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ORIGINAL RESEARCH

Cardiorespiratory Fitness in Individuals Post-stroke: Reference Values and Determinants

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Abstract

Objective: To provide reference values of cardiorespiratory fitness for individuals post-stroke in clinical rehabilitation and to gain insight in characteristics related to cardiorespiratory fitness post stroke.

Design: A retrospective cohort study. Reference equations of cardiopulmonary fitness corrected for age and sex for the fifth, 25th, 50th, 75th, and 95th percentile were constructed with quantile regression analysis. The relation between patient characteristics and cardiorespiratory fitness was determined by linear regression analyses adjusted for sex and age. Multivariate regression models of cardiorespiratory fitness were constructed.

Setting: Clinical rehabilitation center.

Participants: Individuals post-stroke who performed a cardiopulmonary exercise test as part of clinical rehabilitation between July 2015 and May 2021 (N=405).

Main Outcome Measures: Cardiorespiratory fitness in terms of peak oxygen uptake ($\dot{V}O_2$peak) and oxygen uptake at ventilatory threshold ($\dot{V}O_2$-VT).

Results: References equations for cardiorespiratory fitness stratified by sex and age were provided based on 405 individuals post-stroke. Median $\dot{V}O_2$peak was 17.8[range 8.4-39.6] mL/kg/min and median $\dot{V}O_2$-VT was 9.7[range 5.9-26.6] mL/kg/min. Cardiorespiratory fitness was lower in individuals who were older, women, using beta-blocker medication, and in individuals with a higher body mass index and lower motor ability.

Conclusions: Population specific reference values of cardiorespiratory fitness for individuals post-stroke corrected for age and sex were presented. These can give individuals post-stroke and health care providers insight in their cardiorespiratory fitness compared with their peers. Furthermore, they can be used to determine the potential necessity for cardiorespiratory fitness training as part of the rehabilitation program for an individual post-stroke to enhance their fitness, functioning and health. Especially, individuals post-stroke with more mobility limitations and beta-blocker use are at a higher risk of low cardiorespiratory fitness.

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In the general population, cardiorespiratory fitness is the best predictor of all-cause mortality[1,2] and it has been linked to a decreased chance of cardiovascular disease and a higher quality of life.[3] Post stroke, a higher cardiorespiratory fitness has been linked to better walking ability,[4] higher physical activity levels,[5] and decreased stroke recurrence.[6] Improving cardiorespiratory fitness through training is possible post stroke[7,8] and an increase in cardiorespiratory fitness post stroke has been linked to improved functioning.[9] Therefore, insight in cardiorespiratory fitness of individuals post-stroke is important to assess and address potential risks of decreased functioning and health.

Cardiorespiratory fitness of individuals post-stroke is reported to be on average 53% of that reported for able-bodied individuals.[10] This can partially be attributed to the fact that less fit individuals are more prone to experience a stroke.[11] Furthermore,

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cardiorespiratory fitness can decrease because of physical inactivity directly after stroke and the consequences of the stroke itself.[8] In addition, motor and cognitive consequences of stroke can limit the ability to resume normal daily activities and thereby further decrease cardiorespiratory fitness.[12]

The criterion standard to assess cardiorespiratory fitness is peak oxygen uptake ($\dot{V}O_2$peak) derived from a cardiopulmonary exercise test (CPET). To interpret the cardiorespiratory fitness, $\dot{V}O_2$peak is compared with reference values that are often obtained from an able-bodied, asymptomatic population.[13-15] This comparison is valid to provide insight in general fitness and risk of comorbidities and mortality. However, the use of able-bodied reference values also poses problems because most individuals post-stroke fall in the lowest fitness category. This floor effect makes it hard to distinguish between patients and to decide for which individuals fitness training might deserve specific attention. Because we know that individuals in the lowest fitness categories can gain the most by improving fitness,[7,8] it seems important to provide individuals with reference values of their peers.

Although the $\dot{V}O_2$peak of individuals post-stroke has been described in a considerable number of publications,[10] reference values of cardiorespiratory fitness for individuals post-stroke do not currently exist. Furthermore, most publications do not report on ventilatory threshold. At intensities below ventilatory threshold, exercise can be sustained for a prolonged time. Above ventilatory threshold, anaerobic energy pathways are increasingly used, which leads to lactate accumulation and fatigue. Therefore, the ventilatory threshold is often used to prescribe training intensity.

Next to the lack of patient specific reference values, there is limited information on patient characteristics influencing cardiorespiratory fitness post-stroke. A study including 113 individuals after minor stroke or TIA reported that $\dot{V}O_2$peak was significantly associated with physical activity and history of cardiovascular or pulmonary disease, but not with several stroke characteristics.[16] In a study on 59 individuals post-stroke in the chronic phase, both comfortable gait speed and Fugl-Meyer score were shown to be correlated with $\dot{V}O_2$peak but not with $\dot{V}O_2$-VT.[17] Expanding the knowledge on associated factors could reveal which individuals are at risk for low fitness levels and provide clues regarding mechanisms influencing cardiorespiratory fitness post-stroke, which could guide treatment.

