implicate consideration of nutritional intakes. Importantly however, exercise training when combined with antihypertensive pharmacotherapy increases the magnitude of BP reductions compared to medication alone, thus, improving overall cardiovascular disease risk (56). Therefore, a carefully considered exercise program must be prescribed to those taking medications to reduce BP. The mechanisms for exercise exaggerating the pharmacologic BP response are yet to be determined and would benefit from further investigation, but could include concepts such as improved blood flow and transport, increased metabolism, and/or improved translocation and binding.

Metabolic Effects

The immediate consequence of some oral hypoglycemic agents is gastrointestinal distress, and, thus, are recommended to be taken with food. However, it has only recently been presented that the glucose-lowering effects of hypoglycemic agents are more effective when taken before food (57). Similarly, as an exploratory finding of their exercise timing study, Carrillo et al., (58) reported glucose area under the curve (as a measure of glucose tolerance) was reduced when metformin was taken before breakfast and exercise was performed in the morning. Interweaving these findings into exercise guidelines will take further evidence, but collectively demonstrates how the timing of medication, exercise, and meals may be modified to improve individual outcomes.

Single- and dual-agonist hyperglycemic agents (*i.e.*, GLP-1, GIP, GIP/GLP-1) have proven extremely effective for reducing body mass (59–61) but are yet to be extensively studied with exercise (62) in terms of body composition, exercise capacity, or physical function outcomes. In contrast to insulin or sulfonylureas, GIP/GLP-1 agonists or combined agents pose a low risk to cause hypoglycemia due to their once-weekly administration and long half-life. Therefore, it may be less important to prescribe exercise around the administration of these pharmacological agents. In combination though, exercise training and GLP-1 administration has been demonstrated to be more effective for weight management following an 8-wk energy-restricted diet compared to GLP-1 or exercise alone (63). Therefore, it is important to consider how best to prescribe exercise in consideration of nutritional intake to maximize the effectiveness of both GIP/GLP-1 medications and energy restriction for weight management, with minimal considerations required for glucose regulation.

THE INFLUENCE OF NUTRITION (WHAT AND WHEN) ON EXERCISE DOSE

Acute Nutrition and Exercise Effects

The timing of energy intake and physical activity are integral for metabolic health, where energy intake and physical activity interact to manipulate physiological responses. Much of the literature regarding the integration of exercise and meal timing describes fasted versus fed exercise in the morning (64), and pre- versus postprandial exercise throughout the day (65,66). However, a systematic review of adults assessing changes in BP and glucose concentrations found no acute time-of-day exercise benefit (67). Acute exercise can have either appetite-suppressing or increasing effects, depending on the individual (68), thus, it is difficult to ascertain the inferential effects on dietary intake from time-of-day exercise studies. Despite some nuanced findings (69,70), exercise in the postprandial state might be preferred, especially for metabolic outcomes (50,71). When clinical conditions have been investigated, there is some evidence for beneficial effects of afternoon exercise for those with type 2 diabetes (69) and morning exercise for cardiovascular disease prevention (72). Therefore, exercise at any time remains a key recommendation compared to no exercise for any outcome studied (69,70). Considering the barriers to exercise participation, adding a further barrier of requiring prescriptive time-of-day exercise is likely to either exacerbate or have no change to the low participation rates.

Chronic Nutrition and Exercise Effects

Several dietary timing strategies independently impact on health outcomes exclusive of exercise patterns. Daily interventions such as time-restricted eating, often referred to as the 16:8 diet, where energy intake is restricted to 4–10 h during daylight periods, has been demonstrated to improve parameters of metabolic health (such as insulin sensitivity, BP, and 24-h glucose concentrations) without reductions in energy intake (73). Importantly, we measured no impact on muscle protein synthesis when following time-restricted eating compared to a 12-h control diet of the same meals (74). This suggests that time-restricted eating strategies will not negatively impair potential physiological responses to exercise, nor effect dose or dosing. In contrast to time-restricted eating, but usually mentioned under the same umbrella, intermittent fasting interventions such as alternate-day fasting or the 5:2 diet (2 days of very low energy intake) require intentional weekly energy reduction to induce improvements to metabolic health, including reduced body weight (75). However, the beneficial outcomes of intermittent fasting are not superior to those induced by continuous energy restriction, as evidenced by a recent systematic literature review and meta-analysis (76), nor are they going to provide outcomes that reflect those of exercise training studies (*i.e.*, increased

cardiorespiratory fitness, increased strength and mobility). Therefore, intermittent fasting may be utilized if adherence to typical daily energy restriction is low, but consideration of consequential physiological responses to exercise (completed in either a fasted, preprandial, or postprandial state) will be important (77).

SUMMARY

Exercise is an essential component of managing cardiovascular disease and its individual risk factors, demonstrating substantial benefits for reducing morbidity and mortality. The data presented underscores the importance of individualizing exercise prescription based on an initial assessment of physical capacity, to determine the appropriate dose of both aerobic-based and resistance-based exercise and considering nutritional and pharmacological interactions. The data presented demonstrates that exercise intensity is unlikely to be the most important factor to generate improved cardiometabolic health and reduced risk of subsequent cardiac events. This is not to suggest that intensity is not important, but when prescribed exercise appropriately considers mode, time, frequency, and duration to provide the necessary stimulus, and, therefore, concepts such as exercise dose and dosing demonstrate more relevance. Individualizing these factors could enhance exercise adherence to magnify the known positive outcomes.

Considering that any exercise is good exercise, and something should be recommended over nothing, it should be considered that there is a continuum as to which mode of exercise should be prescribed in any specific scenario. Aerobic-based exercise is most likely effective for individuals with moderate to high cardiorespiratory fitness and lower BP. Resistance-based exercise might be more effective for individuals with low cardiorespiratory fitness and exercise capacity and high BP. Although, it is recommended in either circumstance that both aerobic-based and resistance-based exercise are prescribed but it is key to emphasize one mode more than the other to achieve the best outcomes relative to health and adherence. High-intensity interval exercise, although beneficial in most scenarios, induces physiological stress, which might have negative consequences on lipid metabolism, and, therefore, needs careful consideration in those with elevated total and low-density lipoprotein concentrations. It is also apparent that shorter, more frequent exercise dosing (frequent bouts) might be advantageous for some markers of cardiovascular health and should be considered as appropriate. Clinical decision-making will remain to adjust the prescriptions to accommodate multiple risk factors or comorbidities that most individuals will present to cardiac rehabilitation with.

Therefore, it is important to consider the complete individual profile of cardiorespiratory fitness, muscle strength, BP (both at rest and during exercise), blood cholesterol, and glucose profiles to prescribe exercise for cardiac rehabilitation. Further, it is important to align these with the expected responses to optimize the prescription around pharmacologic agent administration and nutritional intake. Although the identified factors are important to consider, the complete individual profile might also include other pathologies not considered in this brief review and sociodemographic factors that might dictate how or when exercise is prescribed. Furthermore, regular reevaluation of these markers is important to guide the progression and adaptation of exercise to ensure the appropriate dosages are prescribed and individuals do not become complacent about the process while maximizing the outcomes.

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