

## Review Article

# Reduced Cardiorespiratory Fitness after Stroke: Biological Consequences and Exercise-Induced Adaptations

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Evidence from several studies consistently shows decline in cardiorespiratory (CR) fitness and physical function after disabling stroke. The broader implications of such a decline to general health may be partially understood through negative poststroke physiologic adaptations such as unilateral muscle fiber type shifts, impaired hemodynamic function, and decrements in systemic metabolic status. These physiologic changes also interrelate with reductions in activities of daily living (ADLs), community ambulation, and exercise tolerance, causing a perpetual cycle of worsening disability and deteriorating health. Fortunately, initial evidence suggests that stroke participants retain the capacity to adapt physiologically to an exercise training stimulus. However, despite this evidence, exercise as a therapeutic intervention continues to be clinically underutilized in the general stroke population. Far more research is needed to fully comprehend the consequences of and remedies for CR fitness impairments after stroke. The purpose of this brief review is to describe some of what is currently known about the physiological consequences of CR fitness decline after stroke. Additionally, there is an overview of the evidence supporting exercise interventions for improving CR fitness, and associated aspects of general health in this population.

## 1. Introduction

Little is known about the biology surrounding decrements in cardiorespiratory (CR) fitness after stroke, but evidence has gradually begun to track the damage caused to multiple physiological systems by stroke-related chronic inactivity [1–8]. Collectively, these changes negatively impact morbidity and mortality prospects and contribute to reduced quality of life [9]. Because CR fitness is a measure that quantifies the ability of the heart, lungs, blood vessels, and skeletal muscles to work together to deliver oxygen and remove metabolic byproducts during exercise, it is indirectly reflective of broad categories of cardiovascular, metabolic, and functional health. Most often, CR fitness is measured using a metabolic cart for gas analysis and exercise equipment (e.g., treadmill,

recumbent stepper, or cycle ergometer) to determine peak oxygen-consuming capacity ( $\text{VO}_2$  peak) and is quantified during exercise to complete exhaustion [10–16].

CR fitness varies according to age, gender, physical activity levels, body composition, and the absence or presence of chronic disease or disability. In the poststroke population, the literature suggests that CR fitness is reduced by as much as 50% when compared to age-matched sedentary counterparts [12, 14]. The extent of deterioration is associated with several clinically relevant biological correlates which were the focus of this review.

It remains unclear whether reduced CR fitness after stroke is due primarily to premorbid conditions, direct effects of the stroke itself, or poststroke physical inactivity. All are likely contributors but understanding the relative

contributions of each will require further research into biological/etiological mechanisms [17]. Whatever the cause, it is important to assess the capacity of stroke survivors to physiologically adapt in response to aggressive rehabilitation therapy interventions. Hence, this review also outlines some of the preliminary progress made in deciphering the physiological benefits of exercise training after stroke. Arriving at a better understanding of the cardiovascular, metabolic, and functional adaptations resulting from a variety of therapy protocols and how these contribute to improved CR fitness is especially important for healthcare providers, rehabilitation specialists, and others working towards the common goal of improving overall health and quality of life in this clinical population.

## 2. Biological Consequences Contributing to Reduced CR Fitness after Stroke

Sequelae of an upper motor neuron lesion include hemiparesis, reduced mobility, impaired balance and in coordination, and diminished proprioceptive feedback [17]. Secondary conditions such as changes in muscle physiology and inflammation [5, 6], impaired hemodynamic response [1, 3, 8], altered metabolic health [18], and, to a lesser extent, respiratory dysfunctions [19] can also negatively influence daily activities and exercise performance. The neuromotor system relies on effective motor unit recruitment and efficient mechanical movement to sustain physical activity and prevent early fatigue [11, 20–22]. Altered neurological input to the periphery and associated disuse profoundly alters skeletal muscle tissue composition in the paretic limb, thereby, contributing to reduced CR fitness and related health problems.