This study aims (1) to provide population specific reference values of cardiorespiratory fitness in terms of both $\dot{V}O_2$peak and $\dot{V}O_2$-VT for individuals post-stroke in clinical rehabilitation and (2) to gain insight in associations between patient characteristics and cardiorespiratory fitness post-stroke.

List of abbreviations:

BBS	**Berg Balance Scale**
BMI	**body mass index**
CPET	**cardiopulmonary exercise test**
FAC	**functional ambulation category**
MI	**Motricity index**
TSI	**time since stroke**
USERm	**Utrecht Scale of Evaluation of Rehabilitation mobility sub-score**
$\dot{V}O_2$	**oxygen uptake**
$\dot{V}O_2$peak	**peak oxygen uptake**
$\dot{V}O_2$-VT	**oxygen uptake at ventilatory threshold**
VT	**ventilatory threshold**

Methods

Participants

This study included adult individuals post-stroke, who were referred for a routine CPET as part of their rehabilitation in Heliomare Rehabilitation Center (Wijk aan Zee, the Netherlands) between July 2015 and April 2021. Individuals post-stroke are referred to Heliomare when they have a prognosis of returning to independent living after multidisciplinary rehabilitation. CPET inclusion was according to ACSM criteria[18] with additional inclusion criteria: ability to perform 10 minutes of unloaded cycling and a functional ambulation category (FAC)>2. This study was reviewed by the medical ethical committee of Vrije Universiteit Medical Centre Amsterdam and approved by the local ethical committee of Heliomare. Participants gave permission to include their data by signing the informed consent or afterward by a no-objection letter.

Participants were selected from Heliomare's CPET database based on ICD9 codes. Individuals were excluded from analysis when they (1) were >1 year post-stroke, (2) presented with either subarachnoid hemorrhage, traumatic head injury, sinus thrombosis, or arterial malformations, or (3) had undergone invasive brain surgery such as craniectomy or bypass.

Primarily, the first CPET for each individual was selected. When this test was not deemed maximal conform the criteria stated below, any available follow-up test that did reach maximal criteria was included for that individual.

Cardiopulmonary exercise test

The CPET was performed under supervision of a physician on an upright or semi-recumbent cycle-ergometer[a] depending on the participants functionality. After 3 minutes rest and 3 minutes warm-up at 0 Watt, a ramp protocol based on the estimated maximum exercise capacity of the participant was used, so that the exercise phase was expected to last about 8-12 minutes. Participants were instructed to cycle at 70 revolutions per minute if possible. The test was stopped if cycling pace dropped below 50 rounds per minute due to patient exhaustion or if the physician deemed it unwise to continue. A cool-down phase of 3 minutes at 10% of maximal power followed. Breath-by-breath gas exchange[b], ECG and arterial oxygen saturation were continuously monitored.

Data analysis

Cardiorespiratory fitness

Cardiorespiratory fitness was expressed both as peak oxygen uptake ($\dot{V}O_2$peak) and as oxygen uptake at ventilatory threshold ($\dot{V}O_2$-VT). Both were determined from CPET data. The maximum of the 30-second averaged $\dot{V}O_2$ was considered $\dot{V}O_2$peak. $\dot{V}O_2$ peak was considered valid when a participant reached a respiratory exchange ratio (RER) >1.1 concurrently (>1.05 and >1.0 for participants over 50 and over 65 years of age, respectively).[19,20]

Two assessors determined VT according to the V-slope method.[21] A plot of the ventilatory equivalents and RER over time was presented after V-slope assessment, to allow the assessor to evaluate the time point of VT. If the assessors did not agree on the $\dot{V}O_2$-VT within 100 mLO_2/min, they conferred to reach consensus.

Determinants

Data regarding age, sex, height, body mass, time since stroke (TSI), and use of beta-blocker medication were obtained before the CPET. In addition, the following characteristics were derived from patient files: stroke characteristics (left or right, ischemic or hemorrhagic, first or recurrent), Utrecht Scale of Evaluation of Rehabilitation mobility sub-score (USERm),[22] Berg Balance Scale (BBS),[23,24] Motricity index (MI),[25] and FAC.[26] The functional tests were administered as part of regular rehabilitation treatment and included when assessed within 30 days of the CPET.

Statistical analysis

Data were analyzed using SPSS (IBM SPSS Statistics version 27.0, IBM Corp). Outcome measures were checked for normality using visual inspection, skewness and kurtosis. A *P* value of <0.05 was considered significant.

Reference equations

Reference equations for cardiorespiratory fitness in the fifth, 25th, 50th, 75th, and 95th percentile of the population were constructed using quantile regression stratified for age and sex. Quantile regression is a statistical model that fits a regression curve to specific percentiles of the distribution of the dependent variable.[27,28]

Associations

To explore the associations of the different patient characteristics with cardiorespiratory fitness, linear regression analyses adjusted for age and sex were performed with both $\dot{V}O_2$peak and $\dot{V}O_2$-VT as dependent variable. The following determinants were explored: body mass index (BMI), TSI, type of stroke (ischemic/hemorrhagic, side of stroke, first or recurrent stroke), use of beta-blocker medication, USERm, BBS (dichotomized: with (BBS<45), or without increased fall risk (BBS>44)), FAC (dichotomized: dependent (FAC=0-4) or independent ambulators (FAC=5)), and MI.

Multivariate regression model

Multivariate models for cardiorespiratory fitness based on the available characteristics were developed with multiple regression analyses. Determinants with associations from linear regression with *P*<.20 were included in the primary model. Because not all determinants were available for all individuals (table 1), multiple imputation was used for missing data. Multiple imputation prevents bias from discarding incomplete cases and prevents loss of power in multivariate analysis.[29] Data were imputed 5 times based on all available data points. Statistical results of these 5 samples were averaged.[30]

After imputation, determinants were checked for multicollinearity based on correlation and the variance inflation factor.[31] Then, 2 multiple linear regression models with dependent variables: $\dot{V}O_2$peak and $\dot{V}O_2$-VT and all applicable determinants were developed using backward elimination technique. A value of *P*<.05 was considered significant for the beta of the determinants. Only main effects of determinants were evaluated. The explained variance of both models was reported.

Results

Inclusion

712 CPETs of 517 individuals were identified based on ICD9 code (fig 1). Eighty individuals were excluded based on exclusion criteria or missing raw data. Of the remaining 437 individuals, 43 first CPETs were excluded for lack of maximal effort. Eleven of these

Table 1 Patient characteristics

		N
Age (y)	63[23-89]	405
Sex (M/F) (%M)	284/121 (70)	405
BMI (kg/m^2)	25.5[17.2-46.1]	405
Time since stroke (d)	31 [6-228]	405
Side of stroke (left/right/other)	204/164/37	405
Stroke type (ischemic/hemorrhagic/other)	340/61/4	405
first/recurrent stroke	347/58	405
Beta-blocker medication (yes/n)	121/255	376
Motricity index*	158 [0-200]	315
Functional ambulation category (0-3/4/5)*	100/100/149	349
Berg Balance Score*	49 [4-56]	346
Utrecht Scale of Evaluation of Rehabilitation mobility*	28 [0-35]	355
CPET protocol (W/min)	10 [5-24]	404
Ergometer type (cycle/recumbent cycle/unknown)	379/19/7	405
$\dot{V}O_2$peak (mL/kg/min)	17.8 [8.4-39.6]	405
$\dot{V}O_2$peak (%predicted)†	75.9 [32.0-137.6]	404
$\dot{V}O_2$-VT (mL/kg/min)	9.7 [5.9-26.6]	399
$\dot{V}O_2$-VT (%predicted maximum)*	40.8 [17.8-88.0]	399
$\dot{V}O_2$-VT (%$\dot{V}O_2$peak)	55.6 (10.6)	399
RER peak	1.18 [1.00-1.52]	405
Peak Power (Watts)	101 [31-282]	405
Peak heart rate (beats/min)	141 [71-200]	399
Peak heart rate (%pred)	93 [46-137]	393

NOTE. Values are presented as mean (standard deviation) or median [range], respectively.
* Functional tests were administered as part of regular rehabilitation treatment and included when assessed within 30 days of the CPET.
† Based on Wasserman et al.[13]

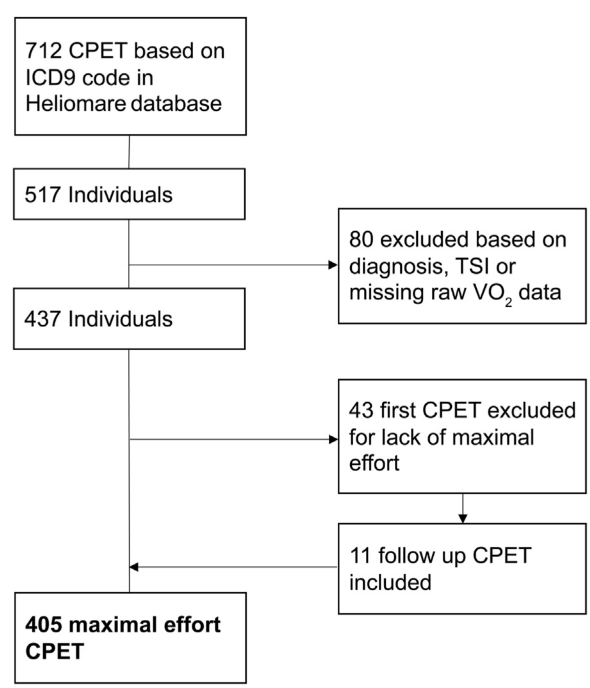

Fig 1 Inclusion flow chart.

individuals performed a maximal effort follow-up test that was then included. Thus, 405 maximal effort CPETs were included in the analysis. In 6 cases, VT could not be determined.