### 2.1. Muscle Physiology after Stroke

**2.1.1. Tissue Composition.** Major structural and molecular abnormalities have been observed in hemiparetic leg muscle [4–7] with serious implications for impairment of strength [23–25], insulin sensitivity [26, 27], mobility function [10, 11, 25], and CR fitness [10, 13, 14, 16, 28]. In addition to severe unilateral muscle wasting and increased intramuscular fat after stroke [7], there is a dramatic shift towards a higher proportion of fast twitch muscle fibers [4, 6], which are more insulin resistant and fatigue prone [29]. There is also preliminary evidence of a reduction in the number of capillaries per muscle fiber in paretic leg muscles with significant relationships between low capillary density and glucose intolerance in this population [30]. Finally, there is a nearly three-fold elevation in the expression of paretic leg muscle tumor necrosis factor-alpha (TNF- $\alpha$ ) [5], an inflammatory cytokine implicated in both muscle atrophy [31], and insulin resistance [32]. These pathological alterations in skeletal muscle represent novel targets for exercise rehabilitation strategies during the poststroke recovery period. Given the increasing numbers of elderly disabled by stroke [33], alternative rehabilitation strategies are needed to specifically address and reverse the effects of paresis on muscle tissue quantity and quality.

On the basis of physiological principles, there is little question that unilateral skeletal muscle changes after stroke contribute to worsening CR fitness and related health changes. A reduction in lean tissue, especially in the larger leg muscles, negatively affects  $VO_2$  and CR fitness [34]. Furthermore, muscle metabolism and the ability to perform specific activities are heavily influenced by fiber type. For example, the ability to successfully engage in endurance activities relies on aerobic metabolism which is primarily driven by slow myosin heavy chain (MHC) isoforms and type I muscle fibers while high-intensity, quick movements depend on the availability of fast myosin heavy chain isoforms and type II muscle fibers [35]. There is evidence that the increased proportion of fast myosin heavy chain isoforms in the paretic limb is inversely correlated with gait speed [6].

These fatigue prone muscle fibers negatively affect community ambulation through decreased gait efficiency and increased energy expenditure. This increased energy expenditure leads to chronic fatigue and can limit ability to perform activity after stroke [36]. Feelings of fatigue and tiredness may further inhibit performance of activities of daily living (ADLs) and instrumental activities of daily living (IADLs).

Sedentary, nondisabled individuals expend approximately 10.5 mL of oxygen/kg/min (3 metabolic equivalents, METS) during light IADLs and about 17.5 of oxygen/kg/min (5 METs) during heavy IADLs and are able to reach a maximum of 8–10 METS [37]. In contrast, people after stroke are only able to reach a maximum of 4–5 METS, making higher level ADLs impossible and lower level ADLs unsustainable [38]. A vicious cycle results when feelings of fatigue during daily activities further reduce activity participation, thereby, compounding CR fitness decline.

**2.1.2. Proinflammatory Markers and Pathways.** Beyond localized up-regulation of inflammatory markers in paretic skeletal muscle, there are also systemic changes in circulating levels with disabling conditions. Specifically, circulating cytokines such as TNF-alpha and IL-6, have been shown to increase with acute myocardial infarction, heart failure, and obesity [39–41]. Elevated levels of proinflammatory markers have also been reported after stroke [42–44] and have been strongly associated with larger infarct size and poor outcomes (i.e., early neurological decline) [44, 45]. Increases in oxidative stress are purported to interfere with vascular function [40, 46, 47] and other aspects of physiology relevant to CR fitness and metabolic health. New onset of hypertension has been reported in individuals after an acute stroke with elevated levels of proinflammatory markers (TNF alpha, IL-6, and VCAM-1) [45]. This suggests that elevated levels of proinflammatory markers may alter peripheral biological mechanisms such as those associated with the endothelial nitric oxide system, contributing to increased vascular resistance, and negatively affecting participation in rehabilitation or adaptive capacity. However, the pathogenesis for the potential relationship between the inflammatory markers and impaired endothelial function after acute stroke is still unclear. Although a detailed description of complex cytokine networks in the context of general health and health

improvement is beyond the scope of this brief review, a more detailed account of this subject is provided in a recent review by Ploeger et al. [48]. Importantly, the causes behind elevated circulating cytokines are complex, and there are gaps in our knowledge about how to intervene against chronic inflammatory disease in stroke and beyond [48].