Descriptives

Patient characteristics and main outcome measures are reported in table 1. Median time between functional tests and CPET was 10 days. Median $\dot{V}O_2$peak was 17.8 mL/kg/min and 76% of able-bodied norm values.[13] Median $\dot{V}O_2$-VT was 9.7 mL/kg/min.

Because both $\dot{V}O_2$peak and $\dot{V}O_2$-VT showed a skewed distribution, they were log transformed in the regression analyses.

Reference values

Quantile regression showed a significant decrease of $\dot{V}O_2$peak with age for all percentiles (fig 2, table 2). Women showed significantly lower $\dot{V}O_2$peak compared with men in all percentiles except for the fifth percentile. Quantile regression showed no significant effects of age on $\dot{V}O_2$-VT except for the 75th percentile. Sex did not significantly affect $\dot{V}O_2$-VT in the fifth and 25th percentiles. However, the effect of sex was significant in the 50th, 75th, and 95th percentiles.

Table 2 Quantile regression parameter estimates

	$\dot{V}O_2$peak (mL/kg/min)			$\dot{V}O_2$-VT (mL/kg/min)		
	Intercept	Sex	Age (y)	Intercept	Sex	Age (y)
q05	15.8*	-0.04	-0.07*	6.40*	0.45	0.01
q25	20.7*	-2.10*	-0.08*	7.85*	-0.47	0.01
q50	28.6*	-2.93*	-0.16*	11.21*	-0.93*	-0.02
q75	35.1*	-3.93*	-0.20*	15.29*	-1.25*	-0.05*
q95	44.2*	-5.71*	-0.23*	20.54*	-2.10*	-0.08

* Significant at the P<.05 level. Sex was coded 0=men, 1=women.