*Altered Glucose Metabolism after Stroke.* Beyond stroke-induced changes to paretic side tissue composition secondary to altered neurological input, sedentary living and reduced CR fitness also partially contribute to a severe decline in metabolic status. Specifically, insulin resistance and glucose intolerance are highly prevalent after stroke [26, 27], leading to progressive cardiovascular disease risks [49] and predisposition to recurrent stroke [50].

Kernan et al. originally identified a high prevalence of insulin resistance during the subacute stroke recovery period [26]. Subsequent findings in chronic stroke [27] revealed a 77% prevalence of abnormal glucose metabolism. This is clinically relevant given that impaired glucose tolerance and diabetes prospectively predict two- and three-fold increased risk for recurrent cerebrovascular events, respectively [50]. Prospective studies showed that fasting hyperinsulinemia [51] and postload insulin areas during an oral glucose tolerance test (OGTT) [52] predicted risk of future stroke and cardiovascular events. Notably, a large Scandinavian study showed that those in the highest quintile of postload insulin area had a greater than two-fold relative risk of stroke than those in the lowest quintile of insulin area [52]. Thus, epidemiologic research based upon surrogate measures of insulin sensitivity provides powerful evidence that insulin resistance is strongly associated with vascular event risk and recurrent stroke. Generally, physical inactivity is a well-recognized contributor to altered glucose metabolism and insulin sensitivity in all aging populations [53] and may play a particularly large role in stroke survivors [26, 27].

## 2.2. Cardiovascular Regulation after Stroke

*2.2.1. Autonomic Control of Cardiac Function.* The central nervous system (parasympathetic and sympathetic branches) regulates heart rate, cardiac contractility, blood pressure, and vasomotor tone of the blood vessels. Impairments related to autonomic control of blood flow and cardiac regulation can occur after stroke, specifically if the stroke occurs around the parietal and insular cortex [54–56]. One study reported that those individuals with left insular stroke had an increase in cardiac events such as heart failure within one year after stroke [57]. These cardiac complications could have significant effects for cardiac function during activity and exercise. It is well known that people post-stroke have lower heart rates and oxygen consumption at peak effort during a graded exercise test when compared to healthy sedentary age-matched peers [12, 14]. This may be a result of impaired autonomic control of the cardiovascular system in addition to pharmacologic therapy (beta blockers).

*2.2.2. Blood Flow and Vascular Function.* Blood flow distribution is governed by central cardiovascular command

(parasympathetic/sympathetic activity) [54] and peripheral mechanisms, such as metabolic demands, peripheral resistance, and changes in pressure [55, 56]. Changes in either central or peripheral regulation can interrupt normal vascular function. Stroke-related changes in the brain, specifically in areas that regulate autonomic function, can have significant implications for blood pressure control and cardiac function during the acute phase of stroke recovery [57, 58].

In chronic stroke, blood flow in the paretic leg is significantly lower at rest [1–4] and during exercise [4], when compared to the nonparetic limb. These unique unilateral adaptations, not observed in nondisabled young and older adults, can influence performance of ADLs and quality of life [59, 60]. Research suggested that reductions in blood flow occur secondary to decreased levels of physical activity [59, 61], which can affect blood flow velocity, endothelial function, and arterial diameter. A recent study determined that vascular remodeling in the femoral artery occurs in the paretic lower extremity after stroke [2]. The femoral artery diameter and blood flow velocity were significantly reduced in the paretic limb when compared to the nonparetic limb. The femoral artery wall thickness was also significantly greater in the paretic limb, potentially contributing to impaired flexibility of the vessel wall to vasodilate during activity to allow for adequate blood and oxygen delivery.