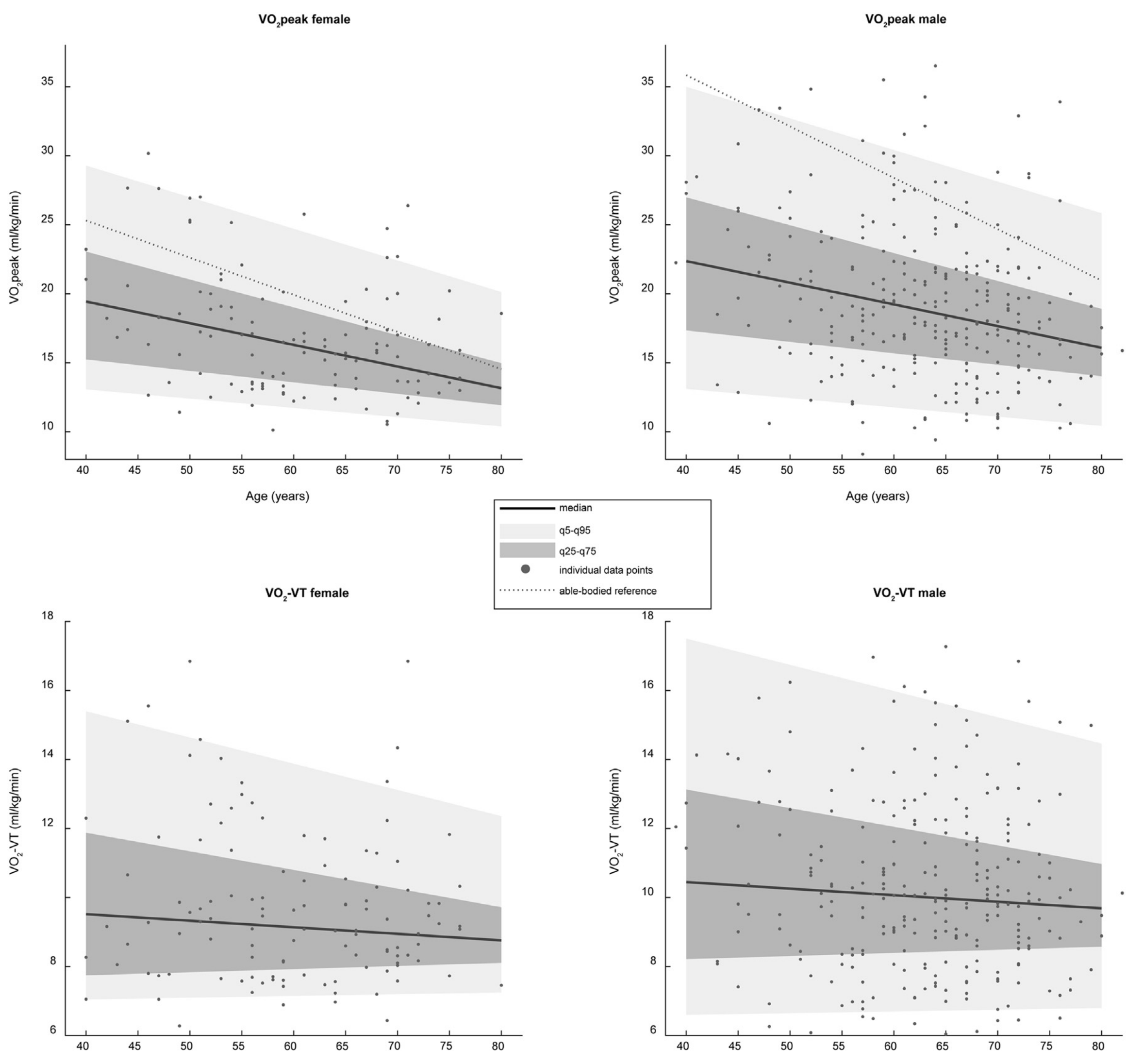

Fig 2 Reference values of peak oxygen uptake (upper panels) and oxygen uptake at ventilatory threshold (lower panels) for women (left panels) and men (right panels) post-stroke. Solid lines represent median values, dark gray patches the 25th-75th percentiles and light gray patches the 5th-95th percentiles of cardiorespiratory fitness. Reference values for able-bodied peak oxygen uptake based on Wasserman et al (2011)[13] are represented as the gray dotted lines in the upper panels.

Associations

The determinant TSI was log transformed because residuals were not normally distributed.

$\dot{V}O_2$peak and $\dot{V}O_2$-VT were significantly lower in individuals with beta-blocker medication, higher BMI, longer TSI, lower MI, and lower USERm when corrected for age and sex (table 3). Additionally, BBS was positively associated with $\dot{V}O_2$-VT, but not with $\dot{V}O_2$peak. FAC, side of stroke, type of stroke, and first or recurrent stroke were not associated with cardiorespiratory fitness.

Multivariate regression model

Significant determinants of $\dot{V}O_2$peak in the final model were age, sex, beta-blocker medication, BMI, TSI, and USERm (table 4). A lower $\dot{V}O_2$peak was predicted for women, older individuals, individuals using betablocker medication, individuals with higher BMI, individuals longer post-stroke, and individuals with a lower USERm. Explained variance was 30% (average r^2=0.298[0.291-0.308], average F=28.2[27.1-29.6]).

Significant determinants of $\dot{V}O_2$-VT in the final pooled model were sex, beta-blocker medication, BMI, TSI, USERm, and MI (table 3). A lower $\dot{V}O_2$peak was predicted for women, individuals using beta-blocker medication, individuals with higher BMI, individuals longer post-stroke, and individuals with lower motor ability. Explained variance was 20% (average r^2=0.195[0.185-0.214], average F=13.5[12.6-15.2]).

Discussion

This study provides population specific reference values of cardiorespiratory fitness for individuals post-stroke corrected for age and sex. The reference values were constructed based on cardiopulmonary exercise tests of individuals post-stroke undergoing rehabilitation care in the Netherlands. Quantile regression showed that cardiorespiratory fitness post-stroke decreased with age and was lower in women. The constructed percentiles can give individuals post-stroke insight in their cardiorespiratory fitness relative to a heterogenous group of individuals post-stroke in clinical rehabilitation. Multiple linear regression analyses showed that cardiorespiratory fitness post-stroke was correlated strongest with age, sex, BMI, use of beta-blocker medication, TSI, and motor ability. These characteristics could indicate which individuals post-stroke are at an increased risk of a low cardiorespiratory fitness.

We found median $\dot{V}O_2$peak values of 17.8[8.4-39.6] mL/kg/min. This is within the range of 8-22 mL/kg/min $\dot{V}O_2$peak reported in a 2012 review on individuals post-stroke.[10] It is comparable with the average of a cohort of individuals 3 months post stroke in Belgium (18.1 mL/kg/min)[9] but somewhat lower than the average of a cohort of individuals in the Netherlands after minor stroke or TIA (22.5 mL/kg/min).[16] However, our cohort scored far below the average values reported in able-bodied populations. For example, median $\dot{V}O_2$peak in our cohort was 76% of the reference value for able-bodied individuals reported by Wasserman et al.[13] Thus, cardiorespiratory fitness of the current cohort was comparable with that of other stroke cohorts, but low compared with the able-bodied population.

We found a large variance in cardiorespiratory fitness post-stroke: $\dot{V}O_2$peak ranged from 8.4 to 39.6 mL/kg/min or 32%-138% of able-bodied reference values.[13] To quantify this variance, we constructed quantile reference values relative to age and sex. Wide ranges in cardiorespiratory fitness between the fifth and 95th percentile show that individual responses vary widely even when corrected for age and sex. The presented quantile regression can give an individual post-stroke or their health care provider insight in how their cardiorespiratory fitness compares to their peers.

To further explain differences between individuals, we explored other factors that might influence cardiorespiratory fitness post-stroke with multivariate regression analyses. Similar to other reports,[14-16] we found that cardiorespiratory fitness was lower in women, older individuals, and individuals with higher BMI. Interestingly, cardiorespiratory fitness was not correlated to stroke subtypes. Boss et al[16] who included more detailed stroke subtypes in their model also did not find any correlations with cardiorespiratory fitness. This suggests that stroke subtyping is not relevant for identifying individuals at risk for low cardiorespiratory fitness.

Stroke characteristics associated with lower cardiorespiratory fitness were use of beta-blocker medication, lower motor ability,

Table 3 Univariate regression parameter estimates

	$\dot{V}O_2$peak (mL/kg/min)				$\dot{V}O_2$-VT (mL/kg/min)			
	β	95% CI	P	r^2	β	95% CI	P	r^2
Age (y)	0.992	0.990-0.995	<.001*	0.117	0.998	0.996-1.000	.062	0.024
Sex (0=men, 1=women)	0.856	0.809-0.910	<.001*	0.117	0.929	0.884-0.985	.006*	0.024
Beta-blocker medication (0=no, 1=yes)	0.863	0.816-0.914	<.001*	0.175	0.906	0.860-0.955	<.001*	0.057
Body mass index (kg/m^2)	0.984	0.978-0.991	<.001*	0.164	0.987	0.981-0.993	<.001*	0.064
Side of stroke (0=left, 1=right)	0.951	0.900-1.005	.076	0.105	0.959	0.912-1.008	.099	0.022
Type of stroke (0=Ischemic, 1=Hemorrhagic)	1.007	0.936-1.083	.852	0.121	1.006	0.941-1.076	.865	0.019
First or recurrent stroke (0=first, 1=recurrent)	0.990	0.919-1.068	.801	0.117	1.036	0.967-1.111	.330	0.027
Ln(time since stroke) (d)	0.984†	0.934-0.963	<.001*	0.144	0.949†	0.932-0.968	<.001*	0.059
Motricity index [0-200]	1.001	1.001-1.002	<.001*	0.176	1.001	1.001-1.002	<.001*	0.098
FAC (0=0-4, 1=5)	1.050	0.994-1.111	.080	0.156	1.038	0.986-1.092	.157	0.038
BBS (0<45, 1>44)	1.011	0.953-1.074	.714	0.138	1.060	1.002-1.120	.041*	0.044
USERm [0-35]	1.006	1.003-1.009	<.001*	0.191	1.005	1.002-1.008	.004*	0.062

NOTE. β indicates the percent change in cardiorespiratory fitness when the determinant increases by 1 unit.
* Significant at the P<.05 level.
† Because of the log transformation of the predictor, this number represents the change when time since stroke is doubled.

Table 4 Multivariate regression parameter estimates

	$\dot{V}O_2$peak			$\dot{V}O_2$-VT		
	β	95% CI	*P*	β	95% CI	*P*
(Constant)	50.45	38.31-66.46	<.001	17.10	13.07-22.36	<.001
Age (y)	0.994	0.991-0.996	<.001	0.998	0.894-0.984	.065
Sex (0=men, 1=women)	0.865	0.822-0.911	<.001	0.938	0.996-1.000	.009
Beta-blocker medication (0=no, 1=yes)	0.875	0.830-0.924	<.001	0.915	0.869-0.964	.001
Body mass index (kg/m^2)	0.984	0.978-0.991	<.001	0.986	0.981-0.992	<.001
Ln(time since stroke [d])	0.936*	0.873-0.946	<.001	0.953*	0.896-0.972	.001
USERm [0-35]	1.008	1.005-1.011	<.001	1.004	1.001-1.007	.017
Motricity index [0-200]	n.s.	n.s.	n.s.	1.001	1.000-1.001	.005

NOTE. β indicates the percent change in $\dot{V}O_2$peak when the determinant increases by 1 unit.
Abbreviations: CI, confidence interval; n.s., not significant.
* Because of the log transformation of the predictor, this number represents the change when time since stroke is doubled.

and longer TSI. These associations existed even though we did not assess all characteristics at the time of the CPET. Potentially, assessing motor function at the time of the CPET might have led to stronger associations. Unfortunately, this was not possible in this retrospective study based on data collected in a clinical setting. Nevertheless, these characteristics could help identify those individuals post-stroke at higher risk of low cardiorespiratory fitness and potentially guide rehabilitation treatment. These characteristics are discussed in the paragraphs below.

Individuals using beta-blocker medication attained a 12% lower $\dot{V}O_2$peak and 8% lower $\dot{V}O_2$-VT in the model. The effect of beta-blockers on exercise capacity has been shown to vary per treated condition, per individual, and per type and dosage of medication.[32] Because we did not record these parameters, it is unclear what direct effect the medication had on cardiorespiratory fitness. Most likely these effects are mixed. Potentially, beta-blockers served as a proxy for comorbidities that were not recorded in the model. Individuals using beta-blockers are likely those with more comorbidities and these comorbidities potentially limit exercise capacity. Because individuals using beta-blockers have been shown to be able to improve cardiorespiratory fitness through physical training, this group could potentially benefit from exercise training in rehabilitation.