Most recently, interhemispheric differences in blood flow velocity (BFV) of the middle cerebral artery (MCA) have been shown [62]. The MCA BFV on the ipsilesional side was substantially lower than the contralesional vessel, suggesting that systemic vascular deterioration extends to the brain. More work is needed to determine how systemic and cerebral vascular functions interrelate and the systemic consequences of each phenomenon.

*Respiratory Function after Stroke.* Although not all patients after stroke have overt pulmonary disease [63], respiration may be compromised as a direct result of the stroke itself (particularly brain stem stroke), associated complications (e.g., weakness of respiratory muscles, impaired breathing mechanics), comorbidities (e.g., chronic obstructive pulmonary disease, cardiovascular dysfunction), or lifestyle factors (e.g., physical inactivity high incidence of smoking) [64]. The excessive fatigue experienced by some people after stroke may be partly due to respiratory insufficiency as manifested by low pulmonary diffusing capacity, ventilation-perfusion mismatching, or decreased lung volumes (e.g., vital capacity, total lung capacity, inspiratory and maximal inspiratory capacity, and expiratory reserve volume) [65, 66]. Impaired breathing mechanics with restricted and paradoxical chest wall excursion and depressed diaphragmatic excursion have been also reported [64, 67]. Expiratory dysfunction appears to be related to the extent of motor impairment (e.g., paresis of the hemi-diaphragm and intercostal and abdominal muscles) [65, 68–70]. Inspiratory limitations, manifested by reduced maximal inspiratory pressure [71], are related to reduced chest wall excursion secondary to the gradual development of rib cage contracture [72].

The physiologic impairments described above reduce the ventilatory reserve or the difference between the maximal available ventilation and the ventilation measured at the end of exercise [73] and contribute to low CR fitness levels in the stroke population. At peak exercise performance, people after stroke have significantly lower minute ventilation and tidal volume, but not respiratory rate, compared with control participants [74]. Reductions in lung volumes and chest wall movements can lead not only to decreased exercise endurance, shortness of breath, and risk of sedentary behavior but also increased risk of recurrent stroke [75]. Therefore, exercise interventions designed to improve respiratory muscle strength and pulmonary function should be encouraged.

*2.3. Exercise-Induced Adaptations in CR Fitness and Associated Aspects of General Health after Stroke.* Exercise is a potent physiological stimulus which could induce a wide range of adaptations. These adaptations include improved CR fitness, changes in vascular function and vascular morphology, reduced respiratory effort, and enhanced glucose metabolism and insulin sensitivity.

The capacity of the stroke population to make cardiorespiratory adaptations to aerobic exercise has been demonstrated in numerous training studies. Table 1 summarizes trials individuals in the subacute (<6 months after stroke) and chronic (>6 months post-stroke) stages of recovery. In these studies, the magnitude of change in peak  $\text{VO}_2$  (mean gain of ~12.5%) was comparable to the 10% to 30% improvements (reported for healthy, sedentary adults) [76, 77] and the 13% to 15% gains observed for participants in cardiac rehabilitation [78, 79]. Even the relatively modest gains in CR fitness reported in some stroke exercise studies (e.g., 8% [80], 6% and [81]) may be sufficient to raise the anaerobic threshold, thereby, extending the time during which muscle contractions can be sustained with oxidative metabolism. Interventions which result in even small changes in aerobic capacity may be of clinical significance on the basis of where stroke survivors stand relative to the range of  $\text{VO}_2$  required for general ADLs [10, 37]. Considering the degree to which  $\text{VO}_2$  peak levels have been compromised after stroke, even modest changes in CR fitness will have a greater impact on activities of daily living for stroke survivors than to their age-matched healthy peers.

The considerable interindividual differences noted in most training studies are attributable to many factors, including severity of stroke, time since onset, variations in intensity and mode of training, and level of compliance with the exercise regimen [11, 21, 22, 90]. In studies of people with stable coronary disease, considerable interindividual differences have been observed, of which only a small portion (about 11%) have been attributed to recognized covariates such as initial fitness status and an even smaller percentage (about 5%) to measurement errors [91, 92]. The most rapid improvements in exercise capacity tend to occur in previously sedentary people [93]. Further, it has long been acknowledged that the highest overall relative gains are usually seen in individuals with the lowest initial values of  $\text{VO}_2$  peak [94].

#### *2.4. Exercise-Induced Muscular Adaptations after Stroke*

*2.4.1. General Adaptations.* Several important studies reported that strength training, provided it is progressive and of adequate intensity, can be effective in combating the losses in muscle mass [95], muscle quality [96], and function [97] which typically occur with advancing age. Strength training results in significant muscle hypertrophy in both healthy elderly and frail elderly populations [95, 98]. Several studies also showed that strength training can affect adaptation in skeletal muscle fibers [99–101]. Strength training with high repetitions and a strong endurance component results in higher proportions of Type IIa (fast oxidative) [102, 103], and Type I [101, 104] myosin heavy chain muscle fiber types and is an effective stimulus for fiber hypertrophy in Type I, Type IIa, and Type IIx muscle fibers [101, 105, 106]. High repetition strength training also results in improved muscle capillarization in peripheral arterial disease patients [99] and in healthy populations [107]. Finally, there is evidence that  $\text{TNF-}\alpha$  levels are successfully reduced with strength training in frail elderly humans [31].

*2.4.2. Post-Stroke.* Patients after stroke have been studied far less in the context of strength training. Of the few trials undertaken none have assessed the capacity of strength training to cause skeletal muscular adaptations. However, the results of a recently completed nonrandomized pilot study in chronic stroke [23] has showed that skeletal muscle hypertrophy accompanied by molecular adaptations occurred in both the paretic and nonparetic limbs. Pilot work suggested that functionally and metabolically relevant skeletal muscle tissue adaptations are possible in this population. There is now a randomized study underway to further test the impact of strength training on paretic limb skeletal muscle after stroke (Ivey, PI).

*Metabolic Adaptations with Exercise in Stroke Survivors.* Over the last decade, major advances have been made in the understanding of the effectiveness of exercise and lifestyle interventions to improve cardiometabolic health and prevent progression to diabetes in high-risk nonstroke populations. The Diabetes Prevention Program showed that lifestyle interventions based upon low-intensity exercise and weight loss were more effective than metformin (58% versus 31%) to prevent progression to diabetes in high-risk individuals, which occurs in ~10% of controls annually by natural history [53]. Preliminary findings in chronic stroke survivors demonstrated that moderate intensity treadmill training reverses impaired glucose tolerance and type 2 diabetes status in 58% of cases [18]. The study investigated the effects of 6-month moderate intensity treadmill training ( $N = 26$ ) versus stretching exercises ( $N = 21$ ) on insulin response during an OGTT and found significant reductions with treadmill training in fasting insulin areas compared to controls ( $-23\%$  versus  $+9\%$ ,  $P < 0.05$ ). Changes in insulin area were inversely related to changes in CR fitness by  $\text{VO}_2$  peak in the two groups combined ( $r = -0.34$ ,  $P < 0.05$ ), but not to body weight or fat mass [18]. This suggested that greater improvements in  $\text{VO}_2$  peak, as with higher intensity training, may

TABLE 1: Cardiorespiratory adaptations to aerobic training after stroke.