In the current cohort, a longer TSI was associated with a lower $\dot{V}O_2$peak, even when accounting for motor ability. Potentially, individuals who can perform a CPET earlier after stroke have been less deconditioned by inactivity directly post stroke. However, this correlation should be interpreted with caution: first, the range of TSI in our study was limited, which limits the generalization of these results. Second, the effect of TSI, was small: a 10% increase was related to a 1.5% decrease in both $\dot{V}O_2$peak and $\dot{V}O_2$-VT. Therefore, including TSI in risk assessment or comparison between individuals post-stroke is not advised based on this study.

Motor ability significantly explained part of the variance in cardiorespiratory fitness. An individual with the highest USERm score in our model would attain a 32% higher $\dot{V}O_2$peak and a 15% higher $\dot{V}O_2$-VT than an individual with the lowest score. It is yet unclear how this relation should be explained. Lower motor ability might lead to more inactivity, which in turn would lead to a decreased cardiorespiratory fitness. Alternatively, a decrease in active muscle mass underlying a low motor ability could directly decrease cardiorespiratory fitness. Lastly, motor ability might directly influence the ability to perform a maximal exercise test.[17] Thus, it is unclear if and how training motor ability will increase cardiorespiratory fitness. Independent of causation, however, motor ability could be considered when assessing individuals at risk of a low cardiorespiratory fitness.

Strengths and limitations

This study's findings are strengthened by a large sample size compared with other cohorts of individuals post-stroke (N=405). Another strength is the use of 2 measures of cardiorespiratory fitness: $\dot{V}O_2$peak and $\dot{V}O_2$-VT. Similar associations between patient characteristics and both $\dot{V}O_2$peak and $\dot{V}O_2$-VT strengthen our findings.

It should be considered that these reference values are determined for individuals post-stroke in the Netherlands during their rehabilitation phase—up to about 7.5 months post stroke—in the age range of 40-80 years. Generalization of these values to other populations is not necessarily warranted.

We did not aim to provide an accurate prediction model for cardiorespiratory fitness post-stroke, but merely investigated the associations with different person and disease-related characteristics. The explained variance of the presented multivariate models was low. Therefore, these models cannot be used to replace actual measurement of cardiorespiratory fitness.

Finally, it should be stressed that a high cardiorespiratory fitness compared with a patient population might imply higher level of functioning but does not imply a low mortality risk. Therefore, these population specific reference values should be applied alongside reference values for an able-bodied population to assess both functional and health-related consequences of cardiorespiratory fitness.

Clinical implications

Previous studies have indicated that individuals post-stroke are limited in physical functioning by a low cardiorespiratory fitness.[4,33] Training cardiorespiratory fitness post-stroke is feasible and effective,[7] and most of the individuals in our cohort would likely benefit from improvements in cardiorespiratory fitness in terms of long-term health benefits and physical functioning. The presented reference values might help to determine the importance of cardiorespiratory fitness training as part of a post-stroke rehabilitation program. Potentially, for individuals scoring lower than median reference values cardiorespiratory training might be prioritized to increase functioning, whereas for others this is of lesser importance than other rehabilitation goals. Also, our results can help identify individuals with higher risk of low cardiorespiratory fitness based on stroke specific characteristics. This study showed that especially individuals with more mobility limitations and beta-blocker use tend to have a low cardiorespiratory fitness.

Conclusions

This study presents reference values of cardiorespiratory fitness for individuals post-stroke undergoing rehabilitation corrected for age and sex. These can give individuals post-stroke and health care providers insight in their cardiorespiratory fitness compared with their peers and guide rehabilitation treatment.

Cardiorespiratory fitness was lower in older individuals, women individuals, individuals with a higher BMI, individuals using beta-blocker medication, and individuals with lower motor ability.

Suppliers

a. Corival; Lode.
b. Jaeger Oxycon CPX; Vyaire.

Keywords

Anaerobic threshold; Cardiorespiratory fitness; Exercise test; Reference values; Rehabilitation; Stroke