Mode	No. of subjects	Program duration weeks	Frequency x/week	Session duration minutes	Intensity	Change in peak VO <sub>2</sub> %
Subacute stroke (<6 months after stroke)						
Cycle ergo meter [82]	E: 44 C: 48	12	3	20–30	40 rpm	E: +9 C: +0.5
Treadmill [83]	E: 6 C: 6	26	5	20	NR	E: +35 C: +1
Cycle ergo meter [21]	E: 23 C: 22	3–4	3	30	50–75% peak VO <sub>2</sub>	E: +13 C: +8
Chronic stroke (>6 months after stroke)						
Cycleergometer [84]	E: 37 C: 24	26	3	10–20	40–50% HRR	E: +18 C: –3
Cycleergometer [85]	E: 24 C: 24	8	2	20	50–60% HRR	E: +13 C: –3
Treadmill [18]	E: 26 C: 20	26	3	40	60–70% HRR	E: +15 C: –3
E1: Mod intensity [86] E2: Low intensity	E1: 18 E2: 19 C: 18	14	3	30–60	E1: 50–69% HRR E2: <50% HRR	E1: +4 E2: +6 C: –3
Treadmill + strengthening [87]	E: 14	12	5	90	80% HR max	E: +19
Treadmill [81]	E: 20*	4	2–5	NR	80–85% HR max or RPE 17	Immediate: +6 Delayed: +6
Cycle ergometer [85]	E: 19 C: 23	10	3	30	50–70 rpm	E: +13 C: +1
Aerobic exercise [80]	E: 29	12	3	30	HR at RER of 1.0	E: +8
Treadmill [13]	E: 23	26	3	20	<60% HRR	E: +10
Aerobic exercise [88]	E: 32 C: 31	19	3	60	<80% HRR	E: +9 C: +1
Water based [89]	E: 7 C: 5	8	3	30	<80% HRR	E: +23 C: +3

E: Experimental; C: control; rpm: revolutions per minute; HRR: heart rate reserve; \*crossover design; NR: not reported; RPE: rating of perceived exertion; RER: respiratory exchange quotient.

produce even greater improvements in insulin sensitivity. These preliminary findings have implications for diabetes prevention after stroke and warrant further investigation in the larger context of improving general health and function in this population.

*Vascular Adaptations with Exercise after Stroke.* During exercise, the arterial wall is chronically exposed to increased blood flow, and the vessel diameter expands to accommodate a larger volume of flow [55, 56]. However, as with the above outcome categories, vascular adaptations to exercise after exercise stroke remain only partially understood, with initial experiments providing encouraging preliminary results. First, the group observed vascular changes after a unilateral training program that focused on exercising only the paretic leg. Beyond demonstrating increased functional performance and strength in the paretic limb with this intervention, there were also substantial vascular changes on the paretic side with the potential for altering regional and systemic physiological health [3]. Specifically, four weeks

of unilateral leg training improved femoral artery blood flow and diameter [3]. More recently, treadmill training over six months has resulted in significantly improved resting and hyperemic blood flow in the paretic and the non-paretic lower extremities, when compared to elements of conventional stroke rehabilitation [8]. Briefly, treadmill training increased both resting and reactive hyperemic blood flow in the paretic limb by 25% compared to decreases in the control group ( $P < 0.001$ , between groups). Similarly, non-paretic leg blood flow was significantly improved with tread mill training compared to controls ( $P < 0.001$ ). CR fitness (VO<sub>2</sub> peak) improved by 18% with tread mill training and decreased by 4% in control ( $P < 0.01$ , between groups), and there was a significant relationship between blood flow change and peak fitness change for the group as a whole ( $r = 0.30$ ,  $P < 0.05$ ). There has been also recently published evidence showing that treadmill exercise training can have a positive impact on cerebral vasomotor function in both hemispheres, particularly in those not taking statin medication [62]. These data provided the first evidence of exercise-induced cerebral vasomotor reactivity

improvements in stroke survivors, implying a protective mechanism against recurrent stroke and other brain-related disorders.

*Respiratory Adaptations.* Although reduced respiratory function has been reported after stroke, therapeutic interventions aimed at improving respiratory muscle strength and function are extremely limited. Two recent randomized controlled trials have examined the effects of inspiratory muscle training (IMT) in people after stroke. One trial examined whether six weeks of inspiratory muscle training would produce significant improvements in cardiopulmonary function when compared to a 6-week intervention consisting of breathing techniques and also a control group [63]. The authors concluded that IMT produced significant improvements in pulmonary function variables and cardiopulmonary outcomes during peak exercise testing. These improvements translated into functional gains as observed by the Barthel Index and functional ambulation scores.

Britto et al. published findings from a double-blind randomized controlled trial in chronic stroke survivors [108]. Individuals were randomized to an 8-week home-based exercise training program using either (1) an inspiratory muscle trainer (IMT) with progressive increases in resistance or (2) an IMT without resistance. Results demonstrated significant improvements in respiratory function (maximal inspiratory pressure and inspiratory muscular endurance) for the experimental group but not the control group. Although the experimental group (IMT with resistance) was able to exercise at a higher workload for the functional performance test, these differences were not significantly different. More work is needed in this area to identify other biologic factors which precipitate respiratory decline, identify therapeutic interventions to improve breathing mechanics, and improve pulmonary function in those individuals post-stroke.

## 2.5. Adaptations in Memory and Cognition after Exercise and Stroke

*2.5.1. Animal Models.* Given the central importance of cognitive health to all aspects of functional and physiological health after stroke [109], researchers are now accumulating evidence related to how exercise impacts this outcome category. Over the past 15 years, progress has been made in understanding the influences of exercise on central nervous system functions (see reviews Kramer, 2007; Devine, 2009). Animal studies have demonstrated favorable effects of aerobic training on neural function through modulation of synaptic plasticity underlying neuroprotective and neuroadaptive processes [110]. For example, learning and memory were enhanced in rats after one week of voluntary wheel running [111], possibly through the upregulation of brain-derived neurotrophic factor (BDNF) [112, 113] or other growth factors, such as vascular endothelial growth factor [114]. In a rodent stroke model, treadmill exercise enhanced gene expression for BDNF and a corresponding reduction in brain infarct volume [115]. Similarly, exercise attenuated the effects of traumatic brain injury, again in a rodent model, through a BDNF-mediated mechanism [116].

These neuroplastic responses appear to be dose dependent [117].

*2.5.2. Human Models.* Human studies have begun to reinforce the findings of the earlier animal work. Evidence of a causal relationship between exercise training and improved cognition has been reported in older adults without known cognitive impairment [118, 119] and in people with cardiovascular disease [120]. Quaney and colleagues [121] provided the first preliminary evidence on the effects of exercise training on cognitive executive function and motor learning in chronic stroke survivors. After an 8-week cycle ergometry exercise program, significant improvements were found in measures of information processing and complex motor learning tasks [121].

## 3. Conclusions

Reduced CR fitness after stroke is well documented with clinically relevant physiologic consequences. Although the precise mechanisms and the consequences of the severe reduction in CR fitness have not been fully elucidated, preliminary evidence points to several noteworthy biological correlates. For example, maladaptive changes to the tissues of the paretic side may both contribute to and be compounded by reductions in CR fitness. These include negative unilateral changes in muscle mass, intramuscular fat, muscle fiber type distribution, hemodynamic function, capillary density, and inflammatory markers. Further, there are systemic disturbances to metabolism and respiration which are exacerbated due to the presence of sedentary living and accompanying CR fitness decline. The evidence in the literature suggests that maladaptive physiologic changes have been observed in the paretic lower limb and these may contribute to the low CR fitness found in people post-stroke.

Exercise training has been shown to be a potent stimulus for improving CR fitness and associated physiological outcomes in both stroke and nonstroke aging populations. Changes in  $\text{VO}_2$  peak, muscle tissue quantity, muscle biology, tissue inflammation, pulmonary function, systemic metabolism, and cognition have all been reported in various elderly and disabled subgroups. Although the body of evidence for exercise-induced adaptation in stroke is limited, great progress has been made over the last decade to show that stroke survivors maintain their capacity to adapt and are capable of performing exercise at levels not previously thought possible. Further work is needed to determine the effects of exercise on attenuating inflammatory responses and improving tissue composition after stroke. While a limited number of exercise training studies have increased pulmonary performance after stroke, it is evident that continued work in this area is needed to improve functional and cardiorespiratory outcomes. Finally, larger randomized research studies aimed at effective exercise prescription and informing best practice in stroke rehabilitation are essential to the advancement of stroke recovery.

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