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References

1. Ross R, Blair SN, Arena R, et al. Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a scientific statement from the American Heart Association. Circulation 2016;134:e653–99.
2. Harber MP, Kaminsky LA, Arena R, et al. Impact of cardiorespiratory fitness on all-cause and disease-specific mortality: advances since 2009. Prog Cardiovasc Dis 2017;60:11–20.
3. Lee D, Artero EG, Sui Xuemei, Blair SN. Review: mortality trends in the general population: the importance of cardiorespiratory fitness. J Psychopharmacol 2010;24:27–35.
4. Blokland I, Gravesteijn A, Busse M, et al. The relationship between relative aerobic load, energy cost, and speed of walking in individuals post-stroke. Gait Posture 2021;89:193–9.
5. Thilarajah S, Mentiplay BF, Bower KJ, et al. Factors associated with post-stroke physical activity: a systematic review and meta-analysis. Arch Phys Med Rehabil 2018;99:1876–89.
6. Ivey FM, Macko RF, Ryan AS. Hafer-Macko CE. Cardiovascular health and fitness after stroke. Top Stroke Rehabil 2005;12:1–16.
7. Saunders DH, Sanderson M, Hayes S, et al. Physical fitness training for stroke patients. Cochrane Database Syst Rev 2020;2020:1–3.
8. Billinger SA, Coughenour E, MacKay-Lyons MJ, Ivey FM. Reduced cardiorespiratory fitness after stroke: biological consequences and exercise-induced adaptations. Stroke Res Treat 2012;2012.
9. Baert I, Daly D, Dejaeger E, Vanroy C, Vanlandewijck Y, Feys H. Evolution of cardiorespiratory fitness after stroke: a 1-year follow-up study. influence of prestroke patients' characteristics and stroke-related factors. Arch Phys Med Rehabil 2012;93:669–76.
10. Smith AC, Saunders DH, Mead G. Cardiorespiratory fitness after stroke: a systematic review. Int J Stroke 2012;7:499–510.
11. Writing Group MembersMozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics-2016 update: a report from the American Heart Association. Circulation 2016;133:e38–360.
12. Tiozzo E, Youbi M, Dave K, et al. Aerobic, resistance, and cognitive exercise training poststroke. Stroke 2015;46:2012–6.
13. Wasserman K, Hansen JE, Sue DY, et al. Principles of exercise testing and interpretation: including pathophysiology and clinical applications. 5th ed. Philadelphia: Lippincott Williams and Wilkins; 2011.
14. van der Steeg GE, Takken T. Reference values for maximum oxygen uptake relative to body mass in Dutch/Flemish subjects aged 6−65 years: the LowLands Fitness Registry. Eur J Appl Physiol 2021;121:1189–96.
15. Koch B, Schäper C, Ittermann T, et al. Reference values for cardiopulmonary exercise testing in healthy volunteers: the SHIP study. Eur Res J 2009;33:389–97.
16. Boss HM, Deijle IA, van Schaik SM, et al. Cardiorespiratory fitness after transient ischemic attack and minor ischemic stroke: baseline data of the MoveIT study. J Stroke Cerebrovasc Dis 2017;26:1114–20.
17. Boyne P, Reisman D, Brian M, et al. Ventilatory threshold may be a more specific measure of aerobic capacity than peak oxygen consumption rate in persons with stroke. Top Stroke Rehabil 2017;24:149–57.
18. Williams Wilkins. American College of Sports Medicine. ACSM's guidelines for exercise testing and prescription. 6th ed. Philadelphia: Lippincott; 2000.
19. van de Port IGL, Kwakkel G, Wittink H. Systematic review of cardiopulmonary exercise testing post stroke: are we adhering to practice recommendations? J Rehabil Med 2015;47:881–900.
20. Edvardsen E, Hem E, Anderssen SA. End criteria for reaching maximal oxygen uptake must be strict and adjusted to sex and age: a cross-sectional study. PLoS One 2014;9:18–20.
21. Beaver W, Wasserman K, Whipp B. A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol 1986;60:2020–7.
22. Post MWM, van de Port IGL. Development and validation of the Utrecht Scale for Evaluation of Clinical Rehabilitation. Clin Rehabil 2009;23:909–17.
23. Berg KO, Wood-Dauphinee SL, Williams JI, Maki B. Measuring balance in the elderly: validation of an instrument. Can J Public Health 1992;83:S7–11.
24. Berg K, Wood-Dauphine S, Williams JI, Gayton D. Measuring balance in the elderly: preliminary development of an instrument. Physiother Can 1989;41:304–11.
25. Demeurisse G, Demol O, Robaye E. Motor evaluation in vascular hemiplegia. Eur Neurol 1980;19:382–9.
26. Holden MK, Gill KM, Magliozzi MR, Nathan J, Piehl-Baker L. Clinical gait assessment in the neurologically impaired. Reliability and meaningfulness. Phys Ther 1984;64:35–40.
27. Cade BS, Noon BR. A gentle introduction to quantile regression for ecologists. Front Ecol Environ 2003;1:412–20.
28. Koenker R, Hallock KF. Quantile regression. J Econ Perspect 2001;15:143–56.
29. Schafer JL. Multiple imputation: a primer. Stat Methods Med Res 1999;8:3–15.

30. Briggs A, Clark T, Wolstenholme J, Clarke P. Missing....presumed at random: cost-analysis of incomplete data. Health Econ 2003;12:377–92.
31. Field A. Discovering Statistics using SPSS Statistics. 3rd ed. London: SAGE Publications; 2009.
32. Gordon NF, Duncan JJ. Effect of beta-blockers on exercise physiology: implications for exercise training. Med Sci Sports Exerc 1991;23:668–76.
33. Blokland IJ, Schiphorst LFA, Stroek JR, et al. Relative aerobic load of daily activities after stroke. Phys Ther 2023;103:pzad005.